CHAPTER

23

ENDOCRINOLOGY

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The endocrine system of birds consists of the hypothalamic-hypophyseal complex, the gonads, pancreatic islet cells, adrenal glands, thyroid glands, parathyroid glands, ultimobranchial glands and the endocrine cells of the gut. All these organs release hormones into the bloodstream, which act on target tissues by interacting with receptors on the surface of the cell (peptide hormones) or within the cytoplasm or nucleus of the cell (steroid hormones).

Although endocrinopathies in birds do occur, endocrinology is a subject that is frequently unfamiliar to the avian practitioner. Endocrine system abnormalities may be more frequently diagnosed as practitioners expand their working knowledge of normal avian endocrinology, and appropriate clinical diagnostic tests can be used to document endocrine abnormalities.

A clinical presentation that suggests an endocrine disorder must always be confirmed before treatment is begun. Confirmation of the diagnosis may be difficult once replacement therapy is initiated, and improper or inadequate endocrine therapy can be fatal. Obesity is a good example of a clinical sign that is often misdiagnosed as an endocrine disorder (hypothyroidism) in birds, but is nearly always caused by malnutrition and lack of exercise instead. Feather abnormalities have also been reported in association with endocrine disorders without supporting evidence for an etiology. Polydipsia and polyuria can be of endocrine origin, but may also be psychogenic in origin. Psychologic factors and generalized organic diseases can profoundly affect endocrine function. Suppression of gonadotropin synthesis and reproductive failure may occur with environmental stress, and there can be an inadequate production of vitamin D in chronic renal failure leading to renal secondary hyperparathyroidism. Occasionally, failure of a target organ to respond to hormones may mimic endocrine disease (eg, nephrogenic diabetes insipidus, pseudohyperparathyroidism).

Furthermore, in man, domestic mammals and possibly also in birds, a number of endocrine syndromes may develop in association with tumors of non-endocrine origin, which form hormones that have a biological activity similar to the natural hormones (eg, paraneoplastic syndromes, ectopic hormone production).

This chapter will provide a review of normal endocrine function in birds (mostly based on gallinaceous species)[28,29,93,101] and discuss reported endocrinopathies in birds and some physiologic phenomena of clinical importance. Because there is a strong tendency among veterinarians to extrapolate knowledge of small animal endocrinology to birds, differences between avian and canine endocrinology will be highlighted.

Therapeutic measures are not given for diseases that have not been reported in birds. Guidelines for specific treatments of all endocrine abnormalities can be found in human and veterinary textbooks of internal medicine.[26,109]

The Hypothalamus and Pituitary Gland

Anatomy and Physiology

The hypothalamus is a relatively small structure that occupies about three percent of the total brain volume and forms a large portion of the ventral diencephalon. Various neural cell clusters can be recognized in the hypothalamus. Anteriorly, the most prominent are the preoptic nucleus, supraoptic nucleus and paraventricular nucleus. The infundibular nucleus and the medial posterior hypothalamic nucleus are found in the posterior or tuberal hypothalamus (see Chapter 28).

The hypophysis or pituitary gland is intimately connected to the hypothalamus. The pituitary gland consists of an adenohypophysis and a neurohypophysis (pars nervosa, neural lobe). In birds, the adenohypophysis can be divided into the pars distalis (anterior pituitary gland) and the pars tuberalis. The pars distalis forms the bulk of the adenohypophysis and is situated ventral to the neurohypophysis. Two distinct cell types can be distinguished in the cephalic and caudal part of the pars distalis, which therefore are referred to as the cephalic lobe and caudal lobe, respectively. A functional pars intermedia, which occurs in mammals, is not present in birds. The neurohypophysis can be divided into the pars nervosa (equivalent of posterior pituitary gland), the infundibular stalk and the median eminence.

The hypothalamic peptidergic neurons control pituitary gland function, whereby a variety of internal and environmental factors exert their influence by afferent neural stimuli and circulating hormone concentrations (eg, negative feedback). The hypothalamus is extensively innervated by ascending and descending afferent fibers from the rest of the central nervous system. Efferent fibers run to the pars nervosa and the median eminence of the neurohypophysis.

The supraoptic and paraventricular nuclei form the neurohypophyseal hormones, mesotocin and vasotocin, which are transported by axoplasmic flow and stored in depots in the neural lobe. The axons converge into a distinct bundle that is called the supraoptico-(neuro)hypophyseal tract. Axons terminating at the median eminence discharge their chemotransmitters into a portal system of blood vessels, which drain into the anterior pituitary gland.

Neurohypophyseal Hormones

Avian neurohypophyseal hormones, arginine vasotocin (AVT) and mesotocin (MT), are similar to the mammalian antidiuretic (arginine vasopressin, AVP) and oxytocic (oxytocin) hormones, respectively. The major effect of AVT in birds is to reduce urine production. This is accomplished by decreasing the glomerular filtration rate through constriction of the afferent arterioles of reptilian-type nephrons, and by increasing the permeability of collecting ducts of mammalian-type nephrons. AVT is released in response to plasma osmolality changes, which are registered by peripheral and central osmolality receptors. Dehydration and infusion of hypertonic solutions cause AVT release, while infusions of hypoosmotic glucose solutions depress plasma AVT concentrations below the detectable limit (<0.5 fmol/ml).

Injections of both AVT and oxytocin increase intrauterine pressure in birds, and a large increase in blood AVT concentration has been observed shortly before oviposition.

Plasma concentrations of AVT can be measured by means of an AVP radioimmunoassay that has been validated for AVT in avian plasma.

Adenohypophyseal Hormones

Adenohypophyseal hormones are either glycoproteins or polypeptides. The glycoprotein hormones are luteinizing hormone (LH), follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH; thyrotropin). They consist of two subunits: α and β.

The β subunit is the same for all three hormones, while the α subunit is hormone-specific.

The adenohypophyseal polypeptide hormones are growth hormone (GH; somatotropin), prolactin- and proopiomelanocortin (POMC)-derived hormones such as adrenocorticotrophic hormone (ACTH) and β-melanocyte stimulating hormone (α- and β-MSH), β- and τ-lipoprotein (β- and τ-LPH), β-endorphin and encephalin.

LH is secreted mainly from the caudal lobe, while TSH is secreted in the cephalic lobe. The secretion site for FSH is undetermined. Prolactin is secreted in the cephalic lobe, while GH is secreted from the somatotrophic cells in the caudal lobe. The POMC-derived hormones, ACTH and α-MSH, are secreted in the corticomelanotrophic cells of the cephalic lobe. This differs in mammals in which MSH is produced in specific cells in the intermediate lobe.

Both LH and FSH stimulate ovarian steroid synthesis and are essential for ovarian function in birds. During the ovulatory cycle, plasma FSH concentration shows little change. However, approximately five hours before ovulation, a rise in plasma LH concentration can be observed. Plasma LH concentration is low during egg laying, incubation and care for the chicks. An increase in LH secretion occurs toward the end of the chick-rearing period to prepare the hen for the next laying cycle.

In males, LH stimulates Leydig cell differentiation and testosterone synthesis, while FSH promotes Sertoli cell differentiation and spermatogenesis. A seasonal pattern of gonadal function that is regulated by daylight length has been described in birds. In male Japanese quail, a rise in plasma LH and FSH concentrations followed by increases in testicular size and gonadal steroid synthesis can be observed when the animals are transferred from 8 to 20 hours of daylight. After 50 days of being exposed to long daylight periods, the birds become refractory to photostimulation. Gonadotrophin synthesis is negatively influenced (suppressed) by other factors, such as aggressive encounters, nutritional deficiencies and the stress of restraint.

A chicken LH radioimmunoassay (RIA) can be used to measure plasma LH in other birds. The RIA for mammalian FSH can be used to measure plasma concentrations of avian FSH.

TSH increases the number of colloid droplets in thyroid cells, stimulates the uptake of iodide by the thyroid and stimulates the release of thyroxine (T_4). A human TSH RIA has been used to detect immunoreactive TSH in plasma of Japanese quail.

Avian GH has effects both on growth and on the short-term control of metabolism. Growth in chicks is markedly depressed after the administration of anti-GH antibodies. GH mobilizes stored lipids and increases free fatty acids, which are then available as an energy source. Lipogenesis is decreased. Muscle glycogen is increased and glucose utilization is reduced. GH seems to spare carbohydrates from use as a precursor for lipid synthesis.

An RIA for chicken GH is capable of detecting this hormone in many avian species (see hormonal involvement in avian growth and development).

In birds, prolactin is known to affect reproduction and osmoregulation. Effects on growth and metabolism have been suggested. In pigeons and doves, prolactin stimulates the production of crop milk. Just before the eggs are to hatch, there is a prolactin-induced proliferation and sloughing of mucosal cells in the crop sac. These cells are then regurgitated to feed the young during the first eight to eleven days of life. In other avian species, prolactin induces broodiness and suppresses ovarian function directly and indirectly via the hypothalamus. Prolactin is released after infusion of hypertonic NaCl solutions, and reduced urine flow occurs following the administration of prolactin.

Plasma prolactin concentrations can be measured by means of a homologous or heterologous RIA.

ACTH stimulates corticosterone and aldosterone production by the avian adrenal cortical (interrenal) cells.

At present, the unavailability of an ACTH RIA for avian plasma is an obstacle to studying the hypothalamic-hypophyseal-adrenocortical axis in birds, and plasma concentrations of corticosterone must be used as an indicator of plasma ACTH concentration. In ptarmigan (grouse), feather pigmentation has been shown to be influenced by MSH.[43]

Hypothalamic Releasing or Inhibiting Hormones or Factors

The hypothalamic-hypophysiotropic factors are released from the median eminence and are transported to the anterior pituitary gland via the portal blood vessels. If the chemical structure of these hypothalamic chemotransmitters is known they are called

hormones, and when the chemical structure is unknown, they are called factors. These chemotransmitters can have a stimulating or an inhibiting action on the release of the trophic anterior pituitary hormones and hence are called releasing or inhibiting hormones or factors.

The secretion of gonadotropin (LH and FSH) is controlled by LH releasing hormone (LHRH) which differs slightly from its mammalian counterpart. Both mammalian and avian LHRH stimulate avian LH secretion both *in vivo* and *in vitro*. LHRH cell bodies are located in the periventricular preoptic nucleus and in the tuberoinfundibular neurons.

The secretion of TSH is under stimulatory hypothalamic control. The hypophysiotropic factors regulating pituitary TSH release are somatostatin and thyrotropin releasing hormone (TRH), which are also physiologic regulators of GH secretion in birds.

GH release from the adenohypophysis is under hypothalamic control by TRH, growth hormone releasing factor (GRF) and somatostatin (somatotropin release inhibiting factor; SRIF), which inhibits GH secretion. Somatostatin is also formed in the avian pancreas.

Contrary to the situation in mammals, prolactin is under stimulatory hypothalamic control. The identity of avian prolactin releasing factor (PRF) remains undetermined.

The secretion of ACTH in birds is presumably under control of corticotrophin releasing factor (CRF).

Hormonal Involvement in Avian Growth and Development

A number of hormones play a major role in the control of growth. These include GH, T_4 (3,5,3',5' – tetraiodothyronine), T_3 (3,5,3' – triiodothyronine) and the sex steroids. The effect of GH on growth is via mediating factors: insulin-like growth factors (IGF) I and II (somatomedins), transforming growth factors (TGF), epidermal growth factors (EGF) and nerve growth factors (NGF).[81] Insulin appears to be available for the embryo all throughout chicken ontogeny, and the gene is expressed before the pancreas differentiates.[88] Plasma concentrations of GH are first detectable on day 17 of chicken embryo development, and responses to injection of GH releasing factor or thyrotropin releasing hormone are not observed until three weeks into incubation.[81]

Three variants of chicken GH have been observed. It has been postulated that some variants are more specific than others for the distinct activities of GH (eg, growth promotion, lipolysis, inhibition of glucagon-induced lipolysis). Independent control of synthesis and release of the variants of GH may exist. Mammalian and avian GH preparations have both lipolytic and antilipolytic activities; fish GH has no lipolytic effect, yet exerts full antilipolytic effect. This has been regarded as tentative evidence for the existence of two types of GH receptors: a GH receptor that does not recognize fish GH ("lipolytic" receptor) and a GH receptor that recognizes mammalian, avian and fish GH ("antilipolytic" receptor).

In chickens, plasma concentrations of GH are highest from hatching up to eight weeks of age, and then decline to reach a low, relatively static level.

Diseases in Relation to the Hypothalamic-Hypophyseal Complex

Although in recent decades major advances have been made in the elucidation of hypothalamic-hypophyseal control of endocrine function in birds, relatively little has been reported with regard to diseases related to the hypothalamic-hypophyseal complex (HHC).

Considering the large number of diseases associated with the HHC in man and domestic animals, and the similarity of the HHC between mammals and birds, it is to be expected that a number of hypothalamic diseases that hitherto have not been reported in birds will be reported in the future.

Diseases may be caused by hypo- or hypersecretion of one or, more commonly, several of the hypothalamic or pituitary hormones. These alterations in secretion may be caused by tumors that are primary or metastatic, benign or malignant, pituitary or parapituitary, or by granulomatous lesions, congenital lesions or trauma. In addition to causing endocrine abnormalities, space-occupying lesions may cause neurologic signs due to pressure on surrounding nerve tissue.

When a diagnosis of hypothalamic disease is based on circulating concentrations of hypothalamic or hypophyseal hormones, it should be considered that primary hypofunction of a target organ will result in hypersecretion of the trophic hormone. This makes it possible to distinguish between a primary disorder of the gland or a disorder of the gland secondary to pituitary dysfunction or a hypothalamic disorder (tertiary dysfunction).

Examples from mammalian medicine of hyperpituitarism include Cushing's syndrome (ACTH), precocious puberty or infertility (gonadotrophin), amenorrhoea in women and infertility in men with galactorrhea (prolactin), hyperthyroidism (TSH), gigantism (GH before puberty) and acromegaly (GH after puberty). Examples of hypopituitarism include dwarfism, secondary hypothyroidism, adrenocortical insufficiency and hypogonadism. An example of a disease associated with a disorder of the hypothalamus or posterior pituitary gland is cranial (central) diabetes insipidus, which is caused by insufficient secretion of antidiuretic hormone.

Dwarfism

Dwarfism has been reported in various avian species such as the fowl,[46] pheasant,[2] Black-headed Gull[42] and Great Crested Flycatcher.[67] Dwarfism is sex-linked recessive in the fowl.[46] Sex-linked dwarf growing chicks have lower concentrations of somatomedin C (insulin-like growth factor, IGF - I) and T_3, whereas GH and T_4 are increased, probably due to a decreased negative feedback effect on GH secretion. The dwarfism is not caused by a defective release mechanism of GH because both TRH and GRF stimulate the release of GH to a greater degree in dwarfs then in normal chickens. In normal chickens, GH and TRH stimulate hepatic 5'-monodeiodination activity (conversion of T_4 to T_3). This conversion does not occur in dwarfs. A lack of GH receptors could be a sufficient cause for deficiencies in IGF-I and T_3 production in dwarfs.[50]

Diabetes Insipidus

In birds, the main physiologic regulator of body water balance is the octapeptide, arginine vasotocin (AVT). Both arginine vasotocin and the mammalian counterpart, arginine vasopressin (antidiuretic hormone, ADH), produce antidiuresis in birds, but the former is considerably more potent.

Diabetes insipidus has been reported to occur in chickens and might also occur in other avian species. The principal clinical signs of this disease are polyuria and polydipsia (PU/PD) (see Color 8).

Water deprivation test can be used in dogs to distinguish between the causes of PU/PD. The principle of the water deprivation test is to determine whether endogenous ADH is released in response to dehydration and whether the kidney responds to this stimulus. With this test, differentiation between central diabetes insipidus, nephrogenic diabetes insipidus, primary (psychogenic) polydipsia and hyperadrenocorticism is facilitated. For healthy racing pigeons, it has been established that a urine osmolality of at least 450 mOsm/kg can be expected after 24 hours of water deprivation, which typifies the normal concentrating capacity of the kidneys. In avian patients with PU/PD in which urine osmolality does not increase in response to water deprivation, administration of exogenous ADH or AVT can be used to differentiate between central diabetes insipidus and other causes of PU/PD.[1] A water deprivation test using plasma AVT concentration has recently been developed for use in birds. Plasma AVT concentrations were measured before and during a 72-hour period of water deprivation. It was concluded that an AVT concentration > 2.2 pg/ml after 24 hours of water deprivation is indicative of a normal AVT release from the neurohypophysis in the pigeon.[61]

Pituitary Tumors in Budgerigars and Cockatiels

Chromophobe adenomas and carcinomas of the pituitary are common in budgerigars (see Chapter 25). In a review of 497 tumors in budgerigars, 156 were either chromophobe adenomas or carcinomas;[85] however, in other reports, the incidence of these tumors was considerably lower.[12] Variations in the reported incidence of pituitary tumors might be caused by the fact that these tumors are easily overlooked during a routine gross necropsy. The pituitary gland is easy to isolate and should always be evaluated. The mandible is removed with the bird in dorsal recumbency. The medial ridge of the sphenoid bone can be broken away with forceps, after which the pituitary will be found lying in the sella turcica of the sphenoid, just posterior to the optic chiasm. The normal pituitary gland from a budgerigar is about 2 mm in diameter,

CLINICAL APPLICATIONS

Pituitary gland tumors should be suspected in clinical cases with:

- PU/PD
- Reproductive failure
- Feather dystrophy
- Pigmentation abnormalities
- Obesity
- Stupor
- Blindness
- Convulsions
- Uni- and bilateral exophthalmos
- Hyperglycemia.

If these signs are present and a bird dies, the pituitary gland should be submitted for histopathology.

while the diameter can be 7 mm if a pituitary tumor is present. Pituitary tumors have been associated with a ten-fold weight increase of the pituitary gland.[8,12,82]

These tumors may be infectious in nature, which could also explain the variation in the reported incidence of disease. Homologous transplantation of pituitary tumors from budgerigars has been reported, and renal adenocarcinomas occurred in ten percent of the birds.[84] Avian leukosis virus antigen has been demonstrated in budgerigars with kidney tumors.[69] A causal relationship between renal tumors in budgerigars and avian leukosis virus, however, has yet to be demonstrated. Pituitary tumors have also been reported in an *Agapornis* spp.[91] and in two cases in the fowl.[15]

Recently, pituitary adenoma and pituitary adenocarcinoma with metastasis to the liver have been reported in cockatiels.[19,106]

Reported clinical signs of pituitary tumors in budgerigars and cockatiels are related to hormonal imbalance (eg, polyuria, polydipsia, reproductive failure, obesity and feather structure and pigmentation abnormalities) and to compression of surrounding nervous tissue (eg, stupor, blindness, uni- or bilateral exophthalmus, convulsions). Although it has been suggested that the PU/PD is caused by hyposecretion of AVT (diabetes insipidus), hypersecretion of ACTH (Cushing's disease, secondary hyperadrenocorticism), TSH (hyperthyroidism) or GH have not been excluded.

Hyperglycemia and obesity occurred in birds with subcutaneous transplants of pituitary tumors.[84] The obesity was characterized by an accumulation of adipose tissue beneath the skin of the breast and abdomen as well as in the peritoneum and mesentery. The liver was often enlarged, and histologic sections revealed an accumulation of fat in hepatic cells.

In budgerigars with large tumor transplants, blood glucose concentrations exceeded 1000 mg% with one value reaching 1768 mg%. At necropsy, the thyroids, adrenal glands and pancreas were normal.

Calcium Metabolism

Anatomy and Physiology

Calcium metabolism in birds is under the control of three major hormones: parathyroid hormone (PTH), calcitonin (CT) and 1,25 dihydrocholecalciferol ($1,25(OH)_2D_3$), the active metabolite of vitamin D_3 (Figure 23.1). Other hormones, however, also alter calcium metabolism, and the amounts of calcium and vitamin D in the diet have profound effects.

Parathyroid Hormone

PTH is secreted by the paired parathyroid glands, which consist of cranial and caudal lobes and can be found caudal to the thyroid glands. In the chicken, the left parathyroid gland is not in contact with the thyroid gland, while on the right side the cranial lobe lies next to the thyroid gland. In companion birds, the parathyroids are normally visible as light-colored areas at the caudal end of the thyroid glands (see Anatomy Overlay). The main tools that have been used for studying parathyroid function in birds have been parathyroidectomy and the use of heterologous (usually bovine) PTH. Currently, a sensitive radioimmunoassay for avian PTH is not available and avian PTH (1-84) or PTH (1-34) is also not commercially available. Heterologous and homologous PTH may act differently in birds.

PTH is secreted in response to hypocalcemia. The primary target organs of PTH are the kidney and bone. Calcium excretion in the urine is decreased by increasing tubular reabsorption of calcium, while circumstantial evidence suggests that calcium resorption from bone is increased. During the egg-laying cycle, PTH functions in the resorption of medullary bone. Under the influence of PTH, renal tubular secretion of phosphate is increased, while decreased tubular reabsorption may occur. The net result is a phosphate diuresis and a decrease in plasma phosphate.

PTH regulates vitamin D by stimulating 1-hydroxylase activity and inhibiting 24-hydroxylase activity in the renal cortex, thereby enhancing the production of the key calcium-regulating hormone $1,25(OH)_2D_3$. Furthermore PTH acts together with $1,25(OH)_2D_3$ to increase calcium absorption from bone.

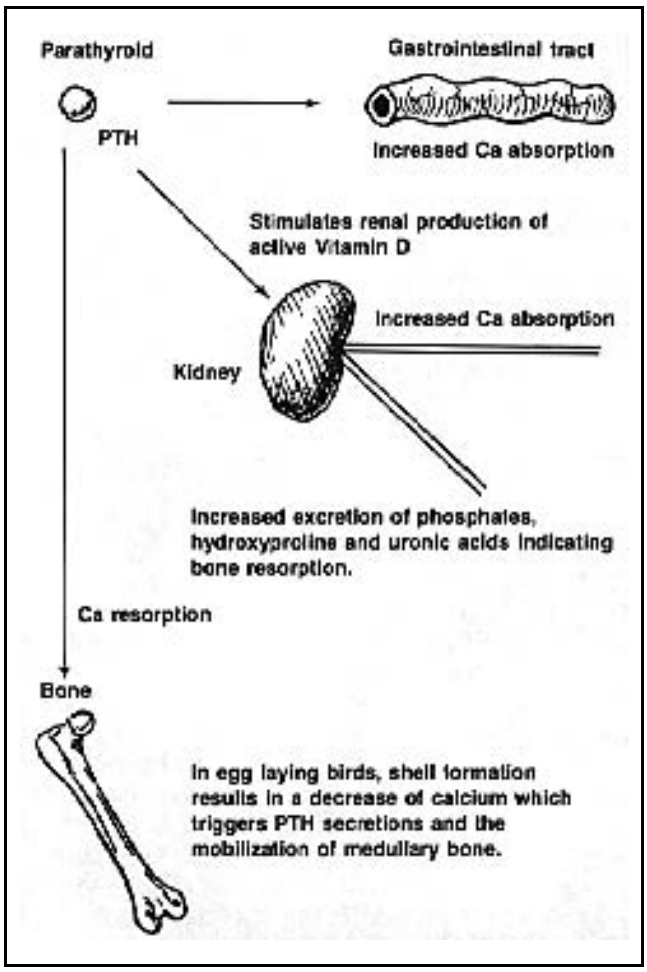


FIG 23.1 Control of calcium metabolism. The parathyroid gland secretes PTH, which increases calcium absorption from the gastrointestinal tract, increases calcium absorption by the kidney and causes calcium resorption from the bone.

Calcitonin (CT)

CT is secreted by the C cells of the ultimobranchial glands. In chickens, the left gland lies caudodorsal to the caudal lobe of the parathyroid gland, while the right ultimobranchial gland lies more caudally and is separate from the caudal lobe of the parathyroid gland. In chickens, the ultimobranchial glands are found in association with the parathyroid tissue; in pigeons, they are found in association with thyroid tissue.

The chromatographic profile of the biologic activity of cultured ultimobranchial glands from embryonic chickens resembles that of purified salmon CT. Furthermore, chicken and salmon CT exhibit immunological identity, which makes it possible to measure avian CT by radioimmunoassay with antibody raised against synthetic salmon CT.[20]

In contrast to its action in mammals, CT does not induce a hypocalcemia in normocalcemic birds. It appears, rather, to control hypercalcemia and to protect the skeleton from excessive calcium resorption.[5] The mode of action is through decreasing calcium resorption from bone.

Vitamin D_3

Vitamin D_3 (cholecalciferol) is converted from its precursor, 7-dehydrocholesterol, under the influence of ultraviolet (UV) light. It has been suggested that this process occurs in birds when the oil of the uropygial gland is spread over the feathers and irradiated by UV light before the vitamin is orally ingested during preening. The mechanism of conversion in birds that lack a uropygial gland has not been proposed. The photolysis reaction converts 7-dehydrocholesterol to pre-vitamin D_3, which is in equilibrium with both its precursor and with vitamin D_3. The next step occurs mainly in microsomal fractions of liver cells and is the formation of 25-hydroxycholecalciferol. The second and more important step in the activation of D_3 occurs in mitochondria of cells in the renal cortex, and involves the conversion to 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$], which is regarded as the key calcium-regulating hormone. When body demands for calcium are low, the major hydroxylation product of $25(OH)D_3$ is $24,25(OH)_2D_3$. There is evidence from studies in mammals that the latter inhibits the secretion of PTH.

Other hormones that stimulate the production of $1,25(OH)_2D_3$ are prolactin and estrogen.

The main role of the active metabolite of vitamin D_3 is to elevate plasma calcium and inorganic phosphorus by increasing small intestinal absorption of these minerals in conditions whereby the plasma concentrations of one of these minerals are too low to sup-

CLINICAL APPLICATIONS

Activities of the parathyroid hormone:

- Decreased renal excretion of calcium
- Increased calcium resorption from bone
- Resorption of medullary bone (egg laying)
- Increased renal excretion of phosphate
- Increased production of active D_3.

Activities of calcitonin and vitamin D_3:

- Calcitonin decreases calcium resorption from bone.
- Vitamin D_3 increases intestinal absorption of calcium and phosphorous
- In conjunction with the parathyroid, vitamin D_3 mobilizes calcium and phosphorous from bone.

port normal mineralization of bone. Therefore, lack of vitamin D_3 in young birds leads to rickets. In addition, $1,25(OH)_2D_3$ acts together with PTH to mobilize calcium and phosphorus from the skeleton when hypocalcemia occurs.

Vitamin D_2

Because ergocalciferol (vitamin D_2) is more rapidly metabolized and excreted than cholecalciferol (vitamin D_3), the antirachitic properties of the former are 10 to 40 times less than those of vitamin D_3, despite the equal rate of initial uptake by the target tissues.

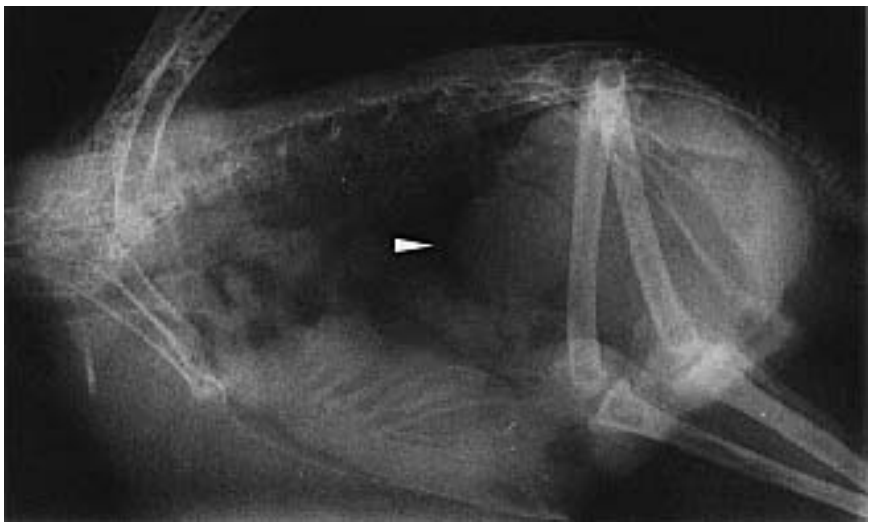


FIG 23.2 Lateral radiograph of a sexually mature Mexican Red-headed Amazon Parrot hen. Note the spherical mass (arrow) cranioventral to the kidneys, representing a solitary large ovarian follicle. Pre-ovulatory bone deposition is apparent in the medullary cavity of the appendicular skeleton (courtesy of Marjorie McMillan).

Calcium in Reproductive Physiology

Two independent physiologic phenomena related to calcium metabolism are seen in hens during reproduction. These normal changes should not be misinterpreted as pathologic.[89]

- ***Estrogen-induced Hypercalcemia:*** About four days before female pigeons are due to ovulate, the blood calcium concentration rises from a normal value of about 2.2 mmol/l (9 mg/dl) to a value of over 5.0 mmol/l (20 mg/dl) at the time of ovulation. This rise is caused by an increase in the protein-bound calcium, secondary to the estrogen-induced transport of yolk proteins to the ovary as calcium complexes. The concentration of ionized calcium remains constant.

- ***Physiologic Marrow Ossification:*** During egg-laying, there is a large increase in the quantities of calcium and phosphorus that are retained from the diet and deposited in the medullary bone. This medullary bone may completely fill the marrow cavity of long bones, particularly those in the limbs (Figure 23.2). This period of bone deposition coincides with increased osteoblastic activity. When the hen starts to secrete the eggshell, the medullary bone is resorbed by osteoclastic activity. Calcium is deposited in the eggshell as calcium carbonate, and the phosphorus is excreted from the body. Normal medullary bone deposits should not be mistaken for a pathologic condition radiographically. The precise details of the hormonal mechanism by which the supplies of calcium from the gut and from the skeleton are regulated in relation to the requirements for shell formation are not fully understood.

Relation Between Total Calcium and Protein in Avian Plasma

The plasma calcium concentration is normally about 2.0-2.8 mmol/l (8-11.2 mg/dl), depending on the species. About one-third of plasma calcium is protein-bound and is biologically inactive. Total calcium concentration is markedly influenced by plasma protein concentrations. The ionized fraction is important with regard to deposition of calcium salts and excitability of nervous tissues. For technical reasons, most laboratories determine only total calcium. Hence, total plasma calcium should be evaluated in conjunction with plasma protein concentrations.

In man and in dogs, there are significant linear relationships between calcium and albumin, and calcium and total protein. In these species, adjustment formulas have been derived for serum total calcium on the basis of the concentrations of albumin and total protein. Recently, a significant correlation was found between total calcium and albumin concentration in the plasma of 70 healthy African Grey Parrots. Approximately 14% of the variability of calcium was attributable to the change in the concentration of plasma albumin (R^2=0.137).[59] A correction formula was derived on the basis of the concentration of albumin:

Adjusted Ca (mmol/l) = Ca (mmol/l) - 0.015 albumin (g/l) + 0.4

A significant correlation was also found between total calcium and total protein concentration in 124 plasma samples of Peregrine Falcons. About 42% of

the variability in calcium was attributable to the change in the plasma total protein concentration. The correlation between calcium and albumin was significant, but significantly smaller than the correlation between calcium and total protein. Only 11% of the plasma calcium concentration was attributable to a difference in concentration of albumin. An adjustment formula for plasma calcium concentration in the Peregrine Falcon was derived on the basis of the total protein concentration.[62]

Adj. Ca (mmol/l) = Ca (mmol/l) - 0.02 Total Protein (g/l) + 0.67

Application of a correction formula in African Grey Parrots and Peregrine Falcons is indicated when extremely low or extremely high plasma protein concentrations are detected. It should be stressed that the correction formulas mentioned above are based on total protein and albumin determinations with specific analytic methods. For total protein, the biuret method is used with human protein as a standard, and albumin is calculated from total protein and plasma protein electrophoresis on cellulose acetate membranes.[59a]

Diseases in Relation to the Metabolism of Calcium and Phosphorus

Hyperparathyroidism

Hyperparathyroidism is a condition whereby there is an increased secretion of PTH. In man primary hyperparathyroidism may occur from hyperplasia, adenoma or carcinoma of the parathyroid gland. The most common presentation is a renal disorder due to recurrent renal calculi (nephrocalcinosis). The second most common presentation is bone disease (osteitis fibrosa generalisata), while the third mode of presentation is related to hypercalcemia. Pseudohyperparathyroidism is a condition characterized by hypercalcemia caused by the release of hormone-like substances from nonendocrine tumors; however, with neoplasm, hypercalcemia may also occur from widespread skeletal deposits of metastatic tumors, with associated increased osteoclastic activity. Contrary to the situation in man and domestic mammals, primary hyperparathyroidism and pseudohyperparathyroidism have not been documented in birds. Because adenoma and carcinoma of the avian parathyroid gland do occur,[36] it is likely that primary hyperparathyroidism will be reported in the future.

Secondary nutritional hyperparathyroidism is commonly reported in birds secondary to a calcium-deficient diet (see Chapter 3).

Diets that contain only seeds or only meat are deficient in calcium. Fruits and most vegetables are also calcium deficient. Nonetheless, many pet food retailers continue to market so-called "complete parrot foods," which consist only of seeds (mainly sunflower seeds). Affected birds have a low or normal plasma calcium concentration, a normal plasma phosphate concentration and increased AP activity. In young birds, rickets or rachitis is seen as a result of calcium-deficient diets, while in adult birds osteomalacia will occur.

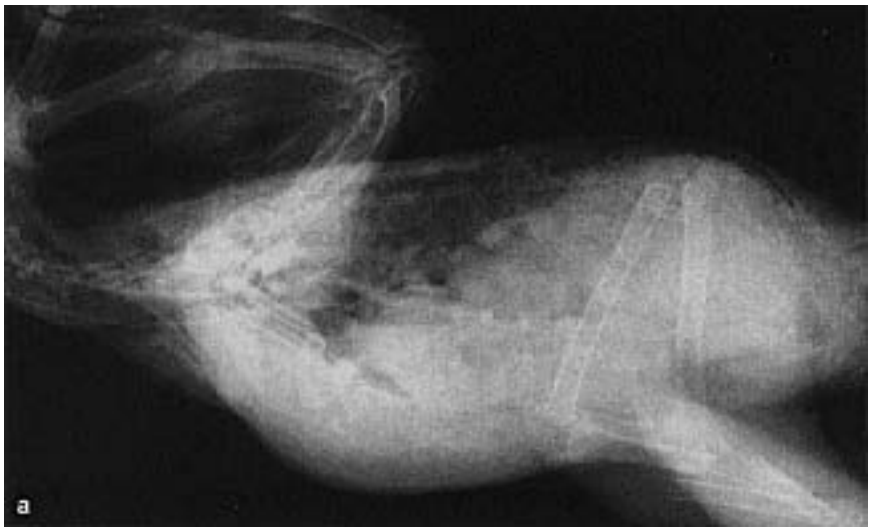
Secondary hyperparathyroidism due to a renal disorder is well known in mammals and possibly occurs also in birds. In chronic renal disease, failure of the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$], the key calcium-regulating hormone, will result in reduced intestinal absorption of calcium. Under these circumstances, a high plasma phosphate concentration may be seen due to decreased tubular secretion of phosphate. Plasma AP activity will be increased.

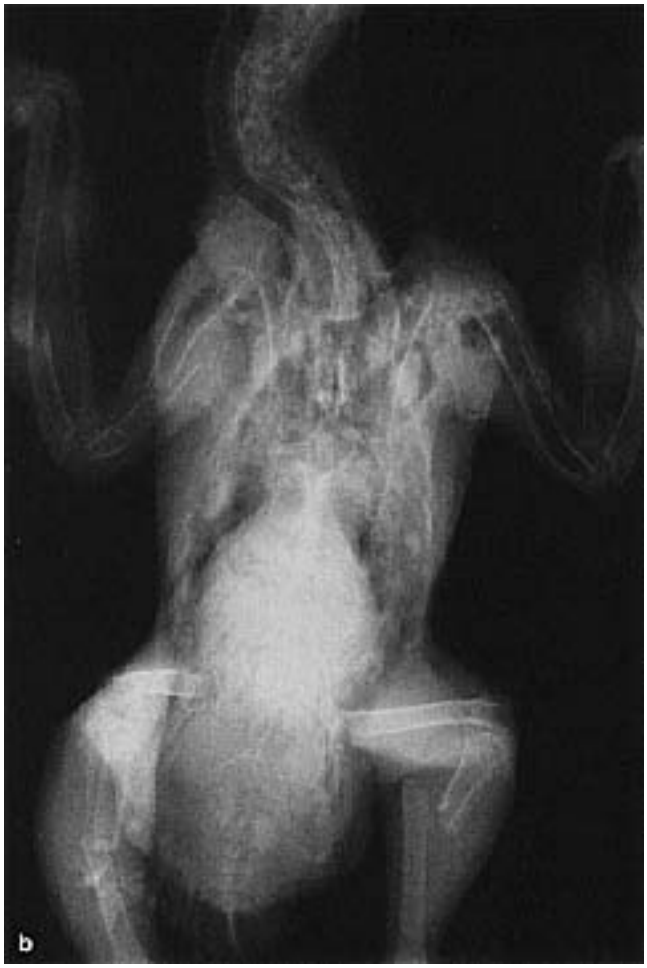
Tertiary hyperparathyroidism is known in man as a pathologic extension of the secondary form when adenomas develop in the previously hyperplastic glands and there is accompanying hypercalcemia due to autonomous PTH secretion. This condition has not been reported in birds.

Rickets

Rickets or rachitis is a metabolically induced bone disease in growing animals. Painful deformities occur throughout the skeleton, particularly in the proximal tibiotarsus, the head of the ribs and sometimes the costochondral junction. The skeleton and the beak (rubber beak) become soft and pliable. Rickets can be caused by inadequate dietary intake of calcium, phosphorus or vitamin D_3 or by an improper calcium:phosphorus ratio. With calcium and vitamin D deficiencies, the resulting hypocalcemia induces enlargement of the parathyroid gland (nutritional secondary hyperparathyroidism). Consistent parathyroid gland changes are not typical with a phosphate deficiency or excessive calcium intake. Histologically, it is possible to differentiate between rickets caused by vitamin D deficiency, hypocalcemia and hypophosphatemia/calcium excess.[53-55]

Tachypnea and polycythemia have been observed in birds with rickets, presumably because of poor rib strength and infolding of ribs.[48] Affected birds died of right ventricular failure, often accompanied by ascites.





Osteomalacia (Osteodystrophy)

In mature birds, calcium deficiencies will result in parathyroid enlargement and PTH-induced activation of osteoclastic activity, which eventually can result in complete demineralization of medullary bone, followed by cortical bone (Figure 23.3). The resorbed osseus tissue can be replaced by fibrous tissue (osteodystrophia fibrosa). The cortical bone can become so thin that spontaneous fractures may occur, especially in the vertebrae, ribs, tibiotarsus, tarsometatarsus and femur. The fractures are typical for demineralized bone and are called "greenstick fractures." The beak becomes soft and pliable. Plasma calcium concentrations remain generally normal until the end stage of the disease, when tetanic convulsions may be observed. Although calcium deficiencies accompanied by pathologic fractures seem relatively common in psittacine birds, nutritional osteodystrophia fibrosa is rarely diagnosed. A possible explanation might be that histologic examination of bones is not often performed.

Osteoporosis

To a certain degree, osteoporosis (cage layer fatigue) is physiologic during egg production. Osteoporosis is characterized by the progressive reduction of bone mass. It is the most important skeletal disease in

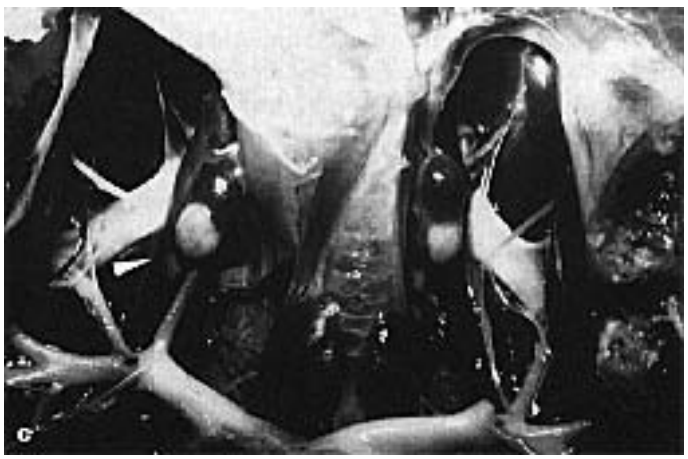
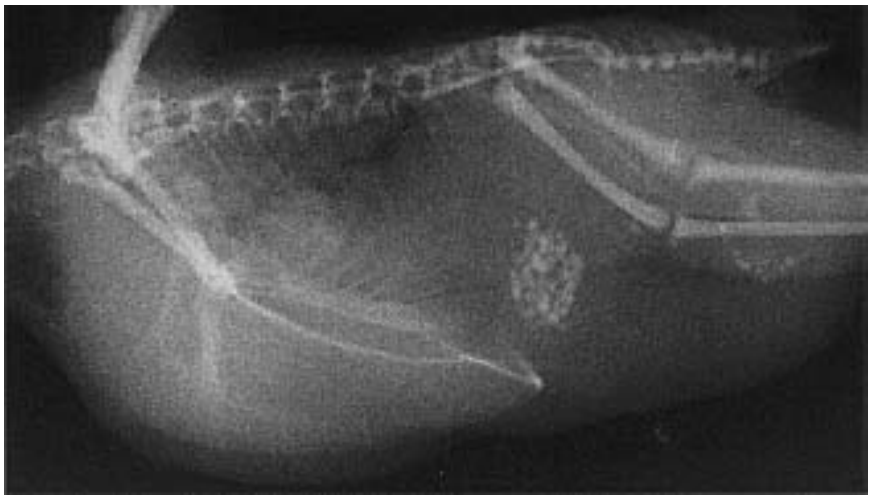


FIG 23.3 An adult female Amazon parrot was referred for evaluation of bilateral tibiotarsal fractures after flying into a wall. The hen had a three-year history of egg laying and had recently laid her second egg of the year. The bird appeared to have head tremors, was unable to stand and both wings were drooping. The diet consisted of a sunflower seed and peanut mix. **a,b)** Radiographs indicated multiple fractures, decreased bone density and soft tissue densities in the abdomen. **c)** At necropsy, the parathyroid glands were dramatically enlarged (arrow), and the abdomen was filled with flocculent debris. Histopathology indicated egg-related peritonitis, parathyroid hyperplasia and severe osteoporosis suggestive of secondary nutritional hyperparathyroidism.

chickens used for egg production and is restricted to birds kept in enclosures. Etiologic factors may be immobilization, which is a well known cause for osteoporosis in man, and marginal nutritional calcium deficiency, which can alter the physiologic osteoporosis from high egg production into severe osteoporosis with associated clinical signs. Affected birds are found paralyzed in their enclosures, and have skeletal deformities and enlarged parathyroid glands. Paralysis may be explained by spinal cord compression due to fractures in the thoracic spine and possibly by hypocalcemia, although the latter has not yet been demonstrated.



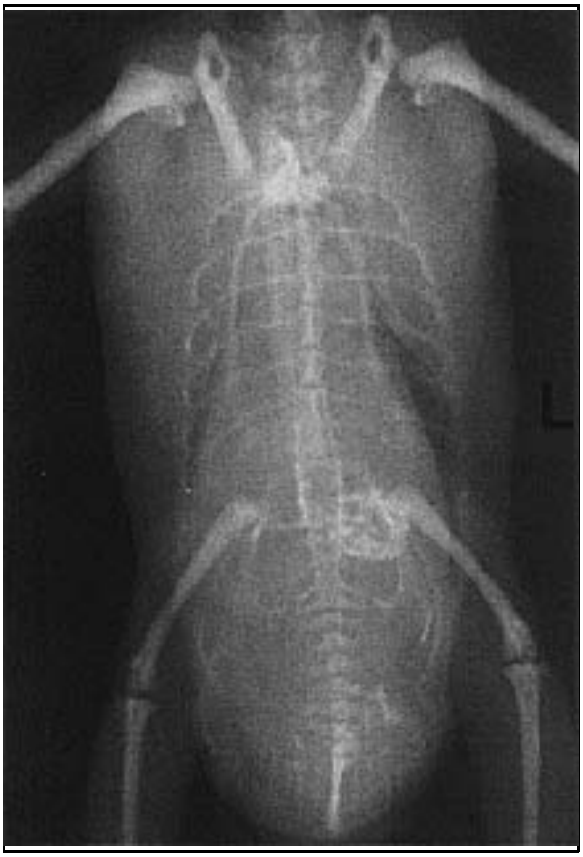


FIG 23.4 Radiographs of a budgerigar hen with increased endosteal bone formation and a distended abdomen secondary to oviductal enlargement. These findings are suggestive of hyperestrogenemia (courtesy of Marjorie McMillan).

Hypervitaminosis D_3

Oversupplementation of the diet with vitamin D_3 (>4 million IU/kg diet) causes dystrophic calcification of kidney tubules. Calcium nephropathy can also occur when birds are raised on diets containing 3% calcium instead of the normal 0.6% (see Chapters 3, 31).

Hypocalcemia Syndrome in African Grey Parrots

Hypocalcemia characterized by seizures has been described in raptors and African Grey Parrots. A unique feature of this syndrome in African Grey Parrots is that demineralization of the skeleton to maintain normal calcium levels does not occur. Hypocalcemia is an important problem to consider in an African Grey Parrot that repeatedly falls off its perch. Administration of parenteral calcium and sufficient dietary uptake of calcium resolves clinical signs. A dietary calcium deficiency is suspected, but not confirmed as the etiologic agent. In a recent study it was shown that African Grey Parrots have significantly lower calcium, albumin and total protein concentrations compared to Amazon Parrots; however, the significantly lower mean and median values for plasma calcium in African Greys could be explained only partially by the difference in albumin-bound calcium.[59] The higher incidence of hypocalcemia in African Grey Parrots might therefore be associated with lower plasma concentrations of free calcium.

Polyostotic Hyperostosis

In female budgerigars, polyostotic hyperostosis (Figure 23.4), which resembles physiologic marrow ossification is often seen in association with ovarian tumors. The condition can also be induced by stilbestrol implantation.[86] Physiologic marrow ossification and polyostotic hyperostosis may be related, and the latter may be a pathologic exacerbation of a physiologic phenomenon caused by hyperestrogenism. Hyperestrogenism has also been associated with abdominal hernias (Figure 23.5).

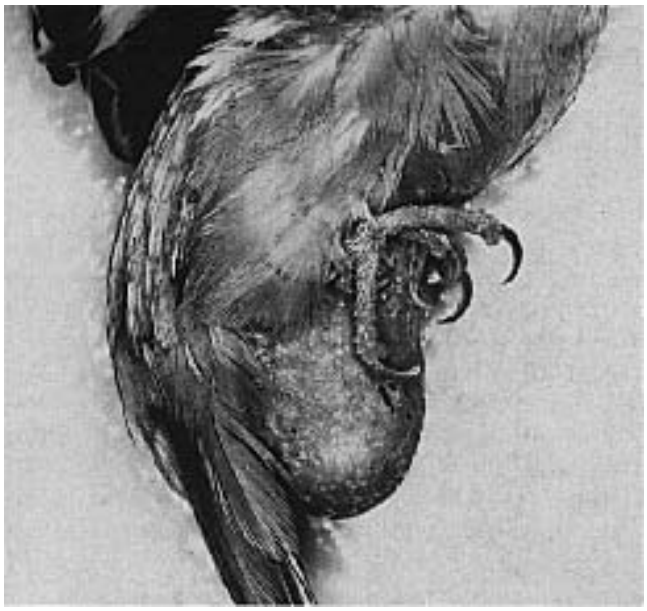


FIG 23.5 A mature budgerigar hen was presented with a progressively enlarging abdominal mass, weight loss and a reduced fecal output despite a normal appetite. Radiographs indicated polyostotic hyperostosis and an abdominal hernia suggestive of hyperestrogenemia.

The Thyroid Glands

Anatomy and Physiology

The thyroid glands in birds are paired organs that lie on each side of the trachea in the thoracic inlet. A connecting isthmus is absent. The thyroids are in close contact with the common carotid artery, just distal to the origin of the subclavian artery and common carotid artery from the brachiocephalic trunk (see Anatomy Overlay). Blood supply is from the cranial and caudal thyroid arteries that originate from the common carotid artery. Venous return is through the thyroid veins, which empty into the jugular vein. Except for doves and pigeons, the avian thyroid gland lacks calcitonin cells, which are located in the ultimobranchial glands.

The thyroid lobes are composed of follicles surrounded by a single layer of epithelial cells enclosed by a basement membrane. The height of the epithelial cells is dependent on the secretory rate and may vary from flat to columnar. The follicles contain a proteinaceous material called colloid, which is mainly thyroglobulin, the storage form of the thyroid hormones.

The basement membrane is in contact with the blood vessels, while the opposite cell membrane faces the colloid. The basement membrane is the site of TSH-stimulated iodide uptake from the plasma and secretion of thyroid hormone into the plasma. The cell membrane facing the colloid is the site of thyroglobulin synthesis, oxidation and organification of iodide onto tyrosine residues of preformed thyroglobulin such as of 3-monoiodotyrosine (MIT) and 3-5-diiodotyrosine (DIT). MIT and DIT residues are coupled to form 3,5,3',-triiodo L-thyronine (T_3) and 3,5,3',5'-tetraiodo L-thyronine (thyroxine, T_4).

Compared to the thyroid gland in mammals, the avian thyroid produces more T_4 than T_3.[3] It is T_3 that is the principally active hormone,[108] produced mostly by extrathyroidal 5'-monodeiodination of T_4 in liver and kidney. The activity of the 5'-monodeiodination enzyme is hormonally controlled by hypothalamic hormones (TRH, GRF) and GH.[50]

Pathology

Histologic examination of the thyroid gland is a useful and reliable means of differentiating between various thyroid disorders.

In primary hypothyroidism, there is a loss of follicles resulting either from thyroiditis or atrophy, while in secondary or tertiary hypothyroidism, the thyroid follicles are distended with colloid and the lining epithelial cells become flattened. The colloid is uniformly dense with complete or nearly complete absence of resorption vacuoles at the periphery of the colloid.

In hyperthyroidism, a diffusely hyperplastic epithelium may be observed, with little or no colloid present and possibly with lymphocytic infiltration.

In endemic goiter (caused by iodine deficiency), the thyroid gland is diffusely enlarged because of cellular hyperplasia as a result of TSH stimulation. The accumulation of thyroglobulin occurs because poorly iodinated thyroglobulin is relatively resistent to digestion by endogenous proteases. Some thyroid areas may atrophy with concomitant fibrosis.[44]

In thyroiditis, lymphocytic infiltration is present. Lymphocytic cells are often so numerous that they dominate the microscopic structure of the gland. Secondly, there is some proliferation of thyroid epithe-

lium. The pathologic changes result in considerable destruction of the thyroid. Lymphocytic infiltration of the thyroid gland is also a common finding with leukosis in chickens, and it may be difficult to differentiate autoimmune thyroiditis from leukosis.

Amyloidosis of the thyroid gland is characterized by amyloid deposits in interfollicular tissue and is often associated with tuberculosis or other chronic infections, especially in Anseriformes.

Normal thyroid histology is also dependent on the stage of plumage development. Increased thyroid activity can be observed in molting pigeons: the height of the thyroid epithelium increases and colloid is resorbed from the follicles.[100]

Thyroid Disorders

Diseases of the thyroid gland may be accompanied by thyroid enlargement (goiter), hyperfunction or hypofunction. Functional disorders may be primary, secondary or tertiary, depending on the location of the lesion (thyroid gland, pituitary gland or hypothalamus, respectively). Only goiter has been adequately documented in birds and may be caused by neoplastic disease or by iodine deficiency. Hypothyroidism has been documented in chickens, pigeons and one parrot, and it has been suggested that hyperthyroidism may be induced by exposure to iodide-containing disinfectants. Thyroiditis occurs frequently in birds,[112] but clinical signs associated with this condition have not yet been reported.

Thyroid Tumors

Thyroid neoplasia is rare in birds. Most thyroid enlargements represent thyroid hyperplasia caused by iodine deficiency. Adenomas and adenocarcinomas have been reported in budgerigars,[12] a Scarlet Macaw and some other birds from zoological collections (see Chapter 25).[83,102] Thyroid adenomas and adenocarcinomas have been reported in chickens.[15,33] Leukotic changes have also been documented in chickens.[42]

Clinical signs associated with thyroid enlargement include regurgitation and dyspnea. Like thyroid tumors in man and domestic mammals, it is to be expected that some avian thyroid tumors will have autonomic hormone production and will cause hyperthyroidism; however, no reports are available in birds.

Goiter in Budgerigars

The most frequent clinical disease of the thyroid gland in birds is goiter in budgerigars, caused by feeding an iodine-deficient diet (usually seed mixtures).[12,49,83] Goiter has occasionally been seen in chickens[33] and other avian species,[12] but is a well known and distinct clinical entity in the domestic pigeon. In budgerigars with goiter, clinical changes are limited to regurgitation and dyspnea caused by gland pressure on the trachea and esophagus (see Color 19). Specific signs of hypothyroid function are absent. Circulatory problems may occur due to compression of the heart and great vessels. The size of the glands can exceed 10 mm compared to a normal size of about 2 mm, while the weight can show a 100-fold increase (normal weight = 3 mg). If the glands are cystic they may weigh 1000 mg and be palpable at the thoracic inlet. Radiographically, a dorsal or ventral displacement of the trachea may be visible.

Goiter can be prevented by placing a bird on a complete formulated diet. The dietary requirement of iodine is about 20 µg per week for a 35 g budgerigar. Affected animals can be treated with a 0.3% Lugol's solution in the drinking water (1 drop per 20 ml water): first week, daily; second week, three times a week; then once weekly.

Goiter in Domestic Pigeons

Goiter can occur in domestic pigeons on an iodine-deficient diet. Certain breeds (eg, White Carneaux) are more susceptible than others.[44] Soybeans and fat-rich corns (like maize) may increase the iodine demand

CLINICAL APPLICATIONS

Clinical findings of thyroid enlargement in budgerigars

- Obesity
- Regurgitation
- Dyspnea
- Dorsal displacement of trachea (radiographs)
- Ventral displacement of trachea (radiographs)
- Circulatory problems

Clinical findings of goiter in pigeons

- Lethargy
- Obesity
- Palpable mass (thoracic inlet)
- Reduced fertility
- Reduced hatching rate
- Unhealthy squabs
- Myxedema
- Dystrophic feathers

and potentiate goiter.[99] Clinical signs in adult pigeons are different from those in budgerigars and include lethargy, obesity and a palpable thyroid gland in the thoracic inlet. Affected birds show a reduced fertility, reduced hatchability and reduced viability of squabs. Signs of hypothyroidism may include a puffy appearance of the facial skin (myxedema) and abnormal feather development. Tail and wing feathers that are too long and narrow or structural defects in the contour feathers may give the bird a ruffled appearance and an irregular or failing molt. Dyspnea accompanied by a respiratory stridor occurs only in severe cases. Although supporting data is not available clinical signs suggest that contrary to the situation in budgerigars, iodine-deficient goiter in White Carneaux Pigeons is accompanied by hypothyroidism.

Hypothyroidism

Primary hypothyroidism is a well recognized disorder in birds. In chickens, it occurs as a hereditary autoimmune disorder.[18,92] Low levels of thyroid hormones have also been associated with a malabsorption syndrome.[77] Experimentally induced hypothyroidism is associated with growth retardation, mental retardation and defective plumage development (fringed and elongated feathers with loss of barbules and color). Chickens with genetic hypothyroidism have low T_4 concentrations, obesity, rather silky plumage, delayed sexual development or delayed maturity (Figure 23.6).[17]

In man and dogs, various non-thyroidal illnesses have been shown to favor the formation of T_3 to protect the body from the catabolic state that accompanies many of these diseases. This phenomenon has been designated the "low T_3 syndrome," though affected subjects remain euthyroidic.[52] The same mechanism seems likely in birds.[23] For this reason, measurement of plasma T_3 is of doubtful value for the diagnosis of primary hypothyroidism and could even lead to false conclusions. The measurement of T_4 would seem to be the most logical choice for evaluating birds; however, even plasma T_4 concentrations can be influenced by drugs, handling, bleeding,[107] food intake, environmental temperature,[108] increased plasma corticosterone concentration[23] and infections with *Eimeria maxima*.[22] Normal plasma T_4 concentrations in birds are about one-fifth to one-tenth those characteristic for mammals.[50] In many birds, resting plasma thyroxine concentrations are below the detection limit of the assay.[110]

Thyroid abnormalities have been frequently reported as a common cause of disease in companion and aviary birds; however, the only support for these statements has been a low plasma T_4 when compared with a reference interval established in a single random blood sample.[75,76] Reports of hypothyroidism are therefore questionable at best (Figure 23.7). Documentation that a low plasma T_4 level is caused by primary hypothyroidism requires a TSH stimulation test to rule out other causes for a decreased T_4 concentration.

A TSH test has been reported for chickens,[107] Psittaciformes[56,110] and racing pigeons.[63] Low T_4 levels were documented in a Hyacinth Macaw that responded to L-thyroxine therapy. For evaluation of thyroid function in racing pigeons, blood samples should be collected before and between 4 and 24 hours after administration of 0.1 IU of TSH.[a] If a dose of 1 IU per pigeon is used, samples can be collected up to 32 hours later. In healthy individuals, at least a 2.5-fold increase will be observed over basal T_4 concentrations using these doses and sampling times.[63] The TSH stimulation test can also be used in other avian species using 1 IU/kg. A diagnosis of hypothyroidism should not be based on low baseline thyroxine concentrations or on a "favorable response to administration of thyroxin."[71-75] A diagnosis is based on suggestive clinical signs, especially defective plumage development, in conjunction with failure to respond to TSH.

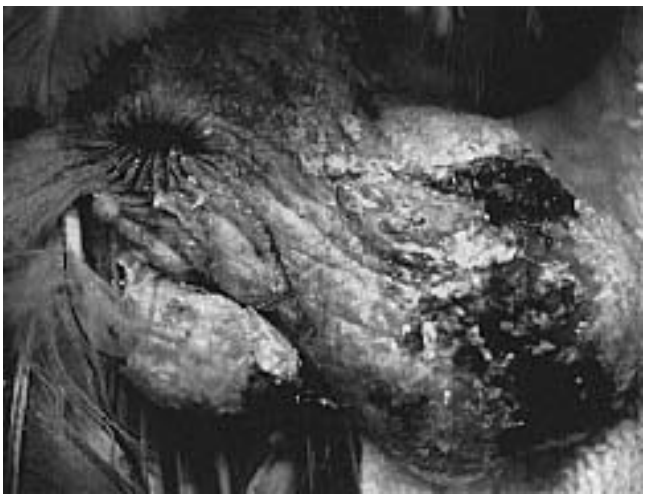


FIG 23.6 A mature, obese Amazon parrot was presented with an asymmetric, ulcerative periabdominal mass. Biopsy indicated a lipoma. Obesity and lipoma formation are frequently discussed as signs of hypothyroidism in companion birds; however, affected birds can rarely be shown to have hypothyroidism by determination of T_4 levels following TSH stimulation. Thyroxine supplementation should be used only in birds with documented cases of hypothyroidism (courtesy of Tom Tully).

If secondary and tertiary hypothyroidism occur in birds, these disorders can probably be diagnosed by performing stimulation tests with both TRH and TSH and by measuring of plasma TSH and thyroxine concentrations.

Hyperthyroidism

Hyperthyroidism or thyrotoxicosis results from oversecretion of thyroid hormones. It is clinically characterized by an increased metabolic rate. In man, it may result from diffuse hyperactivity of the gland (Graves' disease) or as a result of a single hyperplastic nodule (toxic adenoma). Rarer causes are increased TSH secretion from the pituitary gland, ectopic TSH producing tumors, metastatic thyroid carcinoma and ovarian teratoma containing thyroid tissue. The administration of iodides may also induce hyperthyroidism (Jod-Basedow phenomenon), but in these cases the gland is already abnormal.

Two Fairy Blue Penguins developed signs of hyperirritability after the use of iodide-containing disinfectants, and the disease was classified under the term hyperthyroidism.[37,78,79] The histology of the thyroid glands of the affected birds, however, was that of colloid goiter (large follicles with flattened epithelium). Furthermore, it is not likely that excessive amounts of iodide will induce hyperthyroidism. Exposure to excessive amounts of iodide paradoxically may lead to goiter or even hypothyroidism. In normal humans, a small but significant decrease in thyroid hormones with a compensatory rise in serum TSH concentration occured after excessive dietary intake of iodine. This suggests that the inhibitory effects of iodides on the serum concentrations of the thyroid hormones are probably partially overcome by the increased TSH secretion. Iodide-induced goiter, hypothyroidism or both in subjects with normal underlying thyroid function is uncommon. Most patients who develop disease have received large quantities of iodides for a long period of time.[13] In the author's opinion, the affected penguins should be classified as "iodide goiter" and not "hyperthyroidism."

FIG 23.7 An adult Blue and Gold Macaw was evaluated for a chronic feathering problem that had been diagnosed as hypothyroidism. The bird was on an all-seed diet and was restricted to a dark corner of the house. The bird had numerous pin feathers and thin, poorly formed mature feathers. Clinicopathologic, radiographic and TSH stimulation findings were within normal limits. The bird responded to a change in diet and daily exposure to unfiltered sunlight.

Thyroiditis

Various forms of thyroiditis have been described in man. Etiologies include pyogenic organisms, viruses and autoimmune phenomena (Hashimoto's thyroiditis). Clinical signs are variable and may be associated with goiter hyper- or hypothyroidism. Thyroiditis was reported in a large variety of avian species, including an Amazon parrot. At necropsy, 36.9% of avian thyroid lesions were of an inflammatory nature.[112]

In an obese strain (OS) of chickens, circulating thyroglobulin autoantibodies have been shown to be the cause of spontaneous thyroiditis accompanied by hypothyroidism.[17,18] Clinical signs included obesity, silky plumage, delayed sexual development or lack of maturity, thyroid glands that were either smaller or larger than normal and low plasma thyroxine concentrations. Another line of chickens (described as delayed amelanotic, DAM) with similar thyroid abnormalities has been reported.[92] Neonatal bursectomy decreased the incidence and severity of chronic thyroiditis in OS and DAM line chickens.[51] Because neonatal bursectomy, and not thymectomy, prevents the occurrence of the disease, it is likely that the disease is caused by an immunologic response to free particulate fractions of thyroid rather than by antibodies that react with thyroglobulin.[25]

The Use of Thyroid Hormone in Non-thyroidal Disorders

Thyroid hormone has been frequently recommended for the treatment of obesity in birds. However, no controlled studies have been performed to demonstrate the effectiveness of this treatment. Most studies with physiologic doses of thyroid hormone in man have failed to show any significant effect on weight

reduction. Physiologic replacement of thyroid hormone in a euthyroid individual is compensated for by suppression of the hypothalamic-pituitary-thyroid axis with no net hormonal effect. Pharmacologic doses of thyroid hormone sufficient to raise the basal metabolic rate to a hypermetabolic state undoubtedly result in increased weight loss. If caloric intake is not carefully controlled, however, predominantly fat-free tissue may be lost during treatment. The weight loss may be readily and rapidly reversed after discontinuation of therapy.

The occurrence of toxic effects is unavoidable when pharmacologic doses of thyroid hormone are used. In man, cardiovascular complications were seen in 20% of patients treated with pharmacologic doses. In obese birds without proven hypothyroidism, thyroid hormone therapy can be dangerous and should not be used in lieu of providing a well balanced diet and adequate exercise.

Thyroid hormone can induce molt in a number of species. The molt is more pronounced after administration of a single dose compared with daily administration of small doses equal to the sum of the single dose. A decreasing sensitivity to thyroxine-induced molt is seen in guineafowl, pigeons, gallinaceous birds, waterbirds, Passeriformes and birds of prey. A number of members of the latter orders either do not molt in response to excess thyroid hormone or show only slight molting of small feathers in response to large or even sublethal doses of the hormone.

The Adrenal Glands

Anatomy and Physiology

The right and left avian adrenal glands are yellow organs located craniomedial to the kidneys (see Color 21). The glands receive blood from branches of the renal artery, while the adrenal veins drain into the caudal vena cava. The microanatomy of the avian adrenal gland differs from that of mammals in that the avian adrenal gland is not clearly divided into an outer cortex and inner medulla. In birds, cortical and chromaffin tissue are intermingled. Chromaffin tissue accounts for about 25% of adrenal tissue and can be divided by means of cytochemistry into two types of chromaffin cells: those releasing epinephrine and those releasing norepinephrine.

Cortical or interrenal cells are arranged in numerous cords composed of a double row of cells. The cords radiate from the center of the gland and loop against the inner surface of the connective tissue capsule. The arrangement of specific cell types along the cords results in some structural zonation with two zones: a subcapsular zone that produces aldosterone and a more extensive inner zone that produces corticosterone. The zonation is the most distinct when corticotrophic stimulation is suppressed or enhanced. The major function of the avian adrenal cortical cells is to produce glucocorticoid and mineralocorticoid hormones, of which corticosterone is the most important corticoid hormone in birds. Aldosterone production is considerably less.

In avian embryos, other corticosteroids like cortisol and cortisone are also synthesized. These compounds decrease in concentration around hatch and are absent in the adrenals of chickens and ducks older than two weeks.[68,96] The embryonic avian adrenal gland is also a site of sex steroid synthesis.[96] The secretion of corticosterone is regulated by ACTH, which is released from the corticomelanotropic cells from the cephalic lobe of the adenohypophysis in response to hypothalamic CRF. Glucocorticoids exert a negative feedback at the level of the hypothalamus and hypophysis. The hypothalamic-hypophyseal adrenal (HPA) axis has been reviewed by Bayle.[7]

Corticosterone is essential for survival in times of stress and regulates intermediary metabolism and hemodynamic functions. It also has mineralocorticoid activity. Corticosterone balances the production and action of biologically active substances produced during stress (ie, catecholamines, prostaglandins). If left unchecked, the stress-induced release of these compounds would lead to shock. Plasma corticosterone concentrations can reliably be determined using an RIA.

In free-ranging Mallard Ducks living in coastal estuaries and alkaline lake environments, corticosterone functions as an important mineral-regulating hormone. Under these circumstances, it acts simultaneously on three target organs: the small intestine, the nasal salt glands and the kidney. A specific increase in extracellular sodium concentration, an increase in the concentration of an associated anion or an increase in extracellular osmolality activates the hypophysiotropic reflex to cause a release of ACTH.[45,97]

This response is in marked contrast to that seen in birds that do not possess functional nasal glands and cannot tolerate hyperosmotic drinking water. In these birds, as in most mammals, glucocorticoids do not function as mineral-regulating hormones and sodium does not act as a secretogogue for ACTH release.

The regulation of aldosterone secretion in birds and mammals is probably similar. Renin is released from the juxtaglomerular cells of the kidney in response to low plasma sodium concentration or reduced blood volume. The renin acts on circulating angiotensinogen to form angiotensin I, which is converted to angiotensin II. Aldosterone secretion is stimulated by angiotensin II. Angiotensin II appears to stimulate aldosterone synthesis by acting directly on the steroidogenic cells rather than by stimulating the release of ACTH from the adenohypophysis.[45] In contrast to mammals, birds do not release aldosterone in response to elevated extracellular potassium concentrations.[45]

Angiotensin II has been shown to be a potent dipsogen in a variety of birds. However, carnivorous birds that ingest most of their water requirement with food, show a much lower sensitivity to angiotensinogen II. In quail, daily water consumption parallels a pattern of change in plasma angiotensin II. Furthermore, the inhibition of endogenous angiotensin II by captopril or by the receptor antagonist Saralasin, decreases natural water intake in quail. In the xerophilous budgerigar, daily patterns of water intake and plasma concentrations of angiotensin II are not parallel.[95]

Adrenocortical Disorders

Both over- and underproduction of either glucocorticoid (Cushing's syndrome and Addison's disease, respectively) or mineralocorticoid hormones (aldosteronism and hypoaldosteronism) have been reported in man and domestic animals. Although adrenal lesions have been described on postmortem examinations in a high percentage of birds (27% in one study involving psittacine birds), a clinical diagnosis of spontaneous adrenal disease has never been documented. The use of the ACTH stimulation test, dexamethasone screening test and dexamethasone suppression test as reported for dogs[26] should prove useful for the diagnosis of both hypoadrenocorticism and hyperadrenocorticism in birds. The optimal dose for ACTH and sampling times for determination of plasma corticosterone (not cortisol) concentrations have been established for a number of avian species.

Hyperadrenocorticism (Cushing's syndrome)

Spontaneous hyperadrenocorticism has not been reported in birds, but the effects of exogenous glucocorticoids have been well documented. In man and domestic mammals, Cushing's syndrome occurs most commonly in patients receiving glucocorticoids. Hyperadrenocorticism can occur as a result of a primary tumor of the adrenal gland, a pituitary tumor that hypersecretes ACTH, or ectopic ACTH secretion from a nonpituitary tumor. Both of the latter conditions induce bilateral adrenocortical hyperplasia due to continuous ACTH secretion.

Pituitary and adrenal tumors have been reported in birds, and it is not unlikely that a number of these patients were in fact suffering from hyperadrenocorticism. The following conditions have been reported: bilateral adrenal adenoma and adrenal cortical hyperplasia in budgerigar,[8] unilateral adrenal adenoma in a budgerigar,[12] unilateral adrenocortical carcinoma in a pigeon,[33] adrenal carcinoma with metastasis in the liver,[12] and adrenal gland neoplasia in a variety of avian species.[39] An adrenal cortical tumor in an 18-month-old leghorn hen with marked signs of virilism was reported[15] as well as an adrenal cortical adenoma.[16]

Furthermore, a number of stressful situations can increase adrenal size as a result of continuous stimulation by ACTH. Heterotopic adrenal tissue may occur in the ovary, and both cortical and medullary tumors have been tentatively identified in this site.[15]

Hypoadrenocorticism

Adrenalectomy in birds results in renal loss of NaCl and death from hyponatremia and hyperkalemia. Affected birds can be maintained with high NaCl intake or corticosterone injections.

In dogs, the ACTH-stimulation test is used to evaluate adrenocortical function. In adrenocortical insufficiency, administration of ACTH will not lead to an increase in plasma cortisol, while in hyperadrenocorticism, an exaggerated response may be seen. In all avian species studied, corticosterone, and not cortisol, is considered to be the major glucocorticoid; therefore, cortisol is not a valid parameter to evaluate adrenocortical function in birds.

It has been demonstrated that Mallard Ducks consuming petroleum-contaminated food (South Louisiana crude oil) developed structural damage to the

mitochondria of the inner zone cells in the adrenal cortex and had decreased circulating corticosterone concentrations.[32] Adrenocortical testing procedures using corticosterone have been reported in Psittaciformes,[57,104,110] raptors[111] and pigeons.[60] In pigeons, ACTH testing was accomplished by taking blood samples before and at 60 or 90 minutes after stimulation with 50 μg of ACTH[b] or at 30, 60, 90 or 120 minutes after stimulation with 125 μg of ACTH. In healthy individuals, a 10- to 100-fold increase over baseline corticosterone concentrations and absolute concentrations in the range of 2.2 to 15 μg/dl should be considered normal for post-stimulation samples.

The Use of Corticosteroids in Non-endocrine Disease

Glucocorticoids are widely used in human and veterinary medicine for their beneficial effects in a wide variety of diseases, especially those in which inflammation is severe or in which immunologic-induced disease is involved. Occasionally, glucocorticoids are used to reduce hypercalcemia induced by certain types of neoplasms (renal excretion is increased and intestinal absorption reduced). The adverse effects of glucocorticoids should always be considered before they are administered. The clinician has to consider whether the disease is serious enough to warrant long-term glucocorticosteroid therapy.

The majority of knowledge on the effects of corticosteroids on immunity is derived from experimental work on small rodents and rabbits, although some work has also been performed in birds. In mammals the antibody-forming cells ("bone marrow-derived" or "bursa-equivalent" [B-] lymphocytes and plasma cells) are relatively resistant to the suppressive effects of these agents, while thymic-derived (T-) lymphocytes, and therefore cell mediated immunity, are affected.

Pharmacologic concentrations of corticosterone in birds can cause involution of the cloacal bursa, thymus and spleen, resulting in suppression of both humoral and cell-mediated immunity.[35] Corticosterone in the diet causes a dose-dependent lymphopenia in chickens and an increase in susceptibility to viral infections.[35] A single intramuscular injection of dexamethasone or prednisolone in racing pigeons was found to cause lymphopenia.[34] Lymphopenia occurs within a day after glucocorticoid administration,[35] but leukocyte numbers apparently recover.[21] There is a proportional increase in granulocytes that occurs with the lymphopenia. It has been suggested that this may increase the resistance to bacterial infections through enhanced phagocytosis.[21,35] However, studies in mammals have shown that corticosteroids inhibit neutrophil, macrophage and monocyte migration, chemotaxis, diapedesis, interferon production, processing of antigens, phagocytosis and intracellular killing.[6,27,65]

In man, monocytes are more sensitive to functional suppression by steroids than neutrophils, which may impact the formation of granulomas. Granulomatous hypersensitivity diseases are responsive to glucocorticoid therapy, while tuberculosis and certain fungal diseases associated with granuloma formation are prone to exacerbation and relapse following glucocorticoid therapy. Stress-related aspergillosis is common in oil-contaminated waterfowl.[30,31,87] Aspergillosis has been observed in racing pigeons and budgerigars as a complication of long-term administration of glucocorticosteroids (Westerhof I, unpublished).[84] Aspergillosis in recently captured free-ranging birds may be related to stress-induced hypercorticosteronism with associated suppression of monocyte function (Figure 23.8).

A dose-dependent increase in the excretion of coccidial oocysts can be observed after administration of dexamethasone in infected pigeons.[38]

Glucocorticoids (Corticosteroids)

The anti-inflammatory activities of therapeutically used glucocorticoids (Table 23.1) have been assessed in mammals.[4]

Appropriate dosages for glucocorticoids in birds have not been fully established and are currently being investigated. Dosage guidelines are based on data in mammals.

TABLE 23.1 Activity of Glucocorticosteroids Used in Mammals

Glucocorticoid	Equivalent Dose (mg) Based on Anti-inflammatory Potency	Mineralocorticoid Potency
Cortisone	25	2+
Hydrocortisone (cortisol)	20	2+
Prednisone	5	1+
Prednisolone	5	1+
Methylprednisolone	4	0
Triamcinolone	4	0
Flumethasone	1.5	0
Dexamethasone	0.75	0
Betamethasone	0.6	0

Mineralocorticoid activity is an undesired side-effect in some glucocorticoid drugs. Cortisone and cortisol (hydrocortisone) have the highest mineralocorticoid activity and are the corticosteroids of choice for replacement therapy after adrenalectomy or in (iatrogenic) hypoadrenocorticism. Supplemental administration of the mineralocorticoid, fludrocortisone, is suggested in these cases.

The cortisol dosage for replacement therapy is about 0.5-1 mg/kg daily. Cortisol is also indicated when stressful procedures are undertaken in patients who have been receiving long-term treatment with corticosteroids and are suffering from iatrogenic secondary hypoadrenocorticism or iatrogenic hyperadrenocorticism-like disease.

Prednisolone is the agent of choice for anti-inflammatory immunosuppression and antineoplastic therapy to reduce the severity of negative feedback at the hypothalamus-hypophyseal level. Anti-inflammatory doses of prednisolone are 0.5-1.0 mg/kg. Immunosuppressive and chemotherapeutic doses are 2-4 mg/kg prednisolone daily. Corticosteroids are used as chemotherapy for lymphoreticular neoplasia because of their antimitotic effects on lymphoid tissue.

Dexamethasone is the steroid of choice for reducing cerebrospinal edema. Dosages used in mammals are 2 mg/kg TID until improvement occurs.

Cortisone and prednisone must be metabolized in the liver to form cortisol (hydrocortisone) and prednisolone, respectively. Therefore, prednisone and cortisone are not effective when applied topically.

In clinical situations where long-term glucocorticosteroid therapy is indicated, appropriate consideration should be given to exacerbations of subclinical infections (eg, viral, bacterial, mycotic or parasitic) or induction of iatrogenic secondary hypoadrenocorticism or iatrogenic hyperadrenocorticism-like disease. Local corticosteroid therapy should be considered in ophthalmic and dermatologic conditions, and alternate-day therapy should be considered in long-term systemic corticosteroid therapy to reduce these side-effects. However, the clinician should be aware that high or even toxic blood levels of steroids can occur following topical application.

With daily glucocorticosteroid therapy, short-acting agents are used to simulate the normal physiologic corticosterone cycle. Short-acting glucocorticosteroids are administered in man in the morning when endogenous glucocorticoid concentrations are highest. This induces the most profound negative feedback on ACTH secretion. Low levels late at night release the pituitary from feedback inhibition and permit secretion of ACTH. When the same total amount of glucocorticosteroids is given in divided doses, a greater incidence of complications, particularly suppression of the HPA axis, is to be expected. A nocturnal rise in plasma corticosterone concentrations has been demonstrated in pigeons[47] and chickens,[9] with the acrophase towards the end of the scotoperiod, which is suggestive of an increase of the secretion of corticotrophin (ACTH) at night. There is, however, some controversy about the exact timing of the acrophase in chickens.[28] Considering these findings, it seems logical to administer glucocorticoids in the morning hours in diurnal birds. The situation might be reversed in nocturnal birds.

FIG 23.8 A mature Moluccan Cockatoo male was presented for feather dystrophy and progressive inspiratory dyspnea of several weeks' duration. Endoscopy of the trachea revealed a proliferative mass occluding the majority of the lumen. The bird was euthanatized. At necropsy, an aspergilloma was detected in the mid-cervical area of the trachea. The only other gross lesion was bilateral adrenal hypertrophy (three to four times normal size) suggestive of chronic stimulation by ACTH. Blood collected from the bird during the initial evaluation was positive for PBFD virus by DNA probe testing.

Corticosteroid therapy in severe inflammatory diseases is best divided into several doses through the day. Once the desired effects are reached, the regimen should be tapered down to the least toxic dose. The divided daily dose is given in a single daily dose in the morning and gradually decreased to the minimal effective dose. Whenever glucocorticosteroid therapy has to be given for periods over two weeks, alternate-day therapy should be considered. The daily dose is doubled and given every other day, while the dose on the "off" day is gradually decreased to zero. The use of nonsteroidal anti-inflammatory drugs can be used on the "off" days during the tapering period.

Whenever long-term glucocorticoid therapy is discontinued, gradual tapering of glucocorticoid dosage is indicated.

Iatrogenic Hyperadrenocorticism-like Disease

Exogenous glucocorticoids cause hyperphagia while reducing growth and body weight in birds. There is a marked increase in fat deposition (lipogenesis) and a concomitant increase in protein catabolism. Cholesterol levels increase, and true lipemic conditions may develop as a result of glucocorticoid injections. Furthermore, gluconeogenesis is increased (production of blood glucose at the expense of muscle and adipose tissue) and hence plasma glucose concentrations are elevated. Steroid diabetes may be induced with accompanying glucosuria. Hepatic glycogen is increased. Calcium absorption from the intestinal tract is reduced after administration of betamethasone and cortisol. Corticosterone increases the glomerular filtration rate which, together with glucosuria, may be recognized as polyuria and polydipsia.

Iatrogenic Secondary Hypoadrenocorticism

Glucocorticoids exert a negative feedback influence at the hypothalamo-hypophyseal level and suppress basal and stress-induced corticosterone release. Failure of the adrenal gland to respond to stress factors may result in adrenocortical insufficiency. Many stressors are known to induce corticosterone secretion in birds: extreme environmental temperatures, handling, immobilization, anesthesia, infection, frustration, fear, housing, noise, food and water deprivation and hypovitaminosis A. Adrenocortical failure and shock may occur in birds exposed to one or more stressful situation following iatrogenic glucocorticoid administration. Sustained suppression of the HPA axis is common in human patients who have received the equivalent of 30 mg prednisone per day for more than one week. Exposure to high doses over a prolonged period of time may lead to HPA axis suppression for up to one year. It has been shown in pigeons that short-term, high-dose glucocorticoid therapy produces only transient suppression of the HPA axis (Westerhof I, unpublished). An ACTH stimulation test can be performed to evaluate the integrity of the HPA axis. Replacement therapy is indicated in stressed birds with hypoadrenocorticism.

Stress Marks

A common disorder of developing feathers is the symmetrical development of stress marks or hunger traces. These represent a segmental dysplasia in the barbs and barbules. Stress lines can be easily identified by holding the spread wing or tail feathers against a light and looking for bilateral symmetrical lines perpendicular to the feather shaft (see Color 24). These lesions represent a period of malnutrition or stress while the feathers were developing. They can also be induced by a single injection of a glucocorticoid. Administration of glucocorticoids strongly suppresses growth and increases protein catabolism,[24] and these lesions probably reflect a short period of decreased amino acid available to the developing feather. Chronic malnutrition and chronic stress in birds with developing feathers will result in more severely affected feathers.

Adrenomedullary Disorders

Pheochromocytoma (Chromaffinoma)

A benign or malignant tumor of chromaffin tissue may cause hypersecretion of epinephrine or norepinephrine, which in man is known to lead to hypertension and associated symptoms such as profuse sweating and cardiac irregularities. A pheochromocytoma of the adrenal gland in a 14-week-old broiler pullet has been reported.[15] The bird died suddenly. The only obvious abnormality was an enlarged left adrenal gland measuring 15 mm in diameter.

Endocrine Control of Feather Formation

A basic knowledge of endocrine control of feather formation should direct the clinician away from using endocrine abnormalities as a repository for disturbances in feather formation of unknown etiology. Three basic factors have been discussed in feather formation: the feather-forming tissue itself, the neurohumoral factors in the absence of which the feather-forming tissue is unable to fulfill its specific morphogenetic function, and finally the environmental factors, especially the variation in daylight length, which controls the neurohumoral factors.[100] Neural control of feather formation has been demonstrated by growth retardation of feathers when denervation occurs. The metabolic processes that underlie feather formation are regulated by the thyroid and the gonads.

The development of embryonic, juvenile and adult plumage has three phases: the production of germ

cells, their proliferation and development and the renewal of feathers. The first phase can occur in the absence of thyroid hormone. The presence of thyroid hormone, however, is essential for the growth, differentiation of structure and formation of feather pattern. The importance of thyroid hormone for feather formation is generally similar in young and mature birds. In some birds, this thyroid dependence affects the rate of feather growth and formation of vane structure and in others, it affects the pigmentation and development of feather pattern.

In thyroidectomized birds, the lower parts of the feather are underdeveloped, while in hyperthyroidism, these parts develop most vigorously. In hypothyroidism, the vanes of the feathers are narrower and there is a partial reduction of the barbs. In a number of fowl breeds, hypothyroidism is accompanied by partial or complete replacement of black eumelanin by brown pheomelanin, while in hyperthyroidism eumelanin pigmentation is enhanced. The black pigment can be formed in the bird's body at only a certain concentration of thyroid hormone.

Molting is possible only as the result of complex hormonal influences. Molting occurs during a period of depressed sexual activity. It can be suppressed by sex hormones or induced by administration of progesterone (see Chapter 24).

When the duration of light is decreased, or a long period of artificial daylight is suddenly replaced by a short one, sexual activity declines or ceases and molting begins. Numerous experiments in birds of various species have provided similar results. Short periods of daily light associated with declining sexual activity are needed for the proliferation of feather germ cells and renewal of plumage. Sudden transition to darkness after prolonged exposure to lengthened periods of daily light produces vigorous molting in various birds.

It should be remembered that many avian species must be exposed to natural photoperiods to allow a normal hypothalamic-pituitary control of the molting process. Improper photoperiods may be an important cause of feathering disorders in companion birds kept indoors. Additionally, normal feather development requires that appropriate nutrients for feather development are available in appropriate quantities.

An increase in thyroid gland activity during molting does not cause molting but rather is a response to the body's increased requirements of thyroid hormone in connection with the development of new feathers. However, thyroid hormone administration in some species will accelerate the molting process.

In some birds (eg, Galliformes, Passeriformes, Anseriformes), feather color and pattern vary with the age, gender and season, and these characteristics are governed by hormonal influences of the gonads. In these birds, the adult plumage, unlike the juvenile plumage, develops under the influence of at least two endocrine glands. In contrast, the plumage of Fringillidae may or may not differ by gender. In these birds the plumage does not change under influence of plasma concentrations of sex hormones but is governed by the autosome: sex chromosome ratio and cannot be overridden by hormonal imbalance. The influence of sex hormone in the former group in each feather-forming process is realized only at a definitive level of metabolism that is maintained by thyroid hormone (female plumage does not develop in thyroidectomized birds given estrogen). When the bird is adequately saturated with thyroid and sex hormones, the feathers that develop should be termed the thyro-sexual type. Under conditions of hypothyroidism or athyreosis, the feathers that develop are uniform in structure and should be termed the athyreoid type of plumage (and consequently also asexual, juvenile type).

The male plumage is potentially an attribute of both genders, and the female hormones play the principal role in gender differences in the plumage of Galliformes and Anseriformes. When a rooster, drake or cock pheasant is castrated, no changes are produced in the pattern of its plumage. Neutered females, however, develop male-type plumage after molting. When a castrated rooster or a neutered hen undergoes an ovarian transplant, female-type plumage develops.

Diabetes Mellitus

Spontaneous diabetes mellitus has been reported in a variety of granivorous avian species, including the domestic pigeon. One case of spontaneous diabetes mellitus has been reported in a raptor.[103] Budgerigars and cockatiels frequently develop diabetes mellitus. The most striking clinical signs are PU/PD and loss of weight despite a good appetite. A tentative diagnosis can be made by demonstrating glucosuria while a

definitive diagnosis can be made by finding persistent hyperglycemia.

There are some striking differences between birds and mammals with respect to pancreatic control of carbohydrate metabolism. The insulin content of the pancreas of granivorous birds is about one-sixth that of mammalian pancreata, while the glucagon content is about two to five times greater. Circulating plasma concentrations of glucagon are 10 to 50 times higher in birds than in mammals. In mammals, pancreatectomy results in diabetes mellitus. Reported effects of pancreatectomy in birds are controversial. However, recent experiments performed on granivorous birds indicate that surgical extirpation or destruction of the pancreas with cytotoxic agents leads to hypoglycemic crisis and death. The few reported pancreatectomies performed on carnivorous birds have always led to diabetes mellitus.

It is generally accepted that glucagon is more effective in granivorous birds, which exhibit a marked insulin insensitivity. The limited data available on spontaneous diabetes mellitus in granivorous birds suggest that in these species diabetes mellitus is not caused by an insulin deficiency. Birds of prey may be more insulin-dependent than granivorous birds.[103]

There are several case reports of successful treatment of spontaneous diabetes mellitus in birds with daily injections of insulin using dosages comparable to those used in dogs. These reported "successful treatments" of diabetic birds (disappearance of clinical signs) are surprising, considering the relative insulin insensitivity that has been reported to occur in a variety of avian species.

Plasma insulin and glucagon concentrations have been established in three birds with hyperglycemia.[58] It is not clear whether these determinations were accurate. In all cases, insulin concentrations were similar to controls. Glucagon concentrations on the other hand were extremely high or extremely low. This suggests that the hyperglycemia may have been from varying etiologies.

TABLE 23.2 Control of Carbohydrate Metabolism

	Birds (granivorous)	Mammals
Pancreas	Low insulin High glucagon	High insulin Low glucagon
Plasma glucagon	High	Low
Pancreatectomy	Varies (hypoglycemia)	Diabetes mellitus

When speculating on causes of diabetes mellitus in birds, the possible role of the diabetogenic hormones should be considered. Glucocorticoids, epinephrine, glucagon and growth hormone can all induce hyperglycemia and impaired glucose tolerance. Overproduction of these hormones may occur with tumors of the hormone-producing cells or paraneoplastic syndromes ("ectopic" hormone production).

In man, hyperglucagonemia may be associated with bacterial infections, trauma, congestive heart failure, azotemia and functioning tumors of the α-cells of the islets of the pancreas or of the gastrointestinal tract (eg, glucagonoma).[10,72]

Most avian pancreatic carcinomas are the result of secondary invasion usually via serosal implantation on the duodenal loop of tumors arising in the female reproductive tract.[15] The histology can be most misleading because in the pancreas there is often an appearance of gradation and continuity between epithelium and tumor cells. An islet cell adenoma that was identified as an α-cell adenoma has been described.[15] No clinical information on this bird was available.

An islet cell carcinoma has been diagnosed in one case of diabetes mellitus in a parakeet. The cellular origin of the tumor was not identified, but it was suggested that it could be an α-cell tumor.[80] This also may have been a case of a paraneoplastic syndrome. In man, pancreatic islet cell tumors are a well known site of ectopic ACTH production, which can cause an associated Cushing's syndrome.[70] Pancreatic islet cell tumors are also associated with ectopic GH secretion,[70] which can cause diabetes mellitus in dogs.[26] Unfortunately, no endocrine studies were performed in this particular parakeet. Glucagon-like immunoreactivity has been reported from extracts of certain parts of the avian small intestine.[90]

The normal avian pancreas contains extremely high levels of somatostatin (produced in the D-cells of the islets). This compound depresses glucagon secretion (and to a lesser extent insulin and avian pancreatic polypeptide secretion), and it might be hypothesized that elevated glucagon concentrations could be caused by decreased release of somatostatin (SRIF). The hypothesized triggering mechanism for a diminished release of SRIF, however, is not clear.

In intact female dogs, progesterone-induced GH overproduction with subsequent insulin resistance accompanied with hyperinsulinemia can cause diabetes mellitus. The disease can occur spontaneously

during diestrus or as a complication of treatment with medroxyprogesterone acetate. The data available on plasma insulin concentrations in birds with hyperglycemia/glucosuria suggest that the cases were not caused by insulin resistance because insulin concentrations in the birds were similar to controls. Overproduction of GH, therefore, was an unlikely cause of diabetes mellitus in these birds, but might be a cause of diabetes in other birds.

Hyperglycemia was reported in budgerigars with subcutaneous transplants of pituitary adenomas in combination with slightly elevated GH activities.[84]

A cockatiel was reported with what seemed to be subnormal glucagon concentrations and normal insulin concentrations.[58] It is possible that the low glucagon concentration was a response to a hyperglycemia induced by another unknown factor (steroid diabetes caused by primary, secondary or iatrogenic hyperadrenocorticism or ectopic ACTH production).

The association of Cushing's syndrome with carcinoma is the most common ectopic endocrine syndrome in man. Neoplasms associated with this syndrome include lung carcinoma (oat cell and small round cell), pancreas carcinoid and islet cell carcinomas, medullary carcinomas of thyroid and neoplasms derived from the neural crest (pheochromocytoma, neuroblastoma, paraganglioma, ganglioma) (see Color 25). Numerous cases suggest that any carcinoma may induce an ectopic endocrine syndrome. The current theory is that POMC is probably produced in small quantities by all normal nonendocrine tissues. Immunoreactive POMC is found in large quantities in extracts of carcinomas. Some carcinomas metabolize POMC to biologically active ACTH, producing the so-called ectopic ACTH syndrome.[70] Renal carcinomas and pancreatic carcinomas have been seen in association with hyperglycemia in birds, and a paraneoplastic syndrome involving POMC-derived ACTH with subsequent hyperadrenocorticism cannot be excluded.

The single case of diabetes mellitus reported in a raptorial bird was associated with markedly vacuolated B-cells indicative of excessive stimulation.[103] Further findings were four fluid-filled cysts on the kidneys and mildly enlarged adrenals. Histology revealed chronic multifocal lymphocytic interstitial nephritis. The liver had variable-sized, randomly scattered foci of lipidosis.

The pathogenesis of diabetes mellitus in birds remains unclear.

Polyuria/Polydipsia (PU/PD)

A variety of diseases that cause PU/PD in birds has been defined, but the pathophysiologic mechanisms and etiology are not always clear. The minimal database for an avian patient with PU/PD should include dietary history, social and behavioral history, vaccination status (paramyxovirus in pigeons) and recent medications (eg, corticosteroid therapy), urinary glucose, plasma glucose, urea, uric acid, AST, bile acids, total calcium, total protein, protein electrophoresis and HAI-titer for paramyxovirus in pigeons. Diseases that are known to cause PU/PD in other animals, but that have not been diagnosed in birds, are hyperthyroidism, hyperadrenocorticism and hypercalcemia associated with (pseudo)hyperparathyroidism.

Determining the reproductive history is important in hens with PU/PD. Birds with egg-related peritonitis may have previously laid eggs and then stopped because of the egg-related peritonitis. These birds may have a swollen abdomen in association with PU/PD.

Polyuria/Polydipsia Syndrome in Pigeons Feeding Squabs

Pigeons feed their young crop milk during the first 7 to 11 days after hatching, at which time the squabs are fed regurgitated grains. The parent birds and the squabs often develop PU/PD for a couple of days during the transition period. When the parents and squabs are separated from each other, PU/PD continues in the adult birds but subsides in the squabs.

The observed PU/PD in the parent birds may be caused by a decrease in the circulating concentrations of prolactin. Apart from being essential for the production of crop milk, it has been shown that prolactin has an influence on water and electrolyte regulation in birds. Experimental administration of prolactin to Mallard Ducks results in a decreased urine production. In chickens, an increase in plasma prolactin concentrations has been observed after infusion of hypertonic saline and with dehydration.

When water intake is restricted in these birds, the PU/PD stops immediately, indicating that the body is capable of correctly concentrating urine.

TABLE 23.3 Some Conditions Associated with Polyuria/Polydipsia

- Dietary-induced polyuria
- Excitement or nervousness
- Apparent psychogenic polydipsia
- Medications (corticosteroids, diuretics, progesterones)
- Toxins (eg, gentamicin)
- Nephrogenic diabetes insipidus
- Diabetes insipidus
- Diabetes mellitus
- Renal glucosuria
- Pigeons feeding squabs
- Paramyxovirus (racing pigeons)
- Liver disease
- Renal disease
- (Hypercalcemia?)
- (Hyperadrenocorticism?)
- (Hyperthyroidism?)
- Hypervitaminosis D_3
- Elevated dietary sodium
- Excess dietary protein
- Excessive fruit consumption

Renal Glucosuria

Glucosuria is not always associated with hyperglycemia, and the two should occur together to warrant a diagnosis of diabetes mellitus. Glucosuria without hyperglycemia in man is associated with the Fanconi syndrome, which is caused by inherited or acquired damage to the proximal convoluted tubules of the kidney.[105] Glucosuria without hyperglycemia has been observed in an African Grey Parrot.

Apparent Psychogenic Polydipsia

Some avian patients may develop psychogenic polydipsia that results in polyuria. A water deprivation test may be useful in documenting a primary polydipsia or compulsive water drinking. In these patients, water restriction results in disappearance of the clinical signs. It seems that psychogenic polydipsia should be added to the list of behavioral problems that can be encountered in companion birds.[64]

Paramyxovirus Infection in Racing Pigeons

When a pigeon strain of paramyxovirus serotype-1 infects an unvaccinated flock of pigeons, about 80% of the birds will develop severe PU/PD, which can last for several months and then gradually resolve. The pathophysiologic mechanism for these clinical changes has not been defined.

Products Mentioned in the Text

a. Ambinon, Organon, Oss, The Netherlands
b. Cortrosyn, Organon, Oss, The Netherlands

References and Suggested Reading

1. **Alberts H, et al:** A water deprivation test for the differentiation of polyuric disorders in birds. Avian Pathol 17:385-389, 1988.
2. **Ash JS:** Another dwarf pheasant. Bulletin British Ornithological Club 86:95-96, 1966.
3. **Astier H:** Thyroid gland in birds. *In* Epple A, Stetson MH (eds): Avian Endocrinology. London and New York, Academic Press, 1980, pp 167-189.
4. **Axelrod L:** Glucocorticoid therapy. Medicine 55:39, 1976.
5. **Baimbridge KG, Taylor TG:** The role of calcitonin in controlling hypercalcaemia in the domestic fowl (*Gallus domesticus*). Comp Biochem Phys A 68:647-651, 1981.
6. **Baxter JD, Forsham RH:** Tissue effects of glucocorticoids. Am J Med 53:573, 1972.
7. **Bayle JD:** The adrenohypophysiotropic mechanisms. *In* Epple A, Stetson M (eds): Avian Endocrinology. New York, Academic Press, 1980, p 117.
8. **Beach JE:** Diseases of budgerigars and other cagebirds. A summary of post mortem findings. Vet Rec 74:10-15, 63-68, 134-140, 1962.
9. **Beuving G, Vonder GMA:** Daily rhythm of corticosterone in laying hens and the influence of egg laying. J Reprod & Fert 51:169-173, 1977.
10. **Bilbrey GL, et al:** Hyperglucagonaemia of renal failure. J Clin Invest 53:841, 1974.
11. **Blackmore DK:** The pathology and incidence of thyroid dysplasia in budgerigars (*Melopsittacus undulatus*). Vet Rec 75:1068-1072, 1965.
12. **Blackmore DK:** Diseases of the endocrine system. *In* Petrak ML (ed): Diseases of Cage and Aviary Birds 2nd ed. Philadelphia, Lea & Febiger, 1982, pp 479-490.
13. **Braverman LE:** Normal and abnormal responses to iodine: Disorders of iodine excess. *In* Werner SC, Ingbar SH (eds): The Thyroid. A Fundamental and Clinical Text. New York, Harper and Row, 1978, pp 528-536.
14. **Burrow, GN:** Thyroid hormone therapy in nonthyroid disorders. *In* Werner SC, Ingbar SH (eds): The Thyroid. A Fundamental and Clinical Text. New York, Harper and Row, 1978, pp 974-980.
15. **Campbell JG:** Tumours of the Fowl. Philadelphia, JB Lippincot Company, 1969.
16. **Campbell JG, Appleby EC:** Tumours in young chickens bred for rapid body growth (broiler chickens): A study of 351 cases. J Pathol & Bact 92:77-90, 1961.
17. **Cole RK:** Hereditary hypothyroidism in the domestic fowl. Genetics 53:1021, 1966.
18. **Cole RK, Kite JH, Witebsky E:** Hereditary autoimmune thyroiditis in the fowl. Science 160:1357-1358, 1968.
19. **Curtis-Velasco M:** Pituitary adenoma in a cockatiel (*Nymphicus hollandicus*). J Assoc Avian Vet 6(1):21-22, 1992.
20. **Cutler GB, Habener JF, Dee PC, Potts JT:** Comparative immunochemical studies of chicken ultimobranchial calcitonin. Gen & Compar Endocrin 24:183, 1974.
21. **Davison TF, Rea J, Powell JG:** Effects of dietary corticosterone on peripheral blood lymphocytes and granulocyte populations in immature domestic fowl. Res Vet Sci 34:236, 1983.
22. **Davison TF, Chapman HD, Harvey S:** Endocrine changes in the fowl during infection with *Eimeria maxima*. Res Vet Sci 38:296-300, 1985.
23. **Davison TF, Rea J, Freeman BM:** Effect of increased circulating corticosterone on the plasma concentrations of thyroxine and triiodothyronine in chickens. IRCS Med Sci 13:692-693, 1985.
24. **De la Cruz LF, Mataix FJ, Illera M:** Effects of glucocorticoids on protein metabolism in laying quails (*Coturnix japonica*). Comp Biochem Physiol A 70:649, 1981.
25. **Eisen HN:** Immunology. An Introduction to Molecular and Cellular Principles of the Immune System. New York, Harper and Row, 1974, p 591.
26. **Ettinger SJ (ed):** Textbook of Veterinary Internal Medicine Vol 2, 3rd ed. Philadelphia, WB Saunders Co, 1989, pp 1579-1774.
27. **Fauci AS, et al:** Glucocorticosteroid therapy: Mechanisms of action and clinical considerations. Ann Int Med 84:304, 1976.
28. **Freeman BM (ed):** Physiology and Biochemistry of the Domestic Fowl Vol 4. London, Academic Press, 1983.
29. **Freeman BM (ed):** Physiology and Biochemistry of the Domestic Fowl Vol 5. London, Academic Press, 1984.
30. **Fowler ME:** Miscellaneous waterbirds. *In* Fowler ME (ed): Zoo and Wild Animal Medicine. Philadelphia, WB Saunders Co, 1978, p 215.
31. **Fowler ME:** Stress. *In* Fowler ME (ed): Zoo and Wild Animal Medicine. Philadelphia, WB Saunders Co, 1978, pp 33-34.
32. **Gorsline J:** The effects of south Louisiana crude oil on adrenocortical function. *In* Scanes CG, et al (eds): Aspects of Avian Endocrinology. Lubbock, Texas Tech Press, 1982, pp 359-364.
33. **Gratzl E, Köhler H:** Spezielle Pathologie und Therapie der Geflügelkrankheiten [Pathology and Therapy of Poultry Diseases]. Stuttgart, Ferdinand Enke Verlag, 1968.
34. **Groggier U, Grimm F:** Dexamethasone- und Prednisolone Einsatz bei Tauben [The use of dexamethason and prednisolon in pigeons]. VI. Tagung über Vogelkrankheiten der Deutsche veterinarmedizinische Gesellschaft, München, 1988, pp 68-76.
35. **Gross WB, Siegel PB, Dubosse RJ:** Some effects of feeding corticosterone to chickens. Poult Sci 59:516-522, 1980.
36. **Guerin M:** Tumeurs spontanees de la poulle [Spontaneous tumors in poultry]. *In* Tumeurs Spontanees des Animaux de Laboratoire. Paris, Legrand, 1954, pp 153-180.
37. **Gylstorff I, Grimm F:** Vogelkrankheiten [Avian Diseases]. Stuttgart, Ulmer, 1987.
38. **Haas L:** Die Auswerkung des Paramunitätsinducers PIND ORF auf die Flugleistung sowie auf die Ausscheidung von Kokzidienoozysten von normalen und immunsupprimierten Brieftauben (*Columba livia*, Gmel., 1789, var. dom.) [The effect of the paramunity inducer PIND ORF on the racing pigeon performance and the excretion of oocysts on normal and immunosuppressed racing pigeons]. PhD Thesis, University of Münich, 1987.
39. **Halloran PO'C:** A bibliography of references to diseases in wild mammals and birds. Appendix to Am J Vet Res 16:306-405, 1955.
40. **Harrap BS, Woods EF:** Species difference in the protein of feathers. Comp Biochem Physiol 20:449, 1967.
41. **Hazelwood A, Harrison JM:** A note on Larus 'capistratus' Temminck. Bulle-

tin British Ornithological Club 73: 98-100, 1953.

42. **Hazelwood RL:** Carbohydrate metabolism; Pancreas. *In* Sturkie PD (ed): Avian Physiology 4th ed. New York, Springer Verlag, 1986, pp 303-325; pp 494-501.
43. **Höhn EO, Braun CE:** Hormonal induction of feather pigmentation in ptarmigan. Auk 98:189, 1981.
44. **Hollander WF, Riddle O:** Goiter in domestic pigeons. Poult Sci 25:20-27, 1946.
45. **Holmes WN, Cronshaw J, Redondo JL:** The ontogeny of adrenal steroidgenic function in the mallard (Anas platyrhynchos). *In* Wada M, Ishii S, Scanes CG: Endocrinology of Birds. Molecular to Behavioral. Berlin, Springer Verlag, 1990.
46. **Hutt FB:** Sex-linked dwarfism in the fowl. J Heredity 50:209-221, 1959.
47. **Joseph MM, Meier AH:** Daily rhythms of plasma corticosterone in the common pigeon *Columba livia*. Gen & Comp Endocrin 20:326-330, 1973.
48. **Julian RJ, Summers J, Wilson JB:** Right ventricular failure, and ascites in broiler chicks caused by phosphorus-deficient diets. Avian Dis 30:453-459, 1986.
49. **Kronberger H:** Haltung von Vögeln, Krankheiten der Vögel [Aviculture and Diseases of Birds]. Jena: VEB Gustav Fischer Verlag, 1974.
50. **Kühn ER, Decuypere E, Huybrechts LM, Darras VM:** Hormonal control of the hepatic 5'-monodeiodination activity and its relation to the somatomedin production in the chicken. *In* Wada M, Ishii S, Scanes CG: Endocrinology of Birds. Molecular to Behavioral. Berlin, Springer Verlag, 1990, pp 129-142.
51. **Lamont SJ, Smyth JR, Jr:** Effect of bursectomy on development of a spontaneous postnatal amelanosis. Clin Immunol Immunopath 21:407, 1981.
52. **Larsson M:** Diagnostic methods in canine hypothyroidism and influence of non-thyroidal illness on thyroid hormones and thyroxine-binding proteins. Thesis, Uppsala, Sveriges Lantbruksuniversitet, 1987, p 13.
53. **Long PH, Lee SR, Rowland GN, Britton WM:** Experimental rickets in broilers: Gross, microscopic, and radiographic lesions. I. Phosphorus deficiency and calcium excess. Avian Dis 28:460-474, 1984.
54. **Long PH, Lee SR, Rowland GN, Britton WM:** Experimental rickets in broilers: Gross, microscopic, and radiographic lesions. II. Calcium deficiency. Avian Dis 28:921-932, 1984.
55. **Long PH, Lee SR, Rowland GN, Britton WM:** Experimental rickets in broilers: Gross microscopic, and radiographic lesions. III. Vitamin D deficiency. Avian Dis 28:933-943, 1984.
56. **Lothrop CD, Loomis MR, Olsen JH:** Thyrotropin stimulation test for evaluation of thyroid function in psittacine birds. J Am Vet Med Assoc 186:47-48, 1985.
57. **Lothrop CD, Olsen JH, Loomis MR, et al:** Evaluation of adrenal function in psittacine birds, using the ACTH stimulation test. J Am Vet Med Assoc 187:1113-1115, 1985.
58. **Lothrop C, Harrison G, Schultz D, Utteridge T:** Miscellaneous diseases. *In* Harrison GJ, Harrison LR (eds): Clinical Avian Medicine and Surgery. Philadelphia, WB Saunders Co, 1986, pp.525-536.
59. **Lumeij JT:** Relation of plasma calcium to total protein and albumin in African grey (*Psittacus erithacus*) and Amazon (*Amazona* spp.) parrots. Avian Pathol 19:661-667, 1990.

59a. **Lumeij JT, DeBruijne JJ, Krant M:** Comparison of different methods of measuring protein and albumin in pigeon sera. Avian Pathol 19:255-261, 1990.

60. **Lumeij JT, Boschma Y, Mol J, et al:** Action of ACTH$^{1-24}$ upon plasma corticosterone concentrations in racing pigeons (*Columba livia domestica*). Avian Pathol 16:199-204, 1987.
61. **Lumeij JT, Sprang EPM, Mol JA:** Arginine vasotocin measurements before and after water deprivation for the differentiation of polyuric disorders in birds, submitted.
62. **Lumeij JT, Remple JD, Riddle K:** Relation of plasma total protein and albumin tot total calcium in peregrine falcons (*Falco peregrinus*). Avian Pathol 22:183-188, 1993.
63. **Lumeij JT, Westerhof I:** Clinical evaluation of thyroid function in racing pigeons (*Columba livia domestica*). Avian Pathol 17:63-70, 1988.
64. **Lumeij JT, Westerhof I:** The use of the water deprivation test for the diagnosis of apparent psychogenic polydipsia in a socially deprived African grey parrot (*Psittacus erithacus*). Avian Pathol 17:875-878, 1988.
65. **Melby JC:** Clinical pharmacology of systemic corticosteroids. Ann Rev Pharmacol Toxicol 17:511, 1977.
66. **Murton RK, Westwood NJ:** Avian Breeding Cycles. Oxford: Clarendon, 1977.
67. **Murray BG:** A small great-crested flycatcher. Bird Banding 42:119, 1971.
68. **Nakamura T, Tanabe Y, Hirano H:** Evidence of the *in vitro* formation of cortisol by the adrenal gland of embryonic and young chickens (*Gallus domesticus*). Gen Comp Endocrin 25:300-308, 1978.
69. **Neumann U, Kummerfeld N:** Neoplasms in budgerigars: clinical, pathomorphological and serological findings with special consideration of kidney tumors. Avian Pathol 12:353-362, 1983.
70. **Odell WD:** Endocrine manifestations of tumors: "Ectopic" hormone production. *In* Wijngaarden JB, Smith LH: Cecil Textbook of Medicine, 18th ed. Philadelphia, WB Saunders Co, 1988, pp 1100-1104.
71. **Parrott T:** Pododermatitis in three Amazon parrots and treatment with L-thyroxine. Proc Assoc Avian Vet, 1991, pp 263-264.
72. **Rocha DM, et al:** Abnormal pancreatic -cell function in bacterial infections. New Engl J Med 284:621, 1971.
73. **Rosskopf WJ, Woerpel RW, Howard EB, Holshuh HJ:** Chronic endocrine disorder associated with inclusion body hepatitis in a sulfur crested cockatoo. J Am Vet Med Assoc 179:1273-1276, 1981.
74. **Rosskopf WJ, Woerpel RW, Richkind M, Howard EB:** Pathogenesis, diagnosis and treatment of adrenal insufficiency in psittacine birds. Calif Vet 36:26-30, 1982.
75. **Rosskopf WJ, Woerpel RW:** Remission of lipomatous growth in a hypothyroid budgerigar in response to L-thyroxine therapy. Vet Med Sm Anim Clin 9:1415-1418, 1983.
76. **Rosskopf WJ, Woerpel RW, Rosskopf G, Van de Water D:** Normal thyroid values for common pet birds. Vet Med Sm Anim Clin, March 1982: 409-412, 1982.
77. **Rudas P, Salyi G, Szabo J:** Decreased thyroxine, triiodothyronine and 5-deiodination levels in malabsorption syndrome. Avian Dis 30:293-297, 1985.
78. **Russel WC:** Iodine goiter in penguins. J Zoo An Med 1:24-27, 1970.
79. **Russel WC:** Iodine-induced goiter in penguins. J Am Vet Med Assoc 171:959-960, 1977.
80. **Ryan CP, Walder EJ, Howard EB:** Diabetes mellitus and islet cell carcinoma in a parakeet. J Am Anim Hosp Assoc 18:139-142., 1982.
81. **Scanes CG, et al:** *In* Wada M, Ishii S, Scanes CG: Endocrinology of Birds. Molecular to Behavioral. Berlin, Springer Verlag, 1990.
82. **Schlumberger HG:** Neoplasia in the parakeet. I. Spontaneous chromophobe pituitary tumors. Cancer Res 14:237, 1954.
83. **Schlumberger HG:** Spontaneous goiter and cancer of the thyroid in animals. Ohio J Sci 55:23-43, 1955.
84. **Schlumberger HG:** Neoplasia in the parakeet II. Transplantation of the pituitary tumor. Cancer Res 16:149-153, 1956.
85. **Schlumberger HG:** Tumors characteristic for certain animals. A review. Cancer Res 17:823-832, 1957.
86. **Schlumberger HG:** Polyostotic hyperostosis in the female parakeet. Am J Pathol 35:1-23, 1959.
87. **Schultz DJ:** Respiratory diseases. Proc #55 Aviary and Caged Birds. University of Sydney, Australia, 1981, p 493.
88. **Serrano J, Scavo L, de Pablo, F:** The ontogeny of insulin gene expression. *In* Wada M, Ishii S, Scanes CG: Endocrinology of Birds. Molecular to Behavioral. Berlin, Springer Verlag, 1990, pp 85-92.
89. **Simkiss K:** Calcium in Reproductive Physiology. A Comparative Study of Vertebrates. London, Chapman and Hall Ltd, 1967, pp 155-197.
90. **Sitbon G, Mialhe P:** Pancreatic hormones and plasma glucose: Regulation mechanisms in the goose under physiological conditions. Horm Metab Res 11:85, 1979.
91. **Slye M, Holmes HF, Wells HG:** Intracranial neoplasms in lower animals. Studies on the incidence and inheritability of spontaneous tumors in mice. Am J Cancer Res 15:1387-1400, 1931.
92. **Smyth JR Jr, Boissey RE, Fite KV:** The DAM chicken: A model for spontaneous postnatal cutaneous and ocular amelanosis. J Heredity 72:150, 1981.
93. **Sturkie PD (ed):** Avian Physiology 4th ed. New York, Springer-Verlag, 1986.
94. **Suzuki H, Higuchi T, Sawa K, et al:** Endemic coast goitre in Hokkaido, Japan Acta Endocrinologica (Kbh) 50:161, 1965.
95. **Takei Y, Kobayashi H:** Hormonal regulation of water and sodium intake in birds. *In* Wada M, Ishii S, Scanes CG: Endocrinology of Birds. Molecular to Behavioral, Berlin, Springer Verlag, 1990, pp 171-186.
96. **Tanabe Y, Nakamura T, Fujiota K, Doi O:** Production and secretion of sex steroid hormone by the testes, ovary, and the adrenal glands of embryonic and young chickens (*Gallus domesticus*). Gen Comp Endo, 39: 26-33, 1979.
97. **Thomas DH, Philips JG:** Studies in avian adrenal steroid function. IV: Adrenalectomy and the response of domestic ducks (*Anas platyrhynchos*) L.) to hypertonic saline loading. Gen & Comp Endocrin 26:427-439, 1975.
98. **Visser TJ:** Thyroid Hormone Deiodination. Thesis, Rotterdam, Erasmus University, 1980, p 91.
99. **Vogel C:** Taubenkrankheiten [Pigeon Diseases]. Berlin: VEB Deutscher Landwirtschaftsverlag, 1982, pp 303-306.
100. **Voitkevitch AA:** The Feather and Plumage of Birds. London: Sidgwick and Jackson, 1966.
101. **Wada M, Ishii S, Scanes CG:** Endocrinology of Birds. Molecular to Behavioral. Berlin, Springer Verlag, 1990.
102. **Wadsworth PF, Jones DM:** Some abnormalities of the thyroid gland in non-domesticated birds. Avian Pathol 8:279-284, 1979.
103. **Wallner-Pendleton EA, Rogers D, Epple A:** Diabetes mellitus in a red-tailed hawk. Avian Pathol (in press).
104. **Walsh MT, Beldegreen RA, Clubb SL, Chen, CL:** Effect of exogenous ACTH on serum corticosterone and cortisol concentrations in the Moluccan cockatoo (*Cacatua moluccensis*). Am J Vet Res 46:1584-1589, 1985.
105. **Watts RWE:** Metabolic and genetic renal disorders and renal calculi. *In* Scott RB (ed): Price's Textbook of the Practice of Medicine 12th ed. Oxford University Press, 1978, 1056-1074.
106. **Wheler C:** Pituitary tumors in cockatiels. J Assoc Avian Vet 6(2):92, 1992.
107. **Williamson RA, Davison TF:** The effect of a single injection of thyrotrophin on serum concentrations of thyroxine, triiodothyronine and reverse triiodothyronine in the immature chicken (*Gallus domesticus*). Gen & Comp Endo 58:109-113, 1985.
108. **Williamson RA, Misson BH, Davison TF:** The effect of exposure to 40° C on the heat production and the serum concentration of triiodothyronine, thyroxine and corticosterone in immature domestic fowl. Gen & Comp Endocrin 60:178-186, 1985.
109. **Wijngaarden JB, Smith LH: (eds):** Cecil Textbook of Medicine 18th ed vol 2,. Philadelphia, WB Saunders Co, 1988.
110. **Zenoble RD, Kemppainen RJ, Young DW, Clubb SL:** Endocrine response of healthy parrots to ACTH and thyroid stimulating hormone. J Am Vet Med Assoc 187:1116-1118, 1985.
111. **Zenoble RD, Kemppainen RJ, Young DW, Carpenter JW:** Effect of ACTH on plasma corticosterone and cortisol in eagles and condors. J Am Vet Med Assoc 187:1119-1120, 1985.
112. **Zipper J, Tamaschke CH:** Pathologische Schilddrusenbefunde bei Vögeln [Pathologic changes of thyroid glands in birds]. *In* Verhandlungsberichte XIV Intern Symp Krankh Zootiere, Wroclaw. Berlin, Akademie Verlag, 1972, pp 113-122.