Series preface

"Oh! You are a veterinarian? I (or my brother, my sister, my son, my daughter…) always wanted to be a veterinarian." All of us, as veterinary students and later as veterinarians, have often heard comments like this. Becoming a veterinarian seems to be such a wonderful career to nonveterinarians: helping helpless dogs and cats. Veterinarians should be happy and satisfied in their *chosen* profession because they are able to earn a living by caring for loved pets. The journey to satisfaction and happiness for veterinarians, however, never seems to follow an obvious, straight, or level path.

The 1950s witnessed a dramatic growth in the popularity of pet dogs and in the number of veterinarians who cared exclusively for pets. The popularity of cats soon followed. Today, more dogs and cats are considered "members of the family" than ever before in human history, and their owners want to protect their family members from illness or to resolve any illness. There are more veterinarians who care for dogs and cats currently than ever before in human history. Veterinary medicine has evolved remarkably to meet the ever-growing medical care expectations and demands of dog and cat owners.

When learning of a diagnosis, prognosis, treatment, and/or the cost of care for their ill pet, some owners become distressed. These emotions are often directed at the "messenger" of the bad news: the veterinarian. The veterinarian, in turn, may not respect their own knowledge and feel inadequate. One reason that a veterinarian may feel inadequate is the realization that it is impossible for anyone in general practice to be expert and current on all the canine and feline conditions encountered in a day, week, or month: everything from orthopedics to oncology, from vaccinology to dermatology, from ophthalmology to cardiology. Nor is it possible for an internal medicine specialist to be expert and current in each condition they encounter, from endocrinology to gastroenterology or from respiratory conditions to chronic kidney disease. Further, it is clear that cats are not small dogs. Perceived "knowledge deficiencies" can cause veterinarians to feel they are failing to meet their clients' expectations.

The internal medicine textbooks in this new series offer one approach for enjoying veterinary practice. We encourage colleagues to embrace developing expertise in one area. By focusing on and studying one organ system in either the dog or cat, one can achieve greater knowledge and skills and, in turn, greater confidence. Each book in this series offers a clear path to learning current opinions on pathophysiology, diagnosis, treatment, prognosis, and costs associated with illnesses involving one system in one species. Confidence gained in a focused area can be sensed by devoted owners. Further, confidence in one area of internal medicine also creates confidence in sharing limitations: "I am extremely confident in diagnosing and managing some conditions but I lack that level of expertise in all other conditions".

The books in this series have been constructed to help build expertise in one organ system in either the dog or the cat. Each book is edited by one or two specialists with outstanding international credentials. Each editor was tasked with building a text that contains all the information found in general internal medicine textbooks, but with much more in-depth discussions on each condition. Each book has early chapters focusing on differential diagnoses of owner concerns, physical examination findings, and laboratory and/or imaging results. These are excellent for students as they begin to apply their basic knowledge to clinical cases. These chapters also provide a quick review for experienced general practitioners and specialists. Each chapter provides at least one algorithm designed to take the reader from a vague owner concern, physical examination finding, or laboratory abnormality to a specific diagnosis with step-by-step instructions. The "techniques section" in each text teaches currently employed procedures, most with videos. In-depth chapters on known illnesses comprise 70 to 80% of each book's content. The editors have provided a larger number of chapters, a larger number of expert contributors, and greater depth on each organ system than any general textbook can supply. The material has a level of credibility that no internet site can claim. Each book can guide the reader through a more complete journey of understanding than is available in any other veterinary resource.

Edward Feldman
Federico Fracassi

Preface

In the fascinating world of endocrinology, scientific knowledge and technology have advanced greatly in recent years. Alongside, our ability to diagnose, treat, and manage various endocrine disorders has progressed too. The goal of this textbook is to provide an up-to-date, comprehensive, yet accessible resource for understanding and managing endocrine disorders in dogs.

The book is divided into two parts. The first part adopts a problem-oriented approach to the most common clinical and laboratory abnormalities in dogs with endocrine diseases. We provide algorithms that guide veterinarians step by step in diagnostic evaluation and setting up the treatment. This section serves as a quick reference guide in clinical situations. Additionally, part one covers practical topics such as blood pressure measurement and glucose monitoring. The chapters are supplemented by video material, enhancing comprehension of handling and procedures. These videos do not only facilitate learning for the professionals but can also be shared with owners.

Part two focuses on endocrine diseases. Each chapter starts with the basic anatomy and physiology of the specific endocrine glands, followed by detailed discussions on clinical signs, diagnostic methodologies, and management strategies. Chapters are richly supplemented with boxes, tables, algorithms, charts, imaging studies, and illustrations. Each chapter features a key fact box summarizing the most crucial information. The chapters on diabetes mellitus and Cushing's syndrome are broken down into multiple subchapters. This allows for the inclusion of additional experts offering insights on specific subject matter, such as nutrition, radiation therapy, and diagnostic imaging.

In writing this book, we have had the privilege of collaborating with phenomenal veterinary experts from around the globe. While you will encounter well-known authors, you will also discover some new names. One of our key missions was to pair emerging talents with their professional mentors. The expertise and critical attitude of the authors were indispensable throughout the writing process, making editorial tasks both enjoyable and rewarding. Additionally, special thanks to Edra, and particularly Constanza Smeraldi, for providing state-of-the-art visuals in the book. They significantly ensure that the reading material is easy to understand. Finally, whenever we had doubts, we had the privilege of receiving immediate advice from a friend who is one of the "fathers" of veterinary endocrinology. Thank you, Ed Feldman, for the constant positive and professional support you have provided us.

The recommendations provided in our book are based on research, clinical experience, and expertise, but also practicality and cost-effectiveness. Nonetheless, what may be effective today may be improved upon tomorrow. Science encourages curiosity and urges us to challenge existing beliefs. Therefore, while providing a go-to reference book for veterinarians, veterinary students, residents, and enthusiasts of endocrinology, we also aspire for our book to serve as an inspiration, reminding readers to maintain an open-minded attitude.

Sara Galac
Federico Fracassi

Growth retardation

Federico Fracassi
DVM, PhD, DECVIM (SAIM)

Dolores Pérez Alenza
DVM, PhD

Hans S. Kooistra
DVM, PhD, DECVIM-CA (Internal Medicine)

Pathophysiology

Growth is a complex yet tightly regulated process. Genetic factors play a major role in linear growth, with numerous genes involved in its regulation. After the domestication of the dog, the selection of such genes by humans has resulted in breeds with a wide variety of body sizes and growth rates. For example, selection by people for the genes that give rise to angular limb formation and short legs has resulted in chondrodystrophic dog breeds. As these breeds have been created intentionally, they are generally not considered to have growth retardation. Dogs must consume sufficient calories and nutrients to meet the full (genetic) potential for growth. After food intake, food must be digested and absorbed adequately. Next, nutrients must be transported to the tissues for metabolic maintenance and growth. Based on these processes, the causes of growth retardation can be subdivided into three major groups: inadequate intake of calories and nutrients, increased use of energy, and increased loss of energy.

Several hormones are known to be important determinants of linear growth. Consequently, hormonal disturbances at a young age may be associated with growth retardation (Table 1.1).

The intake of insufficient calories and nutrients at a young age is, next to genetic factors, the most important reason for growth retardation, i.e., nutritional deprivation severely impairs growth. Selective deficiencies in vitamins or minerals may also cause growth retardation. In addition to the quantity, food quality and palatability should also be considered.

A poor appetite, e.g., due to a systemic disease, may result in less food intake. Oropharyngeal disorders, including swallowing problems, may cause hyporexia. Regurgitation or vomiting could cause insufficient nutrients to reach the intestines. A vascular ring anomaly due to a persistent right aortic arch should be considered in puppies with stunted growth and chronic regurgitation, especially after weaning. Maldigestion, e.g., due to exocrine pancreatic insufficiency or biliary obstruction, and malabsorption, e.g., due to an intestinal wall disorder in case of an enteropathy, can result in decreased uptake of nutrients. Intestinal parasites may cause inadequate uptake of nutrients, mainly in puppies.

Catabolic processes, such as those associated with inflammatory processes and fever, will increase energy use. Congenital heart anomalies and endocarditis may result in tachycardia, which, in turn, means extra loss of energy, leaving fewer calories for growth. Disorders involving organs that play a central role in metabolism, i.e., the liver and the kidneys, may also result in growth retardation. Both congenital renal disorders and acquired kidney disease, e.g., pyelonephritis, can result in stunted growth. Portosystemic shunting resulting in hepatic encephalopathy is the most common liver disorder associated with growth retardation. Hepatitis and glycogen storage disease have also been associated with stunted growth. Growth retardation in young dogs with chronic anemia may be associated with impaired oxygen delivery to tissues as well as increased cardiovascular effort. Failure to grow normally cannot only be associated with glucosuria due to (juvenile) diabetes mellitus but may also result from glucosuria due to defects in the proximal tubules of the kidneys. Persistent proteinuria and protein-losing enteropathies decrease growth potential.

Diagnostic approach

Algorithm 1.1 shows the approach to the dog with failure to grow.

Algorithm 1.1 Note 1 A detailed nutritional history should be obtained to get information regarding the amount, quality, and palatability of the food offered to the dog.

Algorithm 1.1 Note 2 A poor appetite, despite the feeding of sufficient palatable, high-quality food, suggests a disorder of the gastrointestinal tract or the presence of systemic disease. Growth retardation in dogs with very good or ravenous appetite may point to maldigestion, malabsorption or loss of energy. History-taking may also reveal treatment with steroids for an unrelated problem. Concurrent clinical signs may help identify an underlying cause for the growth retardation. Diarrhea or voluminous stools may be due to maldigestion and/or malabsorption.

TABLE 1.1 Endocrine causes of growth retardation.

Growth hormone and insulin-like growth factor-1 deficiency. (For more information, see chapter 24)	
Physiology	■ Growth hormone (GH), produced and secreted from the anterior lobe of the pituitary gland, plays a central role in the modulation of growth. ■ Although GH directly affects many tissues, most of its growth-promoting actions are mediated by insulin-like growth factor-1 (IGF-1). ■ Circulating IGF-1 is mainly produced in the liver. In other tissues, IGF-1 stimulates anabolic processes in a paracrine or autocrine manner. For example, linear growth largely depends on the local production of IGF-1 in growth plates. ■ In adult dogs, there is a strong linear correlation between the plasma IGF-1 concentration and body size, while basal plasma GH concentrations are quite similar among various breeds. This implies that breed-specific reference ranges must be used to determine whether growth retardation is due to insufficient circulating IGF-1 concentrations.[1-3]
Etiology	■ Congenital GH deficiency or pituitary dwarfism is the best-known example of such a deficiency. ■ In German Shepherd dogs and Czechoslovakian Wolfdogs, congenital GH deficiency is due to a mutation in the gene encoding for the transcription factor LHX3.
Pathophysiology	■ In the case of complete GH deficiency, linear growth occurs at about a third to a quarter of the normal rate. ■ Growth hormone deficiency in a young animal affects the growth of almost all tissues, resulting in "proportionate dwarfism", meaning that all body components are equally small.
Main clinical signs	■ During the first weeks after birth, pituitary dwarfs may be of similar size as their litter mates. ■ Proportionate growth retardation. ■ Retention of puppy hair coat. ■ Bilateral symmetrical alopecia. ■ Skin hyperpigmented and scaly. ■ Pointed muzzle and relatively long pointy ears, resembling the face of a fox.
Hypothyroidism. (For more information, see chapter 27)	
Physiology	■ Thyroid hormones are essential for central nervous system (CNS) maturation, bone growth, and chondrogenesis. ■ Adequate circulating thyroid hormone concentrations appear to be a prerequisite for normal growth. ■ The effect of IGF-1 on cartilage cells is dependent on thyroid hormones. ■ Thyroid hormones exert direct effects on cell metabolism.
Etiology	■ Congenital dyshormonogenesis or thyroid dysgenesis (congenital primary hypothyroidism). ■ Congenital central hypothyroidism due to isolated TSH deficiency.
Pathophysiology	■ Because skeletal growth strongly depends on thyroid hormones that promote chondrogenesis, in synergy with GH and IGF-1, juvenile hypothyroidism is associated with delayed epiphyseal closure, retarded epiphyseal growth, reduced long bone growth and, consequently, "disproportionate dwarfism".[4]
Main clinical signs	■ Growth retardation with disproportionate dwarfism (short and broad skull, shortened mandible and ears, enlarged or protruding tongue, short thick neck, wide/square trunk, shortened limbs). ■ Impaired mental development (cretinism).
Insulin deficiency	
Physiology	■ Insulin is the most important anabolic hormone in the body. ■ The anabolic actions of insulin include stimulation of protein synthesis and cell division.
Etiology/ pathophysiology	■ Insulin deficiency at a young age, i.e., juvenile diabetes mellitus, is associated with growth retardation. ■ The failure of normal growth, typical of dogs with juvenile diabetes mellitus, is also due to a decrease in insulin-dependent transportation of glucose and fatty acids into muscle and fat cells. ■ Juvenile diabetes mellitus results in glucosuria, i.e., loss of energy in the urine.
Glucocorticoid excess	
Physiology/ pathophysiology	■ The catabolic effects of glucocorticoids are increased gluconeogenesis, decreased glucose uptake by muscle and fat cells, increased protein breakdown, and lipolysis. ■ Glucocorticoid excess suppresses pituitary GH secretion, mainly due to stimulation of hypothalamic somatostatin release. ■ Long-term administration of glucocorticoids to young, growing animals may result in growth retardation.
Gonadal steroids excess	
Physiology/ pathophysiology	■ Gonadal androgens and estrogens affect linear growth. ■ Prepubertal gonadectomy may result in taller individuals.[5] ■ Administration of androgens or estrogens at an early age may result in growth retardation due to premature closure of the growth plates.
Other endocrine hypofunctions	
Physiology/ pathophysiology	■ Hypoadrenocorticism may occur at any age. When hypoadrenocorticism develops in a young growing dog, it may result in growth retardation. ■ Hypoadrenocorticism is often associated with a decrease in appetite, vomiting, and diarrhea, resulting in reduced nutrient intake and, consequently, may result in growth retardation. ■ Hypoparathyroidism may also occur at a young age. ■ Parathyroid hormone has an important role in bone metabolism, and therefore, parathyroid hormone deficiency may result in growth retardation. ■ Disorders associated with severe polydipsia, such as central diabetes insipidus, may result in impaired appetite and failure to adequate growth.

Polyuria may point to renal disease, hepatic disease, diabetes mellitus, diabetes insipidus, or other conditions. Mental dullness may point to hypothyroidism or (hepatic or renal) encephalopathy. Symmetrical truncal alopecia can be seen in dogs with growth hormone deficiency or hypothyroidism. Regurgitation since weaning may point to vascular ring anomaly or megaesophagus. A thorough physical examination is essential in dogs with growth retardation, as specific physical findings may point to a specific disorder. For example, dogs with hypothyroidism usually will have a weak pulse. A heart murmur associated with tachycardia may disclose a cardiac abnormality as a cause of growth retardation.

Algorithm 1.1 Note 3 Body proportions must be carefully evaluated in dogs with growth retardation. Relatively short limbs compared to

ALGORITHM 1.1

Diagnostic approach to growth retardation.

the trunk may point to juvenile hypothyroidism or chondrodystrophy. In contrast, growth hormone deficiency causes proportionate dwarfism. It is also important to note the ratio of height to weight. An animal with stunted growth that is overweight for its height is more likely to have an endocrine disorder such as growth hormone deficiency or hypothyroidism. Malnutrition or systemic disorders are more likely to result in underweight dogs.

Algorithm 1.1 Note 4 Urinalysis may reveal proteinuria, glucosuria, or hyposthenuria. Indications for pyelonephritis may be found in the urine sediment. A complete blood count should be performed to detect anemia, inflammation, or eosinophilia. It has to be taken into account that puppies normally have lower red blood cell counts than adults. Eosinophilia may point to parasitism or hypoadrenocorticism. The results of a routine serum biochemistry profile can help identify renal disease, hepatic disease, diabetes mellitus, or hypoadrenocorticism. Decreased serum protein concentrations may indicate hepatic disease, protein-losing enteropathy, or nephropathy.

Algorithm 1.1 Note 5 Laboratory evaluations should include multiple fecal examinations for intestinal parasites, such as *Giardia* spp. A fecal examination may also provide information regarding (mal)digestion and (mal)absorption.

Algorithm 1.1 Note 6 A low serum IGF-1 concentration may point to growth hormone deficiency. The absence of a significant increase in circulating growth hormone concentration after intravenous administration of GH-releasing hormone can be used to demonstrate growth hormone deficiency (see chapter 24).

Algorithm 1.1 Note 7 Radiological evaluation of the thorax and skeleton and abdominal ultrasound or echocardiography are useful in congenital cardiac diseases, respiratory disorders, liver diseases, renal diseases, and bone growth abnormalities.

Algorithm 1.1 Note 8 Pituitary dwarfism in German Shepherd Dogs is quite often caused by a mutation in a gene that encodes for the transcription factor LHX3.[6] The availability of a diagnostic DNA test not only allows for proper diagnosis of dogs with pituitary dwarfism due to this mutation but also enables breeders to prevent dwarfs from being born to identifying carriers of the LHX3 mutation. If all breeding animals were genetically tested for the presence of the LHX3 mutation and a correct breeding policy were implemented, this disease could be eradicated completely.

Algorithm 1.1 Note 9 Several musculoskeletal disorders may cause failure to grow in young animals. Most of them are congenital and inherited, such as dyschondroplasia (especially in Poodles, Scottish Terriers, and Alaskan Malamutes), dystrophy-like myopathies, osteochondrosis, osteochondromatosis, osteogenesis imperfecta, osteopetrosis, angular limb deformities (abnormal development of the radius and ulna), and hypertrophic osteodystrophy and glycogen storage disease. In addition, nutritional imbalances, such as secondary hyperparathyroidism, a deficiency of vitamin D, and/or excessive vitamin A, may cause failure to grow.

Algorithm 1.1 Note 10 Treating canine hyposomatotropism involves administering synthetic progestins: either medroxyprogesterone acetate at a dosage of 5 mg/kg SC initially every 3 weeks and subsequently at 6-week intervals or proligestone at a dosage of 10 mg/kg SC every 3 weeks, both until 12 months of age. There are, however, some adverse effects, including recurrent periods of pruritic pyoderma and, occasionally, the development of mammary tumors. Porcine GH (pGH) is another potential option. Treatment with either progestagens or pGH should be accompanied by thyroid hormone replacement.

References

1. Favier RP, Mol JA, Kooistra HS, et al. Large body size in the dog is associated with transient GH excess at a young age. *J Endocrinol* 170:479-484, 2001.
2. Nap RC, Mol JA, Hazewinkel HAW. Age-related plasma concentrations of growth hormone (GH) and insulin-like growth factor I (IGF-I) in Great Dane pups fed different dietary levels of protein. *Domest Anim Endocrinol* 10:237-247, 1993.
3. Nap RC, Mol JA, Hazewinkel HAW. Growth and growth hormone in the dog. *Vet Quart Suppl* 1:31S-32S, 1994.
4. Saunders HM, Jezyk PK. The radiographic appearance of canine congenital hypothyroidism: skeletal changes with delayed treatment. *Vet Radiol Ultrasound* 32:171-177, 1991.
5. Salmeri KR, Bloomberg MS, Scruggs SL, et al. Gonadectomy in immature dogs: effects on skeletal, physical, and behavioral development. *J Am Vet Med Assoc* 198:1193-1203, 1991.
6. Voorbij AMWY, Van Steenbeek FG, Vos-Loohuis M, et al. A contracted DNA repeat in LHX3 intron 5 is associated with aberrant splicing and pituitary dwarfism in German shepherd dogs. *PLoS One* 6:2011. doi:10.1371/journal.pone.0027940