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# Medical differentials with potential behavioral manifestations

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## How to think logically about situations where so much is unknown

Behavioral medicine is complex. All signs are nonspecific, and we can never hold the behavioral pathologic profile in our hand. We can only assess a verbal, spectral, or chemical manifestation of the behavioral pathologic findings.

Behavior is the great and final integrator between any animal's internal (physiologic/neurochemical, neuroanatomic, and genetic components) and external environments and the extent to which all these environments interact to produce long-term potentiation (cellular/molecular memory and learning) [1–3]. Not only are behavioral problems the most common concerns for pets and veterinary clients [4–7], but when an animal is truly "organically" ill, the mechanism by which the client recognizes the illness involves a change in behavior.

Common documented "organic" or "medical" causes of behavioral changes include congenital, inherited, and genetic infectious, inflammatory or immune-mediated, metabolic and endocrine, nutritional, degenerative, neoplastic, toxic, and traumatic conditions. Known medical conditions with a neurologic or behavioral effect include epilepsy, narcolepsy, hydrocephalus, polyphagia, and some forms of stereotypic behaviors. It is important to remember, especially in light of the recent findings about narcolepsy, that the extent to which these neurologic conditions seem separate from "behavioral" ones may be a function of our ignorance: the same set of regulatory genes that contributes to the narcoleptic pathologic changes may, in fact, be at work in many anxiety-related conditions involving dysregulation of neurochemical systems [8–10].

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It is also equally important to realize that when we evaluate the behaviors involved in a behavioral complaint or pathologic finding, our observational skills and behavioral history allow us to make assessments only at the phenotypic level—the level at we can describe what something looks like. We need to remember that there are many mechanistic "causes" for any behavioral condition and that we are lacking sufficient data for most conditions to evaluate the extent to which they are heterogeneous, polymorphic, multifactorial, or representative of spectrum disorders. In too many cases, we are lacking the heuristic context in which to evaluate various presentations of the same condition, which is why a structured thought process is so critical [3]. For example, obsessive-compulsive disorder (OCD) has many forms. It is likely that the locomotor forms differ from those involving hallucinations or ingestive behaviors in some profound mechanistic ways. Recent research strongly suggests that OCD in human beings is the result of genetically controlled dysfunction of genes involving regulatory systems [11,12]. There are also possible roles for dietary cofactors in affecting subcellular signaling [13]. Such complex regulatory functions having a genetic heritable basis have also been reported for dogs with narcolepsy [10] and warrant further investigation in dogs and cats affected with OCD.

Implicit in the intellectual construct of a truly "abnormal" or "pathologic" behavior is the concept that the behavioral presentation, or the phenotype, is driven by some integrated anomaly that functions in concert with numerous levels from the genomic and subcellular to the neuroanatomic [14–16]. Using this integrated mechanistic paradigm, we can view truly abnormal behaviors as we would metabolic disorders—as another form of an organic condition. Unfortunately, there are few hard data that support the extent to which any specific underlying pathophysiologic mechanism or cause is involved in any behavioral condition, so it is as foolish to assume that every behavioral complaint is purely behavioral as it is to assume that none are. There is no substitute for paying attention to the pattern of the pet's behavior.

## The roles for history and observation: collecting the data

A good behavioral history combined with honed observational skills (and even the most inexpert observer can hone his or her skills by having clients videotape the problem pet) helps to suggest where diagnostic probability should be placed. Pattern recognition is key, and a few tips should help veterinarians with this.

For example, purely behavioral conditions seldom appear quickly, and the early and more subtle signs are often missed by client and veterinarian alike. A cat that cries every time it urinates and still uses its litter box but dislikes entering it since the period when the client noticed the crying is unlikely to have a purely behavioral problem but is likely to have an

underlying medical condition. The cat that does not cry when it urinates but does not use the box at all since a new cat was introduced to the household fits the profile of a cat with a nonmedical behavioral concern. What clues were present in this simple dichotomous case example that allowed us to draw these conclusions? The discomfort experienced by the first cat may be perceived by the cat to be associated with the litter box, and, accordingly, the cat is becoming reluctant to get into the box. The second cat seems to show no signs of discomfort but is demonstrating the extent to which urine, scent, and subtle social interactions can be important in modulating upheavals in feline groups. The veterinarian should perform a urinalysis on both cats; in the latter case, one would be doing so to rule out the complication of a medical contribution. It is unlikely that the urinalysis will be informative regarding the etiology of the underlying problem. To perform a urinalysis in the case of the second cat is to be thorough, but the veterinarian would have a low index of suspicion that the change in behavior was driven by an underlying organic pathologic change associated with the urogenital system. This does not mean that behavioral changes could not aggravate chronic feline lower urinary tract disease (FLUTD), given what we now know about the complexity of stress and neuromyogenic responses, nor does it imply the absence of a concomitant medical condition. In the first case, pathologic findings of the urogenital system warrant a high index of suspicion. A thorough history would examine the potential secondary behavioral complications of pain associated with elimination: the development of anxieties, substrate aversions, and location aversions. Oddly, tricyclic antidepressants (TCAs) may help both cats, because these drugs address inflammation, the receptors involved in myogenic pain, and the anxiety associated with pain and social discomfiture. This also illustrates how examining only one mechanistic level (eg, the neurochemical one) in a vacuum could lead to confusion about the entire "causal" process.

A logical structured thought process allows the veterinarian to acquire the data to pursue tandem treatment of any organic problems and the associated behavioral changes that may be associated with them (and vice versa).

## An organ systems approach to identifying common organic problems that may best be recognized by their behavioral signs

Adequate extant reviews of medical conditions that can be associated with behavioral signs have previously been published with relevant references [14,17,18]. Accordingly, the nonspecific signs and the systems involved are summarized here in tabular form. Table 1 summarizes conditions associated with organ system–specific nonspecific signs and potential underlying causes. Table 2 summarizes age associations with certain medical/organic conditions that may affect behavior or have a primarily behavioral presentation.

Table 1
Non-specific behavioral signs, organ systems potentially involved, and organic pathology associations

| Nonspecific signs/system involved | Underlying "cause" |
|---|---|
| Inappropriate elimination/ urogenital system complains | Degenerative/developmental<br>Vesicourachal diverticula<br>Ectopic ureter<br>Lissencephaly<br>Portosystemic shunting<br>Hydrocephalus<br>Acquired<br>Intraluminal obstruction: urolithiasis, polyps, blood clots, sloughed tissue<br>Extraluminal obstruction: tumor, prostatic disease, stricture, hernia<br>Metabolic/endocrine<br>Diabetes mellitus<br>Renal glucosuria<br>Central diabetic insufficiency<br>Nephrogenic diabetic insufficiency<br>Renal insufficiency/failure<br>Hypercalcemia<br>Hypokalemia<br>Hyperadrenocorticism<br>Hyperthyroidism<br>Hypoadrenocorticism<br>Hepatic insufficiency<br>Renal medullary washout<br>Primary polydipsia<br>Neurogenic: loss of control/voluntary<br>Lesions of the<br>cerebrum<br>basal ganglia<br>thalamus<br>cerebellum<br>external urethral sphincter<br>perineal muscles<br>pudendal nerve<br>Upper motor neuron disease: reflex dyssynergia, large amounts of infrequently produced urine, bladders that are difficult to express because of the increased urethral tone<br>Lower motor neuron disease ($S_1$–$S_3$ or $L_4$–$S_3$): nerve roots and pudendal and pelvic nerves; associated with bladder atony (flaccid, neuropathic bladders), large urinary volumes, and overflow; easy expression of the bladder; may also have fecal obstructions, hind limb/tail deficits, loss of anal tone<br>Inflammatory<br>Prostatitis<br>Vaginitis<br>Cystitis/FLUTD |

Table 1 (*continued*)

| Nonspecific signs/system involved | Underlying "cause" |
|---|---|
| | Urethritis |
| | Enteritis |
| | Colitis |
| | Infectious |
| | Cell-associated herpes virus |
| | Syncytia-forming virus |
| | Feline calicivirus |
| | Pyelonephritis |
| | Pyometra |
| | Parasitemia (primarily concerns involving defecation) |
| Complaints involving aggressive behaviors | Degenerative/developmental |
| | Lissencephaly |
| | Hydrocephaly |
| | Porencephaly |
| | Congenital portosystemic shunts |
| | Congenital urea cycle enzyme defects |
| | Cerebral hypoxia |
| | Seizure activity |
| | Feline ischemic syndrome |
| | Lysosomal storage diseases |
| | Chronic polioencephalomalacia in the piriform lobes and hippocampus |
| | Endocrine/metabolic |
| | HE (possibly associated with changes in perception, fear, and incoordination) |
| | Hyperthyroidism (remember that in cats with hyperthyroidism, serum transaminases and ALP are often increased) |
| | Uremic encephalopathy |
| | high levels of corticotropin (increased aggression) |
| | Low levels of corticotropin (decreased aggression) |
| | Nutritional |
| | Thiamine deficiencies (primarily cats) |
| | Taurine deficiencies (primarily cats) |
| | High-protein diets (may affect some reactivity, caution is urged) |
| | Neoplastic |
| | Intracranial neoplasia, including meningiomas |
| | Temporal lobe, limbic system, and hypothalamic lesions |
| | Lesions in the VMH and PLH in cats |
| | Infectious |
| | Rabies |
| | Toxoplasmosis |
| | Distemper |
| | FIP |
| | Tick-borne conditions |
| | Miscellaneous bacterial and fungal conditions |

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Table 1 (*continued*)

| Nonspecific signs/system involved | Underlying "cause" |
|---|---|
| | Toxicity<br>Heavy metal<br>Psychotropic medication–induced serotonin syndrome<br>Organophosphates<br>Trauma<br>Cerebral injury<br>Cerebral vascular disease<br>Cerebral infarct (cats)<br>*Cuterebra* larval infarcts |
| Complaints involving depression, sleepiness, or listlessness | Degenerative/developmental<br>Lissencephaly<br>Portosystemic shunting<br>Lysosomal storage diseases<br>Endocrine/metabolic<br>HE (can be associated with parenchymal liver disease, [including cirrhosis, acquired portosystemic shunts, toxicity, and neoplasia] congenital portosystemic shunts, and congenital urea cycle enzyme defects)<br>Hepatic dysfunction/failure (postulated to be associated with increased gamma aminobutyric acid resorption from the gastrointestinal tract)<br>Thyroidal illness (primarily canine hypothyroidism)<br>Uremic encephalopathy<br>Hyperkalemia<br>Hypothyroidism<br>Hyperadrenocorticism<br>Neoplastic<br>Thalamic, subthalamic, midbrain, and frontal lobe lesions<br>Intracranial neoplasia (primarily responsible for stupor and coma)<br>Pontine/tegmental lesions (cats)<br>Toxicity<br>Heavy metal<br>Drugs (prescription and human recreational) (anticonvulsants increase alkaline phosphatase, aspartate aminotransferase, and glutamyl transferase and may affect alanine amino-transferase (glutamic pyruvic transaminase); glutamyl transferase has been implicated as a flag for hepatotoxicity and necrosis associated with atypical diazepam toxicity in cats)<br>Trauma<br>Cerebral injury<br>Cerebral vascular disease<br>CCT (can be caused by fights between animals) |

Table 1 (*continued*)

| Nonspecific signs/system involved | Underlying "cause" |
|---|---|
| Complaints involving changes in ingestive behaviors | Endocrine/metabolic<br>Hepatoencephalopathy<br>Hepatic dysfunction/failure<br>Hyperthyroidism<br>Diabetes<br>Hyperadrenocorticism<br>Neoplastic<br>Thalamic lesions (polyphagia, polydipsia, pica, and aphagia)<br>Lesions in the VMH and PLH in cats<br>Infectious<br>Rabies |
| Complaints involving cognition, including dementia and inability to learn | Neoplastic<br>Frontal lobe and internal capsule lesions<br>Nutritional<br>Thiamine deficiencies (primarily cats)<br>Taurine deficiencies (primarily cats)<br>Infectious<br>Distemper<br>Rabies<br>Mycoses<br>Toxoplasmosis<br>Prion-associated conditions<br>Traumatic<br>Frontal lobe and internal capsule lesions |
| Complaints involving ritualistic behaviors | Degenerative<br>Granulomatous meningoencephalitis<br>Cauda equina syndrome<br>Endocrine/metabolic<br>Hypocalcemia<br>Hypomagnesemia<br>Abnormalities of acid-base balance<br>Neoplastic<br>Lesions in the frontal lobe, internal capsule, and basal nuclei (particularly the caudate nucleus)<br>Nutritional<br>Excessively low-protein diet<br>Food hypersensitivity<br>Infectious<br>Rabies<br>Toxic<br>Tetanus<br>Botulism |
| Complaints involving non-specific fear and anxiety | Degenerative<br>Auditory changes (deafness)<br>Visual changes (cataracts)<br>Mobility changes (arthritis) |

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Table 1 (*continued*)

| Nonspecific signs/system involved | Underlying "cause" |
|---|---|
| | Endocrine/metabolic |
| | Hypothyroidism |
| | HPA axis disorders |
| | Disorders involving glucose metabolism |
| | HE |
| | Uremic encephalopathy |
| | Neoplastic |
| | Lesions in the frontal lobe, internal capsule, and basal nuclei |
| | Infectious |
| | Rabies |
| | Toxoplasmosis |
| | Distemper |
| | FIP |
| | Tick-borne conditions |
| | Miscellaneous bacterial and fungal conditions |
| | Prion-associated conditions |
| | Toxicity |
| | Heavy metal |
| | Psychotropic medication–induced serotonin syndrome |
| | Organophosphates |
| | Trauma |
| | Cerebral injury |
| | Cerebral vascular disease |
| | CCT (can be caused by fights between animals) |
| Complaints involving sexual behavior | Neoplastic |
| | Temporal lobe, limbic system, and hypothalamic lesions |

*Abbreviations*: ALP, alkaline phosphatase; CCT, cranial cerebral trauma; FIP, feline infectious peritonitis; FLUTD, feline lower urinary tract disease; HE, hepatoencephalopathy; HPA, hypothalmic pituitary adrenal; PLH, posterolateral hypothalamus; VMH, ventromedial hypothalamus.

There are three issues that concern us when we are faced with the question of whether the presenting nonspecific signs are behavioral or medical:

1. How can we routinely check, by organ system or by clusters on nonspecific signs that are largely associated with specific organ systems, whether the presenting signs are most consistent with a purely nonbehavioral diagnosis?
2. How can we routinely perform a similar check by age?
3. How can we rigorously test newer ideas about the effects of other systems on behavior, given proposed treatments that involve these systems (eg, the thyroid axis role in nonspecific signs associated with anxiety)?

All three of these issues involve assessment of probability. Unfortunately, probability can only be confidently relied on when sufficient data are

Table 2
Age ranges and associations with organic conditions in which behavioral signs are key

| Age group | Common conditions |
|---|---|
| <9 months of age (youngsters) | Congenital hydrocephalus<br>Lissencephaly<br>Lysosomal storage diseases<br>Distemper/FIP encephalitis<br>Viral, fungal, protozoal, and bacterial encephalitis<br>Trauma<br>Toxicity, primarily lead<br>Hypoglycemia<br>HE (portosystemic shunt)<br>Congenital defects and metabolic disease<br>Thiamine deficiencies |
| 9 months (sexual not social maturity) to 5 years | Distemper/FIP encephalopathy<br>Viral, protozoal, or fungal encephalopathies<br>Steroid-responsive meningoencephalitis<br>Granulomatous meningoencephalitis<br>Trauma<br>Toxicity<br>Hypoglycemia<br>HE (acquired hepatopathy/portocaval shunt)<br>Other acquired metabolic disease<br>Acquired epilepsy<br>Cerebral neoplasia |
| >5 years | Distemper/FIP<br>Steroid-responsive meningoencephalopathy<br>Granulomatous encephalopathy<br>Trauma<br>Toxicity<br>Hypoglycemia (insulinoma)<br>HE (acquired hepatopathy)<br>Other metabolic disease<br>Acquired epilepsy<br>Cerebral neoplasia<br>Watch in the future for prion-associated conditions |

*Abbreviations*: FIP, feline infectious peritonitis; HE, hepatoencephalopathy.

available about the nonspecific signs associated with affiliated medical and behavioral conditions [16] and when we know how to elicit the relevant data using a thorough behavioral history designed to ferret out relevant correlations [14,15,19]. The third issue involves more knowledge of complex interactions than is commonly available. The use of algorithms that structure thought processes is essential here.

Finally, discussed briefly as examples are just two of the complicating issues that overlay all concerns for medical differentials: roles of hormones like thyroid hormone and roles of sex and gender.

## The issue of thyroidal function

Hypothyroidism has been postulated to be associated with fear or aggression in dogs and with sudden shifts in these behaviors. Hypothyroidism has been reported to account for 1.7% of canine aggressive behaviors [20]. Dogs with hypothyroid-associated aggression may not show the other classic signs of hypothyroidism, such as a poor hair coat, lethargy, or weight gain. Aggression is gradual in onset, and triggers can be inconsistent. Appropriate thyroid screening should be part of a minimum database on an aggressive pet to rule out thyroid-related diseases; however, caution is urged in over-interpretation of data, given the relative rareness of the condition. The canine prevalence of hypothyroidism is thought to be approximately 0.2%.

Hyperthyroidism in cats has been associated with manic behaviors, inappetence/anorexia, and aggression. The feline prevalence of hyperthyroidism is likely higher than that of hypothyroidism in dogs, but since its first report as a clinical disorder in 1979, the frequency of diagnosis continues to increase [21–23].

It is important to realize that the estimated incidence of behavioral problems is considerably greater than either of these endocrine conditions. Although the age of onset for hypothyroidism overlaps that for the development of most behavioral conditions in dogs (≈12–24 months of age) [19,22,24], the age of onset of hyperthyroidism is greater (middle-aged to older cats) [23] than that for most behavioral conditions in cats (≈24–36 months). These data are important because they show that although behavioral and thyroidal conditions may be comorbid, the patterns involving age of onset strongly suggest that any rule postulating a causal association may be overly optimistic. Furthermore, for cats, environmental factors associated only with learned behaviors (eg, dietary choices and preferences) seem to play some role in the development of hyperthyroidism.

In human beings, an association between thyroid dysfunction and depression has been suggested but is difficult to prove. True hypothyroidism has had clinical depression as one of its nonspecific signs; however, true clinical hypothyroidism seems to be a relative rather than absolute state. True clinical hypothyroidism affects less than 1% of the human population, but "subclinical hypothyroidism," a description rather than a diagnosis of a biochemically measurable degree of relative thyroid failure, affects 5% to 10% of the population, is more common in women and the elderly, and may be associated with autoimmune conditions or conditions involving neuroimmunologic regulatory function [25]. The effect of this subclinical disease on the treatment of depression in human patients may be to retard the intended outcome of psychopharmacologic treatment as a result of these complex interactions.

Decreased thyroid activity in clinical depression in human beings may, paradoxically, be accompanied by an exaggerated thyroid stimulation response to exogenous thyrotropin-releasing hormone (TRH) in approx-

imately 10% of depressed human patients [26,27]. Thyrotropin response to TRH may be reduced in up to one third of all depressed human subjects [28]. These patients seem to be nonresponders to traditional antidepressant medications but can be converted to responders with the addition of thyroxine. This effect has not been noted for the 90% of the human population demonstrating a normal TRH response. Transthyretin is the protein associated with thyroid hormone transport, and it seems to be low in nonresponder depressed patients with normal peripheral $T_3/T_4$ concentrations. The extent to which transthyretin abnormalities are involved in this response is unknown, but in a small sample of patients with major depression who were refractory to treatment with antidepressants, cerebrospinal fluid (CSF) levels of transthyretin were significantly lower than for neurologic controls. The condition would then involve a defect primarily affecting a transporter protein, suggesting that the association between neurotransmitters and depression may be both direct and indirect.

It seems that consistent patterns involving alteration of thyroidal hormones occur in human patients acutely affected with affective illness [29,30]. These patterns may be a function of the brain's ability to regulate thyroid hormone levels independent of peripheral needs, however. Basal thyroid-stimulating hormone (TSH) production and the response of TSH to TRH are influenced by nonthyroid and non-TRH factors, including somatostatin, dopamine, and serotonin [29]. This suggests that no single measurements of thyroidal function can be viewed as an indicator of thyroid axis dysfunction in affective disorders in human beings. Certainly, such implications are important for dogs, where age and breed reference ranges are not fully explored and may vary considerably. Furthermore, correlations between sex, thyroidal function, and affective illness in human beings may be spurious and the result of another more complex association. The c-erb-A family of gene products shares considerable homology at the binding regions for nuclear $T_3$, glucocorticoid, and estrogen receptors. Correlational associations may be the result of poorly or incompletely understood interactions between families of transcriptional factors [30].

That said, although there have been anecdotal suggestions for the use [17], either alone or in combination, of thyroid supplementation for the treatment of canine behavioral conditions, there is currently no good rationale for supplementation with exogenous thyroxin in the absence of specific behavioral clinical signs and aberrant levels or a response to transthyretin in pets with behavioral problems. Such cavalier dispensation of potent medication is particularly problematic given the wide range of breed-specific reference ranges for $T_3$, $T_4$, free $T_3$, and free $T_4$. Resting free $T_4$ levels, if grossly low, may provide a rough gauge to thyroid function, because free $T_4$ is less likely than total $T_4$ to be affected by nonthyroidal illness or drug therapy [31]. Most accurately measured using dialysis methods, low free $T_4$ concentration combined with an increase in TRF is consistent with a diagnosis of hypothyroidism [31]. In the absence of clinical

signs of hypothyroidism (obesity, seborrhea, alopecia, weakness, lethargy, bradycardia, and pyoderma) and low (not low-normal) free $T_4$ (or the equivalent TSH stimulation test result), there is no rational or competent reason to treat dogs with behavioral or any other diagnoses with thyroxin [32]. There may be a small population of dogs for which this generalization might prove false in the future, but they should be rare. These dogs, if they exist, may have anxiety conditions that are affected by cholecystokinin (CCK). In male rats, CCK-A (alimentary) receptor stimulation inhibits TSH secretion at the level of the anterior pituitary [33].

This is not to say that dogs with thyroid disorders do not alter their behavior; they do, but the behavioral changes are nonspecific and should not be confused with a behavioral diagnosis. There may be nonresponders to antidepressant and antianxiety medications in the canine population that are analogous to those in the human population. If so, supplementation with thyroxin in addition to the antidepressant or antianxiety medications may help. Nevertheless, most single-mechanism (ie, thyroid) hypotheses for the underlying cause and treatment of complex behavioral phenomena like aggression and fear are simplistic and invariably wrong. In this case, supplementation is not benign; executed in the absence of a diagnosis, it is a poor reflection on the practice of veterinary medicine. Although the issue of hormonal interaction in behavioral conditions is a complex one, supplementation with thyroxin is largely a popular bandwagon movement for which there are no rigorous data. Collection of these data would doubtless be enlightening.

In human psychiatry, the current view reflects the absence of a specific link between any abnormality of the thyroid axis and the pathophysiology of any affective illness [34]. The presence of a behavioral depression or other affective disorder alone does not warrant full thyroidal assessment or treatment unless the patient is female and older. We would do better to focus on the roles of thyroid hormones in the regulation of neural development and other complex links. In the embryonic or developing hypothyroid brain, morphologic and biochemical alterations of neurons are comparable to those seen in degenerative illness [35]. This is not surprising, given that deficiencies of thyroid hormone in neonates and children lead to abnormal brain development with concomitant deficits in behavior, locomotor ability, speech, hearing, and cognition. These functions may be partially caused by interreliance between thyroid hormones and acetylcholine, nerve growth factor, and hippocampal function [36]. Accordingly, the reported correlation between cognitive decline, age, and thyroid function may be a result of complex interactions between regionally relevant populations of cholinergic neurons, nerve growth factors, and all factors affecting learning. In such cases, thyroid hormones may be best viewed as one cog in a complex neuromodulatory scheme. Certainly, given this, mere supplementation with thyroxine to treat nonspecific behavioral signs is unlikely to be either rational or informative.

## The issue of sex

The most common effects of chromosomal sex determination that are relevant to behavioral medicine are those associated with sex steroid hormonal function. For example, one of the beneficial effects of castration and removal of testicular testosterone is the decrease in roaming behavior that subsequently follows. The decreased roaming may serve to decrease the local canine population, but it may also have indirect effects on longevity for the neutered male: intact males of almost any species exhibit more ''risk-taking'' behavior than do females, usually as a result of the pursuit of mates. In some species of lizards, such behaviors decrease the amount of foraging time available to male lizards. In other species, including many birds, males are more susceptible to predation and parasitism because of their appearance [37–42]. Of course, testosterone raises reactivity, and combined with the search for mates, males of many species are at increased risk for injury and subsequent infection and debility.

The more subtle effects of sex steroid hormones may be immunologic ones that indirectly affect behavior [43]. Male sex steroid hormones, androgens, and their female analogue, estrogens, have immunoneuromodulatory properties. Although estrogens and androgens tend to have similar effects on gonadal tissues, androgens may lower several aspects of immunity, whereas estrogens enhance these same levels [41]. Even in controlled laboratory settings, male rodents are more susceptible to infection than are female rodents. This difference is attributable to differential effects of sex steroid hormones; males are more susceptible to parasitic, bacterial, fungal, and viral infections than are females. In part, this effect is a result of lowered humoral immune responses associated with androgens. There is also a role for T helper (Th) cells: females exhibit higher Th2 responses, which are associated with higher interleukin (IL)-4, IL-5, IL-6, and IL-10 responses, than do males. In general, estrogens seem to enhance both humoral and cell-mediated immune responses. Female rodents also have increased immunologic tolerance to foreign substances compared with male rodents. These subtle effects of sex steroid hormones may cause males and females to seek and respond to risk, social environments, and social interactions differently.

High-affinity androgen and estrogen receptors have been found in the thymus, bone marrow, and spleen of rodents and in human macrophages, and estrogen receptors are present in the cytosol of circulating lymphocytes. Again, differential responses of exposure to infectious agents may directly and indirectly affect normal and abnormal behaviors. Certainly, male cats affected with the feline immunodeficiency virus experience more lymphocyte apoptosis (programmed cell death) than do female cats [44].

In terms of basic Mendelian genetics, animals with only one X chromosome are at increased risk for expression of conditions carried on sex chromosomes; deleterious recessive alleles are more likely to be

expressed in the heterogametic sex, and many genes contributing to both neurochemical synthesis and regulation [45] and immunoregulation are found on the X chromosome [43].

This last category may have the most relevance for veterinary behavioral medicine and human psychiatry. Alcoholism, drug abuse, antisocial personality, attention deficit disorder, Tourette's syndrome, and completed suicide predominate in male human beings with psychiatric conditions, whereas depression, anxiety, eating disorders, and attempted suicide are more common in female human beings with psychiatric conditions [46]. Unfortunately, we do not know to what extent social and cultural mores, socioeconomic factors, and overt and subtle gender roles are responsible for this dichotomy in human beings. In contrast, there is good evidence in many rodent models of anxiety that the behavioral manifestation of anxiety is dependent on the phase of estrus and the relative roles of estradiol and progesterone. In veterinary behavioral medicine, most dogs affected with "dominance" or impulse-control aggression are male. When the afflicted patients are female, however, these dogs exhibit a different subset of signs than do afflicted male dogs, and they exhibit the associated behaviors at a younger age than do male dogs [47]. For OCD, male dogs are overrepresented compared with female dogs. Aggressive behaviors, and some ritualistic ones, are affected by alterations in the neurotransmitters serotonin, norepinephrine, and dopamine. Some of the genes coding for these neurotransmitters or enzymes that metabolize them are on the X chromosome. Accordingly, deletions in these X chromosome genes may be critically important for our understanding of the mechanisms underlying many problematic behaviors [45,48].

It is also possible that in addition to the temporal and cyclic effects of circulating sex steroid hormones, behaviors may have been shaped by effects of these hormones early in ontogeny. Organizational structure of many brain regions and the extent to which lateralization of some functions occurs are dependent on activational effects of estradiol and testosterone [49,50]. Finally, there seem to be sex-associated differences in hippocampal reactivity, which has profound effects for any changes in behavior that have a basis in learning. Baseline excitability of hippocampal slices from male mice is higher than for female mice, testosterone has an augmentative effect on "kindled" or stimulated generalized responses, and both aspects are decreased by castration [51]. The findings warrant careful consideration if neutering and behavior modification are commonly recommended tools of the trade. In this case, neutering may lower reactivity via the excitatory effect on hippocampal tissue. Although there may be a subsequent slower effect for routine behavior modification, such a decrement may be more than compensated for by avoiding the reinforcement of impulsive reactive behaviors.

Those wishing to understand the complex interaction of genomic, molecular, neurochemical, and neuroanatomic mechanisms that influence

suites of behaviors would do well to consider these subtle hormonal effects in addition to the more straightforward effects of genomic sex determination. This is especially true given that hormonal actions work in concert with nuclear proteins. These nuclear proteins or cofactors help to regulate receptor transcription activity at the subcellular level [50]. The relevance for the pathologic findings of behavioral conditions that are largely treated using pharmacologic agents that affect receptor function and transcription (eg, all TCAs and selective serotonin re-uptake inhibitors [SSRIs]) could not be greater.

## Summary

Boundaries between behavioral conditions and medical differentials are likely to blur more rather than less as we learn more about genomic, cellular, and subcellular effects on common conditions. These changes should lead to better treatment but may also require a paradigm shift in how we view behavioral conditions and the mechanisms that contribute to them.

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