ELSEVIER

Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 2000, Vol. 24, pp. 727–776

0278-5846/00/$-see front matter

PII: S0278-5846(00)00104-4

NATURAL ANIMAL MODELS OF HUMAN PSYCHIATRIC CONDITIONS: ASSESSMENT OF MECHANISM AND VALIDITY

KAREN L. OVERALL

Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA

(Final form, June 2000)

Contents

Abstract
1. Introduction
1.1 Why Bother with Animal Models
1.2 Overview of Animal Models - Differences Between Induced and "Natural" Models
2. Hierarchical Thinking and Mechanism
2.1 Making the Diagnosis - Necessary and Sufficient Conditions
3. "Natural" Homologous and Analogous Models for Human Psychiatric Conditions
3.1 Canine Separation Anxiety - Assessment of Face Validity and the Phenotypic Level of Diagnosis
3.1.1 Canine Separation Anxiety - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis
3.1.2 Canine Separation Anxiety - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis
3.2 Canine OCD - Assessment of Face Validity and the Phenotypic Level of Diagnosis
3.2.1 Canine OCD - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis
3.2.2 Canine OCD - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis
3.3 Canine Cognitive Dysfunction - Assessment of Face Validity and the Phenotypic Level of Diagnosis
3.3.1 Canine Cognitive Dysfunction - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis
3.3.2 Canine Cognitive Dysfunction - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis
3.4 Canine Dominance Aggression - Assessment of Face Validity and the Phenotypic Level of Diagnosis
3.4.1 Canine Dominance Aggression - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis
3.4.2 Canine Dominance Aggression - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis
3.5 Canine Panic Disorder - Assessment of Face Validity and the Phenotypic Level of

Diagnosis
3.5.1 Canine Panic Disorder - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis
3.5.2 Canine Panic Disorder - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis
4. What about Schizophrenia?
5. Miscellaneous Conditions
6. Conclusions
Acknowledgments
References

Abstract

Overall, Karen L. Natural Animal Models of Human Psychiatric Conditions: Assessment of Mechanism and Validity. Prog. Neuro-Pyschopharmacol. & Biol. Pyschiatr. 2000, 24, pp. 727–776. ©2000 Elsevier Science Inc.

1. The classic animal models for human psychiatric conditions involves rodents. As prey species, their normal behaviors of avoidance would be considered pathological in humans and dogs. Hence, such models may not be homologous for similar behaviors found in psychiatric pathology in humans.
2. Dogs exhibit pathological behavioral conditions that may be equivalent to certain human psychiatric conditions. These canine conditions appear spontaneously or endogenously in the absence of genetic or neurochemcial manipulation, and as such, may be homologous to the human condition.
3. If canine conditions approach homology with human conditions they should have excellent face, predictive, and construct validity.
4. The canine conditions of separation anxiety, obsessive-compulsive disorder, cognitive dysfunction, dominance aggression, and panic disorder have good to excellent validity at all explored levels for human generalized anxiety disorder, obsessive-compulsive disorder, Alzheimer's disease, impulse control disorders, and panic disorder.
5. Natural canine models can aid our understanding of human psychiatric conditions.

Keywords: animal model, canine model, cognitive dysfunction dog model, dominance aggression, generalized anxiety disorder, impulse control disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, schizophrenia, separation anxiety.

Abbreviations: acral lick granuloma (ALG), adrenocorticotropic hormone (ACTH), American Psychiatric Association (APA), cerebrospinal fluid (CSF), carbon dioxide CO2, generalized anxiety disorder (GAD), high anxiety behaviors (HAB), homovanillic acid (HVA), hydroxyindol acetic acid (HIAA), long-term potentiation (LTP), low anxiety behaviors (LAB), magnetic resonance spectroscopy (MRS), obsessive-compulsive disorder (OCD), panic disorder (PD), positive emission tomography (PET), post-traumatic stress disorder (PTSD), rapid eye movement (REM), selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), weighted average anxiety score (WAAS).

1. Introduction

1.1. Why Bother with Animal Models?

Psychiatric disorders - whether in humans or in domestic animals where they are called behavioral disorders - are among the most complex and incapacitating of all pathological conditions. In the United States 20 million patients suffer from depression, manic depression, and schizophrenia. The direct and indirect cost for the treatment of schizophrenia, alone, is $33 billion per year, similar to the combined costs of the treatment of arthritis and coronary artery disease (NARSAD data, 1996).

The data from the literature on canine and feline behavioral disorders are equally impressive. Behavioral disorders are responsible for the relinquishment and death of more pet animals per year than infectious, neoplastic, and metabolic disease, combined. The average veterinary practice in the United States loses in excess of $17,500 in income annually for services that were not delivered because the pets were relinquished due to behavioral concerns (Sigler, 1991).

Psychiatric conditions, like those in canine and feline behavioral medicine, are devastating, poorly understood, and complex. Any model system that can speed our understanding of any aspect of the disorders involved should be valued (Gainetdinov and Caron, 1999). This paper addresses a class of model that is too seldom considered: the canine behavioral medicine patient. Dogs develop analogous, and possibly homologous, conditions to some human psychiatric disorders possibly including generalized anxiety disorder (GAD), attachment disorders, social phobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic disorder, Alzheimer's disease, and aggressive impulse control disorders (Table 1). This paper briefly reviews the difference between natural and induced animal models, and discusses the potential for the development of animal models for the above conditions. I attempt to focus on the practical application of natural canine models for understanding pharmacology and neuropathology of similar conditions.

Table 1

Human Psychiatric Conditions and Potentially Analogous or Homologous Conditions in Domestic Dogs

Condition in humans (As defined by the APA DSM IV, 1994 where appropriate)	Condition in dogs (As defined by Overall, 1997a)
Social and attachment anxieties, separation anxiety, GAD	Canine separation anxiety
OCD	OCD
Alzheimer's disease	Canine cognitive dysfunction
Impulse control disorders	Canine dominance aggression
Panic disorder	Panic disorder / Noise phobias
Social phobia	(/) Social phobia
PTSD	(?) Canine PTSD associated with abuse, neglect, abandonment
Schizophrenia	(?) Endogenous genetic fear, "nervousness", or "shyness" and withdrawal

1.2. Overview of animal models - differences between induced and "natural" models

From the outset it important to realize that no animal model, natural or induced, can ever fully mirror the human situation which it's modeling; there is no model that is isomorphic with the symptomology in question (Green, 1983). This difficulty is due to (1) the intrinsic problems with defining patient profiles and diagnostic criteria, (2) the variation between patients even when these are defined, and (3) that the level of the disorder that the animal exhibits may not be the level of the disorder that is most pathological. Even when we can be certain that the behaviors or signs are the same, we should remember that humans are unusual among animals in that they are verbal, and so similar behaviors, signals, or signs may have different meaning (Smith, 1965; McKinney and Moran, 1981). Emotional states may be ill-defined, so there is an increased likelihood that the labeling and interpretation of the behavior may be more in the eye of the researcher than in the brain of the animal (Kornetsky and Markowitz, 1978).

A larger problem is that psychiatric conditions in humans, and behavioral conditions in dogs, are

often poorly defined. In humans, a label like "depression" may refer to a symptom, a syndrome, or a nosological entity (Lehmann, 1959; Maser, 1998; Mojtabai and Rieder, 1998; Pincus et al., 1999). Because we assess what we have come to define as depression in humans largely by a series of verbal responses, we use data that are, at best, correlates of underlying pathology. Furthermore, the observable changes in behavior that occur in animals, primarily rodents, which serve as models for depressed states, are treated as secondary symptoms in humans (McKinney and Bunney, 1969), and little effort is made to characterize either human or rodent behaviors in a manner that would allow assessment of analogy or homology. It was this observation that lead McKinney and Bunney (1969) to specify the requirements for a model system (modified to a more general format here): (1) the symptoms of the condition in animals should be reasonably analogous to those see in humans [this is where the biggest criticism of the model lies - avoidant behaviors that we would call pathological in humans are often normal in rodents], (2) there should be observable behavioral changes in both model and patient that can be objectively evaluated, (3) independent observers should agree on objective criteria for drawing conclusions about the subjective state, (4) the treatment modalities effective in reversing the human condition should have the same effect on the animal condition, and (5) the system should be reproducible by other investigators.

Currently, animal models are sought that have 3 types of validity: face validity where the model is phenotypically similar and acts as a good model of specific symptoms (conditions 1-3, above), predictive validity where the model shows the same effect for drugs used in treatment or induction of provocative states (condition 4, above), and construct validity where the model either relies on or elucidates the same basic underlying mechanism responsible for the condition in humans. Often researchers fail to specify if they are seeking a correlational model (e.g., predictive validity; a model that is selectively sensitive to therapeutic agents), an isomorphic model (e.g., face validity; a model that implies the behavioral response in the human and animal is the same), or a homologous model (e.g., true construct validity; a model that implies that the "cause" of the behavioral response in the animal is sufficient to provoke the same response in humans) (Menard and Treit, 1999).

Most animal models seeking to meet the criteria for construct validity rely on induced or manipulative models involving surgical lesioning [includes ablation, spot lesioning, and

cannulation and drug studies] (Kowalska, 1995; Kosmal et al., 1997; Tsukahara et al., 1998), induction of pathology through behavioral alterations [includes crowding, forced swims, and other paradigm encountered seldom, if ever, in nature] (Kornetsky and Eliasson, 1969; Martin et al, 1989; Martin, 1998; Wu et al., 1999), or manipulation of genetic expression, primarily through the development of inbred lines or through knock-out mutations (Cases et al., 1998; Heisler et al., 1998; Okuyama et al., 1999; Parks et al., 1998). The main difficulty with such models is that none of these manipulations truly occur in isolation and the extent to which they interact with other neuroanatomic activity, neurochemistry, synaptic or genetic plasticity, or in other behavioral outcomes is often unknown and unknowable.

In seeking construct validity, we hope that the abnormal behavior shown by the animal reflects a breakdown in a fundamental behavioral process which would result in the symptomology / pathology in question (Green, 1983). True behavioral and psychiatric pathology is complex and probablistic. If we are interested in addressing neurochemical pathology, we have to acknowledge the difficulty implicit in conditions where inter-individual differences in monoamine metabolite levels change over the course of the condition (Constantino et al., 1999). We have no way of evaluating higher order effects of an induced pathology, so we have no way to evaluate how isomorphic an induced model really is. This difficulty is compounded if we ignore behavioral measures altogether, if we use only a single index of the disorder, if the disorder involves parallel systems or networks of pathology at any level, or if we forget that any induced model is predicated on one exaggerated class of normal behavior that may not represent any, let alone, the same pathology for the species being used (Menard and Treit, 1999). If conditions like anxiety are controlled by complex systems of multiple, distributed, and parallel pathways, we need to understand that we seldom explore or evaluate each of those pathways in induced models (Menard and Treit, 1999). Accordingly, we may be evaluating, at best, an incomplete pathology, and, at worst, an artifact. Finally, much of what we may be observing in induced models could be the result of not fully appreciating species-typical normal baseline social responses or due to incorrect inferences drawn from what we perceive to be releases from inhibition (Cohen, 1991; Gershenfeld and Paul, 1998; Stein, 1998), a process that is complex and poorly understood, itself.

The link that may allow isolated, induced, or manipulated systems to be interpreted in the context of the pathological phenotype may be in the comparisons and manipulations of natural

models suffering similar or homologous conditions. These natural animal models meet the requirements for heuristic and predictive value as set by Martin (1998) in that they (1) reproduce the behavioral and pathological features of the disorder in question, (2) allow investigation of neurobiological mechanisms that are not easily amenable to study in humans, and (3) permit reliable evaluation of pharmacological agents. The amount of co-morbidity in human psychiatric diagnoses suggests that there is substantial heterogeneity in the conditions and that different subpopulations can be identified, or that the diagnoses are not sufficiently discretely defined. The same consideration applies in veterinary behavioral medicine. Mechanistic hierarchical thinking can help us to understand what we seek to model, at what level we are addressing the model, and how the different validity constructs may rely on mechanistic interaction.

In many rodent models the face validity is questionable, given that "normal" rodent behavior of hiding are considered pathological in humans and dogs. Rodent models that isolate systems often fail to mimic human function. "Induced" models created through lesioning and knock-out genes may not be sufficiently restrictive and specific. If they change more than one aspect of any level of investigation, we are hard-pressed to evaluate the effects on other levels in complex integrated systems. Natural, more homologous models, like the ones suggested in this paper, are more likely to lead to coherent internally consistent paradigms by which we can understand the diversity and function of different levels - from the genotypic and molecular through the neurochemical and neuroanatomical to the phenotypic - of mechanistic interaction.

Rodent models suffer greatly for three reasons: they have simplified and often uninterpretable construct validity, when compared with human patients the predictive validity model often fails, there is often a disconnect between predictive validity and face validity, especially when compared with human patients. Natural canine models may be the next step in refining the model paradigm.

2. Hierarchical Thinking and Mechanism

When one makes a behavioral diagnosis one is usually making the diagnosis on the basis of some descriptor of the behavior. Such diagnoses are functional, phenotypic, or phenomenological diagnoses *(sensu* Moyer, 1968) and are based on patterns of behavior or on profiles of behavioral sequences. Diagnosis at this level may hint at underlying neuroanatomical, neurochemical, molecular, or genetic forces or mechanisms driving the abnormality, but phenotypic diagnoses are

not pathognomonic for any of these discrete, mechanistic levels. The most common error made in diagnostic approaches that rely on description is to confuse or confound levels of mechanism within descriptions of diagnosis (Mojtabai and Rieder, 1998). It is important to realize that tests for mechanistic hypotheses must occur within the level for which the mechanism is specified. For example, tests of a putative neurochemical basis for a behavioral problem must be conducted at that level, not only at the more gross level of changes in behavior, although the result of the test may be changed behavior. This overall approach is outlined in Table 2.

Table 2

Levels of "Cause" to Consider in Any Behavioral Diagnosis

- Phenotype: (1) Role of underlying, broad genotype x environment interaction; (2) Role of phenomenological, functional diagnoses
  - Neuroanatomy: (1) Role of localization of activity; (2) Role of neuroanatomic diagnoses
    - Neurochemistry: (1) Role of chemical / substrate interaction; (2) Role of most mechanistic pathophysiological diagnoses
      - Molecular: (1) Role of gene regulation and interaction with substrate; (2) Role of etiological diagnostic refinements
        - "Genotype": Role of heritability and genomic plasticity

Table 3 further elaborates this type of mechanistic approach and suggests which data are necessary to understand the interaction between levels.

Table 3

Understanding Patterns of Behavior Within Levels of a Mechanistic Approach

I. Phenomenological, phenotypic, functional diagnoses: must meet necessary and sufficient terminological criteria
    A. Demographic patterns
        1. Global patterns of behavioral change with age, reproductive status, et cetera (requires that individuals are followed through time)
    B. Suites of behavioral patterns
        1. Specific behaviors that occur
            a. Numbers of behaviors that occur (range, mean, predictive value)
            b. Covariation in behaviors to define subtypes or subpopulations (Venn diagrams, r values) - must avoid spurious correlations
            c. Ontogenetic development of specific behavioral suites (ethograms)(must follow individuals)
        2. Elemental behaviors that are shared across diagnoses (may hint at underlying reductionist mechanism - i.e., the neurochemistry of stress)
II. Neuroanatomical diagnoses
    A. Region activated during normal v. Abnormal behavior
        1. Level of activity
        2. Variants in patterns of activity
    B. Neuron behavior
        1. Types
        2. Densities
        3. Overall activity
III. Neurochemical / Neurophysiological diagnoses
    A. Types of neurochemicals
        1. Activities
        2. Receptor types associated with these
            a. Activity of receptor gates
            b. "Metabolism" of receptors
            c. Conformation of receptors
    B. Interactions of neurochemicals
        1. Neuron recruitment
            a. Regional activity
            b. Responses to behavioral changes
IV. Molecular diagnoses
    A. Molecular / conformational chemistry of receptors and neurotransmission
    B. Gene product regulators of expression
    C. Gene product regulators of function
V. Genetic diagnoses
    A. At the level of gene / locus
        1. Overall heritability (Mendelian pattern) Table 3 continued.....

Table 3 continued

a. Codon shifts
b. Errors (loss or addition of part of chromosome - e.g. - Marshall's disease, Down syndrome
c. Coding for different proteins

2. Multi-factorial effects

B. At the level of the genome

1. Gene products
2. Regulator genes
3. Local environmental receptor effects

NB: Tests of any mechanistic hypothesis must occur at the level of focus

Part of the problem in identifying the relative contributions of the different mechanistic levels to overall behavioral presentation is that most of the data available (e.g., behaviors associated with specific environmental stimuli; alterations in behavior in response to drug therapy) are only correlations. Correlational data can suggest tests of potential hypotheses of causality, but such data are not synonymous with "cause" or mechanism, itself. Diagnoses are not diseases; correlation is not causality. The assumption that they are equivalent is the most common error made about most processes, including normal and abnormal behavior.

Conditions for which there is putative etiologic and pathophysiologic heterogeneity (multi-factorial disorders) are complex. All psychiatric conditions and their canine analogues are likely to involve complex neural circuitry within a complex heterogenous disorder. For this reason there will be no "Holy Grail" of diagnosis and treatment (Braff and Geyer, 1991). For example, not all tail-chasing by dogs is due to the same underlying neurophysiological mechanism: some is a sign or outcome of obsessive-compulsive disorder (OCD), but some is a sequela or a response to neurological damage (Table 4).

Table 4a

Example of mechanistic interaction of the phenotypic level with other levels

PHENOTYPE	A Abnormal variant A	B Abnormal variant B	C Abnormal "Normal"	D "Normal"
Neuroanatomical variant	I	I	I	I
Neurochemistry	a	b	a	b
Molecular products	I'	II'	II'	II'
Genotype	b'	b'	b'	b'

In the example in Table 4a the variants in the condition are due to some difference in environmental response. This could be a purely phenotypic effect (Abnormal variant B). Alternatively, the effect could be due to learning and long-term potentiation (in which case the molecular level is affected - Abnormal variant A); this molecular effect also affects neurochemistry. The effect could also be one that is primarily neurochemical, without affecting the molecular level (Abnormal variant C).

In the example in Table 4b the variants in the condition could also be due to some difference in environmental response. This could be a purely phenotypic effect, as presented (C). Alternatively, the effect could be due to learning and long-term potentiation, in which case the molecular level is ultimately affected, illustrating that the signs that we see at any level can be a function of where we sample in the process (B), or the effect could be primarily one of neurochemistry (A), as determined by a change in genetic coding for different molecular products that affect the neurochemistry.

Table 4b
Example of mechanistic interaction of the phenotypic level with other levels

PHENOTYPE	A Abnormal variant A	B Abnormal variant B	C Abnormal "Normal"	D "Normal"
Neuroanatomic variant	I	I	I	I
Neurochemistry	a	a	b	b
Molecular products	I'	I'	II'	II'
Genotype	a'	b'	b'	b'

Phenotypic (functional, phenomenological) diagnoses are open to various mechanistic bases at all lower levels. Some of these more reductionistic levels can be partially tested using treatment (specific pharmacologic agents), but few phenotypic diagnoses can be specifically tested using behavior modification. Regardless, the logic for using very specific phenomenological diagnoses is to (a) enumerate and identify the particular behavioral manifestation that needs to be altered or assessed, and (b) to identify areas where specific behavioral intervention can be useful.

Inherent in the nature of a functional or phenotypic diagnosis is the association of a compilation of relatively non-specific signs. For dogs, growling is no more specific a sign than is an elevation in temperature, yet the distinction between compilations of signs and diagnosis has often been blurred in behavioral medicine, as it has in human psychiatry. Some of the difficulty is the results from the fact that behavior is so complex. Behavior can be both an event and a process, and observable behaviors are the result of the integration of all of the processes ongoing in underlying organ systems, in interaction with the external social and physical environments. The integration of processes inadvertently encourages tautological diagnoses. One mechanism whereby tautology can be avoided is to specify necessary and specific conditions for diagnosis that are divorced from compendia of non-specific signs. Once these conditions are specified, lists of signs and frequencies with which those signs occur can be compiled for each diagnosis, allowing within and among population comparisons. Knowledge of the frequency of specific behaviors is useful for: (1) establishing an overall pattern of the behavior [a. suites of behavioral patterns, b. determining heterogeneity of condition (how variable is it?), c. mechanistic tests of causality], (2) intervention,

(3) danger assessment, and (4) prognosis. These components are not synonymous with a diagnosis.

The approach discussed here keeps track of number and types of diagnoses, number and types of signs, and population level and temporal differences, without confounding these as occurs when diagnosis is indistinguishable from lists of signs. This approach generates data that could then provide hypotheses for which tests could be directed at each individual level. For example, if two diagnoses - or suites of signs - were phenotypically different, but neurochemically indistinct, this suggests that the differences in the phenotypic presentation are due to environmental, social, or cultural effects. If, on the other hand, one diagnosis - or suite of signs - is shown to have two neurochemical bases, the resultant behavior can be due to underlying differences in physiology and genetics plus any overlying effects of the environment (See Tables 4A & 4B for an example). Part of the problem with co-morbidity of diagnoses in human psychiatry is rooted in an under-appreciation of the interplay of these different mechanistic levels and their resultant phenotypes (Kellner and Yehuda, 1999).

Finally, one major advantage to using natural canine models is that breeders of the dogs are often continuously, if indirectly, conducting behavioral / genetic experiments. The development of breeds of dogs results in a form of genetic canalization. Practices of inbreeding or line-breeding further exaggerate this canalization. Many of the models discussed in this paper (OCD, impulsive / dominance aggression, social phobia / fear / panic disorder) address conditions for which there is a putative genetic basis within certain breeds. The approach outlined here permits the use of natural animal models of behavioral pathology to target investigation of specific levels of pathology (i.e., phenotypic, neuroanatomical, neurochemical, molecular, and genetic) and to then evaluate the integration of these in a system that provides greater opportunities to dissect genetic contributions (Gershenfeld and Paul, 1998).

2.1. Making the Diagnosis - Necessary and Sufficient Conditions

In veterinary behavioral medicine diagnoses are made largely on the basis of constellations of non-specific signs. If the words you choose as labels affect your interpretation and thinking about processes for which you have incomplete information, the actual words become very important. This caution is critical because the signs in behavioral medicine have (usually erroneously) been

viewed as "soft", and there are few simple tools that permit reasonably unambiguous comparison. Comparisons be made with regard to population level data only when there is a standardized diagnostic scheme. The fraction of animals afflicted by a specific behavioral problems is real, but the labels we place on those animals may not be consistent across populations, so that demographic data may not, in fact, reflect the underlying frequency or occurrence of the problem. If this is true, comparisons of efficacy of treatment across populations may be suspect. Cultural patterns of human impact of the behavioral problems of pets can only be assayed using multicenter studies. When done well, such studies can detect underlying sources of variation that suggest causal mechanisms for disorders that may not have been previously appreciated, but such comparisons are invalid if the same rules were not used to formulate the diagnoses (e.g., the "data" here).

These same concerns are also central to diagnosis in human psychiatry and for the implications diagnosis will have for understanding the underlying mechanism of the pathology and for treatment (Allgulander, 1999; Evenden, 1999; Kellner and Yehuda, 1999; Pincus et al., 1999).

The implementation of "necessary and sufficient" criteria, using the terms as they are used in logical and mathematical applications, is a refinement over descriptive definitions of terms. A necessary criterion or condition is one that must be present for the listed diagnosis to be made. A sufficient criterion or condition is one that will stand alone to singularly identify the condition. Sufficiency is an outcome of knowledge: the more we learn about the genetics, molecular response, neurochemistry, and neuroanatomy of any condition and its behavioral correlates the more succinctly and accurately we will be able to define a sufficient condition. Definition of necessary and sufficient conditions is not synonymous with a compendium of signs associated with the condition. The number of signs present and the intensity of those may be a gauge for the severity of the condition, or act as a flag when there can be variable, non-overlapping presentations of the same condition. The diagnostic conditions for dominance aggression listed below illustrate this difference. The use of necessary and sufficient diagnostic criteria act as qualitative, and potentially quantitative, exclusion criteria. They allow for uniform and unambiguous assessment of aberrant, abnormal, and undesirable behaviors. In this paper I use the canine diagnostic categories as they are defined by these criteria (see Appendix A) (Overall, 1997a,b).

3. "Natural" Homologous and Analogous Models for Human Psychiatric Conditions

3.1. Canine Separation Anxiety - Assessment of Face Validity and the Phenotypic Level of Diagnosis

Canine separation anxiety is a condition that is manifest as extreme distress when the dog is separated from his owner(s). The presence of other animals in the household does not alleviate the distress. The condition is variable in its triggers and presentation. The triggers may be the absence of only one special person, or the dog may be content to stay with anyone, as long as they are not "alone". Some dogs only react when they are truly left alone in the house (a real absence), while others will react only if they do not have access to the client because of a closed door or a crate (a virtual absence); some dogs react in both circumstances. Escape strategies are closely linked to conditions related to anxiety (King, 1999a) and the intensity of the response may depend on the intensity of the stimulus (King, 1999b). The classic escape paradigm may have some relevance for these dogs, and the extent to which they actively reject being left alone may be related to the functional intensity of their anxiety. . Canine responses to the absence can include elimination, vocalization, destruction, increased or decreased motor activity, withdrawal, salivation, self-mutilation, or increased or decreased vigilance and scanning (McCrave, 1981; Overall, 1997a; Voith and Borchelt, 1985). We know that some of these dogs exhibit increased muscle tension associated with hyper alertness (Overall, 1999a), but the extent to which autonomic responses increase or decrease has not been fully evaluated, although early data indicate mildly increased autonomic responsiveness compared with unaffected dogs (Overall, 1999a). In human GAD muscle tension increases in the absence of augmented autonomic responsiveness (Hoehn-Saric, 1998). Clearly, of the two broad groupings - those dogs who become more active than usual and those who withdraw and become less active than usual - we know more about the former because their behaviors cause clients to complain, seek help, or relinquish or euthanize their dogs.

The human form of separation anxiety is not fully homologous to the canine form because of the requirement that the condition develop before 18 years of age (APA, 1994). Dogs reach sexual maturity at about 6-9 months of age, and enter the phase of social maturity at about 18-24 months (12-36 months = range). While most behavioral conditions, particularly those based in anxiety as are all of those discussed here including aggression, begin sometime during social maturity, separation anxiety in dogs can develop at any age (Overall, 1997a,d). Furthermore, the issue of

"attachment" does not seem to be important in the separation anxiety population (King et al., 1999) but the issue of "abandonment" or being left without human contact is important. Finally, these dogs are willing to go anywhere, as long as their people accompany them, and we seldom have the ability to evaluate the extent to which the condition affects performance in the sense that is true for human children. There is a subpopulation of these dogs that is only content when they are in direct contact with their people, and these dogs show signs of intense distress even when they are boarded or otherwise cared for by other people. This latter subset may be a better model for the human condition of separation anxiety.

The classic manifestation of canine separation anxiety shares features of GAD and panic disorder. The dogs sharing traits associated with panic disorder (both with and without agoraphobia) will be dealt with later. In GAD the key symptom is viewed as cognitive (Maser, 1998). Our assessment of cognition in humans is based ultimately on a shared verbal capacity - a tool missing in our ability to assess dogs. This does not mean that they are not cognitive, and strong inference suggests that these animals experience all the physical and behavioral signs associated with a similar cognitive process noted in distressed humans: muscle tension, restlessness, fatigue, sleep disturbances, and irritability. Sleep disturbances and fatigue can be difficult to evaluate in dogs because they have a different ability to use frequent short sleep cycles involving deep REM sleep than do people (Adams and Johnson, 1994). Regardless, dogs with separation anxiety are often exhausted when their people come home and show a very different sleep-wakefulness pattern on non-work days when compared with work days. Irritability is also difficult to evaluate in dogs, but clients note an enhanced attentiveness and reactivity prior to departures. The key to treating these dogs and to understanding their distress involves increasing predictability without increasing rigidity. This association with predictability is another shared trait with GAD (Akiskal, 1998)

Finally, dogs probably also have a true form of GAD that requires that the signs occur in broad, generalized circumstances regardless of the social or physical environment and regardless of activity. We have no idea how common this diagnosis is, but it may be more common than appreciated if one considers the large numbers of dogs relinquished and euthanized annually. This is partly a diagnosis of exclusion (Overall, 1997a) and in the Behavior Clinic at VHUP we successfully treat these dogs with tricyclic antidepressants and SSRIs, particularly paroxetine,

which has a similar effect to that seen in humans of rendering them less shy and fearful (Allgulander et al., 1998; Lader, 1998).

3.1.1. Canine Separation Anxiety - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis. Few data on neuroanatomical localization of activity exist for human GAD, separation anxiety, or attachment and social disorders, and none exist for dogs. However, there is at least one excellent placebo-controlled, double blind study on the use of the TCA clomipramine for the treatment of separation anxiety in dogs (Simpson, 1997; King et al., 1999). In this study 93 dogs from 3 countries completed a 3 month randomized design to evaluate the efficacy of clomipramine compared with placebo in relieving the signs of separation anxiety. The signs evaluated included: urination, defecation, destruction, and vocalization. A weighted average anxiety score (WAAS) was constructed for each dog at the end of the study based on changes in these signs compared with the first, pre-treatment visit: disappearance of the sign was assigned a score of 4, improvement was assigned a score of 3, no change was assigned a score of 2, worsening of the sign was assigned a score of 1, and signs that were absent at outset and had not changed were assigned a 0. A WAAS score of 2.5 or better was considered improved. There was no difference between placebo and low dose clomipramine group (0.5-1.0 mg / kg po q. 12 h), but beginning at 2 months of treatment, the high dose clomipramine group (1.0-2.0 mg / kg po q. 12 h) differed significantly from the low dose and placebo groups for both WAAS score and the case severity score (average # of target behaviors present before and after treatment) ($P \leq 0.05$; paired t-tests). Long-term treatment with clomipramine resulted in continued improvement for some dogs, while changes in environment / family lifestyle or drug withdrawal resulted in relapse for some dogs (Overall, 1999, unpublished).

At the conclusion of the trial subjective scales for evaluating clinician and owner perception of improvement were constructed. The clinician scale assigns a value of 0 to no change, +1 to improved, +2 to greatly improved, -1 to worse, and -2 to profoundly worse. The client scale assigns a value of 0 to no improvement, 1 to little improvement, 2 to moderate improvement, 3 to much improvement, and 4 to "cured". With few exceptions these scales parallel each other and mirror the WAAS assessment (Overall, 1997c).

These data provide excellent evidence for concomitant good predictive validity paired to good

face validity in a model that is at least analogous to the human condition. The example also illustrates that it is possible to construct reliable, repeatable assessment tools that can be used by a wide variety of researchers to evaluate the actual behaviors, rather than relying on the solely on subjective clinician or owner impression. Regardless, these subjective scales have high concordance with the objective results.

3.1.2. Canine Separation Anxiety - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis. There are currently no data for humans or dogs on underlying molecular or genetic susceptibilities for these conditions. There are some good mouse data which suggest that both genetic susceptibility, and molecular and circuitry changes caused by repetitive stimulation that increase sensitivity and response, may be important in the development of these conditions (Gershenfeld and Paul, 1998; King, 1999a,b).

3.2. Canine OCD - Assessment of Face Validity and the Phenotypic Level of Diagnosis

Obsessive-compulsive disorder in dogs is usually recognized because of the presence of the compulsive component - the ritualistic, stereotypic behaviors. Obsessive compulsive behaviors can include those characterized by circling, tail-chasing, flank sucking (particularly in Dobermans), fence running, fly-biting , self-mutilation (ALG, neurotic dermatitis), hair / air biting, pica, pacing / spinning, staring and vocalizing, some aggressions, self-directed vocalizing, and wool / fabric-sucking / chewing (particularly in cats) (Luescher et al., 1991; Overall, 1994). Because behaviors manifest in OCD are often normal behaviors exhibited in an inappropriate, excessive, or out-of-context manner, history becomes particularly important in elucidating whether the patient truly has OCD. Parallel examples of stereotypic behaviors are found human medicine. These include trichotillomania (hair-pulling), hand washing, and checking (lights, gas jets, locks) (Insel, 1990).

Although the underlying etiology of these disorders is unclear for both dogs and humans, the symptomology and pathophysiology are striking. OCD is characterized by repetitive, ritualistic behaviors, in excess of any required for normal function, the execution of which interferes with normal, daily activities and functioning. Inherent in this description is a behavior that is exaggerated in form as well as duration. Furthermore, the behavior can be perceived by the human patient as abnormal and may be controlled to the extent that the behavior is performed

only minimally, or not at all, in the presence of others. This is probably also true for domestic animals. Dogs who flank suck or tail chase may, after frequent reprimands and corrections, remove themselves from view of the owners, then them commit the behavior elsewhere. Upon approach, the behavior ceases, to be begun again when no one is watching or when the animal removes himself from view. The presence of a cognitive component is not sufficient to rule out OCD, but it does suggest that the problem is rooted at a higher level than the behavior, alone, may indicate (i.e.: the Dobie is flank-sucking, but not because anything is wrong with his flank). This particular class of OCD makes the case for obsessions being a valid component of OCD. We evaluate obsessions in humans by asking them about ruminant, invasive thoughts. The verbal or written component of the response is a translation of the rumination - it is not identical to the ruminant thought, itself. It is inappropriate to apply a criteria to one species that has a divergent phylogeny that prohibits the use of that tool or criteria.

Not all dogs and cats fit a volitional pattern where they can at least temporarily stop their compulsive behaviors. Some dogs continuous stereotypic and ritualistic behavior regardless of distraction or companionship. It is not necessary that the behavior be continuously witnessed for the animal to have OCD, but it is requisite that the offending behavior substantially interfere with normal functioning in the absence of physical restraint. If the desire to exhibit the behavior is present, despite restraint because of punishment, training, or physical incarceration, the condition is present. The key is that if such control is removed and the animal could commit the behavior he will commit the behavior. Ignoring this crucial point will result in under-diagnosis of OCD and under-estimation of its frequency in canine and feline populations.

Obsessive-compulsive disorder in humans frequently appears in adolescence, and continues through mid-life. Human patients are generally clustered into four major groups: washers, checkers, ruminators, and an indistinct group of primary obsessive slowness. In dogs, OCD also appears during social maturity, and left untreated, whether by behavioral or pharmacologic intervention, it worsens.

Standardized behavioral screens and questionnaires can be used as tools to assess severity and progress with treatment (Overall, 1997a) as is true for separation anxiety (Overall, 1997d). The natural canine model for OCD has excellent face validity and can be accurately assessed

phenotypically.

3.2.1. Canine OCD - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis. Studies involving computed tomography have implicated the basal ganglia, particularly in the region of the basal ganglia and the caudate nucleus (Baxter et al., 1992; Coon et al., 1993; Luxenberg et al., 1988; Swedo et al., 1992). These regions have also been implicated in animal models (Davis et al., 1982; Pitman 1989). Changes in cerebral glucose metabolism in the orbitofrontal region have been found to correlate to response to treatment (Insel, 1990). The pathology of OCD appears to be partially attributable to aberrant serotonin metabolism, although some have postulated a tandem role for abnormal endorphin metabolism (Cronin et al., 1986). Neuropharmacological approaches to therapy have sought to address these abnormalities by augmenting serotonin through the use of TCAs and SSRIs (Ananth, 1986). A complete understanding of the integrated anatomical and neurophysiological mechanisms of OCD is not yet a reality.

As is true for humans, OCD appears to be rooted in a neurophysiological abnormality Overall, 1994), and dogs respond well to the tricyclic antidepressant clomipramine (Hewson et al., 1998; Moon-Fanelli and Dodman, 1998; Overall, 1994) and to the SSRI, fluoxetine (Overall, 1997d). In dogs, as in humans, in the absence of behavioral and pharmacological treatment OCD rarely resolves. Should the medication be discontinued, the patient relapses in many cases (Overall, 1997a and unpublished). Symptoms may be worse or more pronounced in stressful or anxiety producing circumstances (APA, 1994; Overall, 1997a) .

3.2.2. Canine OCD - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis. Finally, it has been hypothesized that there is a genetic and heritable component to the condition since it appears to run in some family lines; at least 2-3% of the general human population is afflicted with obsessive-compulsive disorders. First degree relatives have a greater risk for the condition that do members of families in the unaffected human population. Given that dog breeds represent genetic canalization that is further compounded by inbreeding schemes, we would expect the incidence in the canine population to be higher than that in the human population. The breeds in which OCD appears to run in family line that are commonly seen in the Behavior Clinic at VHUP are: great Danes, German short-haired pointers, German shepherd

dogs, bull terriers (see also Moon-Fanelli and Dodman, 1998), Jack Russell terriers, Dalmatians, Bouvier de Flanders, salukis, Cairn terriers, basset hounds, and soft-coated Wheaton terriers (Overall, 1999a). As is true for humans, first degree relatives usually have a different manifestation of OCD than does the proband. These features support the above hypotheses of a neurochemical basis for OCD and confirm that canine OCD is an excellent analogous and - possibly even homologous - model for human OCD, and that it provide insight into the heritability of such conditions.

3.3. Canine Cognitive Dysfunction - Assessment of face Validity and the Phenotypic Level of Diagnosis

Cognitive dysfunction is broadly defined in animals to represent geriatric behavioral changes not attributable to a general medical condition (Overall, 1997a; Ruehl and Hart, 1998). This definition encompasses all of the human geriatric dementias and is not sufficiently specific to delineate a sub-population that may be a good phenotypic model for anxiety. The commonly noted signs of cognitive dysfunction are similar to those noted for canine separation anxiety: elimination in the house and alterations in activity level. The pattern of these changes differs from that seen in true separation anxiety dogs, and the dogs also exhibit behaviors consistent with disorientation. In dogs such signs can be difficult to separate from non-specific changes associated with decreasing function of the visual, auditory, or locomotor systems that occurs with aging. Thirteen of 26 dogs 10 years or older were diagnosed with separation anxiety (i.e., the behaviors occurred only in clients' absence) (Chapman and Voith, 1990), while 6 were attributed to breakdown of house training (i.e., "cognitive dysfunction") that did not meet the necessary and sufficient conditions for separation anxiety. There are currently no published assessment scales that permit objective evaluation of behavioral changes either with the progress of the condition(s) or with treatment. Thus far, data have been collected from opinion surveys of owners. This is an inadequate and insufficient tool, and is neither reliable nor repeatable (Ruehl and Hart, 1998). Future work in the field needs to address quantification and qualification of the specific behaviors noted in cognitive dysfunction.

Regardless, like older people, older dogs have changing physical and emotional needs; accommodating these needs and treating the dogs with medication seems to modulate symptoms (Milgram et al., 1993; Head et al., 1995; Ruehl et al., 1995; Head et al., 1996), but the course of

the underlying condition may be inexorable.

The weakest model argument is the one for face validity: age-related memory dysfunction is extraordinarily difficult to assess in dogs. Longitudinal studies of actual behavioral progressions and changes and responses to provocative memory tests are required to enhance specificity of behavioral correlates and diagnosis.

3.3.1. Canine Cognitive Dysfunction - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis. As is true with human Alzheimer's disease, definitive diagnosis may be ascertainable only post-mortem (Mirra et al., 1991). Aged dogs with cognitive changes show similar lesions, including the deposition of β-amyloid plaques to those seen in human patients (Cummings et al., 1993). The hippocampus and the cerebral cortex are primarily affected (Cummings et al., 1993, 1996), as is true for most humans. Additional changes include ventricular dilation, thickening of the meninges, vascular changes, and reactive gliosis (Uchida et al., 1992; Shimada et al., 1992). Caution is urged about attributing too much weight to such changes: they can be non-specific and may occur in a number of neurodegenerative disorders, as well as in unaffected patients without cognitive signs (Crystal et al., 1993; Davis et al., 1999; Katzman et al., 1988). A study of cognitively unimpaired aged humans found that 51 / 59 subjects had neurofibrillary tangles post-mortem and 46 of 59 subjects had diffuse neuritic, senile plaques throughout the neocortex and entorhinal cortex , and vascular amyloid was present in 44 subject (Davis et al., 1999).

Imaging studies in humans have also produced somewhat non-specific results. Ventricle-to-brain ratio appears to be larger in manic geriatric patients compared with controls (Young et al., 1999), but this is not directly associated with age nor does it correlate well with cortical sulcal widening. Cortical sulcal widening was larger in geriatric manic patients when compared with age-matched controls (Broadhead and Jacoby, 1990; Young et al., 1999). Again, a strong argument can be made for further, more specific investigation.

Treatment with selegiline (L-deprenyl) has a beneficial effect in laboratory tests of aged canine cognitive performance (Milgram et al., 1993; Head et al., 1995; Head et al., 1996) that mirrors improvements similar to those seen in the treatment of Parkinson's disease (Parkinson's Study

Group, 1989, 1993). This effect may be a non-specific and related to augmentation of dopamine via direct effects in the pre-synaptic neuron, or indirect effects on other biogenic amines and neuromodulation. Accordingly, canine cognitive dysfunction has moderate potential for good predictive validity in a model of Alzheimer's disease, but the model is currently too incomplete to be definitive.

3.3.2. Canine Cognitive Dysfunction - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis. Apolipoprotein ϵ studies suggest than some forms of human Alzheimer's disease may be genetically affected. There are no comparable studies in dogs currently; however, in laboratory beagles a congruence of pathology was found within 15/16 litters (Russell et al., 1992). There are few data available for dogs concerning regulatory or structural proteins that have been implicated in normal or pathological brain or in neurological or neuropsychiatric conditions. In humans, synaptic proteins involved in structural plasticity and remodeling of axons and dendrites - debrin [post-synaptic] and GAP-43 [~neuromodulin; pre-synaptic] decline significantly with normal aging (Hatanpää et al., 1999).

The argument for construct validity in the canine cognitive dysfunction model of human Alzheimer's disease is fairly strong; however, the pathology is still relatively non-specific in both conditions. Caution is urged until neuroregulatory proteins, those affecting structure and plasticity, and those affecting receptor function have been investigated. These data will elucidate both the underlying biology of the system and validate or reject the model.

3.4. Canine Dominance Aggression - Assessment of Face Validity and the Phenotypic Level of Diagnosis

Canine dominance aggression is about control or access to control in direct social situations involving humans. The range of behaviors manifest in this condition includes postural threats and stares to sudden stiffening and bites (Overall, 1997a; Podberscek and Serpell, 1996, 1997). This is the primary category of canine aggression in which no warning is given (Borchelt, 1983). The classic dominantly aggressive dog growls, lunges, snaps or bites if they are stared at, physically manipulated - often when reaching over their head to put on a leash, physically disrupted or moved from a resting site - no matter how gently this is done, and when they are physically or verbally corrected. Otherwise, owners report that these are perfectly wonderful and charming

dogs for well over 95% of the time. Owners are further puzzled by the observation that the dog often seeks them out for attention and then bites them when they give it. As for most other behavioral conditions, dominance aggression develops during social maturity, further confusing owners because the dog was "perfect" for the first 1-1.5 years of life. Most dogs exhibiting this behavioral abnormality are male, although there is a female group that exhibits the behavior beginning in puppyhood, leading to questions of *in utero* androgenization (Overall, 1995, Overall and Beebe, 1997). This characterization shares similarities with the human impulsivity and impulse disorders associated with aggression, so further exploration of a model of face validity is warranted.

Impulsivity in humans has been relatively well studied from the behavioral aspect because of the public safety and legal concerns associated with the attendant aggression (Evenden, 1999); however, any behavior that is considered unduly risky or inappropriate has a tendency to be labeled "impulsive". Impulse-control disorders in humans are characterized phenotypically. Intermittent explosive disorder is characterized by failure to resist aggressive impulses that then result in explosive attacks (APA, 1994). The aggression is grossly out of proportion or out of context with any ostensible provocative stimulus. Individuals are remorseful after the event. While it is difficult or impossible to evaluate "resistance" or "remorse" in dogs, those affected with dominance aggression exhibit out-of-context, inappropriate, abnormal - whether in scope or form - behaviors under relatively non-provocative circumstances. This condition is currently viewed as a form of an anxiety disorder (Overall, 1997a,d) where the aggression is a default response to uncertainty about response in social situations involving humans. In the early stages of the condition, the dog improves quickly and dramatically if they are give a kind, reliable rule structure for interaction (e.g., they must sit and be calm before they get any kind of attention). After the outbursts these dogs often withdraw and may be avoided by other family pets.

Dominantly aggressive dogs appear to have excellent face validity for a natural model of impulsivity. The problem is that impulsivity is poorly delineated as a diagnostic category and may, itself, more appropriately be a non-specific sign. Dominance aggression is more selectively defined, but the diagnosis is open to the same criticism. Given the variability in the condition, the extent tow which the dogs struggle for control may be symptomatic of the true pathology.

3.4.1. Canine Dominance Aggression - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis. Little work has been done either post-mortem on neuroanatomy or cytoarchitectural facets of these conditions, or ante-mortem using imaging studies of dominance aggression or impulsivity, *per se*. Limbic system structures, in general, have been related to impulsive risk-taking, behavioral timing, and time judgements (Barratt et al., 1997). Impulsive outbursts are a characteristic of some forms of schizophrenia and will be discussed later. There is a rich literature on neurochemical aspects of both of these conditions.

The serotonin system has been implicated in both canine dominance aggression and in human impulsivity. Affected dogs have lower CSF levels of 5-hydroxyindol acetic acid [5-HIAA] and homovanillic acid [HVA], metabolites of serotonin and dopamine, respectively, post-mortem than do control dogs (Reisner et al., 1996). Although there is evidence that CSF HVA level may be a function of breed, CSF 5-HIAA levels appear to be decreased irrespective of breed. In a screening study seeking to examine urinary metabolites, dominantly aggressive dogs were statistically over-represented, compared with unaffected controls and all other canine patients evaluated for behavioral problems for excess excretion of certain amino acids that may be related to excitatory amino acids (Overall, 1997d). Further refinement of amino acid identification is still needed to interpret these findings. Finally, dominantly aggressive dogs respond to treatment with TCAs (Overall, 1997a,d) and SSRIs (Dodman et al., 1996) when combined with behavior modification.

These neurochemical finding are interesting in light of the putative role of serotonin in impulsivity (Cocarro, 1989). Linnoila et al. (1983) found that CSF 5-HIAA was reduced in aggressive human patients only for those who were impulsive. This correlation between serotonin metabolites and impulsivity has been noted in further studies (Roy et al., 1991; Virkkunen et al, 1994, 1995) that implicate low serotonin turnover rate in impulsive aggression. Treatment for many of these patients involves augmentation of serotonin through use of TCAs and SSRIs, as for dogs. Part of the problem in assessing the relative importance of such changes is that monoamine levels appear to change over the course of development in humans and over the course of the condition (Constantino et al., 1999), so these data may be more relevant than they seem. Finally, monoamine levels may not accurately reflect functioning of receptors or neurons. Coupling with imaging studies could mitigate this concern.

Dominantly aggressive dogs seem to provide an excellent predictive validation model for impulsivity, with the caveat noted above: the diagnosis of impulsivity is a non-specific one, and may be another level of a phenotypic "sign".

3.4.2. Canine Dominance Aggression - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis. Dogs may provide an excellent example of construct validity for impulsivity if the groups of impulsive patients and dominantly aggressive dogs can be better defined phenotypically and neurochemically. Dominance aggression appears to be heritable, and there are some breeds where at least 50% of the members of a line are affected (Overall, 1997d; Reisner, 1996, 1997). Breeds that are commonly represented in the Behavior Clinic at VHUP and for whom the patients are only one of the family with the condition include American cocker spaniels, Dalmatian, English springer spaniel, golden retriever, German shepherd dog, Labrador retriever, and rottweiler (Overall, 1999a). Regardless of what dominance aggression truly is, we have an excellent model of a repeatable form of inherited aggression.

Studies of the genetics of impulsivity in humans have been inconclusive. Some have found no consistent pattern of genetic influence (Plomin and Bergeman, 1991; Plomin et al., 1981), whereas other studies have found that genetic influences account for approximately 50% of the variance in aggression (Rushtown et al., 1986; Tellegen et al., 1988). A recent comparison of impulsivity in monozygotic and dizygotic twins comparing impulsivity and irritability, and impulsivity and assault, found that in there were more over-lapping genetic and environmental influences for those exhibiting impulsivity and irritability (Serocynski et al., 1999).

Clearly, more investigation is warranted, but the sparse data currently indicate considerable hope that the equivalent canine condition may have excellent construct validity for some manifestation of the human condition.

3.5. Canine Panic Disorder - Assessment of Face Validity and the Phenotypic Level of Diagnosis

Approximately 20-30 % of human patients with major depressive disorder have panic attacks. Life-time incidence of panic attacks in depressed groups may reach 50-60 % (Grunhaus et al., 1988). Panic attacks, which are a symptom of panic disorder and not diagnostically codable themselves, and panic disorder are somewhat differently defined (APA, 1994) because non-

specific panic attacks occur in the course of many different anxiety disorders. This finding indicated that the condition of panic may be very fundamental and that the circumstances in which it occurs and the form it takes may contain information about underlying mechanistic variability.

Panic disorder in humans is characterized by intense out-of-context fear or discomfort accompanied by physical symptoms consistent with autonomic sympathetic system stimulation. Life-time prevalence rates of panic disorder in general epidemiological studies range from 1.6-3.5% (Katschnig and Amering, 1998). Patients suffering from panic disorder may experience phobic avoidance (Roy-Byrne and Cowley, 1995). Part of the difficulty in classifying and understanding the disorder is the variability in phenotypes.

Panic attacks are more easily recognizable in pets than is condition like "depression"; however, the covariation in humans suggests that we may be missing the extent to which the signs associated with depression are present in animals. It would be interesting to investigate the extent to which dogs with known panic responses had experienced behavioral changes that can be concordant with depression. Panic may be identifiable as a component of thunderstorm phobia. Interestingly, 40% of canine patients whose owners seek help for thunderstorm and noise phobias have concomitant, and under-appreciated or undiagnosed separation anxiety, while only 8% of patients with a primary noise complaint or thunderstorm phobia have concomitant separation anxiety (Overall, 1997d). This strongly suggests interaction between the phenotype and the neural substrate: something about reacting excessively to noises "predisposes" the dog to have other anxieties (Free et al., 1983).

Dogs that panic exhibit similar symptoms to human with panic: increased heart rate, trembling or shaking, panting - often in short, staccato breaths, salivation - rather than sweating, and flushing of the skin on the pinnae and abdomen. They can exhibit these behaviors while becoming increasingly agitated or increasingly tonic.

A good case can be made for face validity for a natural canine model of panic disorder; however, any such model will be limited by non-specificity in diagnostic criteria and the extent to which the conditions shares signs or co-morbidity with other conditions.

3.5.1. Canine Panic Disorder - Assessment of Predictive Validity and the Neuroanatomic / Neurochemical Levels of Diagnosis. Neuroanatomical studies of panic disorder are closely linked to those pertaining to fear and to peripheral responses. The extent to which learning and memory play roles in fear, anxiety, phobias, and OCD has been poorly studied because it is difficult to do so given the complexity of the neurochemical systems involved. What is known is that: (1) a functioning amygdala is required to learn fear, (2) a functioning forebrain is required to unlearn fear (i.e., to effect habituation), and (3) many human fears appear to be the result of the inability to inhibit a fear response. Accordingly, it has been hypothesized that fear is, in part, due to chronic amygdala over-reaction and, or failure of the amygdala to turn off after the threat has passed.

The specific neuroanatomy of a fear response involves the locus ceruleus (LC), the principal norepinerphrinergic (noradrenergic) nucleus in the brain. Dysregulation of the LC appears to lead to panic and phobias in humans (Charney and Heninger, 1986). The LC directly supplies the limbic systems and may be responsible for many correlated "limbic" signs. Patients with true panic and phobic responses are more sensitive to pharmacologic stimulation and suppression of the LC than are controls (Charney and Heninger, 1986; Ko et al., 1983; Pyke and Greenberg, 1986).

Comparisons of patients with panic disorder with controls indicate that patients have markedly elevated heart rates and substantially elevated levels of plasma epinephrine, cortisol, and growth hormone. In response to isoproterenol challenge these patients have mildly elevated plasma cortisol levels and decreased heart rate suggesting that B-adrenergic receptor response is not increased, possibly because of chronic increased adrenergic function (Nesse et al., 1984). In one study examining the effect of time and activity on patients with panic disorder compared with control patients, the former show no reduction in salivary cortisol measures over the course of the assessment, but the latter do (Stones, et al., 1999). One skin conductance study suggests autonomic instability during quiet sitting in human patients with panic disorder compared with controls (Roth et al., 1998).

The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in anxiety and other disorders. Researchers have variously reported hypercortisolemia and flattening of responses in

patients with panic (Abelson and Curtis, 1996; Rapaport et al, 1989; Roy-Byrne et al., 1986), suggesting that this is another condition that is heterogenous.

Finally, human patients with true panic disorder react in a very specific manner to provocation with either a CO_2 challenge or to an intravenous lactate challenge. Lactate provokes circumscribed episodes of agitation, wariness, and motor responses normally elicited under stressful or threatening conditions in unaffected individuals or during panic attacks in affected individuals, as well as irregular elevation of plasma norepinephrine and cortisol accompanied by central noradrenergic activation (Friedman et al., 1988, DiLorenzo et al., 1987; Liebowitz et al., 1984; Liebowitz et al., 1985; Pitts and McClure, 1967).

PET (positive emission tomography) scans have been used to study regional brain blood flow: increases in blood flow in bilateral temporal poles during anticipatory anxiety have been noted, as has an asymmetry of cerebral blood flow (left < right) in the parahippocampal gyrus (Reiman et al., 1984; Reiman et al., 1986, 1989). The lactate test is an accepted test to provoke (and diagnose) panic attacks in people, but until recently it had not been evaluated in dogs. In human lactate responsive / susceptible patients, parahippocampal blood flow (a marker of neuronal activity), blood volume, and oxygen metabolism are asymmetric when evaluated by PET scans under resting, non-panic conditions (Reiman et al., 1989). This suggests that the abnormality is both biochemical and structural. The biochemical abnormality is postulated to be due to an increase in norepinephrine output from the locus coeruleus, which, in turn, stimulates parahippocampal "over-responsiveness".

Recently, a role for abnormal serotonin function has been substantiated, in part, based on the shared ontogeny and amygdaloid projects of serotonin neurons and those associated with the LC (Coplan and Lydiard, 1998). In this system serotonin is postulated to have a modulatory role that directly or indirectly affects discharge of brain stem nuclei, limbic activation, and prefrontal cortex activation. Such models of complexity and inter-regulation are likely to more closely explain the mechanistic variability underlying population heterogeneity in conditions like panic disorder. Further evidence implicating both serotonergic neurons and benzodiazepine receptors comes from the clinical literature demonstrating the efficacy of TCAs, SSRIs, and benzodiazepines in the treatment of panic disorder and related anxieties (Coplan et al., 1997;

Davidson and Moroz, 1998; de Beurs et al., 1999; Lydiard et al., 1998; Marcourakis et al., 1999; Pohl et al., 1998; Röschke et al., 1999; Sandemann et al., 1998; Spiegel, 1998; Sunderland et al., 1989; Uhlenhuth et al., 1998).

No equivalent imaging studies are yet available for canine patients suffering from panic, noise phobia, or extreme separation anxiety or other disorders that may be excellent models for human panic disorder. Recent experiments employing the lactate sensitivity test in a small sample of dogs (7 with noise phobias, 8 with separation anxiety, 9 unaffected controls) indicates that there was greater lability in neutrophil : lymphocyte ratios, cortisol level, creatine phosphokinase, and heart rate for patients with separation anxiety and noise phobias, than for controls (Overall, 1999; Overall et al., 1999). The most extreme responses were for patients who had both noise phobia and separation anxiety. Dogs in these groups were also the only dogs who showed any behavioral response; non-sedated control dogs slept through the test despite intravenous catheterization and repeated blood sampling. The actual data from the test are less important than its utility as a tool to establish whether the different diagnostic groups have different biological susceptibilities or threshold effects (Sunderland, et al., 1989). The latter is particularly important if there are responders or non-responders within a diagnostic category. This appears to be the case with these patients (Overall, unpublished). For dogs with separation anxiety, alone, the population is extremely variably with some patients requiring SSRIs after not responding to TCAs, while others do well on the older TCAs. The amount of time that the dog has been affected with the condition is not independent of response to drugs (Overall, 1997c), another commonality with human patients. Dogs with noise phobias or other forms of panic require treatment at least sporadically with benzodiazepines and usually benefit from combination treatment with these and SSRI (Overall, unpublished).

Despite our current lack of knowledge of regional brain activity and volume in dogs with panic disorder, these patients appear to provide excellent predictive validity on the basis of the response to medication, physiological data, and pattern of responses demonstrated in preliminary assays of the provocative lactate test. Imaging studies will contribute further evidence in the future.

3.5.2. Canine Panic Disorder - Assessment of Construct Validity and the Molecular / Genetic Levels of Diagnosis. Rodent models suggest areas of future investigation for natural canine

models of panic disorder. Rats bred for high (HAB) or low anxiety-related behaviors (LAB) have provided some insight into possible genetic mechanisms involved in panic disorder. Despite similar basal levels of ACTH and corticosterone HAB rats show higher plasma concentrations of both 5 and 15 minutes after provocative testing and have higher basal and stimulated levels of prolactin than do LAB rats (Landgraf et al., 1999). Transgenic mice that over-produce corticotropic releasing factor (CRF) show increased anxiety-related behaviors that are reversed by central administration of a specific CRF antagonist, suggesting a neuromodulatory role for CRF in the regulation of stress and anxiety (Sajdyk et al., 1999). The *Drosophila* white gene shares significant sequence similarity to a gene regulating tryptophan found on human chromosome 21 (21q22.3); associations between gene polymorphism and mood and panic disorders were significant for human males, suggesting that this gene may at least partially control mood, anxiety, and panic disorders (Nakamura et al., 1999).

Studies using the CO2 test in panic disorder patients indicate that concordance is higher for monozygotic compared with dizygotic twins, suggesting a relevant role for genetic factors in this form or inducible disorder (Bellodi et al., 1998). Parent-of-origin effects, including genomic imprinting, trinucleotide expansion, and mitochondrial inheritance, in panic disorder suggest a role for complex genetic interactions for transmitting mothers and fathers (Haghighi et al., 1999). Linkage studies also suggest complex or multifactorial genetic influences that indicate that subtype identification may not only be possible, but wise in such a heterogenous, "spectrum" disorder (Fyer and Weissman, 1999).

Given the above, it appears that natural canine models may have profound implications for construct validity, and may prove a rich source for linkage analysis.

4. What about Schizophrenia?

Schizophrenia is a debilitating neuropsychiatric disorder that afflicts about 1% of humans (APA, 1994). Schizophrenia now appears to be considered a heterogenous, multifactorial disorder (Arnold and Trojanowski, 1996). The common psychiatric features of schizophrenia include positive and negative signs or symptoms (Andreasen, 1995; APA, 1994; Carpenter and Buchanan, 1994). Positive symptoms appear to reflect an excess or distortion of normal functions; negative symptoms appear to reflect a loss or diminution of normal functions. Accordingly, positive

symptoms can include delusions, visual and auditory hallucinations, bizarre and disorganized language and speech, and profoundly abnormal global behaviors including catatonia. Positive symptoms have been further divided into two groups: the "psychotic dimension", which includes the delusions and hallucinations, and the "disorganization dimension", which includes the disorganized speech and behavior. Negative symptoms are characterized by restrictions in the range and intensity of emotional expression ("affective flattening"), in the fluency and productivity of thought processes and their articulations ("alogia" for the speech deficit), in the initiation of goal-directed behaviors ("avolition"), and in the lack of pursuit of normally pleasurable experiences ("anhedonia"). While there is a form of childhood onset schizophrenia, most schizophrenia is characterized by an onset in the teens or twenties and an insidious course that may begin with social withdrawal and lack of personal care (or awareness of care). Males are over-represented compared with females, they have an earlier age at onset, and may be more profoundly affected. Untreated, normal social and occupational functioning is impossible. The condition is heterogeneous and variable in its presentation. The diagnosis of schizophrenia is, in part, a diagnosis of exclusion since no one sign or pattern of signs is diagnostic for the condition.

The challenge for future research on the pathophysiology of schizophrenia is to link the clinical manifestations to the neural substrates so that treatment strategies can be based on an understanding of the neurotransmitter systems involved. In other brain disorders, such efforts have been helped by the availability of animal models that mimic the human disorder in salient phenotypic and pathological features. There are currently no natural (e.g., non-induced, either via lesioning or drug treatment) models for any of the manifestations of schizophrenia or for any of the symptom clusters. Because the pathology of schizophrenia may involve complex interaction of genetic, neurochemical, and neuroanatomic cytoarchitectural pathologies, a natural model would be desirable. Models produced by lesioning cannot portray the level or degree of complex mechanistic interaction that occurs in conditions for which there is some postulated underlying genetic and molecular pathology. Most lesioning studies have concentrated on the area of the cingulate gyrus of the brain; this is the region that has been postulated to be abnormal both in structure at the microscopic nerve level and at the neurochemical level. Models produced by lesioning cannot mimic the process that creates the pathology.

Schizophrenia has been increasingly recognized as a neurodevelopmental brain disorder with a

strong genetic vulnerability component and some underlying neuroanatomic and neurochemical dysfunction (Arnold, 1999; Arnold and Trojanowski, 1996; Weinberger, 1995). More recently, structural and functional neuroimaging studies have converged to point to tissue loss in fronto-temporal regions and indications of abnormally increased activity in temporal regions (Silbersweig et al., 1995). Studies with magnetic resonance spectroscopy (MRS) have revealed distinct abnormalities in the frontal and temporal regions, the former characterized by decreased n-acetyl-aspartate ratio to creatine (NAA/Cr), increased choline ratios (Cho/Cr) and normal amino acid ratios (AA/Cr), while the latter showed decreased NAA/Cr associated with decreased Cho/Cr and markedly increased AA/Cr. Consistent with the fronto-temporal abnormalities in brain structure and function, neuropsychological studies have shown differential deficits in executive and memory functions linked to frontal and temporal networks, respectively (Bartha et al., 1999; Bertolino et al., 1999; DeQuardo et al., 1999; Honer et al., 1999; Kotrla and Weinberger, 1995; Sedvall and Farde, 1995; Silbersweig et al., 1995). Neuroanatomical findings are not sufficiently consistent to be diagnostic for schizophrenia.

Examination of the pathology at the cytoarchitectural and cell protein level has been illuminating. Proteins like synaptophysin (synaptic vesicle protein) are unique molecular components of neurons. Selective lesions in lab animals can establish the presence of a significant correlation between quantitative assessments of synaptic terminals and levels of immunoreactivity of synaptophysin and SNAP-25 (synaptosomal-associated protein-25). Other proteins like neural cell adhesion molecule (N-CAM) promote cell-cell interactions during development and appear to have important functions in synapses of adult brain. Ratio of N-CAM to synaptophysin may provide an index of synaptic maturity: increased N-CAM to synaptophysin ratios observed in animal models of synaptic formation or proliferation including experimental lesions, genetic models, and during studies of learning and behavior. During long-term potentiation (LTP) initial down-regulation or resorption of N-CAM and related adhesion molecules seems to occur followed by a period of increased synthesis. In cingulate gyrus samples from patients with schizophrenia N-CAM immunoreactivity is increased about 22% compared (Horner et al., 1997, 1999).

At least 4 modes of heritability have been postulated for various "kinds" of schizophrenia (Arnold and Trojanowski, 1996): (1) liability threshold model or polygenic threshold or

oligogenic inheritance, (2) single gene models, (3) mixed model - gene of major effect acting in combination with a background of polygenes, (4) genomic imprinting and mutations involving unstable DNA sequences in the form of expanded trinucleotide repeats. These repeats form dynamic mutations that can expand from one generation to the next. This would account for underlying variability in symptoms and intensity. The first threshold or polygenic model is problematic because we don't know if patients actually meet the postulated normal distribution, but there is heuristic value to this type of model. Single gene models have been largely disavowed across the board, but their main point has been to differentiate mechanisms for early-onset profound cases. The mixed model has only produced inconclusive practical and statistical results to date. The genomic imprinting / mutation model this looks appealing and has lots of potential for the future.

Are there decent natural canine models for this condition, despite our inability to fully evaluate some of the cognitive signs? For example how would we know if dogs heard the canine equivalent of voices? The process could happen but phylogeny prohibits us from assessing it the way do in people - through speech. Fearful, shy, and nervous dogs have been reported in the veterinary behavioral literature for decades (Murphree, 1973; Murphree and Dykman, 1965; Murphree et al., 1967, 1971, 1974, 1977).

Some of these pathologies in behavior have been attributed to genetics, some to environmental conditions, and some to the interaction. No argument for behavioral pathology is ever going to be as simple as nature or nurture, but if the underlying abnormality is based in the genetic / molecular and neurochemical level, environmental influences on behavior will only be available for secondary shaping. Accordingly, a good natural model may be possible for some of the behavioral symptoms or constellations of symptoms of schizophrenia within the population of abnormal canines. There currently exists a colony of genetically "shy" and genetically "nervous" dogs at the University of Pennsylvania. The "nervous" dogs are derived from a much studied line of dogs that were maintained at NIH for almost 30 years (Murphree, 1973). When faced with unfamiliar circumstances or humans these dogs adopt a characteristic freezing posture and profound withdrawal. The "shy" dogs also exhibit avoidance, although their freezing postures are unambiguously different from those dogs in the "nervous" line. The "shy" dogs also salivate profusely and urinate if approach continues. Both sets of dogs tremble and become catatonic and

rigid.

These dogs may be phenotypic (what it looks like), neuroanatomic (the area of the brain causing the problem), and neurochemical (which neurotransmitters are affected and how) models for the disorganized dimension of the positive signs, and perhaps also for the negative signs, of schizophrenia. In addition to the similarities in behaviors, the dogs share other attributes that parallel the hallmarks of schizophrenia in humans. These dogs are normal as puppies and behaviorally indistinguishable from their normal litter mates. For the "nervous" dogs, abnormal behaviors can begin to become apparent by 4-6 months of age; for the "shy" dogs, abnormal behaviors are apparent by 8-10 months of age. The abnormal behaviors continue to worsen until they become fully pronounced and static by social maturity (generally 18-36 months of age in dogs). This mirrors the developmental course seen in humans. There is a genetic component to this condition, and affected dogs generally produce affected dogs in each breeding generation. Males are over-represented in the affected population, and may, in fact, be more severely affected than females. The most profoundly affected dog in the colony was male. The presentation in these dogs is variable and heterogenous, but is always progressive while the dogs are young. Finally, these dogs do not respond to standard tricyclic antidepressants or partial selective serotonin agonists which are helpful in treating many fearful or anxious dogs and humans.

Behavioral and physiological tests, including the lactate sensitivity test, permit affected dogs and their unaffected relatives to be separated into 2 groups. The physiological responses to the lactate test are statistically significantly different between groups (Overall et al., 1999). Furthermore, early data from MRS indicates that the affected dogs may have lower temporal and frontal lobe NAA levels than their unaffected relatives (Overall et al., 1999). Brains of affected and unaffected dogs are being subjected to molecular, cellular, and cytoarchitectural studies similar to those discussed above. All of these studies are ongoing, but the potential exists for these dogs to be used as a natural functional, neuroantomical, and genetic model for the pathology of schizophrenia.

5. Miscellaneous Conditions

Are there good natural canine models for social phobias and post-traumatic stress disorder (PTSD)? Undoubtedly, but we have to seek them. It is likely that dogs with social phobias are

abandoned or euthanized early, because euthanasia and abandonment are options that society condones for our pets, but not for our human families. We occasionally see adopted dogs who show signs that may be very similar to those seen in PTSD. This should be no surprise since many abandoned, rehomed, and shelter dogs have been subject to the very conditions that correlate with PTSD in humans: trauma, abuse, entrapment, and torture. The canine equivalent of PTSD is likely to be shockingly common if we survey for it. Learning more about the canine manifestation of this condition may also help us to understand other human behavioral disorders since child abuse and dog abuse are tightly linked, and children who will grow up to become abusers hone their abuse skills on their pets (Arkow, 1996; Ascione, 1993; Kellert and Felthous, 1985). Unless we actually critically examine the behaviors of distressed humans and distressed pets, we are unlikely to capitalize on these opportunities for natural canine models.

6. Conclusions

The examples listed above make a strong case for an integrated approach using human conditions and natural canine models to test hypotheses generated by induced rodent models. The prevalence of the disorders and morbidity associated with them argue that good homologous and analogous models for face, predictive, and construct validity are badly needed, and may be available for a wide variety of conditions in the canine population afflicted with behavioral disorders. Their prime strength lies in their use is assessing validity of mechanism. If a model has good face validity [the phenotype is virtually the same], and good predictive validity [the response to the same drug is the same], this strongly suggests that the potential for good construct validity is present.

Dogs have virtually identical social and signaling systems as humans, are sexually mature before they are socially mature, can produce another generation in under 2 years, and come in breeds that have already canalized some genetic variation. Furthermore, breeders and owners are highly motivated to understand behavioral problems and to work in a cooperative effort with researchers. Natural canine models of human psychiatric illness provide a unique opportunity for us to understand and help man's best friend, while using him to help and understand ourselves.

In summary, naturally occurring dog models exist. These dog models have excellent face validity. There are few drug studies done on these natural dog models, but those that have been

done have excellent predictive validity. Further investigation into these dog models, particularly if the model already has both face and predictive validity, could lead to excellent construct validity models.

Acknowledgements

I am indebted to Dr. Arthur E. Dunham, University of Pennsylvania, for his input and ideas about integrating mechanistic approaches into Behavioral Medicine, and for his critiques. Many of the veterinary data presented in this paper were collected in studies generously supported by Novartis Animal Health and Pfizer.

References

ABELSON JL, and CURTIS GC (1996) Hypothalamic-pituitary-adrenal axis activity in panic disorder: prediction of long-term outcome by pretreatment cortisol levels. Am J Psychiatry 153:69-73.

ADAMS GJ, and JOHNSON KG (1994) Sleep, work, and the effects of shift work in drug detector dogs *Canis familiaris*. Appl Anim Behav Sci 41:115-126.

AKISKAL HS (1998). Toward a definition of generalized anxiety disorder as an anxious temperament type. Acta Psychiatr Scan 98 (Suppl 393):66-73.

ALLGULANDER C (1999) Anti-anxiety agents: a pharmacoepidemiological review. Hum Psychopharmacol Clin Exp 14:149-160.

ALLGULANDER C, CLONIGER CR, PRYZBECK TR, and BRANDT L (1998) Changes on the temperament and character inventory after paroxetine treatment in volunteers with generalized anxiety disorder. Pyschopharm Bull 34:165-166.

AMERICAN PSYCHIATRIC ASSOCIATION: Diagnostic and Statistical Manual of Mental Disorders. 4th edition. Washington, D.C., 1994.

ANANTH J (1986) Clomipramine: an antiobsessive drug. Can J Psychiatry 31:253-258.

ANDREASEN NC (1995) Symptoms, signs, and diagnosis of schizophrenia. The Lancet 346:477-481.

ARKOW P (1996) The relationships between animal abuse and other forms of family violence. Fam Viol Sex Assault Bull 1:29-34.

ARNOLD SE (1999) Cognition and neuropathology in schizophrenia. Acta Psychiatr Scand 99

(Suppl 395):41-50.

ARNOLD SE, and TROJANOWSKI JQ (1996) Recent advances in defining the neuropathology of schizophrenia. Acta Neuropathol 92:217-231.

ASCIONE F (1993) Children who are cruel to animals: a review of research and implications for developmental psychopathology. Anthrozöos 6:226-247.

BARRATT ES, STANFORD MS, KENT TA, and FELTHOUS A (1997) Neuropsychological and cognitive psychophysiological substrates of impulsive aggression. Biol Psychiatry 21:1045-1061.

BARTHA R, AL-SEMAAN YM, WILLIAMSON PC, DROST DJ, MALLA AK, CARR TJ, DENSMORE M, CANARAN G, and NEUFELD RWJ (1999) A short echo proton magnetic resonance spectroscopy study of the left mesial-temporal lobe in first-onset schizophrenic patients. Biol Psychiatry 45:1403-1411.

BAXTER LR, SWARTZ JM, BERGMAN KS, SZUBA MP, GUZE BH, MAZIOTTA JC, ALAZAKI A, SELIN CE, FERNG H-K, MUNFORD P, and PHELPS ME (1992) Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry 49:681-689.

BELLODI L, PERNA G, CALDIROLA D, ARANCIO C, BERTANI A, and DI BELLA D (1998) CO2-induced panic attacks: a twin study. Am J Psychiatry 155:1184-1188.

BERTOLINO A, KNABLE MB, SAUNDERS RC, CALLICOTT JH, KOLCHANA B, MATTAY VS, BAJEVALIER J, FRANK JA, EGAN M, and WEINBERGER DR (1999) The relationship between dorsolateral prefrontal B-acetyl aspartate measures and striatal dopamine activity in schizophrenia. Biol Psychiatry 45:660-667.

BORCHELT PL (1983) Aggressive behavior in dogs kept as companion animals: classification and influence by sex, reproductive status, and breed. Appl Anim Behav Sci 10:54-61.

BRAFF DL, and GEYER MA (1991) Reply to pitfalls in animal models. Arch Gen Psychiatry 48:380.

BROADHEAD J, and JACOBY R (1990) Mania in old age: a first prospective study. Int J Geriatr Psychiatry 5:215-222.

CARPENTER WT, and BUCHANAN RW. (1994) Schizophrenia. NEJM 330:681-690.

CASES O, LEBRAND C, GIROS B, VITALIS T, DE MAEYER E, CARON MG, PRICE DJ, GASPAR P, and SEIF I (1998) Plasma membrane transporters of serotonin, dopamine, and norepinephrine mediate serotonin accumulation in atypical locations in the developing brain of monamine oxidase A knock-outs. J Neurosci 18:6914-6927.

CHAPMAN BL, and VOITH VL (1990) Behavioral problems in old dogs. JAVMA 196:944-946.

CHARNEY DS, and HENINGER GR (1986) Abnormal regulation of noradrenergic function in panic disorders. Arch Gen Psychiat 43:1042-1058.

COCCARO EF (1989) Central serotonin and impulsive aggression. Br J Psychiatry 155:52-62.

COHEN MR (1991) Pitfalls in animal models. Arch Gen Psychiatry 48:379.

CONSTANTINO JN, MURPHY DL, and MORRIS JA (1999) Family psychiatric history, cerebrospinal fluid monoamine metabolites, and temperament in infants. Biol Psychiatry 45:626-632.

COON H, PLAETKE R, HOLIK J, HOFF M, MYLES-WORSLEY M, WALDO M, FREEDMAN R, and BYERLY W (1993) Use of a neurophysiological trait in linkage analysis of schizophrenia. Biol Psychiatry 34:277-289.

COPLAN JD, and LYDIARD RB (1998). Brain circuits in panic disorder. Biol Psychiatry 44:1264-1276.

COPLAN JD, PAPP LA, PINE D, MARINEZ J, COOPER T, ROSENBLUM LA, KLEIN DF, and GORMAN JM (1997) Clinical improvement with fluoxetine therapy and noradrenergic function in patients with panic disorder. Arch Gen Psychiatry 54:643-648.

CRONIN GM, WIEPKEMA PR, and VAN REE JM (1986) Endorphins implicated in stereotypies of tethered sows. Experientia 42:198-199.

CRYSTAL HA, DICKSON DW, and SLIWINSKI MJ (1993) Pathological markers associated with normal aging and dementia in the elderly. Ann Neurol 34:566-573.

CUMMINGS BJ, SU JH, COTMAN CW, WHITE R, and RUSSELL MJ (1993) β-amyloid accumulation in aged canine brain: a model of early plaque formation in Alzheimer's disease. Neurobiol Aging 14:547-560.

CUMMINGS BJ, HEAD E, and AFAGH AJ (1996) β-amyloid accumulation correlates with cognitive dysfunction in the aged canine. Neurobiol Learn Mem 66:11-23.

DAVIDSON JRT, and MOROZ G (1998) Pivotal studies of clonazepam in panic disorder. Psychopharm Bull 34:169-174.

DAVIS DG, SCHMITT EA, WEKSTEIN DR, and MARKBERY WR (1999) Alzheimer neuropathologic alteration in aged cognitively normal subjects. J Neuropath Exp Neurology 58:376-388.

DAVIS GC, BUSCHBAUM, MS, NABER D, PICKAR D, POST R, VAN KAMMEN D, and BUNNEY WE Jr (1982) Altered pain perception and cerebrospinal endorphins in psychiatric illness. Ann NY Acad Sci 398:366-373.

DE BEURS E, VAN BALKOM AJLM, VAN DYCK R, and LANGE A (1999) Long-term outcome of pharmacological and psychological treatment for panic disorder with agoraphobia: a

2-year naturalistic follow-up. Acta Psychiatr Scand 99:59-67.

DEQUARDO JR, KESHAVAN MS, BOOKSTEIN FL, BAGWELL WW, GREEN WDK, SWEENEY JA, HAAS GL, TANDON R, SCHOOLER NR, and PETTEGREW JW (1999) Landmark-based morphometric analysis of first-episode schizophrenia. Biol Psychiatry 45:1321-1328.

DILORENZO R, BERNARDI M, GENEDANI S, ZIRILLI E, GROSSI G, GUARALDI GP, and BERTOLINI A (1987) Acute alkalosis, but not acute hypocalcemia, increases panic behavior in an animal model. Physiol Behav 41:357-360.

DODMAN NH, DONNELLY R, SHUSTER L, MERTENS P, RAND W, and MICZEK K (1996) Use of fluoxetine to treat dominance aggression in dogs. JAVMA 209:1585-1587.

EVENDEN J (1999) Impulsivity: a discussion of clinical and experimental findings. J Psychopharm 13:180-192.

FREE NK, WINGET CN, and WHITMAN RM (1983) Separation anxiety in panic disorder. Am J Psychiatry 150:595-599.

FRIEDMAN S, SUNDERLAND GS, and ROSENBLUM LA (1988) A non-human primate model of panic disorder. Psychiatry Res 23:65-75.

FYER AJ, and WEISMAN MM (1999) Genetic linkage study of panic: clinical methodology and description of pedigrees. Am J Med Gen (Neuropsychiatric Gen) 88:173-181.

GAINETDINOV RR, and CARON MG (1999) Editorial: Genetic models in pharmacology: present status and future. Pharmacological Res 39:403-404.

GERSENFELD HK, and PAUL SM (1998) Towards genetics of anxious temperament: from mice to men. Acta Psychiatr Scand 98(Suppl 393):55-65.

GREEN S (1983) Animal models in schizophrenia research. In: Animal Models of Human Behavior - Chapter 17. Ed by GCL Davey (Ed.), pp 315-338, John Wiley & Sons, Ltd, New York.

GRUNHAUS L, HAREL Y, KRUGLER T, PANDE AC, and HASKETT RF (1988) Major depressive disorder and panic disorder. Clin Neuropharmacol 11:454-461.

HAGHIGHI F, FYER AJ, WEISMAN MM, KNOWLES JA, and HODGE SE (1999) Parent-of-origin effect in panic disorder. Am J. Med Gen (Neuropsychiatric Gen) 88:131-135.

HATANPÄÄ K, ISAACS KR, SHIRAO T, BRADY DR, and RAPOPORT SI (1999) Loss of proteins regulating synaptic plasticity in normal aging of the human brain and in Alzheimer's disease. J Neuropath Exp Neurology 58:637-643.

HEAD E, HARTLEY J, and KAMEKA AM (1996) The effects of L-deprenyl on spatial short term memory in young and aged dogs. Prog Neuropsychopharmacol Biol Psychiatry 20:515-530.

HEAD E, MEHTA R, and HARTLEY J (1995) Spatial learning and memory as a function of age in the dog. Behav Neurosci 109:851-858.

HEISLER LK, CHU H-M, BRENNAN TJ, DANAO JA, BAJWA P, PARSONS LH, and TECOTT LH (1998) Elevated anxiety and antidepressant-like responses in serotonin 5-HT_{1A} receptor mutant mice. PNAS 95; 15049-15054.

HEWSON CJ, LUESCHER UA, PARENT JM, CONLON PD, and BALL RO (1998) Efficacy of clomipramine in the treatment of canine compulsive disorder. JAVMA 213:1760-1766.

HOEHN-SARIC R (1998) Psychic and somatic anxiety: worries, somatic symptoms, and physiological changes. Acta Psychiatr Scand 98 (Suppl 393):32-38.

HONER WG, FALKAI P, CHEN C, ARANGO V, MANN JJ, and DWORK AJ (1999) Synaptic and plasticity associated proteins in anterior frontal cortex in severe mental illness. Neuroscience 91:1247-1255.

HONER WG, FALKAI P, YOUNG C, WANG T, XIE J, BONNER J, HU L, BOULANNE GL, LUO Z, and TRIMBLE WS (1997) Cingulate cortex synaptic terminal proteins and neural cell adhesion molecule in schizophrenia. Neuroscience 78:99-110.

INSEL TR (1990): New pharmacologic approaches to obsessive-compulsive disorder. J Clin Psychiatry 51(Suppl):47.

KATSCHUNG H, and AMERING M (1998) The long-term course of panic disorder and its predictors. J Clin Psychopharmcol 18[suppl 2]:6S-11S.

KATZMAN R, TERRY RD, and DETERESA R (1998) Clinical, pathological and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. Ann Neuro 23:138-144.

KELLERT SR, and FELTHOUS AR (1985) Childhood cruelty towards animals among criminals and non-criminals. Human Relations 38:1113-1129.

KELLNER M, and YEHUDA R (1999) Do panic disorder and posttraumatic stress disorder share a common psychoneuroendocrinology? Psychoneuroendocrinology 24:485-504.

KING J for the CLOCSA study group (1999) Treatment of separation anxiety in dogs with clomipramine. Results from a prospective, randomized, double-blinded, placebo-controlled clinical trial. J Appl Anim Behav Sci in review.

KING SM (1999a) Escape-related behaviours in an unstable elevated and exposed environment. I. A new behavioural model of extreme anxiety. Behav Brain Res 98:113-126.

KING SM (1999b) Escape-related behaviours in an unstable elevated and exposed environment. II. Long-term sensitization after repetitive electrical stimulation of the rodent midbrain defense system. Behav Brain Res 98:127-142.

KO GN, ELSWORTH JD, ROTH RH, ROFKIN BG, LEIGH H, and REDMOND DE, Jr (1983) Panic-induced elevation of plasma MHPG levels in phobic anxious patients. Arch Gen Psychiat 40:425-430.

KORNETSKY C, and ELIASSON M (1969) Reticular stimulation and chlorpromazine: an animal model for schizophrenic overarousal. Science 165:1273-1274.

KORNETSKY C, and MARKOWITZ R (1978) Animal models of schizophrenia, In: Psychopharmacology: A generation of progress. MA Liptom, A DiMascio, and KF Killam (Eds.), pp , Raven Press, New York.

KOSMAL A, MALINOWSKA M, and WOŹNICKAW A (1997) Diversity of connections of the temporal neocortex with amygdaloid nuclei in the dog (*Canis familiaris*). Acta Neurobiol Exp 57:289-314.

KOTRLA KJ, and WEINBERGER DR (1995) Brain imaging in schizophrenia. Ann Rev Med 46:113-122.

KOWALSKA D (1995) Effects of hippocampal lesions on spatial delayed responses in dog. Hippocampus 5:363-370.

LADER MH (1998) The nature and duration of treatment for GAD. Acta Psychiatr Scand 98 (Suppl 393):109-117.

LANDGRAF R., WIGGER A, HOLSBOER F, and NEUMANN ID (1999) Hyper-reactive hypothalamo-pituitary-adrenocortical axis in rats bred for high anxiety-related behaviour. J Neuroendocrinology 11:405-407.

LEHMANN HE (1959). Psychiatric concepts of depression: Nomenclature and classification. Canad Psychiat Assoc J 4:1-12.

LIEBOWITZ MR, FYER AJ, GORMAN JM, DILLON D, APPLEBY IL, LEVY G, ANDERSON S, LEVITT M, PALIJ M, DAVIES SO, and KLEIN DF (1984) Lactate provocation of panic attacks. I. Clinical and behavioral findings. Arch Gen Psychiatry 41:764-770.

LIEBOWITZ MR, GORMAN JM, FYER AJ, LEVITT M, DILLON D, LEVY G, APPLEBY IL, ANDERSON S, PALIJ M, DAVIES SO, and KLEIN DF (1985) Lactate provocation of panic attacks. II. Biochemical and physiological findings. Arch Gen Psychiatry 42:709-719.

LINNOILA M, VIRKKUNEN M, SCHEININ M, NUUTILA A, RIMON R, and GOODWIN FK (1983) Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sci 33:2609-2614.

LUESCHER UA, MCKEOWN DB, and HALIP J (1991) Stereotypic or obsessive-compulsive disorders in dogs and cats. Vet Clin NA: Sm Animal Pract 21:401-413.

LUXENBERG JS, SWEDO SE, and FLAMMENT MF (1988) Neuroanatomical abnormalities

in obsessive compulsive disorder detected with quantitative X-ray computed tomography. Am J Psychiatry 145:1089-1093.

LYDIARD RB, STEINER M, BURNHAM D, and GERGEL I (1998) Efficacy studies of paroxetine in panic disorder. Psychopharm Bull 34:175-182.

MARCOURAKIS T, GORENSSTEIN C, RAMOS RT, and DA MOTTA SINGER J (1999) Serum levels of clomipramine and desmethylclomipramine and clinical improvement in panic disorder. J Psychopharm 13:40-44.

MARTIN P (1998) Animal models sensitive to anti-anxiety agents. Acta Psychiatr Scand 98(Suppl 393):74-80.

MARTIN P, PICHAT P, MASSOL J, SOUBRIÉ P, LLOYD KG, and PUECH AJ (1989) Decreased GABA B receptors in helpless rats: reversal by tricyclic antidepressants. Pharamcopsychiatry 22: 220-224.

MASER JD (1998) Generalized anxiety disorder and its comorbidities: disputes at the boundaries. Acta Psychiatr Scand 98 (Suppl 393):12-22.

MCCRAVE EA (1981) Diagnostic criteria for separation anxiety in the dog. Vet Clin NA. Sm Anim Pract 21:247-256.

MCGRIFFEN P, OWEN MJ, and FARMER AE (1995) Genetic basis of schizophrenia. The Lancet 346:678-682.

MCKINNEY WT, and BUNNEY WE (1969) Animal models of depression. I. Review of the evidence: Implications for research. Arch Gen Psychiatr 21:240-248.

MCKINNEY WT, and MORAN ET (1981) Animal models of schizophrenia. Am J Psychiatry 138:478-483.

MENARD J, and TREIT D (1999) Effects of centrally administered anxiolytic compounds in animal models of anxiety. Neurosci Biochem Rev 23:591-613.

MILGRAM NW, IVY GO, and HEAD E (1993) The effect of L-deprenyl in behavior, cognitive function, and biogenic amines in the dog. Neurochem Res 18:1211-1219.

MIRRA SS, HEYMAN A, and MCKEEL D (1991) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 41:479-486.

MOJTABAI R, and RIEDER, RO (1998) Limitations of the symptom-oriented approach to psychiatric research. Br J Psychiat 173:198-202.

MOON-FANELLI A, and DODMAN NH (1998) Description and development of compulsive tail chasing in terriers and response to clomipramine treatment. JAVMA 212:1252-1257.

MOYER KE (1968) Kinds of aggression and their physiological basis. Comm Behav Biol A 2:5-87.

MURPHREE OD (1973) Inheritance of human aversion and inactivity in two strains of pointer dogs. Biol Psychiatry 7:23-29.

MURPHREE OD, ANGEL C, DELUCA DC, and NEWTON JEO (1977) Longitudinal studies of genetically nervous dogs. Biol Psychiatry 12:573-576.

MURPHREE OD, DELUCA DC, and ANGEL C (1974) Psychopharmacologic facilitation of operant conditioning of genetically nervous catahoula and pointer dogs. Pav J Biol Sci 9:17-24.

MURPHREE OD, and DYKMAN RA (1965) Litter patterns in the offspring of nervous and stable dogs. I: behavioral tests. J Nerv Mental Dis 141:321-332.

MURPHREE OD, DYKMAN RA, and PETERS JE (1967) Genetically determined abnormal behavior in dogs: results of behavioral tests. Conditional Reflex 1:199-205.

MURPHREE OD, PETERS JE, and DYKMAN RA (1971) Behavioral comparisons of nervous, stable, and crossbred pointers at ages 2, 3, 6, 9, and 12 months. Conditional Reflex 6:91-100.

NESSE RM, CAMERON OG, CURTIS GC, MCCANN DS, and HUBER-SMITH MJ (1984) Adrenergic function in patients with panic anxiety. Arch Gen Psychiatry 41:771-776.

NAKAMURA M, UENO S, SANO A, and TANABE H (1999) Polymorphisms of the human homologue of the *Drosophila* white gene are associated with mood and panic disorders. Molec Psychiatry 4:155-162.

NARSAD (1996) Patient brochure "Someone you know has mental illness".

OKUYAMA S, SAKAGAWA T, CHAKAI S, IMAGAWA Y, ICHIKI T, and INAGAMI T (1999) Anxiety-like behavior in mice lacking the angiotensin II type-2 receptor. Brain Res 821:150-159.

OVERALL KL (1994) Use of clomipramine to treat ritualistic motor behavior in dogs. JAVMA 205:1733-1741.

OVERALL KL (1995) Sex and aggression. Canine Practice. Canine Practice. 20(3):16-18.

OVERALL KL (1997a) Clinical Behavioral Medicine for Small Animals, Mosby, St. Louis, pp 544.

OVERALL KL (1997d) Neurobiology and neurochemistry of fear and aggression. NAVC Proceedings. 11:33-39.

OVERALL KL (1997b) Terminology in behavioral medicine: diagnosis, necessary and sufficient conditions, and mechanism. European Society of Veterinary Clinical Ethology: Proceedings of the First International Conference on Veterinary Behavioural Medicine: 14-19.

OVERALL KL (1997c) The use of clomipramine to treat canine separation anxiety: A placebo-controlled double-blind study. BSAVA / WSAVA Clinical Research Abstracts:298.

OVERALL KL (1999) Animal models of human anxieties disorders. Presentation at the National Institute of Mental Health (NIMH) - Workshop on animal models of anxiety.

OVERALL KL, and BEEBE AD (1997) Dominance aggression in young female dogs: what does this suggest about the heterogeneity of the disorder? European Society of Veterinary Clinical Ethology: Proceedings of the First International Conference on Veterinary Behavioural Medicine:58-63.

OVERALL KL, DUNHAM AE, and ACLAND G (1999) Responses of genetically fearful dogs, patients with separation anxiety, and those with noise phobias to the lactate test: Assessment of the test as provocative index. European Society of Veterinary Clinical Ethology: Proceedings of the Second International Conference on Veterinary Behavioural Medicine: 8-17.

PARKINSON'S STUDY GROUP (1989) Effect of deprenyl on the progression of disability in early Parkinson's disease. NEJM 321:11363-1371.

PARKINSON'S STUDY GROUP (1993) Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. NEJM 328:176-183.

PARKS CL, ROBINSON PS, SIBILLE E, SHENK T, and TOTH M (1998) Increased anxiety of mice lacking the serotonin$_{1A}$ receptor. PNAS 95:10734-10739.

PINCUS HA, WAKEFIELD DAVIS W, and MCQUEEN LE (1999) 'Subthreshold' mental disorders. Br J Psychiatry 174:288-296.

PITMAN RK (1989) Animal models of compulsive behavior. Biol Psychiatry 26:189-198.

PITTS FN Jr, and MCLURE JN (1967) Lactate metabolism in anxiety neurosis. NEJM 25:1329-1336.

PLOMIN R, and BERGEMAN CA (1991) The nature of nurture: genetic influences on 'environmental' measures. Behav Brain Sci 14:373-427.

PLOMIN R, FOCH TT, and ROWE DC (1981) Bobo clown aggression in childhood: environment, not genes. J Res Personality 25:331-342.

PODBERSCEK AL, and SERPELL JA (1996) The English cocker spaniel: preliminary findings on aggressive behavior. Appl Anim Behav Sci 47:75-89.

PODBERSCEK AL, and SERPELL JA (1997) Aggressive behaviour in English cocker spaniels and the personality of their owners. Vet Record 141:73-76.

POHL RB, WOLKOW RM, and CLARY CM (1998) Sertraline in the treatment of panic disorder: a double blind multicenter trial. Am J Psychiatry 155:1189-1195.

PYKE T, and GREENBERG H (1986) Norepinephrine challenge in panic patients. J Clin Psychol 6:279-285.

RAPAPORT MH, RISCH SC, GOLSHAM S, and GILLIN JC (1989) Neuroendocrine effects of ovine corticotropin-releasing hormone in panic disorder patients. Biol Psychiatry 26:344-348.

REIMAN EM, FUSSELMAN MJ, FOX PT, and RAICHLE ME (1989) Neuroanatomical correlates of anticipatory anxiety. Science 243:1071-1074.

REIMAN EM, RAICHLE ME, BUTLER FK, HERSCOVITCH P, and ROBINS E (1984) A focal brain abnormality in panic disorder, a severe form of anxiety. Nature 310:686-685.

REIMAN EM, RAICHLE ME, ROBINS E, BUTLER FK, HERSCOVITCH P, FOX P, and PERLMUTTER J (1986) The application of positron emission tomography to the study of panic disorder. J Psychiatry 143:469-477

REISNER IR (1997) Assessment, management, and prognosis of canine dominance-related aggression. Vet Clin NA: Sm Anim Pract 27:479-495.

REISNER IR, MANN JJ, STANLEY M, HUANG Y-Y, and HOUPT KA (1996) Comparison of cerebrospinal fluid monoamine metabolite levels in dominant-aggressive and non-aggressive dogs. Brain Res 714:57-64.

RÖSCHKE J, KÖGEL P, WAGNER P, GRÖZINGER M, HEVERS W, and SCHLEGEL S (1999) Electrophysiological evidence for an inverse benzodiazepine receptor agonist in panic disorder. J Psychiatric Res 33:1-5.

ROTH WT, WILHELM FH, and TRABERT W (1998) Autonomic instability during relaxation in panic disorder. Psychiatry Res 80:155-164.

ROY A, VIRKKUNEN M, and LINNOILA M. (1991) Serotonin in suicide, violence, and alcoholism. In: Serotonin in Major Psychiatric Disorders. E Coccaro and D Murphy (Eds.), pp 187-208, American Psychiatric Press, Washington, DC.

ROY-BYRNE PP, and COWLEY DS (1995) Course and outcome in panic disorder: a review of recent follow-up studies. Anxiety 1:151-160.

ROY-BYRNE PP, UHDE TW, POT RM, GALLUCI W, CHROUSOS GP, and GOLD PW (1986) The corticotropin-releasing hormone stimulation test in patients with panic disorder. Am J Psychiatry 143:896-899.

RUSHTON JP, FULKER DW, NEALE MC, NIAS DKB, and EYSENCK HJ (1986) Altruism and aggression: the heritability of individual differences. J Personality Soc Psychol 50:1192-1198.

RUEHL WW, BRUYETTE DS, and DEPAOLI A (1995) Canine cognitive dysfunction as a model for human age-related cognitive decline, dementia, and Alzheimer's disease: clinical presentation, cognitive testing, pathology, and response to L-deprenyl therapy. Prog Brain Res 106:217-225.

RUEHL WW, HART BL (1998) Canine cognitive dysfunction. In Psychopharmacology of Animal Behavior Disorders. NH Dodman, and L Shuster, pp 283-304, Blackwell Science, Malden, MA.

RUSSELL JR, WHITE R, and PATEL E (1992) Familial influence on plaque formation in the beagle brain. Neuroreport 2:1093-1096.

SAJDYK T, SCHOBER DA, GEHLERT DR, and SHEKHAR A (1999) Role of corticotropin-releasing factor and uricortin within the basolateral amygdala of rats in anxiety and panic responses. Behav Brain Res 100:207-215.

SANDMANN J, LÖRCH B, BANDELOW B, HÄRTTER S, WINTER P, HIEMKE C, and BENKERT O (1998) Fluvoxamine or placebo in the treatment of panic disorder and relationship to blood concentrations of fluvoxamine. Pharmacopsychiatry 31:117-121.

SEDVALL G, and FARDE L (1995) Chemical brain anatomy in schizophrenia. The Lancet 346:743-749.

SEROCZYNSKI AD, BERGEMAN CS, and COCCARO EF (1999) Etiology of impulsivity / aggression relationship: genes or environment. Psychiatry Res 86:41-57.

SHIMADA A, KUWAMURA M, and AWALURA T (1992) Topographic relationship beteen senile plaques and cerebrovascular amyloidosis in the brain of aged dogs. J Vet Med Sci 54:137-144.

SIGLER L (1991) Pet behavioral problems present opportunities for practitioners. AAHA Trends 4:44-45.

SILBERSWEIG DA, STERN E, FRITH C, CAHILL C, HOLMES A, GROOTOONK S, SEAWARD J, MCKENNA P, CHUA SE, SCHNORR L, JONES T, and FRACKWIAK RSJ (1995) A functional neuroanatomy of hallucinations in schizophrenia. Nature 378:176-179.

SIMPSON B (1997) Treatment of separation related anxiety in dogs with clomipramine. European Society of Veterinary Clinical Ethology: Proceedings of the First International Conference on Veterinary Behavioural Medicine:143-154.

SMITH WJ (1965) Message, meaning and context in ethology. Amer Natur 99:405-409.

SPIEGEL DA (1998) Efficacy studies of alprazolam in panic disorder. Psychopharm Bull 34:191-195.

STEIN MB (1998) Neurobiological perspectives on social phobia: From affiliation to zoology. Biol Psychiatry 44:1277-1285.

STONES A, GROOME D, PERRY D, HUCKLEBRIDGE F, and EVANS P (1999) The effect of stress on salivary cortisol in panic disorder patients. J Affect Dis 52:197-201.

SUNDERLAND G, FRIEDMAN S, and ROSENBLUM LA (1989). Imipramine and

alprazolam treatment of lactate-induced acute endogenous distress in nonhuman primates. Am J Psychiatry 146:1044-1047.

SWEDO SE, PIETRINI P, LEONARD HL, SCHAPIRO MB, RETTEW DC, GOLDBERGER DL, RAPOPORT SI, RAPOPORT JL, and GRADY CL (1992) Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder: Revisualization during pharmacotherapy. Arch Gen Psychiatry 49:690-694.

TELLEGEN A, LYKKEN DT, BOUCHARD TJ, WILCOX KJ, SEGAL NL, and RICH S (1988) Personality similarity in twins reared apart and together. J Pers Soc Psychol 54:1031-1039.

TSULAHARA T, IIHARA K, HASHIMOTO N, NISHIJIMA T, and TANIGUCHI T (1998) Increases in levels of brain-derived neurotrophic factor mRNA and its promoters after transient forebrain ischemia in the rat brain. Neurochem Int 33: 201-207.

UCHIDA K, NAKAYAMA H, TATEYAMA S, and GOTO N (1992) Immunohistochemical analysis of constituents of senile plaques and cerebrovascular amyloid in aged dogs. J Vet Med Sci 54:1023-1029.

UHLENHUTH EH, BALTER MB, BAN TA, and YANG K (1998) International study of expert judgement on therapeutic use of benzodiazepines and other psychotherapeutic medications: V. Treatment strategies in panic disorder, 1992-1997. J Clin Psychopharm 18[suppl 2]:27S-31S.

VIRKKUNEN M, KALLIO E, RAWLINGS R, TOKOLA R, POLAND RE, and GUIDOTTI R (1994) Personality profiles and state aggressiveness in Finnish alcoholic, violent offenders, fire setters, and healthy volunteers. Arch Gen Psychiatry 51:28-33.

VIRKKUNNEN M, GOLDMAN D, NIELSEN DA, and LINNOILA M (1995) Low brain serotonin turnover rate (low CSF 5-HIAA) and impulsive violence. J Psychiatry Neurosci 20:271-275.

VOITH VL, and BORCHELT PL (1985) Separation anxiety in dogs. Comp Contin Educat Pract Vet 7(4):42-53.

WEINBERGER DR (1995) From neuropathology to neurodevelopment. The Lancet 346:552-557.

WU J, KRAMER GL, KRAM M, STECIUK M, CRAWFORD IL, and PETTY F (1999) Serotonin and learned helplessness: a regional study of 5-HT_{1A}, 5-HT_{2A} receptors and the serotonin transport site in rat brain. J Psychiatric Res 33:17-22.

YOUNG RC, NAMBUDIRI DE, JAIN H, DE ASIS JM, and ALEXOPOULOS GS (1999) Brain computed tomography in geriatric manic disorder. Biol Psychiatry 45:1063-1065.

Inquiries and reprint requests should be addressed to:

Dr. Karen L. Overall
Department of Clinical Studies
University of Pennsylvania
School of Veterinary Medicine
VHUP
3850 Spruce Street
Philadelphia, PA 19104-6010, USA

Appendix A: Necessary and Sufficient Criteria for Canine Conditions Discussed

Cognitive Dysfunction

Necessary and sufficient conditions: Change in interactive, elimination, or navigational behaviors, attendant with aging, that are explicitly not due to primary failure of any organ system.

Dominance Aggression

Necessary condition: abnormal, inappropriate, out-of-context aggression (threat, challenge, or attack) consistently exhibited by dogs towards people under any circumstance involving passive or active control of the dog's behavior or the dog's access to the behavior;

Sufficient condition: intensification of any aggressive response from the dog upon any passive or active correction or interruption of the dog's behavior or the dog's access to the behavior.

Noise Phobia

Necessary and sufficient conditions: Sudden and profound, non-graded, extreme response to noise, manifest as intense, active avoidance, escape, or anxiety behaviors associated with the activities of the sympathetic branch of the autonomic nervous system; behaviors can include catatonia or mania concomitant with decreased sensitivity to pain or social stimuli; repeated exposure results in an invariant pattern of response.

Obsessive-compulsive Disorder

Necessary condition: Repetitive, stereotypic motor, locomotory, grooming, ingestive, or hallucinogenic behaviors that occur out-of-context to their "normal" occurrence, or in a frequency or duration that is in excess of that required to accomplish the ostensible goal.

Sufficient condition: As above, in a manner that interferes with the animal's ability to otherwise function in his or her social environment.

Panic Disorder

Necessary condition: sufficient, profound, non-graded, extreme response exhibited out-of-context to the provocative environment, manifest as active avoidance, escape, or anxiety associated with the activities of the sympathetic branch of the autonomic nervous system

Sufficient condition: as above but includes mania or catatonia concomitant with decreased sensitivity to pain or social stimuli; once established repeated exposure results in an invariant pattern of response

Separation Anxiety

Necessary condition: Physical or behavioral signs of distress exhibited by the animal **only** in the

absence of, or lack of access to the client.

Sufficient condition: Consistent, intensive destruction, elimination, vocalization, or salivation exhibited **only** in the virtual or actual absence of the client; behaviors are most severe close to the separation, and many anxiety-related behaviors (autonomic hyperactivity, increased motor activity, and increased vigilance and scanning) may become apparent as the client exhibits behaviors associated with leaving.