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Epilepsy (13-Jul-2004)

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Introduction

Epilepsy is one of the most common neurological disorders in canines and felines. Epilepsy is an episodic illness caused by repeated excessive and hypersynchronous abnormal electrical activity of neurons in the brain. Epilepsy is more than convulsions. A broad variety of clinical phenomena may reflect epileptic seizure activity e.g., behavioural or gastrointestinal signs. Therefore, the recognition of epilepsy implies knowledge of the phenomenology representing different types of seizures. Observations of suspected seizure activity, seizure symptomatology reported by the owner and video documentation of seizures are essential when trying to establish a diagnosis of epilepsy. Electroencephalography, brain imaging and cerebrospinal fluid (CSF) examination among others, may disclose underlying pathological processes causing epilepsy. Animals with epilepsy are time consuming patients. A continued evaluation of the owners' compliance with given instructions concerning actual seizure frequency, antiepileptic treatment, measurement of antiepileptic drug levels, monitoring of potential adverse effects and additional owner counseling is required to manage these patients successfully.

History

The word epilepsy originates from the Greek word epilepsia meaning to be taken, seized or attacked. This condition has been recognized in Man since antiquity. The Greek physician and philosopher Hippokrates (460 - 377 B.C.) believed that the cause of epileptic seizures should be found in the brain. The Greek physician Galén (130 - 210 A.D.) viewed epileptic seizures as a symptom of intracranial dysfunction or systemic disease, caused by an accumulation of mucous in the arterial system. During the Middle Ages epilepsy was thought to be associated with supernatural forces, because of the vigorous symptomatology, especially of convulsions. Humans suffering from epilepsy have been thought to be insane, or possessed by demons in the 16th and 17th centuries. As a consequence, treatment of epilepsy included exorcism and bloodletting, and a variety of substances e.g,. brew of mistletoe, blood from a decapitated man and a pulverized cranium were given to aid the

sick person.

In the 19th century the gap between ignorance and understanding of epilepsy began to close. The physician Calmeil in 1824 made the first attempt to classify epileptic seizures according to their symptomatology. The neurologist John Hughlings Jackson proposed that a classification of epilepsy should be based upon anatomical localization, physiological imbalance and the pathological process [1]. He made a distinction between partial and generalized seizures based upon clinical observations. Electroencephalography (EEG), introduced in 1929 by the German psychiatrist Hans Berger, added immensely to the understanding of epileptogenesis [2].
The influence of human epileptology in veterinary medicine is hard to overlook. Much of what is reported on epilepsy in animals is based upon the study of seizures in Man. An early paper of canine epilepsy is found in "Archiv fur Wissenschaftliche und Praktische Tierheilkunde" [3]. The authors compare the symptomatology of epileptic seizures in Man and dog. The textbook "Die Nervekrankheiten unsere Hunde" [4] uses the terms genuine, essential or idiopathic epilepsy and symptomatic epilepsy as they were used in human epilepsy terminology at that time. In veterinary medicine - EEG was introduced as a laboratory test in the early sixties [5-7]. Terrell A Holliday has contributed greatly to the understanding of canine epilepsy by introducing and refining this investigation in veterinary epileptology [8-10]. However, EEG has never become a routine investigation in the diagnostic management of canine and feline epilepsy patients. Only a limited number of studies have been published on this subject [11-15].

Definition of Epilepsy
Epilepsy is defined as a condition characterized by recurrent seizures (two or more) - a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of a sudden and transitory abnormal phenomenon which may include alterations of consciousness, motor, sensory, autonomic or psychic events, perceived by the patient or an observer [16]. Thus, epileptic seizures are a sign of cerebral dysfunction. Three main characteristics of epileptic seizures are: the loss of control (in various degrees), the episodic (paroxystic) nature of the attacks (they start suddenly and they terminate suddenly), and the repetitive clinical pattern (attacks are identical from episode to episode).

Epidemiology
Epilepsy is the most common neurological disorder in canines. The prevalence of epilepsy in the canine population has been estimated to vary from 0.5% to 5.0% [17-20]. In cats the prevalence of epilepsy has been estimated at 0.5% [20].
No studies exist in a randomly selected cohort, however, of the lifetime prevalence in the general canine or feline population. Investigations of canine epilepsy are often carried out in hospital-referral based or otherwise pre-selected populations [13,21-23]. This is of no concern as long as descriptive studies are performed, i.e., studies focusing on description of seizures, treatment and prognosis of the population investigated [24]. However, when investigating the prevalence and clinical pattern (distribution of seizure types) of epilepsy, a study based upon random sampling is crucial in order to avoid selection bias. A prospective two-phase cross-sectional study of epilepsy, reporting a prevalence of 3.1%, has been conducted in Danish pedigree Labrador Retrievers, a reference population constituting 29,602 individuals [25].
A slight predilection for epilepsy in males has been documented in several studies [18,25-29]. The distribution of idiopathic epilepsy and symptomatic epilepsy has been reported to be 44% and 46% respectively in 50 dogs in an American study (10% experienced non-epileptic seizures) [28]. A Danish study reported a distribution of idiopathic epilepsy, symptomatic epilepsy and cryptogenic epilepsy of 25%, 16% and 45% respectively in a population of 63 dogs (14% could not be classified) [29].
Environmental conditions may provoke seizures in humans and animals suffering from epilepsy. Flashing lights, high sounds, sleep deprivation, stress etc., are known triggers of seizure activity in susceptible individuals.
No relationship between seasons, holidays, days of the week or astrology and seizure frequency has been demonstrated in dogs [23,27,28].

Epilepsy is not necessarily a life long condition. Epilepsy has the potential to be self-limiting. In humans, epilepsy is now regarded as a condition that, for the majority of patients will remit spontaneously or by drug induction [30,31]. The results of a study on Labrador Retrievers suggest that remission of epilepsy also occurs in dogs [25]. In a hospital based population, 30 - 40% of epileptic animals have been reported to achieve seizure freedom on antiepileptic treatment. Seizure reduction was obtained in about 50% [20]. In a study of 30 cats with seizure disorders outcome was documented on the basis of survival and seizure frequency at follow-up (3 - 21 month). In this study 17 cats had a good outcome: eleven seizure free and 6 with a low seizure frequency [32].
Epidemiological research on epilepsy is an excellent tool for studying the characteristics of epilepsy. It provides important information on the natural history of the condition, and thus is useful in the diagnostic and prognostic work with epileptic patients.

The lack of standardized definitions or a defined methodology especially with regard to patient selection bias, diagnostic accuracy and seizure classification in the veterinary literature makes it difficult to compare results among- studies. Different investigators have not used the same definitions of epilepsy and epileptic seizures, along with different case ascertainment methods and classification models, a phenomenon also known from epidemiological studies of epilepsy in humans [16,33,34].

Pathophysiology

The susceptibility for generating an epileptic seizure varies between individuals. Some may have a lower threshold for epileptic seizures and are therefore more likely to develop this condition. If provoked sufficiently any brain can elicit a seizure. Therefore, an animal may experience a single seizure as a sign of transient cerebral overload. Only if seizures become recurrent and are not provoked by systemic disease, is the animal diagnosed with epilepsy.

Seizure phenomenology varies from patient to patient and more than one seizure type can occur within the same patient. No relationship exists between the clinical signs expressed and the underlying etiology.

Irrespective of the fact that epilepsy can be caused by a variety of intracranial structural, cellular or molecular conditions and manifests itself in different ways, the epileptic seizure always reflect abnormal hypersynchronous electrical activity of neurons, caused by an imbalance between excitation and inhibition in the brain. The main representative of excitation in the brain is the excitatory postsynaptic potential (EPSP) whereas that of inhibition is the inhibitory postsynaptic potential (IPSP) [35]. The neuronal membrane potential is regulated by an accurate balance between EPSPs and IPSPs. If this balance is compromised, an epileptic seizure can be generated.

More than 100 neurotransmitters or neuromodulators have been shown to play a role in the process of neuronal excitation. Excitatory amino acids, especially L-glutamate, act at more than half the neuronal synapses in the brain, hereby playing a major role in the spread of seizure activity [36]. There is an increased release of glutamate in the brain associated with epileptic activity.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the CNS. GABAergic inhibition can be pre-synaptic (release of GABA from the GABAergic nerve terminal into presynaptic nerve terminals causing a reduction of neuro-transmitter release) or postsynaptic (caused by the interaction of GABA with specific postsynaptic receptors). GABA released from GABAergic nerve terminals binds to two distinct types of GABA receptors GABA-A and GABA-B receptors to produce neuronal inhibition [37] GABA is catabolized postsynaptically by GABA-transaminase. Dysfunction of the GABA-system can be caused by defects of synaptic GABA release, or of the postsynaptic GABA receptor. Low GABA and high glutamate values have been demonstrated in the cerebrospinal fluid of epileptic dogs [38].

Under normal conditions the excitatory post-synaptic potentials are followed immediately by GABAergic inhibition. Neuronal hypersynchronization occurs if excitatory mechanisms dominate, either initiated by increased excitation or decreased inhibition. As the abnormal neuronal hypersynchronous activity continues, more and more neurons will be activated (high frequency depolarization/repolarization), generating the epileptic seizure. The abnormal hypersynhcronization gives rise to the characteristic abnormalities that can be registered in the electroencephalogram. The physiologic basis of neuronal excitability has been reviewed in detail by March [39].The existence of excitatory connections between pyramidal neurons generating epileptic bursts throgh a positive-feedback mechanism in epileptogenic areas and the fact that neurons in some epilepsy prone regions, (e.g. the structures of the limbic system in the temporal lobe, especially the hippocampal CA3 region), possess the capability to generate "intrinsic bursts", dependent on voltage dependent calcium currents or persistent sodium currents has been identified as key features of epileptogenic circuits [174].

Sex hormones influence the regulation of GABAergic transmission in the CNS. Animal models have shown that the infusion of estrogens, lower the threshold for experimentally provoked seizures, and that this effect of estrogen is intensified if a cortical lesion is already present. Progesterone has been shown to possess an inhibitory effect on spontaneous and experimentally provoked seizures [40,41]. Progesterone probably works through a direct activation of the GABA complex to enhance the effect of GABA. Additionally, progesterone possesses the capability of inhibiting glutamatergic activity. The convulsant/anticonvulsant effects of estrogens and progesterones, respectively, are demonstrated in women with catamenial epilepsy (seizure clustering around the time of menses). There is an increase in seizure frequency, immediately preceding the menstrual period, which correlates to a decrease in progesterone level, and an additional increase in seizure frequency immediately preceding the time of ovulation, correlating with a high estrogen level with no simultaneous increase in progesterone. At the end of ovulation, simultaneously with an increase in the progesterone level, the seizure frequency decreases [42,43]. The relationship between sex hormones and epileptic seizures has not been investigated in natural occurring epilepsy in dogs and cats, but these mechanisms might exist in bitches/mares experiencing clusters of seizures associated with hormonal fluctuations.

Genetics
Epilepsy can occur in any canine and feline breed as well as in mixed breeds. A familial predisposition for epilepsy in dogs has been reported for many breeds, e.g., Beagle, Keeshound, Belgian Tervueren, Golden Retriever, Labrador Retriever, Vizla and Shetland sheepdog [15,18,21,22,25,26,44-46,163,164]. The hypothesis of a polygenic, recessive mode of inheritance has been suggested in the Bernese mountain dog and in Labrador Retrievers [21,47]. It has been suggested that a single locus with a large effect on the incidence of seizures may be segregation in the Belgian Tervueren dog [48]. In Vizslas an autosomal recessive trait has been suggested [164].

Classification of Epilepsy and Epileptic Seizures
Do We Need Classification? - "The Diagnosis of epilepsy is essentially clinical, based on a bonafide history of epileptic seizures. The clinical manifestation consists of a sudden and transitory abnormal phenomenon which may include alterations of consciousness, motor, sensory, autonomic or psychic events, perceived by the patient **or an observer**. Diagnosis should be confirmed by a health professional with expertise in epilepsy, using available medical history, seizure description, and neurological examination. If available, EEG records and other diagnostic tools should also be used, but lack of these instruments should not preclude the diagnosis of epilepsy [16]". As stated by the commission, the clinical signs of epileptic seizures represent the most important criteria for establishing a diagnosis of epilepsy. Not only in veterinary medicine do we deal with the problem that we are dependent on an observer (the pet owner) when identifying signs of seizure activity. A substantial number of human patients as well are not able to recall what happened during a seizure.
Classification based upon seizure phenomenology does more than just serve the purpose of standardizing terminology and thereby making the comparability of data and collaborative research possible. Classifying clinical signs also ensures that many important diagnostic and prognostic clues otherwise lost, will be identified.
Since antiquity, the attempt to classify symptoms has been intended to identify a specific disease, or syndrome. The first known mention of epilepsy is at about 500 - 700 B.C. Stone tablets found in Babylon contain detailed observations of epileptic seizure types, provoking factors and postictal symptoms [49].

Veterinary epilepsy nomenclature has borrowed extensively from its human counterpart, but unfortunately has not actually agreed to standardize terminology. As a consequence, the literature on this subject is often confusing with regard to definitions and interpretations. Classification of epilepsy and epileptic seizures in humans has been established by The Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) [50,51]. The classification is based upon localisation of the seizure focus, the degree of alteration of consciousness, and possible abnormalities recorded in the EEG. Classification of epileptic seizures in dogs, based upon the guidelines of the ILAE, with an emphasis on seizure phenomenology, has been advocated by Schwartz-Porsche and by Berendt and Gram and Licht and co-workers [20,29,165].

Classification of Epilepsy
The classification of epilepsy is based upon the underlying etiology. Classification of the epilepsies deals with three categories, *idiopathic epilepsy, symptomatic epilepsy and cryptogenic epilepsy*.
The term *idiopathic epilepsy* refers to epilepsy of unknown cause (there is no structural cerebral pathology), with a possible familial predisposition. Idiopathic epilepsy is encountered predominantly as primary generalized seizures. However, idiopathic (benign) partial epilepsies of childhood (epilepsy with partial seizures, absence of clinical or neuroimaging evidence of brain damage, characteristic interictal EEG focal sharp waves with variable location, a possible family history of idiopathic epilepsy, onset of seizures between 18 months and 13 years and spontaneous remission of epilepsy during childhood or adolescence) are well described in children and account for about 10 - 15% of epilepsy cases in this age group [52]. Among those is rolandic epilepsy (centrotemporal or midtemporal sharp waves) and epilepsy with frontal or occipital EEG changes [51,52]. Recently, a number of new idiopathic partial epilepsy syndromes with simple inheritance have been described in humans (e.g., familial partial (temporal lobe) epilepsy) [53]. Familial frontal lobe idiopathic epilepsy has been described in the Shetland Sheepdog [15]. In these dogs, the course of the disease was not benign. A substantial number of cases progressed to status epilepticus. Animals suffering from idiopathic epilepsy will interictally appear normal clinically and neurologically.
Symptomatic epilepsy is defined as epilepsy caused by a known/identified disorder of the CNS (focal structural cerebral pathology is disclosed) and presenting as partial seizures with or without secondary generalization. Neuropathology causing symptomatic epilepsy can be gross lesions resulting from congenital or active CNS disease, e.g., congenital malformations, storage disease, inflammatory/infectious disease, space occupying lesions, scar tissue and hemorrhage or minor pathologies such as hippocampal sclerosis, and microstructural changes of the cortex cerebri e.g., cortical neuronal loss and focal

neuronal migration disorders [54-62,175-179]. Cerebral neuronal migration disorders e.g., heterotopias or dysplasias (the majority giving rise to no other neurological signs than seizures) have been shown to represent the underlying etiology of a substantial number of partial epilepsies in humans [63-67]. Heterotopic cell clusters have also been shown to appear in the epileptic dog [68]. Degenerative lesions of the CNS e.g., hippocampus, the piriform lobe, motor cortex, frontal cortex and cingulated cortex and cerebellum have been described, post-mortem, in cats and dogs with epilepsy [15,69-71]. Reversible magnetic resonance imaging (MRI) lesions of the temporal lobe have been demonstrated in humans and in dogs following seizures [72].
The term *Cryptogenic epilepsy* (i.e., of hidden origin) is used as a designation for epilepsy with a suspected symptomatic cause which, however, remains obscure. As in symptomatic epilepsy, cryptogenic epilepsy is characterized by partial seizures. Animals suffering from symptomatic or cryptogenic epilepsy may or may not exhibit focal abnormalities interictally.
In the veterinary literature it is common to refer to epilepsy as "idiopathic epilepsy". According to the suggested classification, the term idiopathic should be reserved for those cases of epilepsy, predominantly presenting with primary generalized seizures, and in which a symptomatic origin is neither detected nor suspected [166].

Classification of Epileptic Seizures
The clinical manifestation of an epileptic seizure reflects the field of activity in the brain areas generating the seizure and the amount and distribution of abnormal electrical activity. Epileptic seizures can be expressed as motor signs, sensory sensations, psychic experiences or autonomic disturbances [50]. Consciousness may be unimpaired, impaired or totally lost. More than one dysfunction may be present and often the clinical signs will progress within the single seizure.
The distinguishing characteristic of epilepsy is a consistent seizure phenomenology reflecting abnormal function of the entire brain or of specific (focal) cerebral areas involved in the epileptic activity. Thus the major characteristic of epilepsy is a phenomenology that occurs repeatedly in an identical manner, every time the individual animal experiences a seizure.
Epileptic seizures are divided into two main categories: Primary *generalized seizures* and *partial seizures*. *Partial* seizures are subdivided into *simple* and *complex partial seizures*. Partial seizures can spread to become *partial seizures with secondary generalization*. Regardless of the kind of seizures the animal experiences, the ictal event is brief (few seconds to few minutes). Interactions between thalamic nuclei and the neocortex working through thalamocortical and corticothalamic projections are involved in the generation of primary and secondary generalized seizures.

Primary Generalized Seizures - Primary generalized seizures are those in which the first clinical changes indicate initial involvement of both cerebral hemispheres (Fig. 1). This is reflected in the ictal EEG by a sudden and simultaneous loss of the normal electroencephalographic background activity in both hemispheres, being replaced by epileptiform discharges, representing hypersynchronous neuronal activity. There is a sudden loss of consciousness combined with a sudden onset of convulsions, without any premonitory symptoms. In the ILAE classification, primary generalized seizures are subdivided into convulsive and non-convulsive seizures and include clonic, tonic, tonic-clonic convulsions, myoclonic and atonic seizures and, in humans, absences expressed solely as repeated episodes of a few seconds' duration with impaired consciousness [50]. Absences have not been documented in dogs or cats.

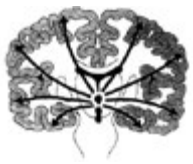

Figure 1. The abnormal impulses originate from centrencephalon and the cerebral cortex. From: Gram L and Dam M. Tæt pà epilepsi. Munksgaard, København, 1993. Illustrator: Lotte Clevin (with permission). - To view this image in full size go to the IVIS website at www.ivis.org . -

In the past, convulsions and absences have been referred to as "grand mal" and "petit mal" respectively. This terminology is no longer used in human epileptology and should not be used in veterinary medicine, since it is non-informative.

Partial Seizures
Partial seizures originate from groups of neurons localized in a specific area of the cerebral cortex (the epileptic focus) and the clinical signs reflect the functions of the area involved (Fig. 2). EEG changes indicate initial activation of neuronal networks of the area in question.

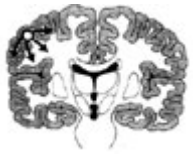

Figure 2. The abnormal impulses originate from a specific area of the cerebral cortex and do not spread. From: Gram L and Dam M. Tæt på epilepsi. Munksgaard, København, 1993. Illustrator: Lotte Clevin (with permission). - To view this image in full size go to the IVIS website at www.ivis.org . -

Simple and Complex Partial Seizures - In humans partial seizures are classified as simple if consciousness is unimpaired, and complex if consciousness is impaired. Consciousness refers to "the degree of awareness and/or responsiveness of the patient to externally applied stimuli. Responsiveness refers to the ability of the patient to carry out simple commands or willed movement and awareness refers to the patient's contact with events during the period in question and its' recall" [50].

The term aura should be used as the synonym for a simple partial seizure. In humans, by tradition, the term aura has been used to denote the symptomatology of the simple partial seizure acting as a signal/warning sign of a forthcoming seizure development into either a complex partial seizure or into secondary generalization (convulsions). In the past, signs described as aura have, in a substantial number of cases of epilepsy described in the veterinary literature, not been recognized as a part of the ictus (namely the partial onset in a partial seizure with secondary generalization), or as the ictus itself (as in partial seizures alone), but have been believed to represent a preictal event. As a consequence, these epileptic seizures have erroneously been classified as primary generalized seizures (the type of seizures predominantly characterizing idiopathic epilepsy).
In animals, signs of confusion or difficulties in recognizing the owner may be interpreted as signs of impaired consciousness. Recognizing diminished consciousness, in dogs and cats, however, can be difficult, and the patients cannot report what they are actually experiencing during a seizure. Whether it is possible from the clinical signs alone (as described by the owner and/or documented by video) - without EEG registration - to discriminate between simple and complex partial seizures in animals, is debatable.
In older terminology, complex partial seizures have been referred to as limbic seizures, psychomotor seizures and temporal lobe seizures.

Partial Seizures with Secondary Generalization - Partial seizures with secondary generalization appear to be the seizure type most commonly observed in dogs [9,23,25,28,29,165]. This is also true in the population of human adults suffering from epilepsy [73].
Secondary generalization of a partial seizure occurs when the seizure activity does not remain focal, but projects rapidly to subcortical structures (mainly thalamic nuclei) to involve other areas of the brain or the entire brain (Fig. 3).

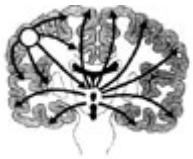

Figure 3. Partial seizure with secondary generalization. From: Gram L and Dam M. Tæt på epilepsi. Munksgaard, København, 1993. Illustrator: Lotte Clevin (with permission). - To view this image in full size go to the IVIS website at www.ivis.org . -

In partial seizures with secondary generalization, the clinical signs are initially characterized by the function of the anatomical site of the seizure focus, rapidly (within seconds to minutes) followed by loss of consciousness and convulsions as seizure activity spreads from the focus to involve the entire brain. In many patients, the onset of the partial seizure is very subtle and is followed by rapid secondary generalization, which can make it difficult to detect the partial onset. Therefore pet owners may not report the signs of a partial seizure onset unless questioned specifically about events preceding convulsions. Partial seizures with secondarily generalised tonic-clonic seizures with the animal retaining consciousness may occur in a very limited number of individuals. This has been described in humans [74].

Clinical Signs in Partial Seizures - The partial seizure itself may appear as motor signs, autonomic signs or paroxysms of behavioral signs (involving the limbic system). Localized motor activity e.g., tonic seizures of one leg or facial twitching and autonomic signs such as pupil dilatation, salivation or vomiting are fairly easy to recognize in dogs and cats whereas abnormal behavior as a sign of epilepsy represent a diagnostic (and differential diagnostic) challenge [75]. In humans, symptoms originating from the somatosensory or special sensory cortex may present, for example, as "pins and needles" sensations, numbness or visual, auditory or olfactory hallucinations/sensations (e.g., flashing light, crude auditory sensations and unpleasant odors). Psychic symptoms (most commonly occurring with impairment of consciousness: complex partial

seizures) may present as e.g., structured hallucinations, depression or rage. The most common symptoms are intense fear or terror, which may lead to running away [76]. Even though we can only hypothesize that a distortion of perception appears in animals, it seems reasonable to believe that it may be such events that give rise to the signs reported as aura, complex partial seizures, psycomotor seizures, temporal lobe seizures or even preictal phase [13,23,29,77-81]. Paroxysms of behavioral signs associated with epilepsy are frequently interpreted as anxiety or fear. The fact that these signs, in the majority of cases, are followed by convulsions is strong evidence that they represent partial seizure activity followed by secondary generalization. They should therefore **not** be regarded as preictal events.
A variety of signs of partial seizures have been reported in humans and in dogs [9,29,76,79-85].

Prodromes - A prodrome is a long-term indication of a forthcoming seizure. Prodromes are long-lasting (hours or days) changes of disposition in humans in the form of anxiety, irritability, withdrawal and other emotional aberrations. In dogs, the most common prodromal signs described are restlessness [29]. Owners of such dogs recognize that a seizure is about to occur within hours or days. In canine patients, up to 11% have been reported to suffer from prodromes lasting from 30 minutes to 24 hours [29]. The nature and origin of prodromes are very poorly understood.
The clinical signs of aura (the partial seizure onset of a partial seizure with secondary generalization) in animals should not be confused with the signs of prodromes, since prodromes by definition are long-lasting (hours to days) events, whereas the time frame in which the aura acts consists of a few seconds to a few minutes. When asking pet owners about prodromal signs, one should very carefully explain to the owner that the signs in question are long-lasting as opposed to signs of partial seizures (which may be followed intoimmediatelly by convulsions (secondary generalization).
Prodromes are considered preictal events, not related to abnormal electrical activity in the EEG. It may be, however, that prodromes actually represent prolonged auras (aura continua) or non-convulsive (partial) status epilepticus. In recent years it has been possible to document EEG related ictal partial seizure activity in a number of patients experiencing prodromes (Alving J. Personal communication. Chief Neurologist, Dianalund Epilepsy Hospital, Denmark, 2002.) EEG evidence of non-convulsive status has also been documented in dogs [14].

Postictal Signs - The epileptic seizure may or may not be followed by a period of abnormal behavior caused by cerebral exhaustion. During this period, the post ictal phase, the animal may appear bewildered, disturbed, ataxic, tired, hungry/thirsty, blind or aggressive. The postictal phase may last from seconds to hours or even days. One should be aware that in many cases the pet owner does not distinguish ictal signs from postictal signs. As a consequence he/she may report that seizures last for a longer period of time than the few minutes' duration of the average epileptic seizure.

Classification of Epilepsy - Future Perspectives - In recent years a revision of the ILAE classification system from 1981 and 1989 has been discussed [50,51]. A semiological seizure classification based exclusively on ictal semiology, either as reported by the patient, by an observer or as analyzed directly by video monitoring has been proposed [86,87]. In this classification system, EEG or other test results do not influence the classification. A new ILAE classification will include more criteria for classification than descriptive terminology for ictal phenomena, e.g., classification of seizures based upon known or presumed pathophysiological and anatomic substrates [88].
It is of great interest for veterinary neurology to follow the development of a revised human epilepsy classification closely. This data can be of value for future endeavors to expand the classification of canine and feline epilepsy.

Diagnostic Evaluation
Differential Diagnosis - The diagnoses of epilepsy in canines and felines are essentially clinical, based upon the owners' observations of seizure activity and seizure phenomenology, video documentation of seizures and diagnostic work-up aimed at distinguishing epileptic seizures from non-epileptic episodes mimicking epilepsy [13,20,23,29,89-92,165].
One should be aware that when pet owners use terms such as epilepsy, seizures, fits, attacks or convulsions they may indicate various clinical phenomena not at all associated with these terms. It is therefore crucial to investigate closely what kind of event the pet owner actually has witnessed.
The primary question, when presented with a canine or feline patient experiencing episodes leading to a suspicion of epilepsy, is whether these are of epileptic nature or not. Many systemic disorders of organic, metabolic, endocrine, toxic or behavioural origin can appear clinically as imitators of epilepsy. However, these diseases will normally be detected provided a thorough diagnostic work-up is done.
Special interest should be given to a number of paroxysmal disorders, which may easily be confused with epilepsy. Among those, narcolepsy, cataplexy and syncope may represent a diagnostic problem as they involve signs that are very common in epilepsy.
Narcolepsy is characterized by disturbance of consciousness accompanied by sudden falling (atonia). The duration of sleep is usually short (a few minutes to 20 minutes). Cataplexy is a short, sudden reduction or loss of muscle tone. Signs may vary

from weakness or head drop to sudden fall to the ground. Attacks last from seconds to a few minutes. Consciousness is fully retained during the episodes. Syncope is an episodic interruption of consciousness due to a diminished blood flow to the brain (the animal "faints"). The causes of syncope may vary greatly, but the clinical signs are rather uniform. The temporary complete arrest of cerebral perfusion causes the animal to collapse and pupils to dilate, followed by convulsive movements. Most commonly, these movements differ from tonic-clonic convulsions by only taking the form of tonic extension of the trunk, clenching of the jaw, or mild clonic jerks of the limbs or trunk and twitching of the face.
Among the most common are vasovagal syncopes (provoked by conditions which favour peripheral vasodilatation such as excitement, fear or pain), cardiac syncopes (often caused by a sudden reduction in cardiac output due to dysrythmia) and tussive syncopes (caused by respiratory conditions e.g., laryngitis or chronic bronchitis, where an increase in intrathoracic pressure interferes with the venous return to the heart).

Diagnostic Work-up - When working with suspected epilepsy patients, the initial clinical work-up should, as a minimum, include a detailed description of the events witnessed by the pet owner, a full physical and neurological examination, hematology and serum biochemistry, urine analysis and survey radiographs of the thorax and the abdomen (to exclude primary neoplasms with the potential to metastazise to the brain). In some cases the diagnosis of epilepsy can be excluded based upon the history or the laboratory test results alone. If no extra cranial causes can be identified, the diagnosis of epilepsy is highly possible.
The next question to ask is what kind of seizures the patient does experience (classification). This is best investigated by analysing seizure episodes and seizure phenomenology. A standardized questionnaire should be used when collecting and recording detailed information on the events reported by the pet owner [75]. The questionnaire should be given orally. The patient history should focus on the previous medical history, including clues of a possible birth trauma and information regarding earlier occurrence of head trauma or febrile disorders affecting the brain. The history should also include age at first seizure, seizure frequency, and a detailed description of seizure development and seizure phenomenology. Since veterinarians, are dependent on second hand information, it is crucial to secure an accurate and detailed report from the owner. The subjective nature of the owner's interpretation is minimized by the use of a standardized questionnaire focussing on ictal events. The questionnaire ensures that details that might otherwise be missed are recorded and help to distinguish ictal from postical events. If the episodes witnessed by the pet owner include convulsions, in the majority of cases the owner will naturally focus on this very dramatic event. However, if questioned thoroughly regarding circumstances preceding convulsions, the owner may describe signs identifying the seizure as partial with secondary generalization.
Since veterinarians rarely have the opportunity to observe seizures in the canine and feline epilepsy patient, home video or video recording during hospitalisation, represent an excellent supplement to the descriptions of seizures given by the owners.
"EEG records and other diagnostic tools should also be used, if available, but lack of these instruments should not preclude the diagnosis of epilepsy. EEG contributes, but does not always confirm a diagnosis of epilepsy: An abnormal EEG must not be considered as a requisite for inclusion since it could be normal (or indicate non-specific abnormalities) in epileptic subjects" [16]. The source of the EEG is electrical potentials generated by cortical neurons. If EEG registration takes place sufficiently close to the populations of abnormal firing neurons, they will produce characteristic pathological changes in the EEG. The disadvantage of surface EEG registration is that only activity from surface areas that are anatomically accessible are recorded. Therefore, an abnormal electroencephalogram can support the diagnosis of epilepsy whereas a normal electroencephalogram does not exclude this diagnosis. EEG is helpful in discriminating between partial and generalized epileptic discharges. Also the EEG may identify a suspected seizure focus [8,10,14,15,180] . Intracranial EEG (electrodes implanted on the dura mater) has proved effective in detecting the epileptic focus in a Shetland Sheepdog [167].

To answer the question of the possible cause of seizures, the following diagnostic methods can be chosen with the specific aim of uncovering seizure etiology: CNS pathology pointing towards a diagnosis of symptomatic/cryptogenic epilepsy may be disclosed by neurological deficits detected at the neurological examination. When dealing with partial seizures (with or without secondary generalization) one should always consider the possibility of identifying cerebral pathology. In the diagnostic work-up of human epilepsy patients, prolonged video-EEG studies and imaging of the brain (CT/MRI) have become a routine investigation in patients with clinical evidence of a partial seizure onset (suspected symptomatic/cryptogenic epilepsy). Computed tomography (CT) and magnetic resonance imaging (MRI) has proven very helpful in the diagnostic management of epilepsy in animals [58,59,72,168].
Cerebrospinal fluid examination should be examined in cases pointing to an active cerebral disorder since CNS pathology may be reflected in the cerebrospinal fluid [57,168].

Diagnostic Work-up in Patients Suspected of Epilepsy - Protocol
- Detailed history (including previous medical history) - Detailed description of events experienced (questionnaire) + home video - Clinical examination • Assess cardiovascular function (if abnormal findings order EKG and ultrasound) • Assess respiratory system (if abnormal findings order endocoscopy) - Hematology and serum biochemistry - Urine analysis - Survey radiographs of thorax and abdomen - Neurological examination • If neurological signs localized to the brain: CSF, brain scan - EEG **Disorders causing signs commonly confused with epilepsy** - Cardiovascular disorders (including syncope) - Respiratory disorders (laryngeal/tracheal/bronchial dysfunction), including syncope - Narcolepsy - Cataplexy - Anemia - Organic disease (e.g., hepatic/renal dysfunction) - Hyperthyroidism (cat) - Hypoglycemia (e.g., insulinoma) - Electrolyte unbalances - Neuromuscular disease (e.g., myasthenia gravis) - Intoxication - Abnormal behavior

Signs of Prodromes
Any warnings of forthcomming seizures i.e., long-lasting changes (30 minutes - several days) in behaviour before seizures emerge

Ictal events (short <2 - 3 minutes episodes)
Duration of signs

Signs of Primary Generalized Seizures
Does the animal experience convulsions
Is consciousness lost from the onset of the seizure
Are convulsions present from the onset of seizure
Are convulsions tonic, clonic or initially tonic followed by a clonic phase
Does the animal experience atonic episodes

Signs of Partial Seizures
Episodic localised motor signs

Paroxysms of behavioural signs: Short (<2 - 3 minutes) stereotyped episodes of change in the dogs behaviour e.g., restlessness, anxiety, attention seeking, hyperactivity, "hallucinations" such as catching or watching imaginary objects, unprovoked aggression, signs of fear, manic behaviour, abnormal vocalising.
Episodic autonomic signs e.g., salivation, vomiting, pupillary dilatation

Partial Seizures with or without Secondary Generalization
If any signs of partial seizure activity - do these signs occur isolated or are they followed by convulsions
Duration of signs

Postictal Signs
Duration of the postictal phase
Description of behaviour during the postictal phase (does the dog appear e.g., disoriented, "blind", hyperactive, exhausted or aggressive)

Long-term Therapy of Epilepsy
General Therapeutic Considerations - The overall consideration is if or when to start therapy in patients with epilepsy. It is commonly stated that early treatment of epileptic seizures significantly increases the success rate with respect to seizure control - an assumption "borrowed" from human medicine. In humans, this assumption has now been contradicted by the results of large population-based cohort surveys, showing that long term outcome is not influenced negatively by the number of seizures experienced prior to institution of treatment [93,94].
The decision of when to start antiepileptic treatment depends on a wide range of factors. Patients that are especially at risk of developing new seizures, e.g., patients with status epilepticus as the first indication of epilepsy or animals with symptomatic epilepsy caused by active CNS disease, should be treated early. In animals experiencing cluster seizures and prolonged seizures, early treatment is also recommendable due to the increased risk of neuronal damage. The pet owners' attitude toward treatment and the question of owner compliance must be taken into consideration. Some owners will tolerate a limited number of seizures a year, while others will accept nothing less than seizure freedom. Some owners may find it hard to accept that epilepsy treatment involves long-term, maybe life-long, treatment and as a consequence may even consider euthanasia as an alternative to treatment. Finally, when antiepileptic treatment is first instituted, the disadvantages of the potential adverse effects of the antiepileptic drug(s) must be counterbalanced against the goal of obtaining seizure freedom.

Antiepileptic Drugs - Ideally, the antiepileptic drug for long-term treatment has a long elimination half-life (needs only dosing once or twice a day), is well tolerated, possesses no adverse effects and is inexpensive. To date, no anticonvulsants have proven to fulfill all these criteria.
Several attempts have been made to apply the broad variety of human antiepileptic drugs in animals. In people, the new anticonvulsants licensed for use as monotherapy or polytherapy are generally well tolerated [95]. It is therefore tempting to assume that they would be effective in canines and felines also. These drugs include carbamazepine, oxacarpazepine, valproic acid, gabapentin, feldbamate, vigabatrin and nimodipine among others. Their pharmacokinetic properties particularly the elimination half-life, toxicity, adverse effects, and to some extend the cost of a potential treatment [96-103] make them generally not applicable in animals. This section shall therefore address only phenobarbital, potassium bromide, primidone, phenytoin and benzodiazepines.

Phenobarbital - Although an "old" drug in veterinary medicine, phenobarbital still holds the position as a first drug of choice. This is a safe anticonvulsant with a high efficacy and a long elimination half-life (dogs: 42 - 89 hours, Beagle 32 +/- 4.6 hours. Cats: 34 - 43 hours), that is generally well tolerated by dogs and cats [104-107].
Several antiepileptic drugs, including barbiturates and benzodiazepines, enhance GABA action at its primary site, the GABA-benzodiazepine chloride-channel complex [108]. Phenobarbital thereby inhibits spreading of seizure activity and elevates seizure treshold.
Phenobarbital is lipid soluble, easily absorbed (maximal plasma concentrations are reached 4 - 8 hours after oral administration) and crosses biological membranes readily. Pharmacokinetic studies have found a bioavailability of 86 - 96% [105]. Protein binding is about 45% [109]. Phenobarbital is for the most part metabolized in the liver. Approximately one third is excreted unchanged renally [96]. The drug possesses strong liver enzyme inducing properties. Elevated liver enzymes, due to enzyme induction, are therefore to be expected [110]. In phenobarbital- treated patients the only reliable measurement of hepatic status is a liver function test (bile acids monitored fasting and postprandial).
Adverse effects include sedation, ataxia, polyphagia, polydypsia, incontinence and hyperactivity. Most animals will develop tolerance to the medication causing the unwanted side effects to disappear within the first weeks of treatment. Hyperactivity is mostly associated with low serum phenobarbital values and can in many cases be eliminated by increasing the drug dosage. The recommended oral dosage of phenobarbital in dogs and cats is 3 - 5 mg/kg/day (one daily dosage or divided and administered twice a day). The ability to metabolize phenobarbital varies greatly between individuals, and the given drug dosage shall, therefore, never be taken as an expression of the effectiveness of the drug [111]. Instead, serum concentration of phenobarbital must be measured, and the drug dosage must be adjusted according to the actual amount of drug in the serum and clinical observations of seizure frequency. Because of the long half-life, it takes about two weeks for steady state to occur

(the time when phenobarbital can first be monitored). Timing of blood collection is not important. It has been shown that there is no therapeutically relevant change in serum phenobarbital concentrations throughout a daily dosing interval [112]. The therapeutic serum concentration (the level within which the drug is expected to be therapeutically active and where toxicity should not be expected) is 15 - 45 µg/ml/65 - 150 µmol/l [113]. Confusingly enough, patients might be seizure free despite serum values ranging beneath the lower therapeutic serum concentration. In this case, the dosage of phenobarbital should only be adjusted if seizure freedom is lost. The serum phenobarbital concentration should always be measured if seizures reoccur (in patients that have achieved seizure freedom), if a known constant (low) seizure frequency suddenly begins to increase and whenever drug dosages are changed.
If using polytherapy with phenobarbital and potassium bromide, the phenobarbital dosage can in some cases successfully be decreased when potassium bromide has reached steady state.

Bromide (potassium bromide/sodium bromide) - Bromide, the first human anticonvulsant (introduced around 1850), was reintroduced for the treatment of refractory epilepsy in children in the nineteen-eighties, and has been used as an add-on drug in refractory canine epilepsy for the last two decades [114]. Most data on bromide in veterinary medicine has been on potassium bromide. The only indication for using sodium bromide is in patients with compromised renal function or adrenal insufficiency. About 25% of phenobarbital resistant canine epilepsy patients become seizure free on polytherapy with phenobarbital and bromide [115,116]. Bromide can also be used as a first drug of choice, e.g., in patients with hepatic dysfunction. There is only limited knowledge (data) of bromide (and its potential adverse effects) in cats. It is therefore recommended that this drug, until further data on cats are available, be used only in the treatment of canine epilepsy [169]. The anticonvulsant action of bromide is not really known. The drug is believed to act through hyperpolarization of postsynaptic membranes [117]. Bromide salts (potassium bromide/sodium bromide) are rapidly absorbed after oral administration. They are unbound to plasma proteins and can therefore diffuse freely across membranes. Bromide has a very long elimination half-life (about 28 days). Steady state will therefore occur about four months after therapy has been instituted. Excretion occurs through the kidneys and is dependent on concomitant chloride intake. Attention should therefore be given to the dietary influence of the excretion of bromides. A high dietary chloride content shortens the elimination half-life causing decreased therapetic serum bromide concentrations and thereby loss of therapeutic efficacy [118].
The recommended oral dosage for bromide is 20 - 40 (60) mg/kg /day (one daily dosage). The therapeutic range of bromide in dogs is 100 - 200 mg/dl when potassium bromide is used as an add-on drug and 250 - 300 mg/dl when used as monotherapy [102].
Mild adverse effects are similar to the ones described for phenobarbital. Signs of bromide toxicosis include ataxia, depression, stupor, anisocoria, muscle pain, dermatological signs such as rash and nodular pustular skin lesions, and gastrointestinal signs such as anorexia, vomiting and constipation [119,120].

Primidone - Primidone is oxidized to phenylethylmalonic acid (PEMA) and phenobarbital. More than 85% of the anticonvulsant effect can be attributed to phenobarbital [104]. The drug is well tolerated by both dogs and cats [121]. Hepatotoxicity has occurred in dogs after long-term treatment with primidone [122,123]. Primidone is also a more expensive drug than phenobarbital. Phenobarbital should therefore be preferred to primidone.

Phenytoin (diphenylhydantoin) - Phenytoin is a potent and effective anticonvulsant. Due to its pharmacokinetics, however, this drug is not a useful drug in dogs and cats [124]. In dogs, the lack of efficacy arises mainly from problems to maintain effective plasmaconcentrations despite of multiple daily dosing [96]. A slow release formula may solve this problem in the future. It is important to know that in cats the drug is eliminated very slowly. As a result, there is an increased risk of accumulation of the drug to toxic levels even at low dosages [125]. Phenytoin may be used for status epilepticus in dogs (2.0 - 5.0 mg/kg given as a slow IV injection).

Benzodiazepines - Benzodiazepines, although excellent anticonvulsants, has no use in long-term treatment of canine epilepsy, due to a short elimination half-life and a rapid (5 - 7 days) development of tolerance to their anticonvulsant effect. In the past, diazepam has been used as a first drug of choice in cats. Severe hepatotoxicity has, however, been associated with this drug in cats, thereby making long-term treatment with diazepam controversial in this species [126]. Thus the primary indication for benzodiazepines is in the management of acute epileptic seizures and status epilepticus. Benzodiazepines are further discussed in the section on Status Epilepticus.

In conclusion, when taking the pros and the cons of the above drugs into consideration, we are mainly left with only two drugs for long-term treatment of dogs, namely phenobarbital and bromide and one for cats, namely phenobarbital.

Complications Associated with Long-term Phenobarbital (primidone) and Potassium Bromide Treatment - Both phenobarbital and primidone can cause hepatotoxicity [113,122,123]. Chronic phenobarbital therapy has the potential to influence thyroxine and thyroid-stimulating hormone. Phenobarbital has been shown to decrease the concentration of T4 without causing clinical signs of hypothyroidism - TSH tests responses were normal [127,128]. Other studies have shown decreased T4 values and increased TSH values without clinical evidence of hypothyroidism associated with phenobarbital therapy [110,129]. Potassium bromide does not seem to influence thyroid function [170]. In the study of Gieger and co-workers serum ALP, ALT, cholesterol, serum albumin and GGT were also monitored. No changes were found for serum albumin and GGT whereas ALP, ALT and cholesterol values were significantly increased. Chauvet and co-workers [130] found that ALP and ALT values increased whereas serum albumin and cholesterol decreased over time [130]. In another study of effects of phenobarbital on serum biochemical tests in dogs it was concluded that phenobarbital causes variable increases in ALP, while bilirubin, cholesterol, albumin and TP concentrations remained normal [131]. A rise in liver enzymes associated with phenobarbital administration has also been demonstrated by other authors [181]. Hojo and co-workers report that long term treatment with phenobarbital significantly induced hepatic CYPs and plasma AGP (hepatic cytochrome P450 and alpha 1-acid glucoprotein) in dogs [171].
Neutropenia and thrombocytopenia can occur with phenobarbital and primidone treatment. A drug-induced agranulocytosis of an immunologic origin (as suggested in humans) may be the underlying cause of the damage to the hematopoiesis, but the precise mechanism is not known [132].
An increased risk for epilepsy patients of developing fatal acute pancreatitis has been shown in a case control study of 70 dogs [133]. The risk of developing pancreatitis is higher in dogs receiving polytherapy with phenobarbital and potassium bromide than in dogs receiving phenobarbital as monotherapy [134]. Superficial necrolytic dermatitis has been reported in dogs receiving long-term phenobarbital administration [182].

Therapeutic Failure - Therapeutic failure may occur because therapy is initially not successful; therapy is successful initially but then becomes less effective or ineffective; or because therapy is only partly successful (seizure frequency and/or seizure severity is reduced but seizure freedom is not achieved).
Common reasons for therapeutic failure

- Dealing with a potentially "difficult" patient (cluster seizures, prolonged seizures).
  Incorrect diagnosis (it is not epilepsy)
- Incorrect choice of antiepileptic drug
- Incorrect dosage of the antiepileptic drug
- Failure to monitor drug levels
- Owner non-compliance
- Presence of epilepsy plus newly developed systemic disease (liver/kidney)
- Patient has gained weight (drug dosage needs to be adjusted)
- The animal has developed a tolerance to the drug (phenobarbital/benzodiazepines)
- Monotherapy is insufficient

Withdrawal of Antiepileptic Drugs - Withdrawing antiepileptic drugs may be considered, if an animal has been seizure free for more that one year.
In humans, epilepsy in remission due to treatment (drug induced remission) is defined as "a prevalent case of epilepsy with no seizures for $\geq$ 5 years and receiving antiepileptic drugs at the time of ascertainment" [16]. Withdrawal of antiepileptic drugs may be considered in human adults who have been seizure free with medication for 5 years. Due to the shorter lifetime of dogs and cats, a time frame of one year of seizure freedom seems reasonable [25]. When considering withdrawal of anticonvulsant medication one must gradually decrease the drug dosage over a longer period of time. A period of 6 - 12 months has been recommended [20].
Before making this choice the potential risk for seizure reoccurrence should be balanced against the advantage of decreasing the risk of the long-term adverse effects that may be experienced with antiepileptic drugs.

Instructions to the Owners - Dogs with epilepsy are very time consuming patients due to the need for close patient monitoring. When dealing with medical treatment of epilepsy it is critical that the owner is instructed very carefully. Patients should be reevaluated yearly and more frequently (+ additional telephone contact 2 - 3 times a year) if seizure frequency increases, if seizure freedom is lost, if signs of systemic disease appear or whenever the owner needs advice.
The owner should be instructed to keep a seizure diary (seizure calendar) to bring along to re-examinations as this insures that important information regarding seizure frequency is not lost. The veterinarian should remember to record dates for prescriptions of drugs and to record the amounts of medicine prescribed.

It is crucial to give the owner a realistic idea of what to expect in terms of side effects and therapeutic success. The owner may thus respond more positively to the question of a possible lifelong antiepileptic treatment and to the fact that seizure freedom in a percentage of cases cannot be achieved. Important information to be given to the owner is that the initial period of treatment can be difficult, with respect to side effects; NEVER to withdraw drugs or change drug dosages without consulting the veterinarian (since this entails a substantial risk of seizure reoccurrence and possible status epilepticus); to always contact the veterinarian in case of unexpected side effects, and always to bring the animal to the veterinarian if signs of status epilepticus occur.

Non-medical Treatment for Epilepsy

Epilepsy Surgery - In humans, surgical management of intractable partial epilepsies has become an efficacious and safe alternative in patients with partial onset seizures (medical therapy resistant or experiencing intolerable side effects). This procedure, however, requires that the epileptic focus be identified - using intracranial EEG, MRI and SPECT scan among others. There are only a few papers on surgical treatment for seizures (not including surgical management of space occupying lesions) in canine epilepsy [135,136]. Computed tomography- guided stereotactic procedures have been used for brain biopsy in dogs. Perhaps similar procedures might be applicable in animals with an identifiable epileptic focus in the future [137].

Vagal Nerve Stimulation - Animal and human studies have shown that vagal nerve stimulation in some cases can prevent or reduce seizures [138,139]. This non-pharmacological treatment may be considered for treatment of medically intractable partial seizures in humans. The exact mechanism of action of vagal nerve stimulation remains unknown. The vagal effects on the EEG, are probably mediated by the NTS (nucleus of the solitary tract) parabrachial-thalamic pathway [140]. Vagal nerve stimulation by digital ocular compression has been investigated as a treatment modality for aborting epileptic seizures in a study of seven dogs. The results of this study suggest that vagal nerve stimulation may be beneficial in some canine epilepsy patients [141]. This has been supported by the results of a study by Munana and co-workers [172].

Ketogenic Diet - The ketogenic diet (a high fat, moderate protein, low carbohydrate diet), utilized as an alternative treatment in some children epilepsies, has been proposed as a therapeutic alternative in the management of canine epilepsy. The anticonvulsant effect is exercised through inducing ketosis and acidosis - similar to what is observed in starvation. In a study of Puchowicz and co-workers the level of ketosis achieved in dogs given the ketogenic diet was lower than the level measured in children whose seizures were controlled by the ketogenic diet [142].

Status Epilepticus (SE)

Status Epilepticus (SE) is a life threatening condition that requires immediate treatment. Small animals with convulsive SE are frequently admitted to the emergency clinic and this condition is one of the most dramatic acute disorders encountered in small animals [143,144]. Signs of CNS damage after SE can persist for weeks, months or be permanent.

In 1993, SE was defined by the Epilepsy Foundation of America's Working Group on Status Epilepticus as "more than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures" [145]. A revised operational definition defines convulsive SE as "generalized convulsive status in adults and older children (>5 years old) refers to $\geq$ 5 min of continuous seizures or two or more discrete seizures between which there is incomplete recovery of consciousness [146]. To apply this definition of SE seems more practical, given that the "normal" tonic-clonic seizure terminates within 5 minutes. The effects of long-lasting seizure activity such as neuronal injury and the risk of dying from the complications of SE may be prevented by early treatment [147-149].

Clusters of seizures (serial seizures), in which there are two or more seizures within a period of minutes to many hours (and where the patient regains consciousness between seizures), should not be confused with status epilepticus. On the other hand clusters of seizures may still represent a potential emergency situation. In cases of continuous serial seizures the patient should therefore be treated as an SE patient.

Classification of SE - Status Epilepticus (SE) can be classified as non-convulsive SE (partial status: limited to partial seizure activity) and convulsive SE.

Non-convulsive SE (simple or complex partial SE) will only be touched on briefly here. This form of SE is scarcely documented in animals as it requires acute EEG monitoring and/or clinical recognition of impaired consciousness. Partial SE has been documented to occur in dogs [14,143].

In cases where partial seizure signs continue or where signs interpreted as postictal are intensive and long-lasting (days), one should consider the possibility that the animal may be in a partial SE.

Convulsive Status Epilepticus -
Why Does Convulsive SE Happen? Animals presenting in SE can be divided into two groups: Patients with known epilepsy and patients for whom SE is the first epileptic event.
In animals presenting with SE as the first epileptic event, SE is often precipitated by cerebral trauma, an intracranial space occupying process, inflammatory CNS disease, intoxication, or acute metabolic disturbance. In animals with an established diagnoses of epilepsy, SE can occur at any time due to the disease itself, but provoking factors such as non-compliance, change in drug regimen, drug toxicity, infections (fever), organ dysfunction, hepatic enzyme induction and weight gain, among others, should also be taken into consideration.
In 58% of human SE patients, SE represents the first indication of epilepsy. Patients at high risk include individuals suffering from symptomatic epilepsy (focal cerebral pathology/partial seizures with or without secondary generalization), intractable epilepsy and frontal lobe epilepsy [150]. This has been shown to be true for the canine also [173]. Prevalence for SE or cluster seizures as a percentage of total hospital admissions of dogs over a period of five years has been reported to be 0.44% [143].

The Pathophysiology of Convulsive SE - The pathophysiology of convulsive SE is closely associated with the duration of the prolonged seizure activity [151,152]. A distinction of SE into early SE (the first 30 minutes) and late SE can be made, based upon the severity of the physiologic and neurophysiologic changes increasing the more prolonged the status becomes [147-149,151,153].
In early SE, the compensatory phase (0 - 30 minutes), the brain manages to compensate for the increased metabolic demand for oxygen and glucose by increasing blood flow greatly. Cardiac output, cardiac rate and blood pressure rise and an increase in circulating catecholamines occurs, resulting in a hypersympathetic autonomic reaction causing hyperpyrexia, bronchial secretion, salivation and vomiting. Additionally, excessive muscle activity contributes to the dramatic rise in temperature often associated with SE [147]. Lactic acidosis from excess anaerobic metabolism develops from the onset of status, due to increased neuronal and muscular activity, accelerated glycolysis, tissue hypoxia, respiratory depression and catecholamine release. Other metabolic disturbances are hypoglycemia, hypo and hyperkalemia and hyponatremia.
During the decompensatory phase (after 30 - 60 minutes of continuous seizure activity) the system fails to meet the continuous high metabolic demand of the epileptic brain. When cerebral autoregulation breaks down, cerebral blood flow becomes dependent on systemic blood pressure, resulting in hypotension, decreased cerebral blood flow, decreased metabolism and thus ischemia and neuronal death.
During the decompensatory phase, systemic and cerebral hypoxia, pulmonary hypertension and edema and cardiac arrhythmia are likely to develop. Cardiac arrhythmias in SE are a result of direct seizure-associated autonomic activation, catecholamine release, hypoglycemia, acidosis and electrolyte disturbances. In late SE, the cumulative hypoxic damage will affect most organ systems with an increasing danger of multiorgan failure. The increase in intracranial pressure will eventually lead to cerebral edema.

Management of Convulsive SE - Animals with SE are high-risk patients! Treating them as intensive care patients and following a standardized protocol therefore greatly increases their survivability. Overall, the importance of having a protocol cannot be stressed enough. One may prefer one anticonvulsant to another, e.g., different benzodiazepines, but what is most important is that the veterinarian is familiar with the drug, that the drug is available in the clinic, and that the complications of SE are addressed.
The patient should, first of all, be stabilized. The airway should be secured, oxygen supplied and an intravenous line (large vein - large catheter) should be established. Anticonvulsants should be administered early (within 5 minutes) and aggressively (blood for monitoring serum levels of phenobarbital should be drawn before administering drugs). Monitor clinical and neurological status, blood pressure, ECG, temperature, blood gasses, pH, blood hematology and biochemistry. Treat complications. Decrease temperature in cases with hyperthermia. In animals with hypoglycemia, glucose should be administered intravenously. The lactic acidosis will reverse with effective control of respiration and motor seizure activity (only on rare occasions is treatment with bicarbonate necessary).
As soon as the patient is stabilized the etiology of the status should be established and investigated, since acute CNS disease calls for therapy aimed at the primary lesion. History should, at a minimum, include information regarding any signs of disease prior to status, previous medical problems, and drugs or toxin exposure.

Anticonvulsive Drugs in SE - The ideal antiepileptic drug in status epilepticus is available for intravenous administration, fast working (highly lipid soluble - fast penetration to the CNS), does not possess sedative side effects, does not interfere with cardiovascular or respiratory functioning and can be used for long-term treatment. Unfortunately such a drug does not exist. Benzodiazepines are the drugs that come closest to the properties mentioned above. Diazepam, clonazepam or lorazepam are the initial drugs of choice due to their rapid onset of action and their effectiveness. Diazepam is metabolized in the liver to

desmethyl diazepam, temazepam and oxacepam. All metabolites are pharmacologically active. Diazepam is highly lipid soluble, and highly protein-bound (94 - 96%). The elimination half-life is about 2 - 4 hours in the dog and 15 - 20 hours in the cat. [154,155], Diazepam penetrates to the CNS faster than lorazepam (within 1 minute after IV injection) due to the higher lipid solubility. The disadvantage of diazepam is that due to this property, the concentration (and effectiveness) of diazepam also decreases more rapidly. Lorazepam is actively retained in the brain and has a longer duration of protection. The unwanted side effects of both drugs are sedation and respiratory depression. Lorazepam produces prolonged period of sedation as compared to diazepam. There is only limited experience with lorazepam [156]. Diazepam can be administered IV, intranasally or rectally [28, 158]. Diazepam is administered as a bolus IV (0.5 - 1 mg/kg) or rectal (1 - 2 mg/kg) and can be repeated once after 5 - 10 minutes.
Continuous benzodiazepine administration in prolonged SE should be avoided. Due to the prolonged seizure activity itself influencing cerebral mechanisms, functional changes occur in GABA-A receptors causing a diminished response of diazepam during prolonged SE [159]. Additionally the risk of side effects increases dramatically with continuous administration due to distribution/redistribution of the drug to/from the lipid compartment. The initial treatment with benzodiazepines should therefore, be followed by a fixed dose of phenobarbital (IV bolus 5 - 10 mg/kg) to secure a long-lasting neuronal protection. Phenobarbital is a very effective anticonvulsant. The disadvantage of the drug is that it penetrates slowly to the CNS (15 - 20 minutes after IV injection). It is therefore not recommendable as a first drug of choice in SE. Phenobarbital naïve patients can be started on a loading dose: Total mg IV = (kg body weight) x (0.8 L/kg) x 20 (this would equal 16 mg/kg) given gradually. The initial treatment with phenobarbital is followed by phenobarbital infusion (constant rate of 2 - 6 mg/dog/hour). Chronic treatment with phenobarbital has shown to reduce the effect of diazepam, presumably due to an increased hepatic clearance [160].
Barbiturates possess the same side effects as benzodiazepines. Adding barbiturates to the above, therefore, increases the risk of serious side effects such as cardiac and respiratory depression.
In cases of refractory SE, the animal must be anesthetized with pentobarbital (barbiturate induced coma). Propofol may also be used to induce anesthesia in refractory SE. Propofol, however, has proven to possess both convulsant and anticonvulsant qualities [161,162].
Steroid therapy is recommended if brain edema is suspected, dexamethasone 0.25 mg/kg (can be repeated 1 - 3 times a day for up to 3 days). In cases of infectious CNS disease the treatment with steroids must be based on an individual assessment of the pros and cons. Once the animal has been seizure-free for 8 - 12 hours, emergency antiepileptic drug treatment can be weaned off slowly.

Therapeutic Failure in SE - In cases of therapeutic failure, the clinical, paraclinical and medical parameters should be reassessed. Common errors leading to therapeutic failure are: The dosage of antiepileptic drugs is not sufficient, continuous injections with diazepam in late SE, failure to identify the underlying cause or failure to identify the complications of the SE itself.

Instructions to Owners - Any successfully treated episode of SE should be followed by steps to prevent SE from happening again. When recovering from SE, continued oral treatment with antiepileptic drug(s) should always be considered (monotherapy or polytherapy in known epilepsy patients already treated with one drug). The owners of animals at risk of recurring SE can be supplied with diazepam for intranasal or rectal administration at home.

Patients with Status Epilepticus are intensive care patients !

Status Epilepticus - Protocol		
Time Table	**Clinic**	**Medical Treatment**
0 - 5 minutes	• History • Clinical examination • Neurological examination • Observe seizure activity • Supply oxygen • IV-line (large catheter) • Hematology, serum biochemistry and blood gasses • ECG, pulsoxymetry **Identify etiology**	• (Diazepam 1 mg/kg IV /rectal bolus)
5 - 15 minutes	• If hypoglycemia: 50% glucose (central vein) • May treat acidosis	• Diazepam 1 mg/kg IV • Can be repeated once after 5 min.
15 - 30 minutes	• Intensive care patient monitoring	• If Diazepam stops seizures: Administer phenobarbital (5 - 10 mg/kg (up to 20 mg/kg) as a bolus (100 mg/min)) - to prevent recurrence of seizures • If seizures continue: Administer phenobarbital (5 - 10 mg/kg (up to 20 mg/kg) as a bolus (100 mg/min)) - to stop seizures
30 - 60 minutes	• Continuous patient monitoring • Intubate • Ventilate (O_2) • Regulate blood pressure • Observe/treat cerebral edema (methylprednisolone/mannitol) • Continuous treatment of complications	If SE continues after IV phenobarbital: lnduce coma with general anesthesia: • Pentobarbital (2 - 8 mg/kg IV as a bolus) • Propofol (4 mg/kg) • Methylprednisolone (30 mg/kg/ IV as a bolus – continous treatment with 15 mg/kg every 2. hour for 24 hours) • Mannitol (1g/kg)

Remember to always consider long-term treatment with anticonvulsive drugs

Closing Remarks

Epilepsy is a most challenging disease with respect to diagnostic approach and therapeutic management. Most animals can live a normal life with antiepileptic drugs. It is important to always remember that, being the family of an epileptic animal will, in many cases, represent an emotional stress factor and that owner counselling - is likely to be inevitable, to prevent the owner from giving up.

Epilepsy: Medical history and seizure symptomatology - check list PRINT

Patient ID:……..... Name:…….
Breed:……..
Sex:……..
Neutralized:…….
Age:……..
Weight:…….

Epilepsy among close relatives……
Known birth complications……
Previous head trauma……
Previous CNS infection……..
Age at first seizure…….
Seizure frequency……..
Distribution of seizures (single/clusters)
……
Circadian distribution of seizures (during sleep, upon awakening, at day, during activity)
……
Seizure provoking factors (e.g., stress, excitement)
……..
Seizure related to hormonal fluctuations or hormonal imbalance
……

Seizure development as described by the owner
……
……
……
……

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