Idiopathic Epilepsy in the Dog: Reasons for Referral and Assessment from the Owners' Perspective

Ya-Pei Chang BVM

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ABSTRACT

Seizures are the most common neurological disorder in small animal medicine, of which 40 to 50% of affected dogs are diagnosed as having idiopathic epilepsy. Dogs with epilepsy represent a large proportion of the caseload for the neurology service of the Small Animal Hospital of University of the Glasgow Veterinary School (SAH-UGVS). The aims of this study were to clarify the reasons for owners requesting a second opinion for dogs with idiopathic epilepsy. This was undertaken by reviewing seizure management regimens instigated at primary veterinary clinics and examining the owners' perspective of the reasons for referral and the seizure management regimen used in SAH-UGVS. Information from the owners' perspective was also thought of value to clinicians in assessing seizure management regimens and could potentially raise issues of relevance to dogs with epilepsy and their owners, which may be the basis for developing an alternative assessment of long-term seizure treatment in veterinary medicine.

A total of 48 dogs referred to SAH-UGVS between March 1999 and April 2001 for evaluation of seizures and diagnosed or tentatively diagnosed with idiopathic epilepsy were included in this study. Breed, gender, age at the onset of seizure activity, seizure type, reasons for referral and previous antiepileptic drug (AED) therapy were reviewed for these cases. For 32 cases, the owners' perspective on reasons for referral to and the seizure management regimen used in SAH-UGVS, as well as the exploration of other issues relevant to dogs and their owners, were sought by mailed questionnaires. Behavioural changes were reported by 11 respondents to the first questionnaire, and the second mailed survey was undertaken to clarify the nature and potential causes of behavioural changes in these patients.

The study demonstrated that "dogs' quality of life", "adequate seizure frequency" and "acceptable AED side effects" were the three main concepts considered important by owners in assessing the outcomes of seizure management. Furthermore, owning an epileptic dog did not have a major impact on owners' work/day-to-day activities and free time. The majority of owners did not consider the administration of the medication a nuisance and coped well with administering medication more than once daily. For more than half of owners, regular veterinary examination and blood sampling for serum AED concentrations monitoring did not cause a significant problem. Further diagnostic procedures did help most owners understand their dogs' condition and provided owners with more confidence in AED therapy adjustment and accepting the balance between AED efficacy and side effects. The majority of owners agreed the cost of further diagnostic procedures was worthwhile.

The study suggests that in both undergraduate and post-graduate education, the value of measuring AED serum concentrations, as well as the use of bromide in canine epilepsy, should be emphasised. The study also demonstrated that dogs on potassium bromide alone exhibited fewer side effects than dogs on phenobarbitone.

A relatively large proportion of cases studied exhibited behavioural changes, which mainly appeared to be AED-related. Clinicians should be aware of the potential for behavioural change in idiopathic epileptic patients on AED therapy. Once patients exhibit AED-related behavioural changes, a dose reduction or discontinuation of the particular AED may be necessary.

TABLE OF CONTENTS

ABSTRACT ii

TABLE OF CONTENTS iii

LIST OF TABLES viii

LIST OF FIGURES xi

ACKNOWLEDGEMENTS xii

DECLARATION xiii

CHAPTER ONE: INTRODUCTION AND THE REVIEW OF LITERATURE 1

1.1 Seizures and Epilepsy 2

1.1.1 Seizures 2

1.1.1.1 Definition 2

1.1.1.2 Phases of Seizure Activity 2

1.1.1.3 Seizure Intensity 4

1.1.1.4 Type of Seizure 4

1.1.2 Epilepsy: Definition, Classification and Causes 6

1.1.3 Functional Aspects of the CNS Related to Seizure Activity 8

1.1.3.1 General Principles and Basic Mechanisms of Neuronal Excitability 8

1.1.3.2 Basic Mechanisms of Epileptogenesis 11

1.2 Epidemiology of Idiopathic Epilepsy 20

1.2.1 Age and Gender 20

1.2.2 Genetic Aspect of Idiopathic Epilepsy 20

1.3 Diagnostic Evaluation 22

1.3.1 Signalment 22

1.3.2 Clinical History 22

1.3.3 Physical Examination 24

1.3.4 Neurological Examination 24
1.3.5 Laboratory Investigation 24
1.3.6 Intra-cranial Imaging 24
1.3.6.1 Structural Imaging 25
1.3.6.2 Functional Imaging 26
1.3.7 Cerebrospinal Fluid Analysis 27
1.3.8 Electroencephalography 28
1.3.8.1 Electroencephalography and Epilepsy 28
1.3.8.2 Electroencephalography in Veterinary Medicine 28
1.3.8.3 Interictal Paroxysmal Discharges 30
1.4 Antiepileptic Drug Therapy 31
1.4.1 General Principles of Antiepileptic Drug Therapy 31
1.4.1.1 When to Initiate Treatment 31
1.4.1.2 Owner Education 32
1.4.1.3 Mechanisms of Action of the AEDs 32
1.4.1.4 Choice of Treatment 33
1.4.1.5 Clinical Pharmacokinetics 35
1.4.1.6 Therapeutic Drug Monitoring and AED Therapy 36
1.4.2 Antiepileptic Drugs 40
1.4.2.1 Phenobarbitone 40
1.4.2.2 Bromide 45
1.4.2.3 Primidone 48
1.4.2.4 Phenytoin 49
1.4.2.5 Benzodiazepines 50
1.4.2.6 Other AEDs 51
1.4.3 AED Therapy Withdrawal 54
1.5 Assessment of Seizure Management 54
1.5.1 Seizure Frequency 54
1.5.2 Quantitative Assessment of Seizure Severity 55
1.5.3 Quality of Life Measures in Epilepsy 56
1.5.4 Related Information in Veterinary Medicine 57
1.6 Aims of the Study 57

CHAPTER TWO: MATERIALS AND METHODS 59

2.1 Criteria for Entry of Dogs in the Study 60

2.2 Investigation Protocol for Patient with Epilepsy 60

2.3 Seizure Disorder Evaluation and Management 67

2.3.1 Categories of Seizure Cases Included in This Study 67

2.3.2 Group One 68

2.3.3 Group Two 70

2.4 Questionnaire Study 71

2.4.1 Questionnaire One: An Assessment of the Seizure Management in Companion Animals from the Owners' Perspective 71

2.4.1.1 Format 71

2.4.1.2 Questionnaire Design 71

2.4.1.3 Pretesting 74

2.4.1.4 Inclusion Criteria and Implementing Mail Surveys 74

2.4.2 Questionnaire Two: Behavioural Changes in Epileptic Dogs 75

2.4.2.1 Format 75

2.4.2.2 Questionnaire Design 75

2.4.2.3 Inclusion Criteria and Implementing Mail Surveys 76

2.4.3 Analysis of Data 76

CHAPTER THREE: RESULTS 77

3.1 Cases Review 78

3.1.1 Breed and Sex Distribution 78

3.1.2 Age at Onset of Seizure Activity 78

3.1.3 Duration of Seizure History When Presented 79

3.1.4 Seizure Type 80

3.1.5 Reasons for Referral 80

3.1.6 AED Therapy at the Time of Referral 81

3.1.7 Behavioural Changes at the Time of Referral 82

3.2 Questionnaire One: An Assessment of Seizure Management in Companion Animals from the Owners' Perspective 86

3.2.1 The Response 86

3.2.2 Detailed Results 86

3.2.2.1 Section A: Establishing the Ideals for Assessing the Outcome of Seizure Management 86

3.2.2.2 Section B: An Assessment of Seizure Management in their Own Dogs ... 89

3.2.2.3 Section C: An Assessment of Quality of Life in Epileptic Dogs 90

3.2.2.4 Section D: An Assessment of Work Associated with Caring for Epileptic Dogs 92

3.2.2.5 Section E: An Assessment of AED Side Effects 93

3.2.2.6 Section F: The Impact of Owning an Epileptic Dog on Owners' Day-to-day Activity 97

3.2.2.7 Section G: The Impact of Owning an Epileptic Dog on Owners' Ability/decision to Stay Away Overnight 98

3.2.2.8 Section H: Owners' Opinions on Further Investigation of Seizures in their Dogs 100

3.3 Questionnaire Two: Behavioural Changes in Epileptic Dogs 105

3.3.1 The Response 105

3.3.2 Detailed Results 105

3.3.2.1 The Behavioural Change and the Frequency (Q-1, Q-15 and Q-16) 105

3.3.2.2 The Onset of the Behavioural Changes (Q-2 and Q-3) 106

3.3.2.3 Trigger Factors or the Reason of the Certain Behaviour (Q-4 to Q-6) 107

3.3.2.4 History of Behavioural Problems (Q-7 to Q-9) 108

3.3.2.5 Behavioural Changes and AED Therapy (Q-10) 108

3.3.2.6 Behavioural Changes and Seizure Activity (Q-11 to Q-14) 109

3.3.2.7 The Response of the Reported Behaviour (Q-17 and Q-18) 110

3.3.3 Summary of Questionnaire Two 111

CHAPTER FOUR: DISCUSSION 113

4.1 General Aspect of the Study 114

The Significance of the Population Surveyed 114

Reflections on the Response Rate to the Questionnaires 114

The Source of Biases 115

4.2 Cases Review 118

The predisposition to idiopathic epilepsy in certain breeds 118

Comparing clinician's perception of reasons for referral with that of owners 119

Factors underlying apparent treatment failure 119

4.3 Assessing Seizure Management from Owners' Perspective 121

4.4 Behavioural Changes in Epileptic Dogs 123

CHAPTER FIVE: CONCLUSIONS 127

APPENDIX ONE

Questionnaire: An Assessment of Seizure Management in Companion Animals from the Owners' Perspective 130

APPENDIX TWO

Questionnaire: Behavioural Changes in Epileptic Dogs 139

REFERENCES 144

LIST OF TABLES

Table 1.1 Summary of the International Classification of Epileptic Seizures 4

Table 1.2 Causes of symptomatic epilepsy 7

Table 1.3 Causes of reactive seizures 8

Table 1.4 Differential diagnosis of nonepileptic paroxysmal disorder and weakness 23

Table 1.5 Mechanisms of action of AEDs (Perucca 1996; Deckers *et al.* 2000) 34

Table 1.6 Pharmacokinetic variables for AEDs in the dog 44

Table 1.7 Recommended doses for AED in the dog 44

Table 1.8 Related information of alternative drugs in dogs 52

Table 1.9 Mechanisms leading to deterioration of a patient's condition 54

Table 2.1 Questions checklist of clinical history 64

Table 2.2 Checklist of physical examination 66

Table 2.3 Routine haematology and biochemistry 66

Table 3. 1 The association between reasons for referral and the duration of seizure history when presented 80

Table 3.2 Current phenobarbitone dose, duration of seizure history and AED history 81

Table 3.3 Database of cases in the study: signalment, seizure history, and previous AED therapy 83

Table 3.4 The response rate at different stages 86

Table 3.5 Evaluation of the importance of factors in the assessment of seizure management in group with AED therapy 87

Table 3.6 Responses distribution of minimal seizure interval in group with AED 87

Table 3.7 Owners' perspective of the importance of issues in assessing seizure management for respondents with pets not on AED therapy 88

Table 3.8 Results of minimal seizure interval (Q-A2) in group without AED therapy 88

Table 3.9 An assessment of seizure management in individual dog of group with AED....89

Table 3.10 An assessment of seizure management in individual dog of group without AED therapy....90

Table 3.11 Results of assessment of epileptic dogs' quality of life in group with AED 91

Table 3.12 Results of question C4 - reasons for the dog's quality of life deteriorating 91

Table 3.13 An assessment of quality of life in dogs of group without AED therapy 91

Table 3.14 An assessment of work associated with caring for epileptic dogs 92

Table 3.15 Reasons of administration of medication is a nuisance 92

Table 3.16 AED side effects in all dogs of the study....93

Table 3.17 The occurrence of side effects in patients with AED therapy....94

Table 3.18 The degree of owners' concern in AED subgroups 95

Table 3.19 The occurrence of side effects in dogs with different phenobarbitone dosages 95

Table 3.20 Reasons for dogs currently with no AED therapy 96

Table 3.21 The impact of owning an epileptic dog on owners' day-to-day activity in group with AED therapy 97

Table 3.22 The impact of owning an epileptic dog on owners' day-to-day activity in group without AED therapy 98

Table 3.23 How owners organised the care of dogs when they stayed away overnight, in the group with AED therapy 98

Table 3.24 Reasons why seizures in dogs affected their owners' ability/decision to stay away overnight....99

Table 3.25 How owners organised the care of dogs when they stayed away overnight, in the group without AED therapy 100

Table 3.26 Reasons why the previous seizure management considered unsatisfactory 101

Table 3.27 Owners' opinions on further investigation of seizure disorder in group with AED 101

Table 3.28 Owners' opinions on further investigation of seizure disorder in group without AED therapy 102

Table 3.29 Owners' opinions on further investigation of seizure disorder from all responses of the study 103

Table 3.30 Responses from cases, on which the full investigation protocol performed 103

Table 3. 31 The association between the duration of seizure history and reasons for referral from owner's perception 104

Table 3. 32 The association between the duration of seizure history and reasons for referral from clinician's perception 104

Table 3.33 General comments 104

Table 3.34 The response rate of the study 105

Table 3.35 Behavioural changes in epileptic dogs 105

Table 3.36 The frequency of the behaviour in each dog (Q-1, Q-15 to 16) 106

Table 3.37 The onset of behavioural changes from Q-2 and Q-3 107

Table 3.38 Behavioural changes and AED therapy 108

Table 3.39 The onset and progress of the behavioural changes 109

Table 3.40 Behaviour and seizure activity 109

Table 3.41 Comparison of certain occurring time of seizure and the behaviour 110

Table 3.42 Responses of the behaviour 110

Table 3.43 Summary of the responses of individual patient 111

LIST OF FIGURES

Figure 2.1 Investigation protocol for dogs with seizures 63

Figure 2.2 The Neurological Examination Sheet of SAH-UGVS 65

Figure 2.3 Seizure diary 69

Figure 3.1 Breed distribution 78

Figure 3.2 Distribution of age at onset of seizure activity 79

Figure 3.3 Duration of seizure history when referred 79

Figure 3.4 Seizure type and number of dogs 80

Figure 3.5 Distribution of serum phenobarbitone concentrations 82

Figure 3.6 Distribution of values for "adequate seizure frequency" 89

Figure 3.7 Distribution of side effects in AED subgroups 94

Figure 3.8 Distribution of occurrence of phenobarbitone side effects in dogs with different range of dosages 96

Figure 3.9 Distribution of answers of question F2 and F4 97

Figure 3.10 The impact of owning an epileptic dog on owners' free time 99

Figure 3.11 The influence of pet insurance to owners in considering the cost of further investigation is worthwhile in group with AED therapy 101

Figure 3.12 The influence of pet insurance to owners in considering the cost of further investigation is worthwhile in group without AED therapy 102

Figure 4.1 The positions of the cut-off points on the VAS in the bias-eliminated calibration versus the discrete seven-point scale (labelled A to G) 116

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DECLARATION

I, Ya-Pei Chang, do hereby declare that the work carried out in the thesis is original, was carried out by myself or with due acknowledgement, and has not been presented for the award of a degree at any other university.

CHAPTER ONE

INTRODUCTION AND THE REVIEW OF LITERATURE

1.1 SEIZURES AND EPILEPSY

1.1.1 Seizures

1.1.1.1 Definition

Seizures are transient and involuntary changes in behaviour or neurological status due to paroxysmal, functional disturbances of the forebrain caused by excessive and hypersynchronous electrical activity (March 1998; Thomas 2000). Depending on the localisation and extent of these discharges, impairment of consciousness, motor function, sensory perception, autonomic nervous system function, or behaviour may be observed in different types of seizures, as well as at different times in the course of a single seizure (Aird *et al.* 1984; Braund 1994; Oliver *et al.* 1997).

1.1.1.2 Phases of Seizure Activity

Seizure activity may be divided into components on the basis of clinical findings.

1.1.1.2.1 Prodrome

The ***prodrome*** is a long-term indication of a forthcoming seizure. Many human patients with generalised seizures experience headache, insomnia, irritability, mood changes, lethargy, unusual appetite and a variety of other symptoms for hours to days before a seizure. The longer the patient has had seizures the more likely he or she is to be able to recognize such prodromal signs (Laidlaw & Richens 1976; Thomas 2000). In a study of epilepsy and seizure classification in 63 dogs, 11% of dogs were described as exhibiting changes consistent with prodromal behaviour prior to the onset of seizures. In this study, signs lasted for between one and twenty-four hours, during which the dogs would try to be with owners, appeared anxious, were generally restless and expressed atypical behaviour e.g. chewing the carpet (Berendt & Gram 1999). The pathophysiology of prodromes is not well understood, but prodromes are not associated with abnormal electroencephalographic activity and are not part of the ictus (Thomas 2000).

1.1.1.2.2 Aura

The ***aura*** is that portion of the seizure which occurs before consciousness is impaired and thus is synonymous with a simple partial seizure, which may or may not develop to secondary generalisation. It may be that, as in mild partial seizures, the aura is the whole seizure (Commission on Classification and Terminology of the International League

Against Epilepsy-ILAE 1981). The aura represents the initial abnormal discharge of a single group of neurons and usually lasts seconds to minutes (Laidlaw & Richens 1976). In human patients with epilepsy, the aura is often reflected clinically by a stereotyped sensation, e.g., sensory, visual, auditory, or vertiginous (Berendt & Gram 1999). Animals may appear restless, hyperexcitable, anxious, pace, lick unpurposefully, salivate inappropriately, hide without reason, or express attention–seeking behaviour (Podell 1996; March 1998).

1.1.1.2.3 Ictus

The ***ictus*** is the main part of the seizure event. The ictus is characterised by involuntary muscle tone or movement and/or abnormal sensations or behaviour and usually lasts from seconds to minutes (Podell 1996). Classifications of seizure type are based on presenting symptoms and electroencephalographic changes during ictus and aura.

1.1.1.2.4 Postictal period

The postictal period is the period immediately following the ictus and represents transient clinical abnormalities in brain function that are caused by the seizure activity (March 1998; Thomas 2000). The length of the postictal phase varies from minutes to days. There is no correlation between the severity of the seizure and the duration, nature, or severity of the postictal phase (DeLahunta 1983). Animals may exhibit unusual behaviour, disorientation, inappropriate urination/defaecation, excessive or depressed thirst and appetite and specific neurological deficits of weakness, blindness, or sensory and motor disturbances (Podell 1996). Postictal paralysis or Todd's paralysis refers to the transient paralysis that may occur following some partial seizures with focal motor components or with somatosensory symptoms (Commission on Classification and Terminology of ILAE 1981). There is presently no reliable way to determine clinically whether focal weakness after a seizure is because of postictal paralysis or because the patient developed secondary cortical ischaemia (Fiser & Schachter 2000).

1.1.1.2.5 Interictal period

The interictal period is the time between resolution of any postictal signs and the beginning of the next ictus (Thomas 2000).

1.1.1.3 Seizure Intensity

There are several terms used to describe the intensity of seizure activity. Isolated seizures are seizures with an interictal period over 24 hours (Podell 1996). Cluster seizures (serial seizures, acute repetitive seizures) are two or more seizures occurring over a brief period (minutes to 24 hours) but with the patient regaining consciousness between the seizures. Status epilepticus has been defined as a seizure that persists for a 20 to 30 minutes, based on the duration thought necessary to induce irreversible brain damage. However, as isolated seizures rarely last longer than a few minutes, a more clinically applicable definition of status epilepticus is a continuous seizure lasting at least 5 minutes, or two or more discrete seizures without full recovery of consciousness between seizures (Thomas 2000). Status epilepticus is a medical emergency and requires urgent intensive treatment to reduce neurological injury (Laidlaw & Richens 1976; Platt & McDonnell 2000).

1.1.1.4 Type of Seizure

According to the International Classification of Epileptic seizures (ICES) (Commission on Classification and Terminology of ILAE 1981) seizures can be classified into three broad categories: partial seizures, generalised seizures and unclassified seizures (Table 1.1).

Table 1.1 Summary of the International Classification of Epileptic Seizures

I. Partial seizures
- A. Simple partial seizures (consciousness not impaired)
  1. With motor symptoms
  2. With somatosensory or special sensory symptoms
  3. With autonomic symptoms
  4. With psychic symptoms
- B. Complex partial seizures (consciousness impaired)
  - B.1. Simple partial onset followed by impairment of consciousness
    - With features as in A 1-4
    - With automatisms ϕ
  - B.2. With impairment of consciousness at onset
    - With features as in A 1-4
    - With automatisms
- C. Partial seizures secondarily generalised

II. Generalised seizures
- A. Convulsive seizures
  - Tonic-clonic seizures
  - Tonic seizures
  - Clonic seizures
  - Myoclonic seizures
  - Atonic seizures
- B. Nonconvulsive seizures
  - Absence seizures

III. Unclassified seizures

ϕ Automatisms are described as "coordinated adapted involuntary motor activity occurring during the state of clouding of consciousness either in the course of, or after a seizure".

1.1.1.4.1 Partial seizures

Partial seizures originate in a small group of neurons that constitute a seizure focus (Westbrook 2000). Partial seizures are classified as simple partial seizures (without alteration of consciousness) or complex partial seizures (with impaired consciousness). Impaired consciousness is defined as the inability to respond normally to externally applied stimuli by virtue of altered awareness and/or responsiveness. There is considerable evidence that simple partial seizures usually have unilateral hemispheric involvement and only rarely have bilateral hemispheric involvement; complex partial seizures, however, frequently have bilateral hemispheric involvement (Commission on Classification and Terminology of ILAE 1981).

The symptomatology of partial seizure depends on the location of the focus within the brain (Westbrook 2000). In patients with complex partial seizures, aberrations of behaviour (automatisms) may occur (Commission on Classification and Terminology of ILAE 1981); jaw snapping, fly-biting, chewing or swallowing movements, gastrointestinal signs, vocalisation, running, hiding, tail chasing, aggressive behaviour have been described (Crowell-Davis *et al.* 1989; Dodman *et al.* 1992; Dodman *et al.* 1996). Impaired consciousness may be the first clinical sign of a partial seizure, or the neuronal discharges in a simple partial seizure may spread to those area involved in maintaining consciousness, resulting in a complex partial seizure (Commission on Classification and Terminology of ILAE 1981; Thomas 2000). Both simple and complex partial seizures may generalise. This spread may occur so rapidly that the initial focal component is not observed. However, with close observation, including videotaped review of the seizures, it has become apparent that many dogs with idiopathic epilepsy suffer partial seizures with secondary generalisation (Thomas 2000).

1.1.1.4.2 Generalised seizures

Generalised seizures are those in which the first clinical changes indicate initial involvement of both hemispheres (Commission on Classification and Terminology of ILAE 1981). Generalised seizures are subdivided into convulsive and nonconvulsive events. Generalised convulsive seizures are the most common seizure type seen in veterinary medicine and are characterised by impaired consciousness coupled with bilateral motor signs of either a tonic-clonic, tonic, clonic, myoclonic, or even atonic nature (Podell 1996).

In a generalised tonic-clonic seizure, the first part of the ictus is the tonic phase, during which there is sustained contraction of voluntary muscles. The animal typically loses consciousness and falls to its side in opisthotonus, with the limbs extended. Muscles associated with respiration are also affected and irregular respiration usually occurs, which may lead to secondary cyanosis. The tonic phase lasts for a minute or so and progresses to the clonic phase, during which there is rhythmic contraction of muscles, which is manifested as paddling or jerking of the limbs and chewing movements. The clonic phase lasts a variable period of time but usually no more than several minutes (Thomas 2000). During the ictus, the autonomic nervous system may be disturbed, which leads to the signs of salivation, urination and defecation. In a tonic seizure, motor activity consists only of generalised muscle rigidity, without a clonic phase. Clonic seizures are less common, in which there is no tonic component. Atonic seizures consist of a sudden and often brief loss of muscle tone, and myoclonic seizures are characterised by brief shock-like contractions that may be generalised or confined to individual muscle groups (Commission on Classification and Terminology of ILAE 1981; Thomas 2000).

The major form of nonconvulsive seizure activity is the absence seizure manifested as impaired consciousness only (Podell 1996). In man, these are characterised by a sudden onset interruption of ongoing activities, a blank stare and possibly a brief upward rotation of the eyes (Commission on Classification and Terminology of ILAE 1981). Absence seizures are poorly documented in animals (Podell 1996).

1.1.1.4.3 Unclassified seizures

The category of unclassified seizures should be used only when it is impossible to classify seizure because of a lack of adequate information (Commission on Classification and Terminology of ILAE 1981).

1.1.2 Epilepsy: Definition, Classification and Causes

Epilepsy refers to a chronic brain disorder characterised by recurrent seizures (Knowles 1998; Thomas 2000). Epilepsy can be classified into three categories: idiopathic, symptomatic and cryptogenic. Idiopathic epilepsies are those in which there is no identifiable brain abnormality other than seizures; in human medicine, they are defined by age-related onset, clinical and electroencephalographic characteristics, and a presumed genetic aetiology. Symptomatic epilepsies are considered the consequence of an identifiable cerebral lesion or other specific disease of the central nervous system.

Potential causes of symptomatic epilepsy are listed in Table 1.2 (page 7) (Oliver *et al.* 1997; Thomas 1998; Thomas 2000). Cryptogenic epilepsy refers to recurrent seizures that are presumably symptomatic, but for which the aetiology is not known (Hopkins *et al.* 1995; Berendt & Gram 1999; Thomas 2000). In veterinary epilepsy nomenclature, cryptogenic epilepsy has been rarely mentioned. Most authors define idiopathic epilepsy as seizures with no identifiable brain abnormality and the diagnosis is made by ruling out extracranial and intracranial causes (DeLahunta 1983; March 1998). In this review the common definition in veterinary medicine is used.

Table 1.2 Causes of symptomatic epilepsy

Anomalous	Hydrocephalus Lissencephaly
Degenerative	Storage diseases
Neoplastic	Primary brain tumor Metastatic brain tumor
Inflammation	Viral: canine distemper, rabies Bacterial: any type Fungal: cryptococcosis, coccidioidomycosis Protozoal: toxoplasmosis, neosporosis Rickettsial: ehrlichiosis, Rocky Moutain spotted fever Granulomatous meningoencephalitis Necrotising encephalitis Steroid responsive meningitis-arteritis
Traumatic	(head injury)
Vascular	Intracranial haemorrhage Brain infarction

A reactive seizure is defined as a reaction of the normal brain to transient systemic insult or physiological stress (Podell *et al.* 1995; Berendt & Gram 1999; Thomas 2000). A patient with recurring reactive seizures is not defined as having epilepsy because no primary chronic brain disorder underlies the seizure activity (Podell 1996). Potential causes of reactive seizures are listed in Table 1.3 (page 8) (Collins 1994; O'Brien 1998).

Table 1.3 Causes of reactive seizures

Metabolic	Alkalosis	
	Hypoglycaemia	
	Hypoxaemia	
	Hyperosmolality: hypernatraemia, nonketonic hyperosmolar diabetes mellitus	
	Hyponatraemia	
	Hypocalcaemia	
	Hypercalcaemia	
	Hepatic encephalopathy	
	Renal encephalopathy	
	Hyperlipidaemia	
	Polycythaemia	
	Hypothyroidism	
Immune	Allergy	
Toxic	Toxins	Animal toxins
		Caffeine and other methylxanthines
		Hydrocarbons and petroleum distillates
		Lead and other heavy metals
		Mycotoxins
		Pesticides
		Plant toxins
	Drug toxicoses	Antibiotics: metronidazole, penicillins, cephalosporins
		Anticholinergics
		Antihistamine and phenothiazines
		5-Fluorouracil
		Iodinated contrast agents
		Ketamine, phencyclidine and other dissociated anesthetics
		Lidocaine
		Methylxanthines
		Nonsteroid anti-inflammatory drugs: ibuprofen, salicylates
		Piperazine
		Sympathomimetics
		Tricyclic antidepressants
		Withdrawal of sedatives, hypnotics or anticonvulsants

1.1.3 Functional Aspects of the CNS Related to Seizure Activity

1.1.3.1 General Principles and Basic Mechanisms of Neuronal Excitability

1.1.3.1.1 The action potential

Neuronal excitability is a function of active and selective distribution of ions across cell membranes. In the resting state, the neuron is polarised with the inside of the cell being more negative than the outside of the cell. Intracellular fluid contains a high concentration of potassium and low concentration of sodium, calcium and chloride and the reverse is true for the extracellular fluid. The resting membrane potential (RMP) of approximately -70mV is maintained by selective permeability of the plasma membrane to certain ions, the

retention of more anions intracellularly than extracellularly and by an energy-dependent sodium-potassium pump (Aird *et al.* 1984).

A change in the permeability of the cell to sodium and/or calcium results in an influx of positive charge and a state of depolarisation and generates an excitatory postsynaptic potential (EPSP). If the plasma membrane becomes selectively permeable to the chloride anion, it results in an influx of negative charge and a state of hyperpolarisation and generates an inhibitory postsynaptic potential (IPSP). The same hyperpolarisation is achieved if outward potassium channels are activated (Fiser & Coyle 1991; March 1998). The neuron integrates the EPSPs and IPSPs in a manner determined by neurotransmitters and neuromodulatory substances acting on the dendritic zone and reaches a state of net depolarisation or hyperpolarisation. Neuronal membrane potential is dependent on a balance of excitatory and inhibitory forces determined by glutamate, gamma-aminobutyric acid (GABA) and a multitude of other neuromudulatory substances acting on neurons (see 1.1.3.1.2 Neurotransmitters, page 9). If the net depolarisation is greater than the threshold, an action potential is generated at the axon initial segment region and propagates down the axon to the axon terminal or presynaptic site. Activation of voltage-sensitive calcium channels here leads to neurotransmitter release. If the neuron is glutamatergic, glutamate is released. The released neurotransmitter traverses the synaptic cleft and activates postsynaptic receptor(s) on the dendrite of another neuron (March 1998). Both released glutamate and GABA are inactivated by uptake into neurons and glia through a sodium-dependent, high affinity transport process (Fiser & Coyle 1991; Westbrook 2000).

1.1.3.1.2 Neurotransmitters

There are over 100 neurotransmitters or neuromodulators which are known to play roles in the system of neuronal excitation. Amongst these, glutamate is the most important excitatory neurotransmitter and GABA is the most important inhibitory neurotransmitter (Hopkins *et al.* 1995).

Glutamate and its receptors

Glutamate mediates most excitatory postsynaptic potentials in the CNS; consequently, excitatory amino acid receptors have become known as "glutamate receptors". There are three major subtypes of glutamate receptors: kainate (KA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA), named according to the types of synthetic agonists that activate them (Westbrook 2000). The KA

and AMPA receptors primarily open sodium channels in the membrane (non-NMDA channels) (March 1998).

The NMDA receptor subtype has a different role. Under normal physiological conditions, magnesium ions produce a block of the NMDA channel. This block is voltage-sensitive so that if the neuron depolarises to 10-30mV, magnesium ions are extruded and the channel becomes open to the influx of calcium and sodium ions, which results in further depolarisation. Calcium influx into neurons also initiates a multiplicity of neuronal changes. Amongst these events are changes in second messenger processes critical to long-term potentiation and physiological processes related to learning and memory. Excessive calcium in the intracellular environment can lead to cell injury and death. The voltage-sensitive blockade decreases the response to NMDA at resting membrane potentials with sensitivity being restored at depolarised potentials. Thus, an NMDA-mediated component of an EPSP is small at resting potentials and maximal during periods of sustained neuronal activity and contributes to greater membrane depolarisation (Fiser & Coyle 1991; Hopkins *et al.* 1995).

GABA and its receptors

GABA is the predominant inhibitory neurotransmitter of the cortex and other forebrain structures, and its actions at the GABA receptor result in the generation of an IPSP (March 1998). Recent studies indicate that there are two subtypes of GABA receptors: denoted $GABA_A$ and $GABA_B$.

The $GABA_A$ receptor complex is a macromolecular entity with numerous components, including a GABA binding site, a chloride channel and several positive and negative modulatory sites sensitive to benzodiazepines, barbiturates, beta-carbolines, picrotoxin, penicillin and zinc. Binding of GABA to the postsynaptic $GABA_A$ receptors changes the postsynaptic membrane's permeability to ions, such as chloride, calcium and potassium; however, chloride permeability changes are most significant (Fiser & Coyle 1991). The intracellular concentration of chloride is about 15-fold lower than the extracellular concentration. Equilibrium potential for chloride ions is usually slightly negative to the resting membrane potential (Fiser & Coyle 1991; Hopkins *et al.* 1995). The opening of chloride channels leads to chloride influx, and therefore produces hyperpolarisation and a decrease in the state of excitability of the cell (Hopkins *et al.* 1995; Kandel & Seigelbaum 2000). Opening of the chloride channel in the $GABA_A$ receptor-channel complex can be modulated by several factors in addition to binding of GABA to the receptor. For example,

the $GABA_A$ receptor appears to desensitise with continued exposure to GABA. This phenomenon may be important in the origin and spread of neuronal activity associated with seizure development (Fiser & Coyle 1991). Numerous substances can influence the probability of the channel opening at the $GABA_A$ complex, including agonists and antagonists. Benzodiazepines and barbiturates are of major clinical importance as modulators of the $GABA_A$ receptor complex. Representatives of each of these classes of compounds increase the potency of GABA-mediated inhibition (Fiser & Coyle 1991; Hopkins *et al.* 1995) (see 1.4.1.3 Mechanisms of Action of the AEDs, page 32).

The receptors involved in mediating GABA's presynaptic inhibition are termed $GABA_B$ receptors. In spinal ganglia cells, $GABA_B$ receptor activation reduces calcium influx, which in turn reduces (excitatory) neurotransmitter release into the synaptic cleft. However, the functions of $GABA_B$ receptor in the brain may not be the same as in spinal ganglion. The activation of the $GABA_B$ receptor opens the potassium channels. Since the potassium equilibrium potential of neurons (E_K = -80mV) is always negative to the resting potential, the opening of potassium channels leads to an outward (hyperpolarising) potassium current (Kandel & Seigelbaum 2000).

1.1.3.2 Basic Mechanisms of Epileptogenesis

The mechanisms of epileptogenesis are not well understood. The pathogenesis of epilepsy is multifactorial. Seizures are a symptom of disordered brain function and represent the end-point of many different pathological pathways (Avanzini *et al.* 1992; Podell 1996). The pathophysiology of partial seizure and generalised seizure are different (Westbrook 2000). Most of the current knowledge of epilepsy derives from studies of partial seizures or partial seizures with secondary generalisation, following structural cerebrocortical damage. Minor changes in brain circuits or neuronal properties can give rise to partial seizures (March 1998).

1.1.3.2.1 Partial seizure

The defining feature of partial seizures is that the abnormal electrical activity originates from a seizure focus. This seizure focus is a small collection of neurons that exhibit enhanced excitability. Enhanced excitability may result from many different factors, such as altered cellular properties or altered synaptic connections caused by a local scar, blood clot, or tumour (Westbrook 2000). It is suggested that the development of focal epileptogenic discharges in a population of neurons is due to the interaction of several

factors: (a) the existence of intrinsic membrane properties which lead to burst-generating capacities in specific subsets of neurons, (b) the reduction of inhibitory control mechanisms, and (c) excitatory coupling among neurons of an epileptogenic region (Avanzini *et al.* 1992). The phases in the development of a partial seizure can be arbitrarily divided into the interictal period, followed by neuronal synchronisation, seizure spread and finally, secondary generalisation (Westbrook 2000).

Intrinsic burst generation in neurons within a seizure focus

Experimental studies of partial seizures have revealed that individual neurons within an epileptic focus have a stereotypic and synchronised electrical response termed the paroxysmal depolarisation shift (PDS). Compared with the typical EPSP, the PDS consists of a sudden, large (20-40mV), long-lasting (50-200ms) depolarisation, which triggers a train of action potentials at the peak of the PDS (Hopkins *et al.* 1995; Westbrook 2000). Both influx of calcium through voltage-gated calcium channels and influx of sodium through non-NMDA and NMDA receptor gated channels are believed to give rise to the PDS (March 1998). The NMDA receptor gated channel is particularly suited to enhance excitability because its contribution is increased by membrane depolarisation and it allows Ca^{2+} to enter the neuron (Westbrook 2000). During the interictal period, the PDS is followed by an after-depolarisation spike hyperpolarisation (after-hyperpolarisation, AHP). Voltage- and calcium-dependent outward potassium currents, as well as feedback inhibition of the neuron (both $GABA_A$-receptor mediated IPSPs and $GABA_B$-receptor mediated activation of outward potassium currents), contribute to this hyperpolarising event (March 1998; Westbrook 2000).

Most neurons normally do not exhibit PDS behaviour. However, pyramidal neurons in lamina V of the cerebral cortex and in the CA3 area of the hippocampus are described as exhibiting this bursting characteristic under normal physiological conditions (Avanzini *et al.* 1992; March 1998; Westbrook 2000; Ure & Perassolo 2000). Normally, intact inhibitory systems prevent excessive excitation of the adjacent zones (March 1998).

Many factors can influence the excitability of neurons within the seizure focus. Injuries to the brain appear to change the intrinsic membrane properties, which alter the input-output relationships of single cells, making them intrinsically more excitable and capable of firing at higher frequencies during depolarisation (Avanzini *et al.* 1992). Changes in glutamate receptor type, number, spatial distribution and/or sensitivity are found after an injury. Following neuronal damage, voltage-gated calcium channels may become abnormally

sensitive and the sodium-potassium pump may become dysfunctional. Pump failure results in partial membrane depolarisation, activation of both voltage-gated calcium channels and NMDA receptor-mediated channels and enhanced neuronal excitability (March 1998).

As long as the PDS is restricted to approximately 1000 neurons that constitute the seizure focus, there are no clinical manifestations (Westbrook 2000). The synchronised activity of multiple neurons produces marked regional extracellular negativity due to an influx of positive ions into the depolarising neurons. This can be detected at the surface of the skull and underlies the interictal spike or sharp on the electroencephalogram (Hopkins *et al.* 1995).

Breakdown of surrounding inhibition

During the interictal period, the PDS is confined to the seizure focus by the after-hyperpolarisation. As mentioned above (see Intrinsic burst generation in neurons within a seizure focus, page 12), the after-hyperpolarisation is partly generated by feedback inhibition of the neuron (Westbrook 2000). Post-synaptic inhibition, mediated by release of GABA, is powerful and widespread in cortical circuits and serves as a control mechanism that prevents development of synchronous epileptiform discharge (Avanzini *et al.* 1992). Inhibition circuits include "feedback inhibition" and "surrounding inhibition" or "lateral inhibition". In feedback inhibition, activated pyramidal neurons excite inhibitory interneurons, which then feedback to inhibit the pyramidal neurons that had caused them to be activated. In surrounding inhibition, in addition to inhibiting neighbouring neurons, many interneurons also send an extensive network of collateral axons to pyramidal neurons in adjacent cortical zones, resulting in the formation of an unexcitable area outside the primary excited zone and restricting the lateral spread of epileptiform activity across the cortex (March 1998).

Computer modelling of neuronal networks suggests that only small decrements of inhibition are required to make a system discharge excessively. Inhibition is a dynamic process, which is altered with use (Hopkins *et al.* 1995). Repetitive activation of cortical circuits causes a depression of synaptic inhibition in normal brain tissue through decreases in the IPSP due to increased intracellular chloride concentration and presynaptic inhibition of GABA release (Avanzini *et al.* 1992). In addition, the $GABA_A$ receptor appears to desensitise with continued exposure to GABA (Fiser & Coyle 1991). In a teleological sense, it is an advantage to reduce inhibition in a pathway under heavy use. If the decrease of inhibition is excessive, it may result in seizures (Hopkins *et al.* 1995). Injuries to the

brain can lead to both morphological and functional loss of inhibition, which includes loss of GABAergic neurons and synapses (the breakdown of feedback and surrounding inhibition), reduced cerebrospinal fluid (CSF) and tissue GABA concentrations, and decreased GABA receptor expression and sensitivity (Avanzini *et al.* 1992; March 1998). All of these factors make inhibition less effective and, in turn, cause increased activity in excitatory circuits, activation of latent excitatory connections, and increased triggering of burst discharges (Avanzini *et al.* 1992).

Changes in excitatory neuronal connectivity

The number of recurrent excitatory connections in a population of neurons is a vital element in the development of epileptogenesis. For example, cortical injury might lead to epileptogenesis through development of new recurrent excitatory circuitry due to axonal sprouting (Avanzini *et al.* 1992). Damaged excitatory axons or excitatory axons that have lost their postsynaptic neurons may sprout new axon collaterals that form abnormal connections with other excitatory neurons or with the dendritic processes of the excitatory neuron itself (March 1998).

Factors related to synchronisation

A dynamic enhancement of synaptic excitability due to recurrent activity in excitatory circuits may be a critical factor in epileptogenesis. Augmentation of glutamate-induced postsynaptic effects, especially in NMDA receptors, would increase EPSP amplitudes, enhance the PDS and generally increase neuronal excitability (March 1998). Changes in the density and distribution of glutamate receptor subtypes on postsynaptic neurons and alterations in the NMDA subtype of glutamate receptors are also found following repetitive seizures (Avanzini *et al.* 1992).

Large increases in extracellular potassium commonly occur after excessive neuronal activity, mainly due to the outward movement of potassium during repolarisation. Defective potassium uptake by astrocytes and dysfunction of the sodium-potassium pump may also be involved in increasing extracellular potassium (March 1998). Increased extracellular potassium directly depolarises neighbouring axon terminals and reduces outward potassium currents during the hyperpolarisation following PDS, leading to longer duration PDS. Increases in extracellular potassium also interfere with transport of chloride out of neurons and indirectly depresses synaptic inhibition (Avanzini *et al.* 1992). Poor glutamate uptake by dysfunctional or energy-deprived astrocytes causes high

concentrations of glutamate to accumulate at excitatory synapses, with subsequent excessive activation of postsynaptic glutamate receptors (March 1998). Other synchronising mechanisms include burst discharges in the axonal terminal arborisations of neurons, electrical interactions between groups of tightly packed cells (ephaptic interaction) and direct conduction of currents from cell to cell through non-chemical synapses (gap junctions) (Avanzini *et al.* 1992).

Regional spread and diffuse generalisation of epileptiform activity

If inhibition is reduced, other neuronal aggregates are excited through different pathways. Successful recruitment of a critical number of areas with synchronised depolarisation leads to a seizure (Podell 1996). The spread of epileptiform activity from the focus generally follows the same pathways as normal cortical activity. Generalisation of a partial seizure to ipsilateral and contralateral cortical areas occurs along intra- and interhemispheric pathways (Westbrook 2000). An important mechanism of secondary generalisation involves thalamocortical circuits. Excitatory events in the cortex result in depolarisation of thalamocortical axon terminals. Antidromic activity in these axons causes excitation of thalamic nuclei, which subsequently project back to multiple cortical areas. Orthodromic activation of corticothalamic fibres also contributes to thalamic recruitment. Activation of the midbrain reticular formation may also promote secondary generalisation due to its known diffuse projection back to the cerebral cortex (March 1998).

Interictal –Ictal Transitions

Six steps lead from focal epileptogenesis to clinical epilepsy: (1) the generation of enhanced physiological responses; (2) PDS (observed as interictal spikes on EEG); (3) focus spread to perifocal neurons; (4) the utilisation or breakdown of control mechanisms within brain circuits that limit the propagation of seizure discharges via preferred routes of spread; (5) the appearance of secondary foci in regions synaptically linked to the primary focus; (6) the emergence of clinical seizures (Ure & Perassolo 2000).

Reasons for transition from interictal discharges to ictal episodes associated with clinical signs of seizures are unknown (Avanzini *et al.* 1992). A combination of increased NMDA receptor function and depressed GABAergic transmission due to reduced release of GABA and receptor desensitivisation may well be responsible for the onset of a clinical seizure (Ure & Perassolo 2000).

Other factors involved in interictal-ictal transition might be the release of substances that cause long-term increase in neuronal excitability through activation of intracellular second messenger systems, coupled to changes in the conductance of membrane ion channels (Avanzini *et al.* 1992). The decrease or blockade of potassium currents produced by acetylcholine increases neuronal excitability and depresses the after-hyperpolarisation (AHP) that normally follow repetitive discharges, and thus it may result in higher firing frequencies (Fiser & Coyle 1991; Avanzini *et al.* 1992). Serotonin, although generally viewed as more inhibitory than excitatory, also has the effect of AHP blockade (Aird *et al.* 1984; Fiser & Coyle 1991; Avanzini *et al.* 1992). Other factors contributing to synchronisation, such as non-synaptic mechanisms, may also be important for interictal-ictal transitions (Avanzini *et al.* 1992).

1.1.3.2.2 Generalised seizure

A primary generalised seizure shows simultaneous disruption of normal brain activity in both cerebral hemispheres from the onset (Westbrook 2000). The discharge synchronisation mechanisms generating this seizure type are poorly understood (Ure & Perassolo 2000). A "centrencephalic" concept has been proposed, in which paroxysmal discharges arise from brain stem and project to the cerebral cortex (March 1998). Furthermore, in generalised tonic-clonic seizures, the discharge synchronisation mechanisms of the tonic phase may correlate with epileptogenic circuits in the brain stem and the clonic phase may relate to the limbic system (Ure & Perassolo 2000). However, current theories focus on the cerebral cortex as the primary generator of generalised tonic-clonic seizures (Niedermeyer 1996).

The generalised nature strongly indicates a diffuse cerebrocortical problem. However, the brain can dynamically change over time even if the original epileptogenic area was focal (March 1998). EEG recordings in human patients with primary generalised epilepsy have revealed that bilateral synchrony is not precise and small time differences exist between discharges from each side (Niedermeyer 1996). Studies of idiopathic epilepsy in Labrador Retrievers have found an initial asymmetry in epileptiform activity (Heynold *et al.* 1997). It may be possible that, in patients with primary generalised seizures, an early subclinical hyperexcitable focus gradually induces hyperexcitability of neurons in other cortical and subcortical areas over time through the process of activity-dependent long-term potentiation (see 1.1.3.2.4 Long-term effects of epileptic activity, page 18) (March 1998).

The pathogenesis of generalised epilepsy may arise from morphological abnormalities or functional defects. In morphological abnormalities, multifocal (e.g., cortical dysplasia) or diffuse changes in neurons or their connectivity may be present (Hopkins *et al.* 1995), and recurrent and anomalous excitatory connections between these groups of neurons have been hypothesised to lead to the diffuse paroxysmal epileptiform discharges. Functional defects at neurochemical or cellular level can affect the cerebral cortex diffusely. In idiopathic epilepsy, a generalised neurotransmitter imbalance due to abnormalities of synthesis, release, or re-uptake probably plays an important role (March 1998). Decreased GABA concentrations and increased glutamate concentrations in the CSF were found in dogs with idiopathic epilepsy (Podell & Hadjiconstantinou 1997). This suggests that altered GABA and glutamate values might be indicative of a state of chronic over excitation in the brain of dogs with idiopathic epilepsy, although whether this finding is a cause or consequence of recurrent seizures is unknown. Deficits at the synaptic, membrane receptor and ion channel level (ion channelopathy) could alter intrinsic neuronal excitability. A diffuse dysfunction of ligand or voltage-gated ion channels could also predispose to seizures (March 1998).

1.1.3.2.3 Seizure termination

The factors that determine seizure duration and termination are not completely understood. Reduction of presynaptic glutamate release, restoration of sodium-potassium ATPase pump and inhibitory system function are necessary for seizure termination (March 1998). The release of transmitters may be depleted with ongoing stimulation. In addition, prolonged exposure to glutamate produces a reduction of the depolarising response of a neuron (Fiser & Schachter 2000).

Intracellular acidification may be another factor resulting in termination of epileptiform discharges. During seizure activity, neurons accumulate hydrogen ions, resulting in acidification of the intracellular environment (Xiong *et al.* 2000). Hydrogen ions compete with other ions at the ion channel associated with NMDA. This competition may partially attenuate NMDA receptor and channel-mediated hyperexcitability. The pH shift associated with neuronal activity serves as a local feedback signal due to the marked pH sensitivity of many ion channels, enzymes and even receptors. Thus, intracellular acidification may be an important restraining force preventing neuronal activity from reaching concentrations that threaten the integrity of normal brain function (Fiser & Schachter 2000).

Increased extracellular potassium after a seizure also affects brain excitability. In general, mild increases in potassium lead to hyperexcitability, but increases to concentrations greater than 20-30 mM produce a spreading depression and cessation of neuronal activity (Fiser & Schachter 2000; Xiong *et al.* 2000).

The neuromodulator adenosine is another key compound in inhibiting the initiation and continuation of seizure activity, as well as regulating the postictal state (Avanzini *et al.* 1992; Fiser & Schachter 2000). Adenosine has prominent inhibitory actions on synaptic transmission. During a seizure, adenosine is released in large quantities (Avanzini *et al.* 1992). In addition, adenosine A1 receptor density increases after repeated seizures in young rats. Both of these represent an attempted control mechanism for the seizures (Fiser & Schachter 2000).

Prolonged seizure activity (status epilepticus) can cause deleterious physiological changes, including hypertension, tachycardia, hypoglycaemia, acidosis and hyperthermia. The initial physiological response is a massive release of adrenaline and noradrenaline into the circulation (Platt & McDonnell 2000). Respiratory compromise due to convulsive activity of muscles associated with respiration can cause cyanosis and acidosis (Thomas 2000). The release of systemic lactate during generalised convulsive activity also contributes to acidosis. However, although hyperthermia, hypoxia, hypertension and acidosis play a role in creating neuronal damage, the ongoing seizure activity also contributes substantially to neuronal damage (Platt & McDonnell 2000). Excessive stimulation with the release of glutamate causes NMDA receptors to open cation channels to calcium, leading to excessive increase in intracellular calcium. Increased intracellular calcium can activate a self-destructive cellular cascade involving many calcium-dependent enzymes, such as phosphatases, proteases and lipases. Lipid peroxidation can also cause production of free radicals, which damage vital cellular proteins and lead to cell death (Westbrook 2000).

1.1.3.2.4 Long-term effects of epileptic activity

As mentioned previously (see Breakdown of surrounding inhibition, page 13 and Factors related to synchronisation, page 14), recurrent activity will potentiate excitatory synapses and depress inhibitory synapses over time. Activity-dependent synaptic plasticity refers to the enhancement of synaptic strength (increased EPSP amplitudes) after periods of recurrent activity. A use-dependent increase or long-term potentiation of NMDA receptor efficacy is believed to occur during normal processes, such as learning and memory, but this may also occur during epileptogenesis (March 1998). Furthermore, changes in the

density and distribution of glutamate receptor subtypes on postsynaptic neurons and alterations in the NMDA subtype of glutamate receptors are also found following repetitive seizures (Avanzini *et al.* 1992).

Mirror Focus

Interictal cortical spiking may propagate via association tracts to the homologous region of the opposite hemisphere and evoke secondary spiking. If this secondary spiking becomes independently active, it is called a mirror focus and may persist even after the primary focus becomes inactive (March 1998).

Kindling

Kindling refers to a phenomenon related to both development of epilepsy and to the normal physiological processes concerned with learning and memory, in which the short, intermittent and subthreshold electrical stimulation of a brain structure induces a progressive increase in brain excitability (Aird *et al.* 1984; Avanzini *et al.* 1992; Hopkins *et al.* 1995). Kindling is a process in which, following the initial subconvulsive stimuli, a nonepileptic region of the brain evokes electrical discharges, which become more extensive and prolonged with repeated stimuli and develop seizure activity. Once present, the enhanced sensitivity to electrical stimulation is lifelong (Westbrook 2000; Najm *et al.* 2001). NMDA receptor activation seems to play a major role in kindling. Also, many neurotransmitters or neuromodulators are probably involved, e.g. GABA, norepinephrine, serotonin and acetylcholine. Sprouting, axonal growth and synaptic reorganisation have been described in the kindled structure. Such plasticity would be likely to involve second messenger system (Avanzini *et al.* 1992).

A combination of the effects mentioned above in a patient which continues to have seizures would increase the number of areas of the brain able to initiate a seizure. Consequently, the successful medical management of such a patient may be more challenging (Podell 1996).

1.2 EPIDEMIOLOGY OF IDIOPATHIC EPILEPSY

Idiopathic epilepsy is the most common cause of recurrent seizures in dogs (Podell *et al.* 1995). The reported prevalence in different breeds ranges between 0.5 percent and 4.1 percent (Kathmann *et al.* 1999). Most dogs with idiopathic epilepsy (75 to 90 percent) exhibit generalised tonic-clonic seizures with loss of consciousness. Other types of seizures, including simple and complex partial seizures and partial seizures with secondary generalisation, have been reported; some patients have more than one type of seizures (Jaggy & Bernardini 1998; Thomas 2000).

1.2.1 Age and Gender

The first seizure in dogs with idiopathic epilepsy usually occurs between the age of six months and five years of age and most commonly between one and three years of age (Heynold *et al.* 1997). Occasionally, dogs outside the expected age range are affected (Knowles 1998). According to other reports, the first seizure occurs between the age of two months and ten years, with approximately 50 percent to 60 percent of cases between one and three years old (Podell *et al.* 1995; Heynold *et al.* 1997; Jaggy & Bernardini 1998; Kathmann *et al.* 1999).

Male dogs have been reported to be slightly more affected than female dogs in most studies (Thomas 2000). Recent studies of genetic aspects in single breeds have revealed different results. In Labrador retrievers, Golden retrievers and Belgian tervueren, males and females were equally affected, and in Bernese mountain dogs, males were significantly more affected than females (Jaggy *et al.* 1998; Kathmann *et al.* 1999; Famula & Oberbauer 2000).

1.2.2 Genetic Aspect of Idiopathic Epilepsy

In most breeds suspected of having a genetic basis for epilepsy, evidence for heritability is based on encountering recurrent generalised seizures in dogs of certain breeds more frequently than those breeds appear in the general population (Knowles 1998). However, the exact mode of inheritance has not been defined (Jaggy *et al.* 1998). Those breeds of dogs which have been reported to have a genetic factor or high incidence of idiopathic epilepsy include the Beagle, Belgian Tervuren, Keeshond, Dachshund, German shepherd dog (Alsatian), Labrador retriever, Golden retriever, Bernese mountain dog, Border Collie, Scottish shepherd dog, horaks laborhound, toy poodle, Cocker spaniel, Irish setter,

miniature schnauzer, Siberian husky, St Bernard, wire haired fox terrier and boxer (Falco *et al.* 1974; Cunningham & Farnbach 1988; Famula *et al.* 1997; Knowles 1998; Jaggy *et al.* 1998; Kathmann *et al.* 1999; Famula & Oberbauer 2000; Quesnel 2000).

A pedigree analysis in keeshonds suggests that the predisposition to idiopathic epilepsy in this breed appears to be determined by a single autosomal recessive gene (Hall & Wallace 1996). Results of pedigree analyses in Labrador retrievers and Bernese mountain dogs support the hypothesis that idiopathic epilepsy has a polygenic, recessive mode of inheritance in these two breeds of dogs (Jaggy *et al.* 1998; Kathmann *et al.* 1999). In addition, the clinical expression of idiopathic epilepsy is variable in terms of onset, frequency and severity of seizures. Therefore, other factors that trigger seizures must play a role. Seizures in dogs with idiopathic epilepsy may be triggered concomitantly by internal stress including mental tension and physical stress. Studies in retrievers have shown that a multifactorial mode of inheritance, including both genetic as well as environmental factors, could be responsible for the transmission and expression of idiopathic epilepsy (Heynold *et al.* 1997). Furthermore, some differences were noticed between Labrador retrievers and Bernese mountain dogs. It was found that, in Bernese mountain dogs, the offspring of epileptic parents had a significantly earlier onset of seizures than the offspring of healthy parents. In addition, males were significantly more affected than females. It was concluded that idiopathic epilepsy in Bernese mountain dogs might have a different mode of inheritance compared to retriever breeds. The variable expression of the disease is probably influenced either by modifier genes or an additive gene effect (Kathmann *et al.* 1999).

Studies in the Belgian tervueren suggest that, although in this breed seizures have a complex pattern of inheritance, a single major locus model with a general effect on seizure expression is likely. A single putative locus with a large effect appears to increase the risk of seizures with homozygous individuals exhibiting seizures and heterozygotes having an increased susceptibility to seizure. The data also support the concept that seizure disorders are likely to be polygenic (Famula *et al.* 1997; Famula & Oberbauer 2000). However, additional objective test-mating programmes would be necessary to define the exact mode of inheritance (Jaggy *et al.* 1998; Kathmann *et al.* 1999).

In the case of canine idiopathic epilepsy, genetic factors are largely presumed to influence a patient's basic threshold of seizures (Knowles 1998). In the threshold value model, each animal inherits a genetically determined predisposition to seizures and, if a certain threshold of stimulation is exceeded, seizures may occur (Cunningham & Farnbach 1988).

The genetic mechanisms involved in a predisposition to seizures are not clearly understood. Based on the hypotheses outlined above, it is likely that different modes of inheritance and expression may exist between breeds, possibly reflecting different aetiologies. Such factors may result in differences in the clinical expression of disease in terms of onset, frequency and severity of seizures, as well as responses to standard treatments between breeds.

1.3 DIAGNOSTIC EVALUATION

The diagnosis of idiopathic epilepsy is based on the ruling out of other extracranial and intracranial diseases that may cause seizures. No positive diagnostic finding can substantiate the diagnosis (Oliver *et al.* 1997).

1.3.1 Signalment

As described above (see 1.2.1 Age and Gender, page 20), the first seizure in dogs with idiopathic epilepsy usually occurs between the age of six months and five years, but dogs outside the expected age range can also be affected. Certain breeds of dogs have been described as having a high incidence of idiopathic epilepsy, although idiopathic epilepsy can occur in any breed of dogs.

1.3.2 Clinical History

Acquiring a thorough and accurate history is important in approaching a seizure case. The first group of questions includes general health details and information related to familial history of seizures, vaccination status, travel, trauma and toxin exposure potential, previous medical and surgical treatment (including anaesthetics), evidence of allergy (especially food allergy) and drug administration (Podell 1996). The next group of questions relates to seizure activity and the first issue to be addressed is whether the patient is having seizures. The major differential diagnostic consideration is paroxysmal or syncopal disorders listed in Table 1.4 (page 23) (Podell 1996; Feldman & Nelson 1996; Knowles 1998; Thomas 2000). Information related to seizure type, duration, frequency, preictal phase, postictal phase and trigger factor should be recorded. The status of the patient's cerebrocortical function between seizures should be ascertained, looking for evidence of abnormalities such as behavioural changes, visual disturbances and gait abnormalities. The existence of

interictal signs is strongly indicative of structural cerebral problems (Podell 1996; Thomas 2000).

In a study of seizure classification in 50 dogs from a nonreferral-based population, a diagnosis of idiopathic epilepsy was statistically more probable when the dog was between 1 and 5 years of age at the first seizure, when the dog was a large breed (> 15 kg), when the seizure occurred between 8 AM and midnight, or when the interval between the first and second seizure was longer than 4 weeks. A diagnosis of symptomatic epilepsy was statistically more probable when the dog was less than 1 or more than 7 years old at the first seizure, when the first seizure was a partial seizure, or when the first seizure occurred between midnight and 8 AM. A diagnosis of reactive seizures was statistically more probable only when the interval between the first and second seizure was shorter than 4 weeks (Podell *et al.* 1995).

Table 1.4 Differential diagnosis of nonepileptic paroxysmal disorder and weakness

Neuromuscular disorders
Myasthenia gravis
Narcolepsy or cataplexy
Normal or abnormal movements during sleep, rapid eye movement sleep disorder
Vestibular dysfunction
Tremor disorders
Canine distemper myoclonus
Behaviour disorders (stereotype)
Tetanus
Discospondylitis
Idiopathic polyradiculoneuritis (Coon Hound paralysis)
Polymyositis
Polyarthritis
Idiopathic polyneuropathy
Pain (e.g., cervical disc disease)
Cardiovascular disorders
Congenital: anatomical defects
Acquired: tachyarrhythmias or bradyarrhythmias, bacterial endocarditis
Neoplasm: haemangiosarcoma
Coagulopathy (warfarin-induced)
Metabolic disorders
Polycythaemia
Hypoadrenocorticism
Hyperviscosity syndrome
Phenochromocytoma
Normal insulin, hypoglycaemia
Anaemia

1.3.3 Physical Examination

A thorough physical examination is important to detect signs of systemic illness that might suggest an underlying cause for seizures (Thomas 2000). The information from physical examinations also helps to differentiate seizures from nonepileptic paroxysmal disorders. In addition, funduscopic examination may provide indirect evidence of active or inactive systemic infections, optic nerve oedema, retinal haemorrhage, or optic nerve infiltration (Knowles 1998).

1.3.4 Neurological Examination

A complete neurological examination should be performed to detect any persistent neurological deficits. Cerebral lesions often cause focal and relatively subtle deficits such as proprioceptive deficits in one side or blindness in one visual field (Thomas 2000). Other cranial nerve function tests are also important as other cranial nerve deficits may suggest a multifocal or diffuse problem. When performing a neurological examination shortly after a seizure, any deficits (usually generalised), such as ataxia, depression, or blindness, may be a result of postictal disturbances, such as postictal paralysis or Todd's paralysis(see 1.1.1.2.4 Postictal period, page 3), and may not indicate underlying brain disease. If focal or generalised deficits are detected, the examination should be repeated in 24 to 48 hours to differentiate postictal effects from persistent interictal deficits (Knowles 1998; Thomas 2000).

1.3.5 Laboratory Investigation

Complete blood counts, platelet count, standard biochemical profile and urinalysis are usually performed. Results of these investigations help to rule out extracranial causes for seizures and also provide baseline values for assessing possible side effects of antiepileptic drug therapy (Knowles 1998). Further metabolic screens, such as serum bile acid concentrations, thyroid function tests, lead concentrations and serum antibody tests for toxoplasmosis, neosporosis and canine distemper virus, should be performed if the history and/or examination are suggestive (Thomas 2000).

1.3.6 Intra-cranial Imaging

The purpose of intra-cranial imaging in epilepsy is to screen for potential intracranial disease as a potential cause of seizure activity. Brain imaging in epilepsy can be divided

into structural or functional imaging (Hopkins *et al.* 1995). Currently in veterinary medicine, the emphasis is on structural brain-imaging modalities, which include computed tomography (CT) and magnetic resonance (MR) scanning. In human medicine, besides structural imaging, functional imaging plays an important and growing role in the clinical assessment and research investigation of patients with epilepsy. Techniques include single photon emission computed tomography (SPECT), positron emission tomography (PET), functional MR imaging (fMRI) and magnetic resonance spectroscopy (MRS). Epilepsy is particularly challening from an imaging interpretation perspective as, in addition to fixed abnormalities, transient abnormalities related to interictal electroencephalographic spikes or seizures may be detected with a variety of functional imaging techniques (Richardson 2001).

1.3.6.1 Structural Imaging

Computed tomography is a specialised radiographic technique that generates transverse images (Oliver *et al.* 1997). It utilises a series of narrow, highly collimated X-ray beams that pass through the patient and are collected by an array of sensitive detectors. The X-ray source is rotated around the patient to produce multiple projections of the same anatomical region (Braund 1994). CT excels in the detection of osseous changes within the cranium. Modern CT scanners can differentiate the ventricular system, the grey and white matter of the cerebral cortex, the thalamus and the basal nuclei.

The principles of interpretation of CT scans and conventional radiography are similar. Changes in size, shape, position, density and margins of organs determine the presence of abnormalities (Braund 1994). Distortion of the lateral ventricles, midline shift of the falx cerebri and displacement of brain parenchyma are typical findings in many brain lesions (Tucker & Gavin 1996). Lysis or proliferative lesions in bones of the calvarium also help ascertain the presence of a lesion (Braund 1994). Abnormal brain tissue is described as hyperdense, isodense, or hypodense relative to normal surrounding brain tissue. Pathological conditions that cause hyperdense areas within the brain parenchyma include mineralisation, haemorrhage, increased cellularity and scar tissue formation. Oedema and acute haemorrhage cause hypodense areas within or around the brain (Tucker & Gavin 1996). Further visual enhancement of blood vessels, organ parenchyma and lesions can be accomplished with intravenous injection of iodinated contrast agents during imaging. The use of contrast media usually enhances the meninges, choroid plexus and the pituitary gland because their capillaries are fenestrated and permit passive diffusion of contrast medium into the surrounding parenchyma. Contrast medium does not normally enter the

brain parenchyma because of the blood brain barrier (BBB). After intravenous administration, iodine leaks out of damaged capillaries and outlines the vascular portions of the lesion (Braund 1994). Lesions with relatively homogeneous cellularity and vascularity show a uniform enhancement pattern. A heterogeneous or ring pattern of enhancement is associated with lesions lacking cellular uniformity or undergoing focal necrosis and haemorrhage (Tucker & Gavin 1996).

In human medicine, structural imaging with MR is the dominant technique in the routine clinical investigation of patients with epilepsy (Richardson 2001). MR imaging is based on detecting the electromagnetic emissions of hydrogen nuclei after a strong magnetic field is applied and released (Tucker & Gavin 1996). The number of hydrogen protons and their local chemical environment affect the signal received by the MR scanner and ultimately determine the appearance of the image (Braund 1994). MR imaging improves differentiation within soft tissues with similar density (improved contrast resolution); however, dense bone and air lack signals for imaging because of the inability of the protons to relax in the dense bone matrix and the relative lack of hydrogen nuclei in air. Two principal forms of image, termed T1- and T2-weighted, are produced (Oliver *et al.* 1997). Air and cortical bone appear dark on both T1- and T2-weighted images. Fluid (oedema, CSF) appears dark on T1-weighted images and bright on T2-weighted images. Most lesions result in an increase in fluid within the lesion and/or oedema in surrounding brain parenchyma and thus appear bright on T2-weighted images (Braund 1994). The most commonly used contrast agent is the paramagnetic element gadolinium (Gd) in the form of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA). The contrast agent acts in a manner similar to the iodinated contrast agents used in CT. The main difference is that MR does not visualise the gadolinium but produces an image of the protons that their relaxation are influenced in the presence of Gd (Tucker & Gavin 1996). After contrast medium administration, many brain lesions are enhanced on T1-weighted images and the bright area can be differentiated from the surrounding dark-appearing brain oedema (Braund 1994).

1.3.6.2 Functional Imaging

Imaging of cerebral blood flow with SPECT and imaging of cerebral metabolic rate with 18-flurodeoxyglucose (^{18}FDG) PET are widely used in human epilepsy centres. Other techniques, such as MRS, fMRI and neuroreceptor imaging studies with both PET and SPECT, are in occasional clinical use, are undergoing clinical development, or have been used in research studies (Richardson 2001).

SPECT has been the most widely used functional imaging technique in epilepsy. This technique uses isotope-labelled tracers to image the distribution of cerebral blood flow. In addition, there have been a few studies of specific receptors in the brain (benzodiazepine receptors). Cost, availability and ability to image ictal events are the advantages of this technique; relatively low resolution, lack of quantification of measured parameters and relatively limited choice of measurable variables are the disadvantages (Hopkins *et al.* 1995; Richardson 2001).

Some principles of PET are similar to those of SPECT, but PET relies on short-lived positron-emitting isotopes and on simultaneous detection of pairs of photons. Quantification and high resolution have been strengths of PET in comparison with SPECT. Blood flow, metabolic rate and a very wide range of receptor, enzyme and transporter parameters can be measured accurately and with high spatial resolution (Hopkins *et al.* 1995; Richardson 2001).

Functional imaging is said to give better results than structural imaging in patients with partial seizures in terms of lateralisation and localisation, and the results of functional imaging appear to correlate better with clinical and electrophysiological data. However, these techniques may be demonstrating the effects and not the cause of epilepsy in some cases (Hopkins *et al.* 1995). The presence of a focal abnormality in the brain of a patient with epilepsy may give rise to a reorganisation of the topographical representation of cortical functions, which may be of research interest or may be of clinical importance when mapping essential functions prior to resective surgery. It is essential that all functional imaging studies should be interpreted with reference to high-quality high-resolution MR structural imaging (Richardson 2001).

1.3.7 Cerebrospinal Fluid Analysis

If imaging is non-diagnostic, CSF should be collect for analysis. CSF should not be collected if increased intracranial pressure is suspected or such anaesthetic techniques that may reduce intra-cranial pressure should be used and the owner appraised of the potential risk. Removal of CSF from cerebellomedullary or lumbar cistern causes a pressure gradient, and herniation of the cerebellum through the foramen magnum and/or herniation of the temporal cortex trough the tentorial notch may occur (Oliver *et al.* 1997). Space-occupying lesions, including neoplasms and abscesses, haemorrhage, noncommunicating hypertensive hydrocephalus, cerebral oedema associated with brain injury and generalised brain inflammation, can cause increased intracranial pressure (DeLahunta 1983). Thus,

performing imaging prior to CSF collection to rule out potential causes of increased intracranial pressure is necessary for decreasing the risk of CSF collection.

One ml per 5 kg of body weight of CSF can be safely removed (Chrisman 1992). Basic CSF analysis includes cell-counts, cytology and total protein concentration. Analysis should be performed within 30 minutes of collection for accurate cell counts and cytology because CSF cells deteriorate rapidly (Oliver *et al.* 1997). If CSF analysis reveals abnormalities, CSF culture, titres for infectious causes of encephalitis, protein electrophoresis and/or immunoelectrophoresis may be helpful (Chrisman 1992; Thomas 2000).

1.3.8 Electroencephalography

1.3.8.1 Electroencephalography and Epilepsy

Electroencephalography (EEG) is a record of the spontaneous electrical activity of the cerebral cortex (Holliday 1999). In human medicine, EEG remains a test of fundamental importance in epilepsy as it provides unique functional information. In patients with an established seizure disorder, the EEG findings may help to confirm the diagnosis of epilepsy, assess the type of epilepsy, identify a lateralised epileptogenic focus, indicate the most appropriate medication that should be prescribed, provide a guide to prognosis and provide a means to document the course of the disorder. In patients with behavioural or other disturbances that could be epileptic in nature but over which there is some uncertainty, the presence of paroxysmal discharges on EEG increases considerably the likelihood that attacks are indeed epileptic (Hopkins *et al.* 1995). Although EEG generally only records electrical potential at the scalp surface, a number of techniques have been devised to allow a three-dimensional reconstruction of the origin of EEG electrical activity (source localisation). These techniques have a number of inherent assumptions and disadvantages. Therefore, in the situation of pre-surgical evaluation, invasive electrode studies or functional imaging are often used to add further anatomical information (Richardson 2001).

1.3.8.2 Electroencephalography in Veterinary Medicine

In veterinary medicine, a number of articles dealing with the technical aspects of EEG, or case reports using EEG as a diagnostic aid in the diagnosis of canine epilepsy, have been published (Srenk & Jaggy 1996; Jaggy & Bernardini 1998; Holliday & Williams 1998). In addition, the use of EEG to link episodic abnormal behaviour and seizure activity has been

reported (Breitschwerdt *et al.* 1979; Crowell-Davis *et al.* 1989; Dodman *et al.* 1992; Dodman *et al.* 1996). Veterinary EEG technique has been adapted from the accepted human "international 10-20 system" of electrode placement on the scalp and subsequently modified (Berendt *et al.* 1999). Certain characteristics in skull anatomy and the nature of animals substantially affect the use of EEG in veterinary medicine.

The frontal sinus, which is located chiefly between the outer and the inner tables of the frontal bone, interrupts the EEG recording from frontal lobe of cerebral cortex. As the size and form of the frontal sinus are dependent on skull form and age, the locations of EEG electrodes need to be modified in different ages and breeds of dogs. In addition, the facial and substantial masticatory muscles have the potential to generate muscle potentials during EEG recording, which are the most common and often the most troublesome artefacts observed. Muscle activity causes intermittent or continuous relatively high frequency activity that can partially or completely obscure background rhythms (BGR) (Holliday 1999).

Unlike EEG recording in humans, animals usually require restraint to perform the procedure. Artefacts caused by movements of the patient and by muscles in the region of the recording electrodes are significant problems in non-sedated patients (Holliday 1999). Different protocols for sedation or anaesthesia for EEG recording have been described to resolve the problem. However, certain anaesthetic agents can induce spikes and other drugs can suppress spikes thus confusing interpretation (Srenk & Jaggy 1996; Holliday & Williams 1998; Holliday 1999). Chlorpromazine (2 mg/kg intravenous injection) has been reported to increase the incidence of interictal paroxysmal discharges in epileptic dogs (Redman *et al.* 1973). Although it has similar pharmacological characteristics, acepromazine has not been established as having a similar effect (Holliday & Williams 1998).

There is a body of veterinary neurologists who prefer to perform EEG recording in dogs with sedation as they believe that the use of anaesthesia is best avoided as it is likely to mask significant abnormalities. Furthermore, sedative drugs in doses sufficient to render the animal drowsy when undisturbed minimise or eliminate difficulties with movement and muscle artefacts and permit recording during all stages of sleep, which is an important part of the protocol (Holliday 1999). There is another group of neurologists who prefer to record EEG in dogs under general anaesthesia (medetomidine for premedication and propofol for anaesthesia). Based on the observations of a transient pattern of paroxysmal discharges (spindles) with asymmetrical distribution, it was concluded those findings

reflect neuronal discharges caused by epilepsy, rather than activity induced by anesthetic agents (Srenk & Jaggy 1996).

1.3.8.3 Interictal Paroxysmal Discharges

The recording of EEG during the patient's clinical episodes may be particularly helpful in determining whether the episodes are indeed seizure disorder in nature and whether they have a focal or lateralised origin (Hopkins *et al.* 1995). As episodes usually occur unpredictably, the likelihood of obtaining ictal recordings is not high unless prolonged recordings are made or episodes are provoked. However, even if a episode can be recorded, as mentioned above, the EEG recording may be so obscured by muscle and movement artefacts that little useful information can be gained from it (Holliday 1999).

The interictal EEG recording is potentially abnormal in epileptic dogs and may exhibit features that help to establish the diagnosis. Possible findings include paroxysmal discharges and are composed of one or more of the following in epileptic dogs: spikes, multiple spike complexes, sharp waves, multiple sharp-wave complexes, spike-and-slow-wave complexes (Holliday & Williams 1998). Such epileptiform activity may be focal, multifocal, or diffuse and may appear unilaterally or bilaterally; if bilaterally, it may be synchronous or asynchronous and symmetrical or asymmetrical (Aminoff 1986).

The routine EEG may be normal in some patients with epilepsy and may, also, occasionally show apparent epileptiform changes in people with no history of epilepsy (Hopkins *et al.* 1995). In human studies, epileptiform activity has been observed in the initial EEG of 2.2-4% of patients without seizures (Aminoff 1986). The probability of demonstrating abnormal interictal epileptiform activity in a human patient increases with the number of EEG recordings in the individual patient. Approximately 50% of the patients demonstrated abnormal epileptiform activity in the first EEG recording, increasing to 84% by the third and to 92% by the fourth recording (Berendt *et al.* 1999). In studies of EEG in dogs with epilepsy, abnormal EEG activity was identified in the first EEG in 65-86% of the dogs and no paroxysmal discharges were found in healthy dogs (Jaggy & Bernardini 1998; Berendt *et al.* 1999). The proximity of a seizure to the EEG examination may influence the amount of epileptiform activity present in the EEG. The closer the examination to a seizure and/or the higher the seizure frequency, the greater the probability that EEG findings will be positive (Berendt *et al.* 1999).

EEG has been suggested to be a valuable diagnostic aid in confirming a clinical diagnosis of canine epilepsy by some veterinary neurologists. In addition, results from some studies show that similarities exists between dogs and humans with epilepsy (Berendt *et al.* 1999). However, veterinary EEG technique has not been standardised and different veterinary neurologists use different modifications of human electrode placements, EEG montages and anaesthesia protocols. Due to these factors, comparing the results from different EEG laboratories and assessing the value of EEG in canine epilepsy is difficult.

1.4 ANTIEPILEPTIC DRUG THERAPY

1.4.1 General Principles of Antiepileptic Drug Therapy

Once a diagnosis of idiopathic epilepsy has been established, the decision on whether antiepileptic drug (AED) therapy should be instigated is based on the frequency and severity of the animal's seizures, as well as the owner's needs and willingness to comply with recommendations for treatment regimens and monitoring (Lane & Bunch 1990). The ideal outcome of AED therapy for patients with epilepsy is to be seizure-free without side effects. However, in human medicine, even with the advent of new AEDs, a significant number of people with epilepsy still cannot achieve this goal (Glauser & Pippenger 2000). A more realistic goal is perhaps to decrease the number of seizures, the severity of individual seizures and postictal complications to a level that does not substantially compromise the quality of life for the dog and family, whilst avoiding serious side effects associated with the use of AED therapy (Podell 1996; Thomas 2000). Most authors agree that one isolated seizure every 6 to 8 weeks is acceptable and seizure control represents a 50% decrease in seizure frequency without concomitant AED intoxication (Knowles 1998).

1.4.1.1 When to Initiate Treatment

In general, it is not suggested to instigate AED therapy after the first isolated seizure in dogs, as evaluation of the underlying seizure pattern and any response to AED therapy will be compromised (Knowles 1998). In dogs with idiopathic epilepsy, AED therapy is usually started when (a) two or more isolated seizures have occurred within a 6-week period, (b) two or more cluster seizure episodes occur within an 8-week period, or (c) status epilepticus has occurred (Podell 1996). It should be remembered that a prolonged

delay in starting AED therapy might result in progressive seizure activity associated with development of mirror foci and kindling, as mentioned above. In a long-term study of idiopathic epilepsy in 54 Labrador retrievers, the authours concluded that dogs with a low total number of seizures prior to treatment responded significantly better to phenobarbitone treatment (Heynold *et al.* 1997).

1.4.1.2 Owner Education

Proper owner education is an important factor in seizure management in companion animals. Owners must understand AED therapy is not curative and that seizure control does not equal elimination (Lane & Bunch 1990; Podell 1996). They must be informed that AED therapy may involve a lifetime, daily treatment regimen and that regular administration of medication is important. Potential side effects of AED therapy must be explained, including the potential deleterious effects of long-term use and the mild side effects that commonly occur when first starting AED therapy, which may precipitate an alarmed owner to cease therapy prematurely (Thomas 2000). Owners should always be warned not to stop AED suddenly due to the risk of precipitating seizures. Regular re-evaluation and drug serum concentration monitoring are necessary and keeping a seizure diary, which includes the time, date and characteristics of each seizure, any side effects and other relevant comments, is helpful in assessing seizure management (Lane & Bunch 1990; Knowles 1998). Finally, owners should be informed not to alter treatment without the advice of the veterinarian (Thomas 2000).

1.4.1.3 Mechanisms of Action of the AEDs

Antiepileptic drugs block seizure initiation and propagation by blocking abnormal events in a single neuron or the synchronisation of related neurons (Boothe 1998). Mechanisms of AED action can be classified into three broad categories: (a) enhancement of inhibitory processes via facilitated action of GABA, (b) reduction of excitatory transmission and (c) modulation of membrane cation conductance. Binding of GABA, benzodiazepines or phenobarbitone to the $GABA_A$ receptor will result in increased chloride permeability and subsequent membrane hyperpolarisation. Drugs that increase the availability of GABA to receptors by inhibition of degradation or re-uptake pathways will also enhance inhibitory neurotransmission. Reduction of excitatory neurotransmission can also be accomplished by altering glutamate-mediated neurotransmission. Drugs that block sodium channels prevent depolarisation of the presynaptic neuronal membrane and thus reduce release of the excitatory neurotransmitter glutamate. Some drugs may be able to block the function

of the NMDA receptor and thus prevent post-synaptic depolarisation (Podell 1998). Drugs acting on more than one mechanism tend to be most effective (Boothe 1998). The probable main mechanisms of action of antiepileptic drugs are listed in Table 1.5 (page 34) (Perucca 1996).

However, there is no clear correlation between the putative primary mechanism of action of different drugs and their efficacy in different seizure types. These inconsistencies may be explained by the fact that available information on mechanisms of action is still scarce and fragmentary, with many drugs probably having additional actions apart from those listed in Table 1.5 (page 34) (Perucca 1996).

1.4.1.4 Choice of Treatment

Criteria for selection of suitable AED for use in dogs includes: a preparation that can be administered two to three times per day, has documented efficacy and is well tolerated by the canine patient (Podell 1998). Several limitations exist in the selection of AEDs for use in veterinary medicine: (a) toxicity, (b) tolerance, (c) inappropriate pharmacokinetics, and (d) expense. Many AEDs that work directly at the sodium membrane ionic level to prevent neuronal depolarisation cannot be used in veterinary medicine because of either a high risk of toxicity or a short elimination half-life. Therefore, most drugs used in veterinary medicine are in the same mechanistic category and work by hyperpolarising the resting neuronal cell membrane (Podell 1996).

Monotherapy is the goal of treating dogs with idiopathic epilepsy to reduce possible drug-drug interactions and adverse effects (Podell 1998). There is little evidence of synergistic action amongst the AEDs and polytherapy has several potential disadvantages, including increased cost, the need to monitor and interpret serum concentrations of multiple drugs, potential drug interactions and more complicated dosing schedules (Thomas 2000). Usually, a drug given as monotherapy is titrated to a maximally tolerated dose before the decision is made to try another drug. If the dog responds to the second drug, the veterinarian should attempt to withdraw the first drug gradually and only if this is unsuccessful should polytherapy be continued (Thomas 2000; Deckers *et al.* 2000).

Table 1.5 Mechanisms of action of AEDs (Perucca 1996; Deckers *et al.* 2000)

AED	Na^+ channel blockade	Ca^{2+} channel blockade	GABA mimetic drugs	Antiglutamate action	Probable main mechanisms of action in detail
Benzodiazepine	+	+	+++		Potentiation of GABA responses through binding with a modulatory site of the benzodiazepine $GABA_A$ receptor complex
Bromide					Neuronal hyperpolarisation and chloride channel alterations (replacement of negatively charged chloride with bromide)
Felbamate	+	+	+	++	Blockade of voltage-dependent Na^+ channels Antagonism of excitatory transmission through an action at the glycine modulatory site of the NMDA receptor Potentiation of GABA responses
Gabapentin	+		++	+	Potentiation of GABA responses Blockade of voltage-dependent Na^+ channels
Nimodipine		++			Ca^{2+} channel antagonist
Phenytoin Mephenytoin	+++	+	+		Blockade of voltage-dependent Na^+ channels
Phenobarbital Primidone	++	+	++	++	Potentiation of GABAergic transmission partly through enhancement of GABA activated chloride conductance
Valproic acid	++		++	+	Blockade of voltage-dependent Na^+ channels Potentiation of GABAergic transmission
Vigabatrin			+++		Potentiation of GABAergic transmission through inhibition of GABA-transaminase

+++ Well-documented action believed to account for a major part of the drug's antiepileptic effect; ++ effect probably of clinical significance; + effect only tentatively characterised or seen only at supratherapeutic concentrations.

However, in one review of AED polytherapy based on mechanisms of action, it was concluded that the AED polytherapy with different mechanisms of anticonvulsant action may in fact enhance effectiveness. In particular, combining a sodium channel blocker with a drug enhancing GABAergic inhibition appears to be advantageous. Combining two GABA mimetic drugs or combining a kainate antagonist with an NMDA antagonist may enhance efficacy, but tolerability is sometimes reduced. Combining two sodium channel blockers seems less promising (Deckers *et al.* 2000). However, this approach cannot be fully applied with the current inadequate state of understanding of the pathophysiology of seizures in the canine patient and the basic mechanisms of action of AEDs (Perucca 1996).

1.4.1.5 Clinical Pharmacokinetics

Desirable pharmacokinetic properties for an AED include high oral bioavailability, negligible plasma protein binding, efficient penetration across the blood-brain barrier, a half-life compatible with once or twice daily dosing and linear kinetics. Lack of extensive biotransformation is also advantageous because it is normally associated with predictable kinetics and low susceptibility to drug interactions (Perucca 1996).

Most AEDs are well absorbed following oral administration, but food will slow the rate of absorption of some drugs (Boothe 1998; French & Gidal 2000).

The extent of protein binding has pharmacokinetic importance since it is the unbound fraction of the drug that readily crosses cell membranes during the processes of distribution, receptor interaction and renal or hepatic elimination (Perucca 1996). Most AEDs are lipid-soluble and are distributed to a volume that exceeds total body water (i.e., greater than 0.6 l/kg) (Boothe 1998). Protein binding, lipid solubility and degree of ionisation at physiological pH affect penetration of AED into CSF, which would influence the speed of onset of therapeutic effect (Perucca 1996). Lipid solubility is the most important factor that influences AEDs' entry into CSF. At equilibrium, however, the CSF concentrations of these drugs are directly proportional to the non-protein-bound fraction in the serum (Lane & Bunch 1990).

Because they are lipid-soluble, most AEDs must be eliminated by hepatic metabolism. Some reactive Phase I metabolites can interact with and damage surrounding tissues. Hepatotoxicity is a common effect of long-term use of AEDs metabolised by the liver (Boothe 1998). Any drugs metabolised by the liver can potentially influence drug metabolising enzyme systems and interactions are common. Some AEDs are enzyme

inducers, some are inhibitors, whereas some are both, with the nature of the interaction depending on the drug and that with which it interacts (Glauser & Pippenger 2000). Hepatic inducers increase the synthesis of enzymes that are associated with a proliferation of hepatocyte smooth endoplasmic reticulum. Enzyme induction is a gradual, dose-dependent process, and the time to complete manifestation of an induction interaction depends on the half-life of the inducing drug and the synthesis rate of the metabolising enzymes (French & Gidal 2000). An increased rate of drug metabolism will increase clearance and elimination half-life of many drugs in patients on chronic therapy (Boothe 1998). Phenobarbitone is an auto-inducer, causing a progressive reduction in its own elimination half-life with long-term use (Podell 1996). Drugs that impair or inhibit drug metabolising enzymes, such as cimetidine, ketoconazole and chloramphenicol, will decrease drug metabolism of AEDs and thus potentially increase serum concentration (Boothe 1998).

After initiation of long-term oral therapy, drug accumulates in the body until the rate of clearance equals the rate of administration, at which point a steady-state equilibrium is achieved. The maintenance dose is the daily dose necessary to maintain steady-state equilibrium. Within one half-life, approximately 50% of a steady-state equilibrium is achieved and 97% occurs after five half-lives have elapsed (Boothe 1998). Complete steady-state equilibrium is achieved at the completion of seven half-lives (Glauser & Pippenger 2000). The full clinical effectiveness of an AED is not achieved, nor should it be evaluated, until steady state has been achieved after any dosage change (Glauser & Pippenger 2000). When therapeutic serum concentrations are required earlier, a loading dose can be administered. Simplistically, the loading dose is a sum of all the daily doses that would have been administered prior to steady-state concentration minus the amount that would be eliminated during this period (Thomas 2000). The major disadvantages of a loading dose of an AED is that there is no time for tolerance to the sedative side effect to occur, thus, lethargy and ataxia occur more commonly than with gradual increases in drug concentration. Both loading and maintenance dose are based on population deposition parameters. Individual differences in drug elimination may result in therapeutic failure with either dosing regimen (Boothe 1998).

1.4.1.6 Therapeutic Drug Monitoring and AED Therapy

Variability amongst patients makes the relationship between dose and serum drug concentrations unpredictable for the individual patient (Boothe 1998). In addition, the correlation between the observed clinical effects of AEDs and their serum concentrations is

much better than that between the AEDs' observed clinical effects and total daily dose (Glauser & Pippenger 2000). Blood drug concentration monitoring can be selectively and appropriately utilised to help optimise drug administration, determine if tolerance is present, detect poor compliance and minimise side effects, especially when it may be related to patient-specific pharmacokinetic or pharmacodynamic problem (Podell 1998; Glauser & Pippenger 2000).

Clinical AED monitoring is useful in the following situations.

Establishing "baseline" effective concentrations

When the patient has achieved the goals of therapy, a trough serum concentration of AED should be obtained to document the serum concentration associated with the successful outcome (Boothe 1998). If the patient later develops breakthrough seizures or toxicity, repeat AED serum concentrations can be compared to an individual's "baseline" previously effective non-toxic concentration to help determine the cause of the new problem (Glauser & Pippenger 2000).

Evaluating potential causes for lack of efficacy

In a large population, the distribution of AED serum concentrations after a fixed dose should be a bell-shaped curve. The vast majority of patients exhibit concentrations within the target range (mean ± 2SDs) expected from a dosage based on body weight. Patients with AED concentrations < mean - 2SDs for the fixed dose can be considered genetically "fast metabolisers" (Glauser & Pippenger 2000). Persistent, unusually low and variable serum concentrations may suggest a "fast metaboliser" or poor owner or patient compliance (Podell 1998; Glauser & Pippenger 2000). Detailed history and close supervision of AED intake help to distinguish between these two situations. AED serum concentrations increase sharply with a monitored AED intake at a constant daily dose in patients with noncompliance, whereas fast metabolisers demonstrate no change in serum concentrations (Glauser & Pippenger 2000).

Evaluating potential causes for loss of efficacy

The most common situation underlying a loss of AED efficacy is drug tolerance. It can be either metabolic or functional in nature and the relationship between drug dose and serum concentration helps to distinguish them (Podell 1998). Metabolic tolerance occurs with AEDs that are inducers of hepatic metabolising enzymes. The auto-induction allows a progressive reduction in elimination half-life with long-term use and higher doses are progressively needed to maintain the same therapeutic concentration (Podell 1996). With

metabolic tolerance, there is no parallel increase in serum concentration as the dose increases. In contrast, with functional tolerance, there is a parallel increase in serum concentration as the drug dose increases (Podell 1998). The lack of response can develop for several reasons: (a) the BBB can develop altered transport mechanisms to limit drug entry into the brain, (b) phenobarbitone receptors in the brain can down-regulate with chronic exposure and (c) pathophysiological progression of brain pathology resulting in multiple seizure foci or changes in neurotransmission may lead to loss of drug efficacy (Podell 1996).

Administration of either multiple AEDs or a combination of AED and drugs for other conditions can modify any of the processes of absorption, metabolism, distribution and elimination, possibly resulting in complex interactions (French & Gidal 2000). Hepatic induction may be one of the impacts of drug-drug interaction. As discussed above, the rate of drug metabolism will increase clearance and elimination half-lives of many drugs if a patient receives continuous therapy with the inducing drug (Podell 1998; Glauser & Pippenger 2000).

Noncompliance is also a potential cause of loss of efficacy. A reduction in trough serum concentration of 20% or more is suggestive of a compliance problem (Podell 1998). In human medicine, breakthrough seizures in neonates, infants, young children and pregnant women can be due to altered or changing AED pharmacokinetics resulting from their physiological circumstances (Glauser & Pippenger 2000). In dogs, occasionally, unspayed bitches experience an increase in seizure frequency during oestrus. The same effect can happen in neutered dogs on oestrogen therapy for urinary incontinence (Knowles 1998).

Judging " room to manoeuvre" or when to change AED therapy

In many cases of refractory epilepsy, inadequate dosages, incorrect dosing intervals or insufficiently high serum concentrations are the causes of unacceptable seizure frequency (Knowles 1998). Peak and trough samples can be collected and used to calculate the AED half-life so that the dosing interval can be modified if necessary (Boothe 1998). If a patient is titrated to and above a reasonable "target dose" and no response is seen, evaluation of a serum concentration may be helpful to determine the next step as whether increasing the dose of the AED should be considered or changing AED should be undertaken (Glauser & Pippenger 2000).

Evaluating potential causes for toxicity

Patients with AED levels > mean + 2SDs for a fixed dose can be considered genetically "slow" metabolisers. They require lower doses of an AED to achieve the same plasma concentration and the desired therapeutic effect. Therapeutic drug monitoring facilitates identification of the slow metabolisers, so their medication regimen can be appropriately adjusted to fit their individual metabolic patterns (Glauser & Pippenger 2000).

The normal process of maturation involves a large number of physiological changes that can dramatically alter drug utilisation. In human medicine, children utilise drugs at a faster rate than adults and therefore require more medication on a body-weight basis than adults to achieve the same therapeutic drug concentration. As the maturation process continues, the ability to bind drugs to plasma protein decreases. Geriatric patients often exhibit reduced rates of drug elimination and therefore require reduced drug dosages. Failure to adjust the therapeutic regimen to compensate for the associated physiological changes may result in exposure to unnecessary and prolonged drug toxicity (Glauser & Pippenger 2000).

Acute or chronic uraemia can dramatically decrease the elimination of a drug that is primarily dependent on urinary excretion, and renal failure can alter the protein-binding to albumin characteristics of many drugs (French & Gidal 2000). In both situations, the ratio of free drug to total drug concentration is high enough to produce a clinically evident toxic effect, even if the total serum drug concentrations are within optimal therapeutic range. Hepatic disease can extensively alter a given therapeutic response by impairing a patient's ability to metabolise drugs. In all these situations, therapeutic drug monitoring provides means of accurately calculating and correcting dosage regimens to coincide with the disease status of the patient (Glauser & Pippenger 2000).

Drug-drug interaction is another potential cause of AED toxicity. In a patient receiving AED polytherapy and exhibiting side effects, therapeutic drug monitoring can assess which AED is most likely to be causing the problem (Glauser & Pippenger 2000). As mentioned above, drugs that impair or inhibit drug metabolising enzymes will decrease the metabolism of an AED and thus potentially increase the serum concentration of the drug (Boothe 1998). Protein-binding interactions commonly occur when two highly protein-bound drugs (>90% bound) are administered and compete for a limited number of binding sites. When one drug displaces another highly bound drug from its plasma protein-binding site, the free fraction may dramatically increase. The unbound drug is available to interact not only with pharmacological receptors but also with hepatic enzymes, thus total systemic

clearance also increases. The net effect is difficult to predict and free serum drug monitoring may be useful (French & Gidal 2000).

Circumstances or intervals for measuring serum concentrations are summarised here: (a) at steady state when seizures are controlled, to establish baseline for future comparisons; (b) each time AED therapy fails to control seizures; (c) anytime following dose alteration, to establish a new steady state; (d) every 6 months, in order to detect changes proactively that might indicate potential therapeutic failure; and (e) for drugs that have a long half-life, blood concentrations should be monitored at one drug half-life and at steady state.

Sampling at one drug half-life is proactive since drug concentration will be only halfway to final steady-state concentration. If a loading dose is used, besides the two blood concentrations mentioned above, samples should be taken 1 or 2 days after loading dose. By comparing the post-loading dose blood concentration and that after one half life, failure to maintain the target concentration with the maintenance dose can be detected earlier (Boothe 1998). In general, trough serum concentrations should be measured if there is poor seizure control to determine if an inadequate dose is being given, and peak concentrations measured when there is a concern of drug toxicity (Podell 1998). Fasting samples are preferred as lipidaemia will render the results of many tests invalid (Boothe 1998).

Special handling precautions are not necessary for samples intended for therapeutic drug monitoring. However, serum separator tubes should be avoided as silicon contained in these tubes may bind AED. These tubes should either not be used or serum should be withdrawn from the tubes immediately after centrifugation (Boothe 1998).

1.4.2 Antiepileptic Drugs

1.4.2.1 Phenobarbitone

Clinical use of phenobarbitone

Phenobarbitone is reported to be effective in 60% to 80% of dogs with epilepsy if serum concentrations of the drug are maintained within recommended therapeutic ranges (Boothe 1998). The mechanism, pharmacokinetics and clinical use of phenobarbitone are detailed in Table 1.5 (page 34), Table 1.6, and Table 1.7 (page 44). The initial dose is 2-3.5 mg/kg every 12 hours with serum concentration measured after 2 weeks (Podell 1996; Podell 1998; Boothe 1998; Thomas 2000). If seizures are not controlled, doses can be increased gradually until the maximum range has been reached or adverse effects become apparent

(Boothe 1998). Two methods are suggested as to how to adjust the dose in such circumstances: (a) increase the dose 25% each time, (b) adjust the dose with the following formula in order to increase serum concentration by 5 μg/ml (Podell 1998; Boothe 1998).

$$\text{New total \# mg daily} = \text{Current \# mg daily} \times \frac{\text{Desired concentration}}{\text{Actual concentration}}$$

Due to auto-induction, it is usually necessary to increase the initial dose to maintain a stable trough therapeutic serum concentration (Thomas 2000). In some patients, auto-induction may eventually shorten the half-life to 36 hours or less and an 8-hour dosing interval may be necessary to minimise fluctuation of serum concentrations. Measurement of both peak and trough concentrations is required to estimate current half-life (Boothe 1998).

In general, trough serum concentration is useful to determine if an inadequate dose is being given. Different serum concentration monitoring programs are suggested. In one program, it is suggested that trough serum concentrations are measured at 14, 45, 90, 180, 360 days after the initiation of treatment, at 6-month intervals thereafter and if a dog has more than two seizure events between these times (Podell 1998). Another program suggests that serum concentrations are measured at 2 weeks (peak and trough), at 8 to 12 weeks (trough) to detect induction, then 6-month intervals (trough) and when a dog has breakthrough seizures (peak and trough) (Boothe 1998). In one study of the effect of timing of blood collection on serum phenobarbitone concentrations, it was revealed that there is no therapeutically relevant change (defined as 30% change in this study) in serum phenobarbitone concentrations using the 12 hourly dosing interval in most epileptic dogs (91% of dogs with stable serum concentrations). Nine percent of dogs with therapeutically relevant changes in serum concentrations were found to have relatively short elimination half-lives (Levitski & Trepanier 2000).

Side effects of phenobarbitone

Polyphagia, polydipsia, polyuria, lethargy and sedation are the most commonly documented side effects of phenobarbitone (Podell 1996). Polyuria is primarily due to an inhibitory action on the release of antidiuretic hormone, however, dogs may develop an apparent psychogenic polydipsia with associated polyuria (Podell 1998; Boothe 1998). Sedation is the main dose limiting effect of phenobarbitone, and hindlimb weakness and ataxia may occur in some dogs (Boothe 1998; Thomas 2000). All these effects may be long lasting and may persist in some cases for the duration of treatment. However, often they resolve after 1 to 2 weeks of therapy (Boothe 1998).

Hyperactivity and restlessness can occur, especially during the first few weeks of therapy (Thomas 2000). It is also described as an infrequent problem that appears not to be dose related and which will resolve typically within 1 week of starting the treatment (Podell 1996). In human medicine, it is reported that hyperactivity occurs in 50 to 80% of children, even with low serum phenobarbitone concentrations. This paradoxical effect has also been described in the elderly (Harden 2000).

As discussed above, in dogs, phenobarbitone is a potent hepatic microsomal enzyme inducer by causing proliferation of the hepatocyte endoplasmic reticulum, which in turn increases the synthesis of cytochrome P450 enzyme (French & Gidal 2000). The same mechanism can cause increased serum liver enzyme activation without causing actual hepatocellular damage or biliary stasis, making it difficult to distinguish increases caused by enzyme induction from those caused by hepatic disease during phenobarbitone treatment (Muller *et al.* 2000a). The extent of the enzyme-inducing effect on hepatic enzymes varies among individuals. A few studies of effects of long-term phenobarbitone on the liver in dogs revealed that alkaline phosphatase (ALP) and alanine transaminase (ALT) can increase significantly over long time, whilst γ-glutamyltransferase (GGT) may increase transiently and albumin may decrease transiently. There are no significant changes in aspartate transaminase (AST), bilirubin and fasted bile acid (Chauvet *et al.* 1995; Foster *et al.* 2000; Muller *et al.* 2000a). This suggests that ALP, ALT and GGT are of limited diagnostic value because of the effects of enzyme induction (Muller *et al.* 2000a). The increased concentrations of ALT caused by enzyme induction are commonly smaller than those found after hepatocellular necrosis or bile duct occlusion (Dayrell-Hart *et al.* 1991; Muller *et al.* 2000a). Abnormal values for AST, serum albumin, total bilirubin and fasting bile acids in dogs treated with phenobarbitone cannot be attributed to the enzyme-inducing effect of the drug (Muller *et al.* 2000a).

Phenobarbitone can cause non-pathological changes in hepatic clinical laboratory tests, but hepatotoxicity is also a potential side effect (Boothe 1998). It is still unclear whether phenobarbitone-induced hepatotoxicity represents an idiosyncratic drug reaction or the extreme of a spectrum of toxicosis that develops in all dogs on chronic phenobarbitone treatment (Muller *et al.* 2000a). It is reported that a serum phenobarbitone concentration above 35 μg/ml had the highest correlation with the development of hepatotoxicity (Dayrell-Hart *et al.* 1991). Finding greater increases in ALT activity than in ALP activity might be useful in recognising hepatic toxicosis, but this only occurred in 50% cases in a report of 18 dogs with phenobarbitone toxicosis. In addition to hepatic function tests (sulfobromophthalein excretion, pre- and post-parandial bile acid concentrations, resting

plasma ammonia concentration and ammonia tolerance test), toxicosis also can be associated with an increased serum concentration with unchanging dose (Dayrell-Hart *et al.* 1991). Hepatotoxicity may be reversible if detected early and the phenobarbitone is withdrawn, however, this adverse effect can be irreversible and ultimately fatal (Thomas 2000). The incidence of serious hepatotoxicity can be reduced by avoiding combination therapy (of more than one drug metabolised by the liver), using therapeutic drug monitoring to achieve adequate serum concentrations at the lowest possible dose and by evaluation of clinical pathology every 4 to 6 months while the patient is on therapy (Boothe 1998).

It is also found that phenobarbitone treatment at therapeutic dosages in dogs can significantly decrease total thyroxine (TT_4) and free thyroxine (FT_4) after 5 weeks of treatment, and thyroid-stimulating hormone (TSH) may have a delayed compensatory increase after 27 weeks of treatment (Gaskill *et al.* 1999; Muller *et al.* 2000b). These changes are not necessarily associated with clinical signs of hypothyroidism or the degree of seizure control (Gaskill *et al.* 1999). Clinical trials evaluating the effects thyroid hormone supplementation in phenobarbitone-treated dogs with low serum T_4 concentrations have not been reported (Gaskill *et al.* 1999). Changes in markers of thyroid function (TT_4, FT_4 and TSH) can persist for 1 to 4 weeks after discontinuation of phenobarbitone. To avoid false positive results, it is recommended that thyroid testing should be performed at least 4 weeks after discontinuation of phenobarbitone administration (Gieger *et al.* 2000). In addition, in studies of effects of long-term phenobarbitone treatment on the adrenal axis and adrenal function tests in dogs, it revealed that phenobarbitone treatment does not affect the adrenal axis or two adrenal function tests, the ACTH stimulation test and low-dose dexamethasone suppression test (Chauvet *et al.* 1995; Muller *et al.* 2000b).

Phenobarbitone has been associated with bone marrow dyscrasias causing depression of one or all bone marrow cell lines, which are rare side effects and may represent an idiosyncratic reaction rather than a dose-related effect (Boothe 1998; Jacobs *et al.* 1998). It has been reported that neutropaenia, thrombocytopaenia and/or anaemia have developed after phenobarbitone or primidone treatment for 2 to 5 months (Jacobs *et al.* 1998). These changes resolve with withdrawal of the drug (Boothe 1998; Jacobs *et al.* 1998; Thomas 2000). The possible underlying mechanisms include drug-induced immune-mediated disease or a direct cytotoxic effect on committed stem or circulating cells due to toxic drug metabolites (Jacobs *et al.* 1998).

Table 1.6 Pharmacokinetic variables for AEDs (Podell 1998; Boothe 1998; French & Gidal 2000)

AED	F (%)	Vd (l/kg)	Prot bind. (%)	$T_{1/2}$ (h)	Tss (d)	Metabolism	Site of clearance
Phenobarbital	86-96	0.7	45	56-102 h	14-21 d	Hepatic	75% hepatic, 25% renal
Bromide	>90	0.3	0	25-46 d	83-120 d	-	Mainly renal
Primidone	>90	0.75	<20	8-15 h	N/A	Hepatic	50% hepatic, 50% renal
Phenytoin	36	N/A	75-85	3.65-7.8 h	N/A	Hepatic	>90% hepatic
Clorazepate	N/A	1.6	N/A	4-6 h	1d	Hepatic	N/A

F, bioavailability; Vd, volume of distribution; Prot bind, fraction bound to serum protein; $T_{1/2}$, elimination half-time; Tss, steady-state time; N/A, not available.

Table 1.7 Recommended doses for AEDs in dogs (Braund 1994; Podell 1998; Boothe 1998)

AED	Indication	dose	Dosing time	Therapeutic range
Phenobarbitone	Initial	2-3.5 mg/kg	q12h	20-35 µg/ml
Bromide	Initial	30-40 mg/kg	q24h	0.8-2 mg/ml in combination with PB <3 mg/ml alone
Primidone	Not recommended	35-70 mg/kg	q12h	Phenobarbital 20-35 µg/ml
Phenytoin	Not recommended	6.6-11, 30-35 mg/kg	q8h	10-20µg/ml
Clorazepate	Add-on	1-2 mg/kg	q12h	300-500 ng/ml; 0.5-1.5 µg/ml

1.4.2.2 Bromide

Clinical use of bromide

The primary indication for the use of bromide as an AED in veterinary medicine has been in combination with phenobarbitone in refractory epilepsy, which has been reported to improve seizure control in about 58 to 83% of dogs with idiopathic epilepsy (Schwartz-Porsche 1992; Podell & Fenner 1993; Trepanier *et al.* 1998). Because bromide is not subject to hepatic metabolism and is not bound to plasma protein, it is the choice of AED in patients that have developed liver disease. Bromide is also effective as monotherapy (Thomas 2000).

The mechanism of the antiepileptic action of bromide is not completely understood. Like chloride ions, bromide ions are distributed mostly to the extracellular space, however, bromide does accumulate intracellularly in neurons and appears to cross neuronal chloride channels more readily than chloride. GABA enhances this influx of bromide, leading to neuronal hyperpolarisation, and thereby stabilises neurons against excitatory input from epileptic foci (Trepanier 1995). In humans, the antiepileptic effects correlate with plasma concentration. The data for the pharmacokinetics and clinical use of bromide in the dog are described in Table 1.6 and Table 1.7 (page 44) (Boothe 1998). Bromide is not metabolised by the liver, excreted predominantly by glomerular filtration and reabsorbed by the renal tubules in competition with chloride (Trepanier 1995). High chloride intake increases bromide elimination, which increases the dose requirement (Trepanier & Babish 1995; Shaw *et al.* 1996). Renal insufficiency decreases bromide elimination, thus, if bromide is administered in dogs with mild renal dysfunction, a reduced dose should be used and serum bromide concentration should be monitored closely to avoid toxicity. Bromide should be avoided in dogs with more serious renal dysfunction (Trepanier 1995). In humans, the variability between therapeutic and toxic serum bromide suggests that individuals differ in their tolerance of bromide. As in humans, dogs show individual sensitivity differences (Schwartz-Porsche 1992). Overall, factors which may affect bromide sensitivity include the physical condition of the dog, food and salt intake, dehydration, vomiting, diarrhoea, impaired renal function and individual variability (Yohn *et al.* 1992).

Bromide is available as potassium bromide or sodium bromide (Boothe 1998). There is no difference in efficacy for the potassium or sodium salt although sodium bromide is more difficult to dissolve in water compared to potassium bromide (Trepanier 1995; Podell 1998). If sodium bromide is used, the dosage (usually reported in the literature for

potassium bromide) should be decreased by 15% to account for the higher bromide content of the sodium salt (Boothe 1998; Thomas 2000). Potassium bromide is preferred when sodium intake must be restricted (e.g. congestive heart failure, hypertension, or hepatic disease) and sodium bromide should be used if hypoadrenocorticism or renal disease exists that may prevent normal potassium homeostasis (Trepanier 1995; Podell 1998; Thomas 2000).

The suggested initial dose is 30 to 40 mg/kg daily with the dose subsequently being adjusted based on the clinical effects and the results of therapeutic monitoring (Schwartz-Porsche 1992). The target range of serum bromide concentration is approximately 1 to 2 mg/ml when used in combination with phenobarbitone and 2 to 3 mg/ml when used as monotherapy (Trepanier 1995; Thomas 2000). In a retrospective study of therapeutic serum drug concentrations in 122 epileptic dogs, it was revealed that, in dogs treated with bromide and phenobarbitone, the reasonable therapeutic range (the lower 10^{th} and upper 90^{th} percentiles of the dogs in the study) for serum bromide concentrations is 0.81 to 2.40 mg/ml, and for bromide treatment alone, the range is 0.88 to 3.00 mg/ml (Trepanier *et al.* 1998). Some dogs may require or be tolerant of doses of 80 mg/kg/day or serum bromide concentrations of 4 mg/ml, however, the maximum dose is always dictated by the patient's clinical response and side effects of the bromide (Knowles 1998; Thomas 2000) .

As the time for steady state equilibrium of bromide is 3 to 4 months, a loading dose is recommended to achieve therapeutic concentrations more rapidly. The maintenance dose must also be given each day. Based on a volume of distribution of 0.3 L/kg and a target concentration of 1.0 to 1.5 mg/ml, the suggested loading dose of bromide is 450 to 600 mg/kg. In addition, a "mini" loading dose of 225 to 250 mg/kg is suggested to increase the serum bromide concentration by about 0.5 mg/ml. The loading dose is split over 5 days to reduce the side effects of sedation and gastrointestinal irritation (see Side effects of bromide, page 47).

As mentioned above (1.4.1.6 Therapeutic Drug Monitoring and AED Therapy, page 36), if a loading dose is used, the first serum bromide concentration should be measured at 1 or 2 days after the loading dose finished. Whether or not a loading dose is given, serum bromide concentrations should be measured at 1 month (one half-life) and 3 to 4 months (steady state) after the initiation of treatment (Boothe 1998). If serum bromide concentrations are within therapeutic range, and seizures are well controlled, therapeutic drug monitoring can be performed every 6 to 12 months unless problems arise. Monitoring should be more frequent in dogs with abnormal renal function, a fluctuating diet, or in

geriatric dogs (Trepanier 1995). Given the long half-life of bromide, the timing of the blood samples is not critical (Thomas 2000).

Side effects of bromide

Bromide toxicosis (bromism) has been well described in humans and is associated with neurological (headache, lethargy, partial amnesia, hallucinations, delirium, ataxia, stupor), gastrointestinal and dermatological signs (erythematous dermatitis) (Trepanier 1995; Podell 1996; Nichols *et al.* 1996). In one experimental study, dogs given sodium bromide at 100 mg/kg for 6 weeks had minimal side effects, whereas those given the drug at dosages of 200 to 500 mg/kg for 4 to 26 weeks developed shivering, ataxia, skin lesions, stupor, coma and death (Nichols *et al.* 1996).

Due to the primary indication of bromide in veterinary medicine as adjunctive AED to phenobarbitone, most of the documented side effects in dogs are observed in combination with phenobarbitone, which include polydipsia, polyuria, polyphagia, transient sedation, ataxia and hind limb weakness (Schwartz-Porsche 1992; Podell & Fenner 1993). Polydipsia, polyuria and polyphagia are well-documented side effects of phenobarbitone treatment in dogs, and it is difficult to ascertain whether or not bromide is exacerbating these effects (Podell & Fenner 1993). Sedation, ataxia and hind limb weakness are related to the anticonvulsant actions of the drug and dogs with higher concentrations are more severely affected, suggesting a dose-dependent effect (Podell & Fenner 1993; Boothe 1998). Vomiting can occur probably because of the direct gastric irritation caused by the hypertonic bromide salt (Thomas 2000). Administering the drug with food, dividing the daily dosage into multiple doses and the use of sodium bromide instead of potassium bromide are helpful in preventing vomiting (Trepanier 1995; Boothe 1998). Skin lesions have not been reported in dogs treated with pharmacological doses of bromide (Trepanier 1995). Abnormal behaviour such as irritability or restlessness has also been reported and usually requires a reduction in dose (Thomas 2000).

Most of the adverse neurological effects of bromide associated with therapeutic doses in dogs are mild and appear to resolve with a reduction in the dosage of any concurrent AED (Trepanier 1995). Bromide intoxication to the point of stupor is rare, especially with close monitoring of serum bromide concentrations (Podell 1996). In cases of bromide intoxication, bromide elimination may be increased by administering 0.9% NaCl intravenously or feeding a high-chloride diet. Loop diuretics also enhance bromide elimination by blocking chloride and bromide reabsorption (Nichols *et al.* 1996). Dogs

should be monitored carefully for seizure breakthrough as serum bromide concentrations decrease (Trepanier 1995).

1.4.2.3 Primidone

Clinical use of primidone

In dogs, primidone is primarily metabolised in the liver to phenobarbitone and phenylethylmalondiamide (PEMA), with a small residual serum concentration of primidone (Cunningham *et al.* 1983). All three compounds have some anticonvulsant effect. Primidone is rapidly eliminated in the dog and shows considerable fluctuations in its plasma concentrations. PEMA is only weakly active and does not play a major role in the anticonvulsant effect in the canine patient (Schwartz-Porsche *et al.* 1985). Compared with primidone and PEMA, phenobarbitone has longer a half-life and is much more potent in its anticonvulsant effect, and it is thought to be responsible for more than 85% of the total anticonvulsant activity of the primidone in dogs (Cunningham *et al.* 1983; Boothe 1998). Correlating with this is the observation that serum phenobarbitone concentrations in patients on primidone therapy can be correlated with primidone efficacy and should be monitored rather than those of primidone (Cunningham *et al.* 1983). Target therapeutic ranges are the same as for phenobarbitone (Boothe 1998).

Some clinical studies suggest there is no advantage to the use of primidone over the use of phenobarbitone as an AED in most dogs (Farnbach 1984a; Schwartz-Porsche *et al.* 1985). If primidone is used, it probably should be given TID for maximal effectiveness, since it and PEMA both have shorter half-lives than phenobarbitone and presumably any additional benefit from this drug would be due to the presence of these additional anticonvulsants (Farnbach 1984b).

The conversion ratio of primidone to phenobarbitone is 3.8:1. A patient should receive approximately 65 mg of phenobarbitone for each 250 mg primidone (Farnbach 1984a).

Side effects of primidone

The side effects of primidone are similar to phenobarbitone (Boothe 1998). In one study comparing the therapeutic efficacy of phenobarbitone and primidone in dogs, serum measurements of ALP, ALT and glutamate dehydrogenase (GLDH) were increased in approximately 70% of dogs treated with primidone, whereas such changes were only observed in 6.7% of dogs on phenobarbitone medication (Schwartz-Porsche *et al.* 1985). Histopathological changes after 6 months of primidone treatment include hepatocellular

hypertrophy and necrosis, lipidosis and extramedullary haematopoiesis (Bunch *et al.* 1985).

1.4.2.4 Phenytoin

Clinical use of phenytoin

Phenytoin is very effective in controlling seizures in man. However, it has not proven to be an effective AED in dogs due to the poor absorption (average bioavailability 36%) and too short a half-life to maintain adequate serum concentrations (Farnbach 1984b; Boothe 1998). In humans, the commonly stated therapeutic range for phenytoin is 10 to 20 μg/ml. Laboratory studies indicate that, in dogs, at least 35 mg/kg TID are needed to reach therapeutic concentrations (Oliver *et al.* 1997). In one clinical study of 77 dogs given phenytoin with the daily dose ranging from 3 to 129 mg/kg/day, it was observed that even high dosages are incapable of sustaining serum concentrations adequate for seizure control (Farnbach 1984b). In addition, phenytoin is an inducer of hepatic microsomal P450 enzymes. Even if a therapeutic serum concentration was achieved, the likelihood is this would only persist only for 2 to 3 days (Boothe 1998).

Due to strong protein-binding at therapeutic concentrations, saturation kinetics for its metabolism and hepatic microsomal enzymes induction, phenytoin has narrow therapeutic index and high risk for drug-drug interactions in humans (Boothe 1998; Glauser & Pippenger 2000). As dose adjustments produce disproportionately large changes in serum concentrations and its metabolism varies considerably between individuals, many human patients show symptoms and signs of intoxication at some point (Feely 1999). Serum phenytoin concentration should be monitored closely (Glauser & Pippenger 2000).

Side effects of phenytoin

Polyphagia, polydipsia and polyuria may be seen in animals medicated with phenytoin. Phenytoin can cause changes in hepatic clinical laboratory tests, which include increased ALP activity and decreased albumin concentration (Bunch *et al.* 1985). Histopathological changes after 6 months of phenytoin treatment include hepatocellular hypertrophy and necrosis, lipidosis and extramedullary haematopoiesis. A toxic hepatopathy with intrahepatic cholestasis has been reported with phenytoin administration when combined with either phenobarbitone or primidone (Bunch *et al.* 1985; Boothe 1998). Toxicity may be related to generation of toxic metabolites, and induction of enzymes may increase the formation of toxic metabolites that may contribute to hepatotoxicity (French & Gidal 2000).

1.4.2.5 Benzodiazepines

Clinical use of benzodiazepines

Benzodiazepines, such as diazepam, clonazepam and clorazepate, are potent AEDs, but several characteristics limit their use for long-term therapy (Podell 1998; Thomas 2000). The half-lives are short and frequent administration is required to maintain adequate serum drug concentrations (Thomas 2000). Due to hepatic induction, benzodiazepines' serum concentrations tend to decrease with time when in chronic use; thus, subsequent dose increases are usually necessary. Tolerance to the anticonvulsant activity of diazepam and clonazepam develops rapidly within 1 to 2 weeks in dogs (Boothe 1998). Cross-tolerance to benzodiazepines may occur with long-term use, and it prevents effective use of diazepam or midazolam to stop status epilepticus in emergency situation (Podell 1998; Thomas 2000). Benzodiazepines are also known to develop physical dependence. After prolonged treatment, sudden withdrawal of benzodiazepines can precipitate seizures and clinical signs including anorexia with weight loss, lethargy, tremor and, in some dogs, hyperthermia may occur (Scherkl & Frey 1986).

Diazepam and clonazepam are not effective AEDs for long-term therapy due to the features listed above. However, as clorazepate has a longer half-life and tolerance to anticonvulsant activity does not develop so rapidly as with diazepam and clonazepam, it is more suitable for chronic use and can be used as an add-on AED (Boothe 1998). However, similar problems may arise as with chronic oral use of short-acting benzodiazepines (Podell 1998). In addition, there are other features of clorazepate that may influence its clinical value. The half-life of clorazepate is less than 12 hours and doses that are accidentally missed can result in seizures (Boothe 1998). As the half-life is short, measurement of both peak and trough drug concentrations are recommended to document fluctuations in plasma drug concentrations. Clorazepate often increases serum phenobarbitone concentrations, which can lead to side effects; thus, serum phenobarbitone concentrations should also be monitored closely (Boothe 1998; Thomas 2000). These increases are usually evident by the first month of therapy but may take longer. Furthermore, clorazepate concentrations tend to decrease with time despite no change in dose, and increases of the dose are usually required to maintain the baseline serum drug concentration. In some animals, 8-hourly rather than 12-hourly dosing may be necessary to avoid both toxic and subtherapeutic concentrations (Boothe 1998). Serum concentrations of phenobarbitone and clorazepate should be monitored at 2 and 4 weeks after initiating clorazepate administration (Boothe 1998; Thomas 2000).

Side effects of benzodiazepines

Side effects of benzodiazepines include sedation, ataxia, polyphagia and, in some cases, hyperactivity. Multiple oral doses of 2 mg/kg at 12-hour intervals for 3 weeks caused significant decreases in serum albumin and increases in serum urea nitrogen, but concentrations were within normal reference ranges (Boothe 1998).

1.4.2.6 Other AEDs

In human medicine, up to 1993, five AEDs have predominated in seizure management. However, despite their remarkable effectiveness, these drugs fail to produce complete seizure control in about 30% of cases. These drugs are also far from ideal in terms of side effects and adverse drug interactions, and there is a need for new drugs with improved efficacy or tolerability (Perucca 1996). Several new AED have been approved for use in man since 1993.

In veterinary medicine, the choices of AED are much more limited. Phenobarbitone and bromide are the best AEDs documented for efficacy and tolerance in dogs. In general, clinicians should avoid the use of primidone, phenytoin and short-acting benzodiazepines for the reasons outlined above. Clorazepate may be a choice of add-on AED, but the potential cross-tolerance and physical dependence limit its use.

Refractory epilepsy is not uncommon in dogs. Approximately 30% of dogs are never well controlled with phenobarbitone and/or bromide (Knowles 1998) and alternative AEDs are still in demand. Some new AEDs have been applied in veterinary medicine recently but, for most of them, further clinical studies are needed to confirm their efficacy and tolerability in dogs (see Table 1.8, page 52).

Table 1.8 Related information of alternative drugs in dogs

Drug	Probable mechanisms of action	Use in man	Reported use in dogs	Pharmacokinetics in dogs
Felbamate	Blockade of voltage-dependent Na^+ channels Antagonism of excitatory transmission through the NMDA receptor Potentiation of GABA responses	Effective in partial and generalised seizures Become the last add-on drug due to idiosyncratic side effects	Add-on AED Monotherapy	$T_{1/2}$: 5.9 h Higher metabolic rate in pediatric dogs Specific inducer and specific inhibitor in human
Gabapentin	Potentiation of GABA responses Blockade of voltage-dependent Na^+ channels	Add-on AED in partial seizures with or without secondary generalisation	No reported clinical studies for long-term use	Excreted unchanged by the kidneys $T_{1/2}$: 2.2 h
Valproic acid	Blockade of voltage-dependent Na^+ channels Potentiation of GABAergic transmission	All types of seizures	Not proven effective for seizure control	$T_{1/2}$: 1.2-3.7 h Relatively high concentrations of some metabolites with anticonvulsant activity Higher conc. entered the central nervous system due to lower protein binding fraction Inhibitory drug interactions in human
Nimodipine	Calcium channel antagonist	Controversial results from clinical trials	Not proven effective for seizure control	Metabolised by the liver and may be affected by phenobarbital hepatic enzymes induction
Vigabatrin	Potentiation of GABAergic transmission through inhibition of GABA-transaminase	Partial seizure with or without secondary generalisation	Not proven very effective for seizures control	N/A $T_{1/2}$ is less critically related to its duration of action due to the irreversible GABA inactivation
Mephenytoin	Blockade of voltage-dependent Na^+ channels	Effective in seizure control, but infrequent use due to side effects	Add-on AED but no reported clinical studies	Anticonvulsant activity coming from its main metabolite, nirvanol Nirvanol $T_{1/2}$: 25 h

Table 1.8 Related information of alternative drugs in dogs (Continued)

Drug	Suggested dose in dogs	Therapeutic ranges in dogs	Side effects in human	Side effects in dogs	References
Felbamate	15-20 mg/kg q8-12 h then increased in 15-mg.kg increments until seizures are controlled.	Not been established in dogs	Dose-related: anxiousness, anorexia, nausea, headache, and other personality changes. Idiosyncratic: aplastic anemia and hepatotoxicity	Mild, reversible blood dyscrasia, including thrombocytopenia, lymphopenia, and leukopenia Hepatic disease in some dogs in combination with phenobarbital.	Perucca 1996 Dichter & Brodie 1996 Podell 1998 Boothe 1998 McGee *et al.* 1998 Thomas 2000 French & Gidal 2000 Ruehlmann *et al.* 2001
Gabapentin	100-300 mg per dog q8h, maximum: 1200 mg q8h (regimen extrapolated from human patients).	Not been established in dogs	Lethargy, ataxia, dizziness, and gastrointestinal upset	No related information	Perucca 1996 Dichter & Brodie 1996 Podell 1998 Boothe 1998 Thomas 2000
Valproic acid	60 mg/kg q8h	40-100 μg/ml	Sedation, tremor, and hepatotoxicity	Alopecia, gastrointestinal upset	Loscher 1981 Nafe *et al.* 1981 Boothe 1998 Feely 1999 Thomas 2000 French & Gidal 2000
Nimodipine	N/A	N/A	Dizziness, hypotension, headache, digital dysesthesia, and nausea due to excessive vasodilation	Lethargy, weakness, anorexia, and hypotension	O'Brien *et al.* 1997
Vigabatrin	N/A	N/A	Behavioural changes, depression, sedation, fatigue, weight gain, gastrointestinal upset, and psychosis	Reversible intramyelinic edema, hemolytic anemia, emesis, loose stool, anorexia, and sudden death	Speciale *et al.* 1991 Dichter & Brodie 1996 Mandigers 1999
Mephenytoin	10 mg/kg q8h	Nirvanol: 25-40 μg/ml	Dermatitis, bone marrow dyscrasias, fever, lymphadenopathy, and hepatopathy	Hepatotoxicity in dogs in combination with phenobarbital	Braund 1994 Boothe 1998

N/A: not available

1.4.3 AED Therapy Withdrawal

In most dogs, a lifetime AED therapy is usually necessary to control seizures. However, attempted withdrawal of AED medication is reasonable in some dogs that have been seizure-free for 1 to 2 years. The dose should be gradually tapered over a period of about 6 months (Thomas 2000). In some situations, the use of AEDs aggravates epilepsy (acute idiosyncratic side effects, chronic dose-related side effects and inverse pharmacodynamic effects may occur) and withdrawal of AED therapy may be desirable. The mechanisms leading to deterioration of a patient's condition are listed below (in Table 1.9) (Genton 2000). If AED withdrawal is undertaken, this should be done gradually. It is recommended that AED dosage is decreased in 25% decrements with 2- to 4-week intervals (Boothe 1998).

Table 1.9 Mechanisms leading to deterioration of a patient's condition

	Consequence	Suggested approach
Maladjustment to disease/ limited access to AED	Refusal of diagnosis or AED Irregular intake of AED Low compliance Repeated withdrawal Seizure, serial seizures Non-conventional treatments Increased side-effects of AED	Global approach; counselling
Overdose	Side-effects Increased seizure frequency New seizure types	Reduce dosage (monitor blood concentrations)
Acute idiosyncratic side effects	Acute illness	Withdraw quickly; use other AED
Chronic dose-related side effects	Chronic illness	Withdraw slowly; use other AED
Tolerance	Secondary increase of seizure frequency withdrawal seizure	Substitute slowly with other AED
Inverse pharmacodynamic effect	Increased seizure frequency new seizure types	Withdraw quickly; revise diagnosis; use other AED

1.5 ASSESSMENT OF SEIZURE MANAGEMENT

1.5.1 Seizure Frequency

Within the field of epilepsy, seizure frequency is used as a clinical assessment tool and reduction in seizure frequency is considered a key outcome measure in clinical practice and

in trials of antiepileptic therapy. Measures of seizure frequency include seizure frequency or transformation of such data into percentage change from a baseline frequency or a rate based on frequency per specified time period (e.g., number per month). In clinical trials, key measurements have included the number or the proportion of patients whose seizure frequency or rate decreased or reached a specified range, as well as the number of months patients have been seizure free. The standard end point has been the proportion of patients whose seizure frequency decreases by ≥50% from baseline (Cramer & French 2001). From a clinical point of view, a compelling measure of efficacy would be the number of patients who are seizure free during the study. However, because many patients enrolled in clinical trials have demonstrated refractoriness to medical therapies, 100% seizure reduction is rarely achieved and is therefore not a useful end point for comparing treatments in a single trial (Lesaffre *et al.* 2000).

1.5.2 Quantitative Assessment of Seizure Severity

In human medicine, there is increasing recognition that traditional measures such as seizure counts do not capture the broad range of outcomes that may be relevant in evaluating the clinical impact of the growing number of medical and surgical interventions now available (Birbeck *et al.* 2000). Two aspects are considered to also be important for outcome assessment: seizure severity and quality of life measurement (Birbeck *et al.* 2000; Cramer & French 2001). Quality of life measurement is discussed in the next section (1.5.3 Quality of Life Measures in Epilepsy, page 56).

Several seizure rating scales are designed for quantitative assessment of seizure severity in human medicine, and the core components that most scales focus on include seizure frequency, seizure type, seizure duration, postictal events, postictal duration, automatisms, seizure clusters, known patterns, warnings, tongue biting, incontinence, injuries and functional impairment. Initially, questionnaires were designed from physician-based assessment, followed by patient-based assessment, to evaluate both the severity of ictal events and the impact of seizures from the perspective of the patient. However, the usefulness of the existing scales is limited by lack of data on responsiveness (Cramer & French 2001).

Responsiveness is a measure of the degree to which an instrument is capable of detecting change over time with alterations in disease state or in response to treatment and an indicator of longitudinal validity (Birbeck *et al.* 2000). Another limitation is appropriateness. All scales suffer from having a limited number of questions that may or

may not cover seizure severity for an individual. In addition, some items in the scales may not relate to treatment effect at all. All the scales also suffer from an arbitrary scoring system. For most scales, further work is needed to define how much change in the total score would indicate a clinically appropriate requirement to change therapy. The application of such scales in clinical trials is also complicated by the questions over their appropriateness. Frequency of administration, consistency among interview technique, interpretation of marginal situations and other problems complicate the use and scoring of scales (Cramer & French 2001).

1.5.3 Quality of Life Measures in Epilepsy

A number of quality of life measures for epilepsy have been developed in human medicine over the last several years (Birbeck *et al.* 2000). Within the health field, quality of life has been variously defined as the emotional response to circumstances, the impact of illness on social, emotional, occupational and family domains, personal well-being, the match between expectations and reality, satisfactory functioning in physical, social and emotional terms and the ability of a person to meet his or her needs (Hopkins *et al.* 1995). Studies of patients with epilepsy have provided information pertinent to all the above definitions. Measurement of aspects of the experience and activities of epileptic patients is generally carried out by means of questionnaires. Questionnaires may be completed by patients, clinicians, or relatives of patients (Hopkins *et al.* 1995; O'Donoghue *et al.* 1998; Birbeck *et al.* 2000; Sabaz *et al.* 2000). Generally, a measure of quality of life, based on a clear conceptual model and with a content derived directly from patients themselves, would be of great value in optimising care and treatment (Birbeck *et al.* 2000).

The assessment of quality of life in epilepsy should take account of issues that have been identified as being relevance to people with epilepsy. Ideally, such assessments should be based on questionnaires designed for self-completion, based on a clear theoretical model of quality of life where the content has been generated directly from interviews with wide variety of people with epilepsy (Hopkins *et al.* 1995). There should be a clear idea of precisely what is being measured by the questionnaire and its applicability to the patients and their current situations (Sabaz *et al.* 2000). The measure should be thoroughly tested for reliability, validity and its sensitivity to differences in epilepsy severity (Hopkins *et al.* 1995; Sabaz *et al.* 2000). Measurement analyses that do not take into account seizure frequency may be overestimating the quality of life impairment of seizure-free patients and underestimating the impairment of those experiencing one or more seizures per month (Leidy *et al.* 1999). There are considerable differences in expectations, values and

perceptions of health between cultures and misleading results may be obtained by using culturally inappropriate measures. Therefore, the questionnaire should be developed, or retested in the country in which it is to be used (Hopkins *et al.* 1995).

Despite the desirability of assessing epilepsy outcomes more broadly, a recent literature review revealed only four AED randomised trials for epilepsy that included a comprehensive measure of health-related quality of life (Birbeck *et al.* 2000). Apart from the problems related to measurement design (described above), epilepsy has several features that make measurement of quality of life particularly difficult. Patients vary enormously in the problems they experience and in the way they adapt to their condition. In addition, problems may arise less from the condition itself than from the perception of epilepsy by others as well as by the patient (Hopkins *et al.* 1995).

In general, it can be said that attempts to measure quality of life in epilepsy have suffered from an overemphasis on measurement and an under emphasis on quality of life. There has been a gap between quantitative and qualitative research (Hopkins *et al.* 1995).

1.5.4 Related Information in Veterinary Medicine

In veterinary medicine, reduction in seizure frequency is the main outcome measure both in clinical practice and in trials of antiepileptic therapy. Neither seizure rating scales for quantitative assessment of seizure severity nor quality of life measures have been developed in veterinary medicine. One study was undertaken, in the Columbus Ohio area, to evaluate owners' perception of the effect that epilepsy and long-term phenobarbitone therapy had on the quality of pet and owner lifestyle (Lord & Podell 1999). This study has revealed the concerns of owners in canine epilepsy and the information may be useful for the design of quality of life measure in dogs.

1.6 AIMS OF THE STUDY

Seizures are the most common neurological disorder in small animal medicine. Many dogs are effectively managed in primary veterinary clinics; however, dogs with epilepsy represent a large proportion of the caseload for the neurology service of Small Animal Hospital of University of Glasgow Veterinary School (SAH-UGVS). It is proposed that referral relates to dissatisfaction with the outcome of seizure management or a desire to

confirm the diagnosis as far as possible. This study was undertaken to clarify the reason for requesting further assessment.

Seizure management regimens instigated at primary veterinary clinics and SAH-UGVS were reviewed in the study. Owners' perspective of the reasons for referral and seizure management regimen used in SAH-UGVS were also explored, as such information was of potential value to clinicians in assessing seizure management regimens. Furthermore, information from the owners' perspective could potentially raise issues of relevance to other dogs with epilepsy and their owners, which may be the basis for developing an alternative assessment of long-term seizure treatment in veterinary medicine.

CHAPTER TWO

MATERIALS AND METHODS

2.1 CRITERIA FOR ENTRY OF DOGS IN THE STUDY

Dogs that were referred to Small Animal Hospital of University of Glasgow Veterinary School between March 1999 and April 2001 for evaluation of seizures and satisfied one of the following criteria are included in this study: (a) dogs diagnosed with idiopathic epilepsy by full seizure investigation, (b) dogs with unremarkable physical and neurological examination as well as blood clinicopathological analyses, and tentatively diagnosed with idiopathic epilepsy without specific investigation of intracranial diseases. Patients found to have symptomatic epilepsy or reactive seizures were excluded from the study.

2.2 INVESTIGATION PROTOCOL FOR PATIENT WITH EPILEPSY

The diagnosis of idiopathic epilepsy is one of exclusion of other likely causes of seizures (see 1.3 DIAGNOSTIC EVALUATION, page 22). The full diagnostic protocol for canine seizure disorders at the SAH-UGVS includes history, physical and neurological examinations, haematology and biochemistry, specified serological tests, CT scan, and CSF analysis. The processes are detailed in Figure 2.1 (page 63).

History details for dogs included in this study are summarised in Table 2.1 (page 64). A full physical examination was performed after history taking to detect clinical signs that may relate to nonepileptic paroxysmal disorders or extra-cranial causes of seizures (Table 2.2, page 66).

Full neurological examination (detailed in Figure 2.2, page 65) is carried out to detect interictal neurologic deficits. When this was performed shortly after a seizure and focal or generalised abnormalities were obtained, neurological examination was repeated in 24 hours in order to differentiate postictal effects from persistent interictal deficits.

Laboratory investigation was performed to rule out extracranial causes of seizures. Tests of haematology and biochemistry are listed in Table 2.3 (page 66). Further serological

tests include fasting and post-prandial bile acids, serum titres of toxoplasma, neospora, and canine distemper virus, and serum lead concentration.

CT and CSF sampling were performed under general anesthesia. Even though most dogs in the study (with seizures only and no interictal signs) had normal neurological status between seizures, the anaesthetic protocol should still concentrate on not causing deterioration of neurological function in these patients. In patients with deteriorated neurological status, the ideal anaesthetic agent should provide general anaesthesia while reducing cerebral metabolic oxygen requirement (CMO_2R), reduce cerebral blood flow (CBF), and should not promote seizures (Golder 1999).

Protocol described below, with some variation, was used in dogs in this study, depending on individual patient's requirement. Patients were premedicated with pethidine (2 mg/kg IM). Prior to induction, the dog was pre-oxygenated by facemask with 100% oxygen for 5 minutes and administered 1 mg/kg IV of lignocaine. Diazepam at 0.2-0.5 mg/kg IV and thiopentone or propofol (with dose to affect) were used for induction. Maintenance was with low concentration of isoflurane in 100% oxygen or propofol infusion with high-inspired oxygen concentration supplement. Diazepam was administered prior to thiopentone or propofol to reduce the required dose of these two anaesthetic agents, as well as for its anti-epileptic properties. Benzodiazepines also decrease the incidence of myoclonus induced by propofol. Barbiturates decrease CMO_2R and CBF at induction doses. In addition, barbiturates maintain the cerebral vascular responsiveness to changes in mean arterial blood pressure and Pa CO_2. The effect of propofol on CMO_2R and CBF is similar to barbiturates. Inhalation agents decrease CMO_2R but increase CBF by depressing vascular autoregulation. This effect is much greater with halothane than isoflurane, and isoflurane increases blood flow more evenly throughout the brain compared to halothane (Golder 1999).

Intra-cranial imaging was performed by a third generation transverse slice CT unit (Excel 2400 Elite®, Elscint Ltd, Haifa, Israel). The dog was positioned in sternal recumbency with forelimbs pulled alongside the chest, and the head was extended and supported on a radiolucent headrest. Scanning was undertaken at 120 KV, 300 mAs, with a 240 mm diameter scan field size, 256x256 image matrix, standard resolution and soft tissue reconstruction filter. In medium and large size of dogs, a bed increment of 5 mm and 5 mm slice width were used, and in small size of dogs 2.5 mm bed increment and 2.5 mm

slice were selected. The scanning area extended from the occipital protuberance to the cribriform plate. Images were acquired using a scan angle of 360° and a scan time of 2 seconds. Post-contrast scans were performed following intravenous administration of 2 ml/kg of non-diffusible iodinated compound sodium iothalamate (70% weight/volume, 420 mg iodine/ml, Conray 420, Mallinckrodt Medical Ltd, Northampton, England, UK). Post-contrast slices were taken at the same levels as the initial study, starting around 20 seconds after injection of contrast media finished.

CSF analysis was performed if the result of intra-cranial imaging was unremarkable. Three-inch 20 gauge or 1.5-inch 22 gauge spinal needles were used for CSF sampling and fluid was collected in plastic plain tube. CSF examination included physical appearance, cellularity (total and differential cell count) and protein content. Manual (haemocytometer) and/or machine count were performed for total cell count. The differential cell count was determined following cytocentrifugation (cytospin3 R^8). If results of all tests were unremarkable, the diagnosis of idiopathic epilepsy was made.

Figure 2.1 Investigation protocol for dogs with seizures

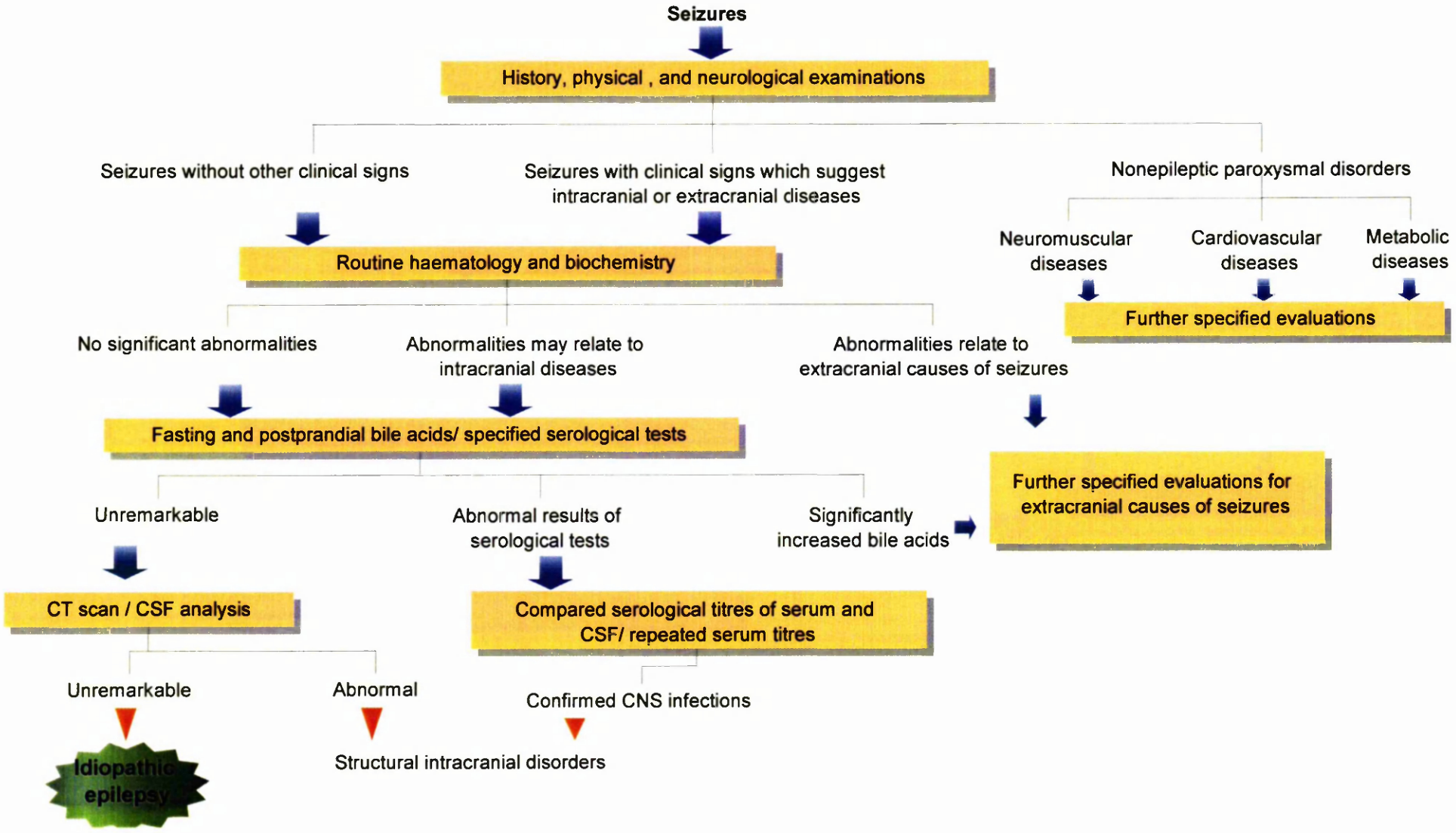


Table 2.1 Questions checklist of clinical history

Signalment	Breed
	Age
	Sex
History related to the cause of seizure	History of seizures in related animal
	Vaccination status
	Previous illnesses
	Traumatic incidents
	Previous medical and surgical treatment -including anaesthetics
	History of changing diet -any indication of food allergy
	Possibility of toxin exposure -including prior antiparasitic treatment
	Whether other animals or people in the same environment had had seizures
	Current illness and treatment
	Behavioural changes
History related to seizure activities	Age at onset of seizures
	Seizure types
	Signs of prodrome and postictal periods -differentiating between seizures and nonepileptic paroxysmal disorders
	Interictal signs
	Trigger factors
	Special occurring time during the day
	Seizure frequency ▸ Interval time between 1st and 2nd seizure ▸ Pattern of seizure frequency
	Antiepileptic drug therapy ▸ Drug, dosage and dosing time ▸ Serum drug concentration monitoring ▸ Side effects ▸ Response of seizure frequency and severity

Figure 2.2 The Neurological Examination Sheet of SAH-UGVS

1) ***SUBJECTIVE***.....
.....

2) OBJECTIVE

Observation

Mental	Alert		Depressed		Disorientated		Stupor		Coma	
Posture	Normal		Head Tilt		Tremor		Falling			
Gait	Normal		Ataxia		Stiffness		Dysmetria		Circling	
Limbs affected	Pelvic Limbs		Tetra		Hemi		Mono			
Other (e.g. fits)										

Key: 4=exaggerated; 3=increased; 2=normal; 1=decreased; 0=none; NE=not evaluated

Weakness	Left Fore	Right Fore	Left Rear	Right Rear
Hopping				
Wheelbarrow				
Ext. postural thrust				
Hemistand/walk				

Proprioception	Left Fore	Right Fore	Left Rear	Right Rear
Paw Position				
Reflex Step				
Hip Sway				
Placing-tactile				
Placing-visual				

UMN or LMN	Left Fore	Right Fore	Left Rear	Right Rear
Muscle Bulk				
Muscle Tone				
Ext. Carpi Rad.				
Patellar				
Pedal				

Panniculus and Sacral Segments

Panniculus	Cut-off		If Yes: Level on L		Level on R	
Anal reflex	Left		Right			
Tail	Voluntary movement					
Bladder	Control		Bladder size		Ease of expression	

Pain

Hyperaesthesia	Cervical		Thoracic		Lumbar		L-Sacral	
Superficial Pain	L-Fore		R-Fore		L-Hind		R-Hind	
Deep pain	L-Fore		R-Fore		L-Hind		R-Hind	

Cranial Nerves	L	R
Vision **2**		
Menace **2,7**		
PMR-stim L **2,3**		
PMR-stim R **2,3**		
Pupil size **2,3 Symp.**		
Fundic Exam		
Vest.eye move.		
Strabismus **8,3,4,6**		
Nystagmus **8,3,4,6**		

	L	R
Facial Sens. *max*		
mandibular		
Ophthalmic **5**		
Mast. Muscle **5**		
Facial muscle **7**		
Palpable **5,7**		
Gag **9,10**		
Tongue **12**		
Sympathetic		

Comments CN

Summary of Neurological Exam: .....
.....

Table 2.2 Checklist of physical examination

General	❑ Pyrexia
	❑ Weight loss
	❑ Anorexia
	❑ Lethargy
	❑ Weakness
	❑ Polydipsia/polyuria
	❑ Dehydration
	❑ Oedema
	❑ Foul-smelling breath
	❑ Bruising or bleeding tendencies
	❑ Retarded growth
	❑ Enlargement of the calvaria
	❑ Persistent sutures and fontanelles of the skull
Mucous membranes	❑ Pale mucous membrane
	❑ Oral ulcers
Circulatory	❑ Heart murmurs
	❑ Arrhythmia
Respiratory	❑ Dyspnoea
	❑ Sneezing
	❑ Nasal discharge
Eyes	❑ Uveitis
	❑ Chorioretinitis
Digestive	❑ Vomiting or diarrhoea
	❑ Icterus
Abdominal palpation	❑ Mass palpated
	❑ Ascites

Table 2.3 Routine haematology and biochemistry

Haematology

RBC	WBC	PLT
Hb	Band neutrophils	MPV
HCT	Neutrophils	PCT
MCV	Lymphocytes	PDW
MCH	Monocytes	
MCHC	Eosinophils	
RDW	Basophils	

Biochemistry

Sodium	Urea	Total bilirubin	Total protein
Potassium	Creatinine	Alkaline phosphatase	Albumin
Na: K ratio	Glucose	Aspartate transaminase	Globulin
Chloride	Cholesterol	Alanine transaminase	Albumin: globulin ratio
Calcium	Triglyceride	γ-glutamyltransferase	
Phosphate			

2.3 SEIZURE DISORDER EVALUATION AND MANAGEMENT

2.3.1 Categories of Seizure Cases Included in This Study

Cases included in this study are divided into two categories.

Group One

Group One included dogs referred to SAH-UGVS with recent-onset seizure disorder (shorter than 6-month history) and diagnosed as idiopathic epilepsy following evaluation as described in 2.2 INVESTIGATION PROTOCOL FOR PATIENT WITH EPILEPSY (page 60). A total of 27 dogs were included in this group. In three cases, the diagnostic procedures were only performed to achieve the level of tentative diagnosis of idiopathic epilepsy due to lack of intra-cranial imaging facility (n=1) or owners' decision of not performing specific intra-cranial investigation (n=2). In these dogs, no history and clinical signs suggested extra-cranial or intra-cranial causes of seizures, and no significant abnormalities were determined on haematology, biochemistry, and/or specified serological tests. All dogs had had greater than 2-year seizure history when data collecting for the study finished in April 2001. Given to the chronic seizure history without any interictal signs, diagnosis of seizure disorder in these cases were thought likely to be idiopathic epilepsy, and it was decided to include these cases in the study.

Group Two

This group included dogs referred to SAH-UGVS with a chronic history of seizures (greater than 6-month history). A total of 21 dogs were included in this group. In 14 cases, the full investigation was undertaken to make the final diagnosis of idiopathic epilepsy. In 7 patients, the diagnostic procedures were only performed to achieve the level of tentative diagnosis of idiopathic epilepsy due to owners' decision of not performing intra-cranial investigation. In this subgroup, no history and clinical signs suggested extra-cranial or intra-cranial causes of seizure disorder, and no significant abnormalities were determined on routine haematology, biochemistry, and/or specified serological tests.

2.3.2 Group One

Seizure frequency and seizure type

After the diagnosis of idiopathic epilepsy was made, if the dog had had only one isolated seizure, seizure monitoring was suggested. In cases which had had generalised seizures and the frequency of these had been more than two or more isolated seizures occurring within a 6- to 8-week period, two or more cluster seizure episodes within an 8-week period, or status epilepticus, treatment was indicated. In dogs with partial seizures, due to the variety in seizure severity between dogs, the decision of whether to medicate relied on individual cases and owners' attitude after seizure management and AED side effects were discussed with owners.

AED regimen

In most cases, phenobarbitone was the first-line AED used in SAH-UGVS, with initial starting dose as 3 mg/kg q12h. Trough serum phenobarbitone concentration was monitored in 2 weeks. Phenobarbitone dosage was adjusted depending on individual response. When the serum phenobarbitone concentration was within the upper therapeutic range but seizure frequency was still unacceptable or severe side effects of phenobarbitone had shown, potassium bromide was added as the second AED. Potassium bromide was also used as a first-line AED in young and geriatric dogs due to its perceived lower toxicity. The initial starting dose of potassium bromide used was 30 mg/kg daily, with a loading dose 450 mg/kg divided into 5 days. Serum bromide concentration monitoring was suggested at day 6 or 7 and week 4. If the paired serum concentrations were within the therapeutic range, or seizure frequency responded to bromide, it was suggested that serum bromide concentrations were measured again in month 3 to 4, and then every 6 months. If serum bromide concentration was lower than the therapeutic range, or seizure frequency was not satisfactory, the maintenance dose was increased in a 10 mg/kg increment alone or with a minimal loading dose 250 mg/kg divided into 5 days.

If the dog had had cluster seizures or status epilepticus for most seizure activities, the use of diazepam 0.5 to 1 mg/kg per rectum when a seizure occurred was prescribed to the owner for the control of cluster seizures or status epilepticus at home.

In order to monitor the clinical response, owners were requested to record seizure episodes and severity in a seizure diary (Figure 2.3, page 69).

Figure 2.3 Seizure Diary

University of Glasgow Veterinary School/ Seizure Diary **Animal's name**_____ **Owner's name**_____

Month: **Year:**

Date	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
Seizure number										
Duration										
Phenobarbital *										
KBr dose *										
Comments †										
Date	11th	12th	13th	14th	15th	16th	17th	18th	19th	20th
Seizure number										
Duration										
Phenobarbital *										
KBr dose *										
Comments †										
Date	21st	22nd	23rd	24th	25th	26th	27th	28th	29th	30th	31st
Seizure number											
Duration											
Phenobarbital *											
KBr dose *											
Comments †											

* Record the changes of dose

† Record the changes e.g. ① delayed the time for medicine ② seizure type is different from other episodes ③if the dog is on KBr, record the chloride content in food when changing diet.

2.3.3 Group Two

Investigation of cases with chronic seizure history can be divided into two parts: confirming the diagnosis of idiopathic epilepsy and seizure management evaluation.

In addition to the historical questions listed in Table 2.1 (page 64), further information was sought relating to potential causes of uncontrolled seizure activity, which included dog / owner compliance with medication requirement, history of sudden withdrawal of AED, details of AED therapy and clinical responses on seizure frequency and severity. Full seizure investigating procedures were performed, and at the same time, serum drug concentrations were measured (trough and/or peak level for phenobarbitone). As mentioned previously, in some dogs, diagnostic procedures were only performed to make the tentative diagnosis due to owners' decision not to go further, but based on the age of seizure onset, no history and clinical signs that suggested intra-cranial diseases, and unremarkable results of routine haematology, biochemistry and/or specified serological tests, idiopathic epilepsy was the most likely diagnosis.

In cases treated with phenobarbitone, if phenobarbitone was given with a rough treatment time, a strict 12-hour interval medication was requested. If a high serum phenobarbitone concentration was not obtained (>30 μg/ml), increased phenobarbitone dosage was suggested. If serum phenobarbitone level was within the upper therapeutic range and seizure frequency was still unacceptable, or the dog showed undesired side effects, potassium bromide was added as the second AED with the regimen described previously (2.3.2 Group One, AED regimen, page 68). Potassium bromide was titrated until a high serum bromide concentration was achieved (up to 3.5 mg/ml) or unacceptable side effects occurred. Owners were informed about the influence of chloride content in the diet to serum bromide concentration in order to minimise the fluctuation of serum bromide concentration.

Diazepam was prescribed, if thought necessary, via rectal administration. The use of a seizure diary (Figure 2.3, page 69) was recommended to produce an objective record of the patent's progress.

2.4 QUESTIONNAIRE STUDY

2.4.1 Questionnaire One: An Assessment of the Seizure Management in Companion Animals from the Owners' Perspective

Owners' perspective on reasons for referral to and the seizure management regimen used in SAH-UGVS, as well as the exploration of other issues relevant to dogs and their owners, were sought by mailed questionnaires.

2.4.1.1 Format

The questionnaire was designed as an A5-size booklet by using a landscape orientation on A4-size paper and folded along the midline. Responses are thought to be higher if questionnaires are presented in a booklet format with front and back covers reserved for contents, aiming at stimulating interest rather than obtaining information from the respondent (Dillman 1978).

On the front cover, a title of 'Your Pet, Its Seizures, and You' and a subtitle of 'An Assessment of Seizure Management in Companion Animals from the Owners' Perspective' were placed. A brief introduction was provided, including aims of the study, the topics of the questionnaire, and an invitation for further comment. The University of Glasgow logo was placed at the top of the front cover, the name and address of the department at the bottom, in order to establish greater trust among subjects. On the back cover, a statement of appreciation, an invitation to make additional comments and plenty of blank space were provided. At the bottom, a question as to whether the respondent would like to receive a copy of questionnaire results was asked. The effect of sending results to respondents is thought to increase response (Dillman 1978).

2.4.1.2 Questionnaire Design

Question types used in the questionnaire included open-ended questions, closed-ended questions with ordered answer choices, and partially close-ended questions (Dillman 1978). In addition, the visual analogue scale was used, which is a technique to measure subjective phenomena. The visual analogue scale is a self-reporting device, consisting of a straight line anchored at either end by the extremes of the measured phenomenon, which provides a continuous range of possible values. Respondents were required to indicate the extent of the measured variable on a visual analogue scale by marking a cross somewhere on the line corresponding to the amount of the phenomenon (Hopkins *et al.* 1995;

Svensson 2000). The visual analogue scale has been established as valid and reliable in a range of clinical and research applications, although there is also evidence of increased error and decreased sensitivity when used with some subject groups (McCormack *et al.* 1988).

The whole questionnaire included a total of ten sections. At the beginning of each section an instruction of how to answer questions was described. The topic of each section and related questions are listed below.

Section A designed/aimed to evaluate, in the broad term, how owners assess seizure management. Several factors were suggested and subjects were asked how important they felt each factor was by using a visual analogue scale. Factors provided in the section included:

- Seizure frequency.
- AED side effects.
- The animal's quality of life.
- Influence of caring for an epileptic dog on owners' lifestyle.
- Cost of seizure management.

In order to understand more about how important subjects feel that seizures are controlled to an adequate degree, one question of what seizure frequency subjects consider reasonable was asked. Two more questions were designed to explore additional factors, also important to subjects, and how important they are.

Section B designed/aimed to evaluate, by visual analogue scales, how subjects perceive their own dog's seizure management with the same factors listed in Section A.

Section C designed/aimed to elicit information on the animal's quality of life subsequent to the onset of seizure by close-ended question and partially close-ended questions. Questions were related to:

- General daily activity.
- Interaction between the animal and family members.
- Overall assessment of the animal's quality of life and, if perceived to have deterioration, to explore the reason.

Section D designed/aimed to explore how owners perceive the extra-work associated with caring for their epileptic dogs by visual analogue scales. Basic information was obtained at first, including numbers of people who are primarily responsible for caring for the epileptic

dog and relationship of these people. Extra work related to caring for an epileptic dog included:

- The administration of the medication.
- Regular veterinary examination and blood sampling to monitor serum drug concentration.
- Seeking emergency veterinary treatment due to breakthrough cluster seizures or status epilepticus.

If subjects perceived the administration of the medication is a nuisance, one further question (partially close-ended question) was asked to explore the reason.

Section E designed/aimed to assess AED side effects and how owners are worried about it. Questions included which side effects the dog has shown (close-ended questions) and how these specific side effects worry the owner (visual analogue scales). Listed side effects were:

- Increased appetite
- Drinking more
- Urinating more
- Sleeping much more than before
- Ataxia
- Restlessness
- Itchiness
- Vomiting and/or diarrhoea

Section F designed/aimed to evaluate the influence of caring for an epileptic dog on their owners' work. Questions were separated into two groups by whether the owner is in employment / education / training.

Section G designed/aimed to evaluate the influence of caring for an epileptic dog on owners' free time, in which questions were focused on if the epileptic dog affects owners' ability or decision to stay away from home overnight.

Section H designed/aimed to explore owners' concerns about their dogs' seizures by visual analogue scales. Questions were related to three aspects:

- Concerns about the ability to control seizures.
- Concerns about their dogs having further seizures.
- Concerns about seizures leading to injury or death of their dog.

Section I designed/aimed to elicit information on the reason for referral, owners' opinions on further investigation, and the influence of pet insurance on owners' decision to pursue further investigation.

Section J designed/aimed to assess how owners perceive the details of seizure management have been explained by clinicians of SAH-UGVS. Subjects of seizure management included:

- The reason for precise timing of drug administration.
- The potential side effects of medication.
- The value of monitoring the serum drug concentrations.
- The likely long term nature of treatment.
- The long term prospects for the dog.

2.4.1.3 Pretesting

Two pretests were undertaken. The first pretest was professional peer review. Five clinicians in SAH-UGVS were recruited for the first pretest. In the light of their comments, changes were made in the wording of instructions and questions, the order of questions, and more questions were added to elicit clearer information. In Section E, a question about detailed current AED therapy was added at the beginning in order to interpret reported AED side effects. Section H and J were deleted due to concerns about the length of the questionnaire. After correction, a revised version of questionnaire was drafted and the second pretesting was undertaken.

The second pretest was a lay review. The panel of five included veterinary nurses, owners of dogs without epilepsy, and a human doctor. In addition to completing (as appropriate) and commenting on the questionnaire, they were requested to record the length of time needed for completing the questionnaire. Few changes of wording and format were made according to their comments. The final questionnaire is in presented in APPENDIX ONE (page 130).

2.4.1.4 Inclusion Criteria and Implementing Mail Surveys

A total of 37 dogs from Group One or Two who were alive in May 2001 were included in the questionnaire study.

Mailing packages, containing the questionnaire, a covering letter explaining the reasons for undertaking the study, and a stamped, addressed return envelope, were posted. Three

weeks later, second mailing packages, containing another covering letter as a reminder, the questionnaire, and a stamped, addressed return envelope, were mailed to non-respondents.

2.4.2 Questionnaire Two: Behavioural Changes in Epileptic Dogs

After results of the first questionnaire were analysed, approximately 30% of respondents (12/33) reported behavioural changes in their dogs, which included repetitive compulsive behaviour, overactivity, or more attention seeking. In the veterinary literature, it is known that these behavioural changes may relate to seizure activity itself (prodrome and postictal period) or AED side effects. Furthermore, in human medicine, psychosis of epilepsy (POE) can be classified into interictal POE, postictal POE, alternative psychosis (forced normalisation), and AED-related psychosis (Kanner 2000; Stagno 2001). In order to clarify the causes of behavioural changes in our patients and explore the problem further in veterinary medicine, a questionnaire was designed to elicit more detailed information in these certain patients.

2.4.2.1 Format

This questionnaire was created in portrait orientation of A4-size, designed as a different format from the first questionnaire in order to clarify the different issues addressed by the questionnaire. At the top of first page, the University of Glasgow logo was placed. A title of 'Behavioural Changes in Epileptic Dogs' and a subtitle of 'A Further Study of Seizure Management Assessment in Companion Animals from the Owners' Perspective' were displayed under the logo, followed by an invitation to make further comments. Spaces were placed between the introduction and the first section to achieve the same effect of an introduction as the front cover in the booklet of Questionnaire One. On the last page, the same content of the back cover as the first questionnaire was placed at the bottom.

2.4.2.2 Questionnaire Design

Question types used in the questionnaire included open-ended questions, closed-ended questions with ordered answer choices, and partially close-ended questions. The questionnaire consisted three sections. At the beginning of each section, an introduction of the topic in this section was described.

The first section was intended to elicit information detailing reported behavioural changes, when they started, and to assess whether any trigger factors or associated events were likely to be involved. In human medicine, it is found that psychosis of epilepsy occurs

with higher percentage in patients who have had psychotic problems prior to seizure onset. Due to this finding in human patients, questions related to behavioural problems in the past history were included in this section.

The second section evaluated whether these behavioural changes were associated with treatment, seizure frequency, or the direct consequence of seizure activity. Detailed frequency and duration of these specific behaviours were requested to compare with frequency of seizure activity. The last section was related to how these dogs responded to owners when the behaviour occurred. The detailed questionnaire is presented in APPENDIX TWO (page 139).

2.4.2.3 Inclusion Criteria and Implementing Mail Surveys

Respondents to the first questionnaire who reported restlessness or other behavioural changes in their dogs were included in the second questionnaire study. One dog was excluded due to sudden death that occurred soon after the first questionnaire was returned. A total of 11 dogs were included in this questionnaire study.

Mailing packages, containing the questionnaire, a covering letter explaining the reason for undertaking the further study, and a stamped, addressed return envelope, were posted. Three weeks later, second mailing packages, containing another covering letter as a reminder, the questionnaire, and a stamped, addressed return envelope, were sent to non-respondents.

2.4.3 Analysis of Data

The visual analogue scale (VAS) was applied as a 100-point measurement in the study. In responses to questions with VAS, the total length of the scale divided by the length from the left end to the cross, obtaining a value of percentage, which in turn was transformed into the VAS score in the range from 0 to 100. As scores of all responses to the certain question were obtained, a statistical software package (Microsoft Excel 97) was applied to obtain the mean, standard deviation (SD), and range of scores on VAS. In responses to questions with ordered answer choices, the data were presented as the percentage. In responses to question F2 and F3, the Spearsman rank correlation coefficient was applied to understand the association between the degree of the impact from owners' perspective and the frequency of time off or been late for work due to caring for an epileptic dog.

CHAPTER THREE

RESULTS

3.1 CASES REVIEW

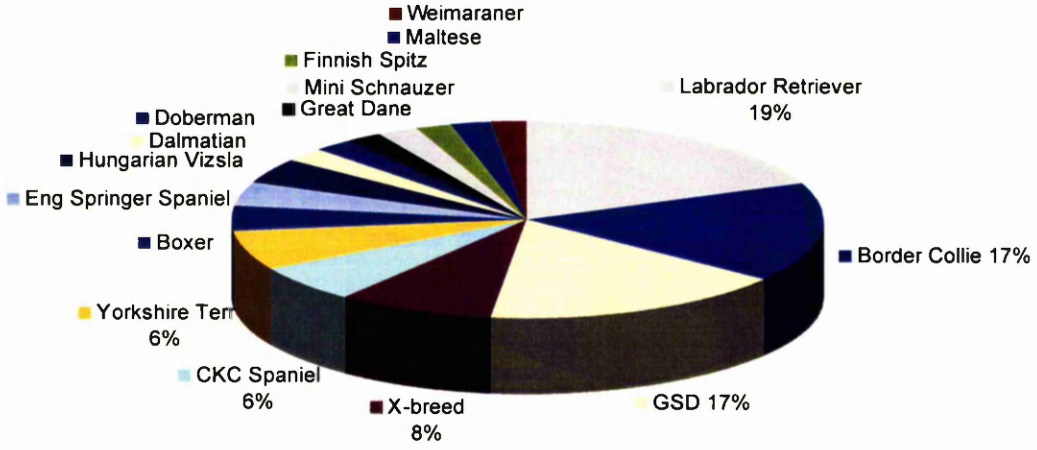
A total of 48 dogs were referred to Small Animal Hospital of University of Glasgow Veterinary School (SAH-UGVS) between March 1999 and April 2001 for evaluation of seizures and that satisfied the criteria for inclusion in either Group One or Two (see 2.3.1 Categories of Seizure Cases Included in This Study, page 67). Detailed data are presented in Table 3.3, page 83.

3.1.1 Breed and Sex Distribution

Sixteen breeds were represented with a preponderance of three specific breeds: Labrador retriever (9/48), Border collie (8/48) and German shepherd dog (8/48). Breed distribution is illustrated in Figure 3.1.

Twenty-two of the dogs were male (18 entire and 4 neutered) and twenty-six dogs were female (5 entire and 21 neutered).

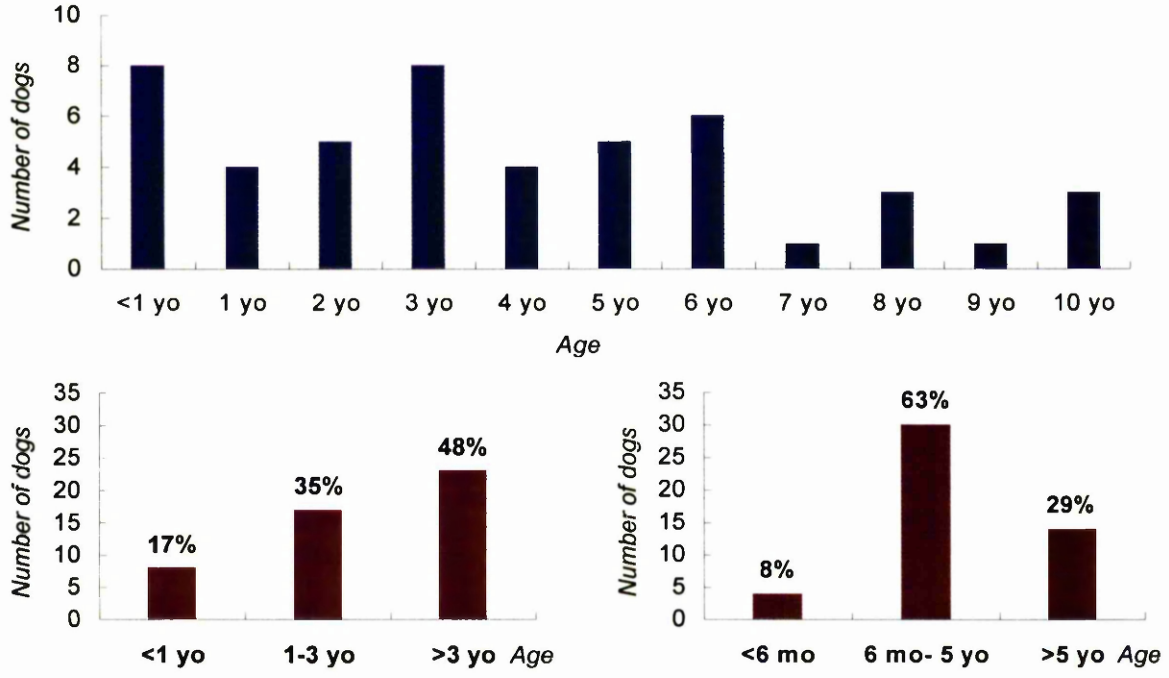
Figure 3.1 Breed distribution



3.1.2 Age at Onset of Seizure Activity

Age at the onset of seizure activity was in the range of 2 months and 10 years old, with a mean of 47 months (Figure 3.2, page 79). In the present study, 35% (17/48) of dogs had first seizure between 1 and 3 years old, and in 63% (30/48) of dogs the first seizure occurred between 6 months and 5 years old.

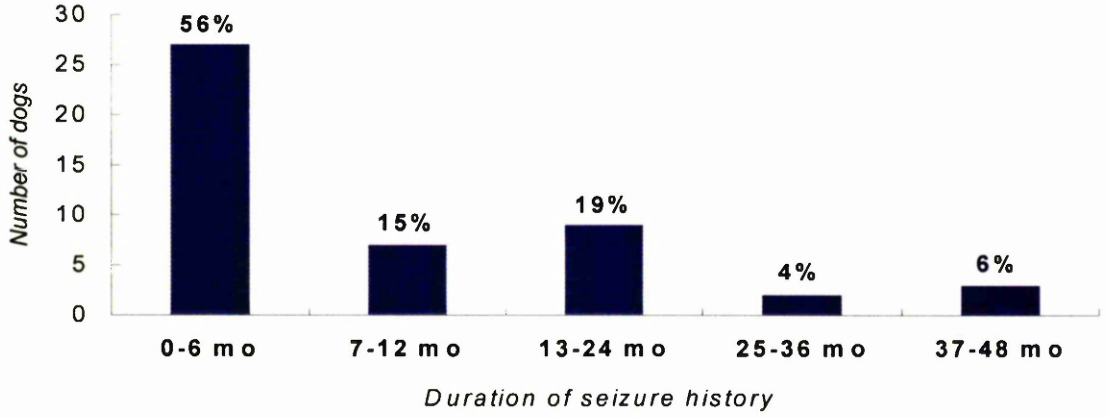
Figure 3.2 Distribution of age at onset of seizure activity



3.1.3 Duration of Seizure History When Presented

The duration of recurrent seizures at the time of referral ranged between 1 day and 48 months, in which the mean was 9 months and the median 5.5 months. Fifty six percent (27/48) of dogs presented with a duration of seizure activity of less than 6 months (Group One) and 44% (21/48) greater than 6 months (Group Two) (see Figure 3.3).

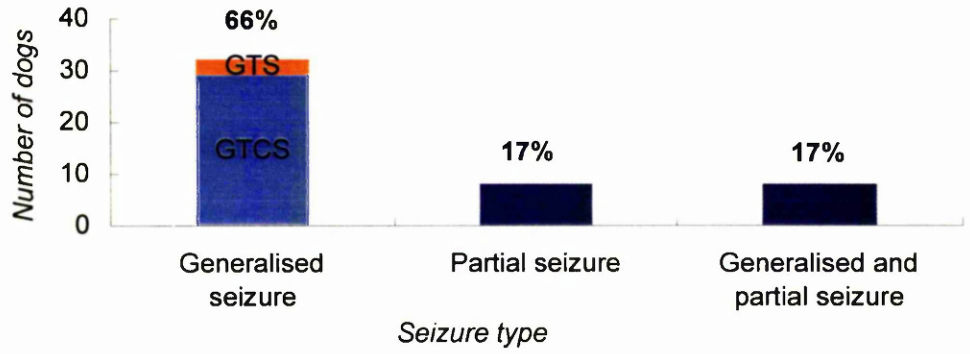
Figure 3.3 Duration of seizure history when referred



3.1.4 Seizure Type

Sixty-six percent (32/48) of dogs exhibited generalised seizures, of which 91% (n=29) had generalised tonic clonic seizures (GTCS) and 9% (n=3) had generalised tonic seizures (GTS). Seventeen percent (8/48) of all the dogs included in the complete study presented with partial seizures, and 17% (8/48) of dogs exhibited both isolated generalised seizures and partial seizures (see Figure 3.4).

Figure 3.4 Seizure type and number of dogs



3.1.5 Reasons for Referral

A retrospective review of the cases seen by clinicians at SAH-UGVS attributed the reason for referral to three broad groups: a desire on the part of the owner for increased confidence in the diagnosis of idiopathic epilepsy (50%, 24/48 cases); owners perception that seizure control was inadequate on the AED regimens (46%, 22/48); concern over the apparent side effects associated with AED therapy (4%, 2/48). In individuals with a less than 6-month history of recurrent seizures (Group One), reasons for referral in 70% of dogs (19/27) were the desire for further diagnosis; in dogs with seizure history greater than 6 months (Group Two), 76% of patients (16/21) were referred due to owners perception that seizure control was inadequate (detailed in Table 3. 1).

Table 3. 1 The association between reasons for referral and the duration of seizure history when presented

Reasons for referral	Group One Duration of seizure history < 6 mo		Group Two Duration of seizure history >6 mo	
The desire for further diagnosis	19/27	70%	5/21	24%
Seizure control was inadequent	6/27	22%	16/21	76%
Concern of AED side effects	2/27	8%	0/21	0%

3.1.6 AED Therapy at the Time of Referral

At the time of accession, 69% (33/48) of patients had been treated with or were currently on anticonvulsant drug therapy. In individuals with a less than 6-month history of recurrent seizures, 52% (14/27) had been treated with AED, and in dogs with seizure history of greater than 6 months, 86% (18/21) were on AED therapy.

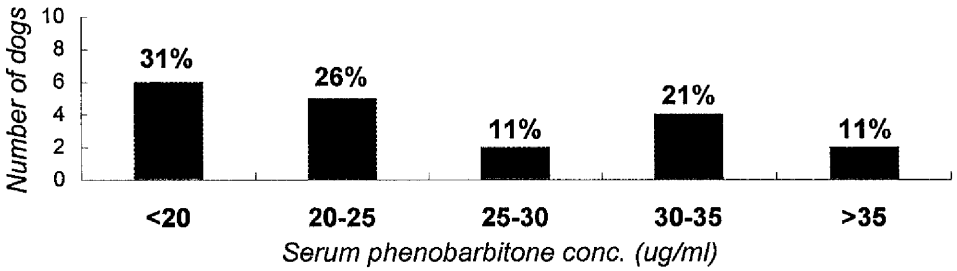
Phenobarbitone was the predominant AED prescribed, with 63% of dogs (30/48) being on phenobarbitone treatment at the time of accession. In the majority of patients (90%), phenobarbitone was administered every 12 hours, in one dog every 24 hours, and in 2 dogs every 8 hours. Dosages administered ranged from 1.2 to 14.7 mg/kg/day, with a mean 5.9 mg/kg/day. Phenobarbitone dose categorised by duration of recurrent seizure history and AED history is presented in Table 3.2.

Table 3.2 Current phenobarbitone dose, duration of seizure history and AED history

	Duration of seizure history		Duration of AED history		Total
	<6 mo	>6 mo	<6 mo	>6 mo	
			Number of dogs		
<4 mg/kg/d	4	6	5	5	10
4-7 mg/kg/d	6	4	8	2	10
>7 mg/kg/d	3	7	3	7	10
			Phenobarbitone dose (mg/kg/day)		
Range	1.6- 9.2	1.2- 14.6	1.6- 9.2	1.2-14.6	1.2-14.6
Mean	5.2	6.5	5.0	7.0	5.9
SD	2.3	3.9	2.2	4.0	3.3

In 19 out of 30 dogs on phenobarbitone therapy, serum phenobarbitone concentrations had been measured immediately prior to or at the time of referral (range 4.4 – 39.5 μg/ml, mean 24.3 μg/ml). In 31% (6/19) of these patients, serum phenobarbitone concentrations were lower than 20 μg/ml (therapeutic range: 20 –35 μg/ml, 1); in 26% (5/19) of dogs the concentrations were within the one-third lower end of therapeutic range (20 –25 μg/ml) and 21% (4/19) were within the one-third upper end (30 - 35 μg/ml); in 11% (2/19) serum phenobarbitone concentrations were higher than 35 μg/ml. The distribution of serum phenobarbitone concentrations is presented in Figure 3.5 (page 82).

Figure 3.5 Distribution of serum phenobarbitone concentrations



Other antiepileptic drugs that had been used in the previous history included primidone (n=2), KBr (n=6), diazepam (n=1), phenytoin (n=1), and clonazepam (n=1). The dose of KBr ranged from 13.9 to 44.1 mg/kg/day, with the mean 26.4 mg/kg/day. Serum bromide concentrations were in the range from 0.5 to 1.2 mg/ml at the time of referral, with the mean 0.8 mg/ml (therapeutic range 1 – 3 mg/ml) (Boothe 1998).

3.1.7 Behavioural Changes at the Time of Referral

At the time of accession, 15% of patients (7/48) exhibited behavioural changes that had developed since seizure disorder started. The behavioural changes reported included repetitive and compulsive behaviour, destructive behaviour, overactivity and excitability, and aggression. The information from clinical records was not detailed enough to determine the possible cause or pattern of behavioural changes.

Table 3.3 Database of cases in the study: signalment, seizure history, and previous AED therapy

Case no.	Breed	Sex	Age of seizure onset	Duration of seizure history	Duration of AED history	Seizure type	Reason for referral*	PB mg/kg daily	Serum PB conc. (μmol/l)	Other AED
120705	GSD	M	2.5 yo	7.5 mo	7 mo	GTCS	2	None	93	Primidone 31.97 mg/kg/d
125509	X-bred	M	6 yo	19 mo	0	GTCS, PS	1	None	N/A	None
127816	Labrador	FN	10 yo	1 mo	0	GTS	1	None	N/A	None
133841	Doberman	MN	4 yo	16 mo	16 mo	GTCS, PS	2	1.15	19	None
134204	Border Collie	M	10 yo	2 mo	0	GTCS	1	None	N/A	None
135317	Border Collie	FN	2.5 yo	8 mo	8 mo	GTCS	2	6.43	105	None
135684	Eng springer spaniel	FN	3 yo	1 mo	0	GTCS	1	None	N/A	None
136193	Mini. Schnauzer	M	1 yo	5 mo	0	GTCS, PS	1	None	N/A	None
136220	Labrador	FN	3 mo	2 mo	2 mo	GTCS	2	3.53	N/A	None
136705	Dalmatian	M	6.5 yo	3 mo	3 mo	GTCS	1	4.80	N/A	None
136950	Labrador	FN	6 yo	1 mo	1mo	GTCS, PS	1	None	N/A	None
137098	GSD	FN	8 yo	6 mo	6 mo	GTCS	2	4.39	138.67	None
137266	Yorkshire Terr	M	6 yo	1 day	0	PS	1	None	N/A	None
137543	CKC spaniel	M	2 mo	0.5 mo	0	GTCS	1	None	N/A	None
137554	Labrador	FN	3 yo	37 mo	13 mo	GTS	1	3.75	69	None
137839	CKC spaniel	F	4.5 yo	3 mo	1 mo	GTCS, PS	2	6.67	N/A	None
137916	Yorkshire Terr	FN	2 yo	14.5 mo	3.5 mo	GTCS	2	5.45	74	None
137944	Boxer	F	5 yo	3 mo	1.5 mo	PS	2	9.23	N/A	Diazepam 0.38 mg/kg tid
138262	Hungarian Vizsla	F	4 yo	9 mo	5 mo	GTCS	2	5.22	107	None
138388	Labrador	FN	3.5 yo	5 days	0	GTCS	1	None	N/A	None
138435	Yorkshire Terr	FN	5 yo	4 yr	4 yr	GTCS	2	14.63	101	None
138469	GSD	M	1 yo	3 mo	2 mo	GTCS	1	8.00	124	None

Table 3.3 Database of cases in the study: signalment, seizure history, and previous AED therapy (Continued)

138493	Great Dane	M	4 mo	7 mo	7 mo	GTCS	2	8.73	144	KBr 27.27 mg/kg/d for short term
138523	Border Collie	FN	3 yo	16.5 mo	15 mo	GTCS	1	1.62	N/A	None
138833	Finnish Spitz	M	7 yo	2.5 mo	2.5 mo	GTCS	1	1.94	N/A	None
138951	Border Collie	FN	2 yo	13 mo	2 mo	GTCS	2	2.00	N/A	None
139073	GSD	M	10 mo	40 mo	20 mo	GTCS	2	8.85	73 for 5.90 mg/kg/d	None
139330	Border Collie	F	10 mo	4.5 mo	4.5 mo	GTCS	2	6.32	N/A	Switch primidone 78.95 mg/kg/day to phenobarbital 6.32 mg/kg/day
139613	GSD	FN	4 yo	19 mo	18 mo	GTCS	2	12.12	139	KBr 20.20 mg/kg/day; serum bromide conc. 0.5 mg/ml
139744	GSD	M	6 mo	1 mo	0.5 mo	GTCS	1	3.33	N/A	None
139977	Labrador	MN	1.5 yo	9 mo	0	PS	1	None	N/A	None
140193	Eng springer spaniel	M	3.5 yo	27mo	23 mo	GTCS	2	8.00	N/A	KBr 26.67 mg/kg day; serum bromide conc. 1.2 mg/ml
140277	X-bred	M	6 yo	4 mo	3 mo	GTCS	2	6.10	89 for 4.07 mg/kg/d	None
140748	CKC spaniel	FN	6 yo	5 mo	1 mo	PS	3	None	N/A	None
140850	Labrador	M	5 yo	19 mo	11 mo	GTCS	2	3.33	41	KBr 2 ml/day, phenytoin 2.78 mg/kg tid; serum bromide conc. 1 mg/ml; serum phenytoin conc. 0.2 µmol/l
140915	Labrador	FN	5 yo	13 mo	12 mo	GTCS	2	8.33	157	KBr 13.89 mg/kg/day, serum bromide conc. 0.5 mg/ml when referred

Table 3.3 Database of Cases in the Study: Signalment, Seizure History, and Previous AED therapy (Continued)

140968	Border Collie	M	3.5 yo	3 mo	0	GTCS, PS	1	None	N/A	None
141152	Maltese terr	FN	10 yo	4 mo	2.5 mo	PS	3	4.29	N/A	None
141210	GSD	FN	1 yo	12 mo	12 mo	GTCS	2	3.64	110	None
141389	X-bred	MN	7 mo	3 yr	0	PS	1	None	N/A	None
141576	Border Collie	M	3 yo	16 mo	14 mo	GTCS, PS	2	5.00	82 for 4 mg/kg/d	Clonazepam 0.27 mg/kg tid
141931	X-bred	FN	8 yo	1 mo	0	PS	1	None	N/A	None
141994	Border Collie	FN	2 .5 yo	6 mo	0.5 mo	GTCS, PS	1	1.58	N/A	None
142041	Hungarian Vizsla	FN	3 yo	2 mo	0	GTS	1	None	N/A	None
142067	Boxer	FN	8 yo	5 day	4 day	GTCS	1	7.74	170	None
142133	GSD	FN	7 mo	11 mo	11 mo	GTCS	2	12.35	150	KBr 44.12 mg/kg/d; serum bromide conc. 0.6 mg/ml
142177	Weimaraner	M	9 yo	1.5 mo	0	GTCS	1	None	N/A	None
142222	Labrador	MN	5 yo	6 mo	0	GTS	1	None	N/A	None

GSD: German Shepherd Dog; X-breed: Crossbreed; CKC spaniel: Cavalier King Charles spaniel
M: male; MN: male neutered; F: female; FN: female neutered
GTCS: generalised tonic clonic seizure; GTS: generalised tonic seizure; PS: partial seizure
PB: phenobarbitone
N/A: not available
Reason for referral*: 1-final diagnosis, 2-uncontrolled seizures, 3-AED side effects

3.2 QUESTIONNAIRE ONE: AN ASSESSMENT OF SEIZURE MANAGEMENT IN COMPANION ANIMALS FROM THE OWNERS' PERSPECTIVE

3.2.1 The Response

A total of 37 questionnaires were mailed in the study. Twenty-three questionnaires were returned within 3 weeks of the original mailing date and 10 questionnaires were returned after the follow-up mailing. A total of 33 questionnaires were received. One questionnaire was not completed, as the respondent considered it inapplicable to their pet which had not been administered AEDs, leaving 32 useable questionnaires. Therefore, the useable response rate was 86% (32/37) (Table 3.4).

Table 3.4 The response rate at different stages

	Response rate of useable questionnaires	
Original Mailing	22/37	59 %
Follow-up	10/37	27%
Total	**32/37**	**86%**

3.2.2 Detailed Results

The questionnaire had specific sections related to AED therapy, and responses are divided into those concerned with patients to which AED therapy had been administered (n=25) and a group with no exposure to AED therapy (n=7).

3.2.2.1 Section A: Establishing the Ideals for Assessing the Outcome of Seizure Management

Responses from owners with pets on AED therapy

A summary of the descriptive statements of the answers to the questions (A1, A3-6) is presented in Table 3.5 (page 87). The issue attributed the greatest significance was "the dog's quality of life", followed by "adequate seizure frequency", "acceptable AED side effects", and "concern of the cost of seizure management". "Influence of caring for an epileptic dog on owners' lifestyle" was of least concern, although answers to this question exhibited the greatest variation in this section.

Table 3.5 Evaluation of the importance of factors in the assessment of seizure management in group with AED therapy

	Question	Response	Range	Mean	SD±
A1	Adequate seizure frequency	24/25	42-100	88.2	15.4
A3	Acceptable AED side effects	25/25	41-100	82.9	17.4
A4	The dog's quality of life	25/25	56-100	92.8	9.1
A5	Minimal influence from caring for an epileptic dog on the owner's lifestyle	25/25	0-100	58.3	35.5
A6	Concern of the cost of seizure management	25/25	0-100	65.9	32.9

In the 24 responses to question A2, a minority of respondents (4/24, 17%) identified a "reasonable" outcome as the patient being totally free from seizure activity with the greater proportion of responses (20/24, 83%) suggesting the concept of "reasonable" outcome included some seizure activity. Approximately one-third of respondents (8/24) considered decreased cluster seizures to isolated seizures as representing a reasonable outcome. Excluding cluster seizures, the minimal seizure interval suggested as "reasonable" (as described by the statements 1-6) varied from "one seizure every 2 weeks" (statement 2) to "less than one seizure every 6 months" (statement 6). The distribution of responses is in Table 3.6, with the most popular response (8/24, 33%) as "one seizure every 3 to 6 months.

Table 3.6 Responses distribution of minimal seizure interval in group with AED

	Statement- seizure frequency	Number of responses	Percentage
1	One seizure / 1 week	0 / 24	0
2	One seizure / 2 weeks	1 / 24	4
3	One seizure / 1 month	1 / 24	4
4	One seizure / 2 months	4 / 24	17
5	One seizure / 3-6 months	8 / 24	33
6	Less than one seizure / 6 months	6 / 24	25
7	Seizure free	4 / 24	17

In the 11 responses to question A7, most owners repeated one of the factors which had been described in previous questions, including AED side effects (2/11), the dog's quality of life (5/11), and seizure control (1/11). Other factors indicated by respondents were the interaction between owners and clinician (1/11), control of behavioural changes (1/11), and the importance of diagnosis (1/11). In summary, this question didn't reveal additional factors important for most owners in assessing seizure management.

Responses from owners with pets not on AED therapy

A summary of the answers is presented in Table 3.7. "The dog's quality of life remained the most important factor to owners in assessing the outcome of seizure management, and the order of factors was the same as group with AED therapy.

Table 3.7 Owners' perspective of the importance of issues in assessing seizure management for respondents with pets not on AED therapy

	Question	Response	Range	Mean	SD±
A1	Adequate seizure frequency	7/7	70-100	92.0	11.9
A3	Acceptable AED side effects	7/7	45-100	90.9	18.8
A4	The dog's quality of life	7/7	94-100	98.6	2.1
A5	Minimal influence from caring for an epileptic dog on the owner's lifestyle	6/7	0-100	40.7	44.3
A6	Concern of the cost of seizure management	6/7	0-100	78.3	36.0

In the 6 responses to question A2, one third of owners (2/6) considered being seizure free as a "reasonable" outcome and a similar proportion included "seizure free" in a range of variable seizure frequency as a reasonable outcome. Only one respondent considered decreasing cluster seizures or status epilepticus to isolated seizures as "reasonable". The range in responses to the minimal acceptable seizure interval perceived as "reasonable" was the same as that for owners with pets on AED therapy. Detailed results of minimal seizure interval are presented in Table 3.8.

Table 3.8 Results of minimal seizure interval (Q-A2) in group without AED therapy

	Statement- seizure frequency	Number of responses	Percentage
1	One seizure / 1 week	0/6	0
2	One seizure / 2 weeks	1/6	17
3	One seizure / 1 month	1/6	17
4	One seizure / 2 months	0/6	0
5	One seizure / 3-6 months	1/6	17
6	Less than one seizure / 6 months	1/6	17
7	Seizure free	2/6	32

3.2.2.2 Section B: An Assessment of Seizure Management in their Own Dogs

Responses from owners with pets on AED therapy

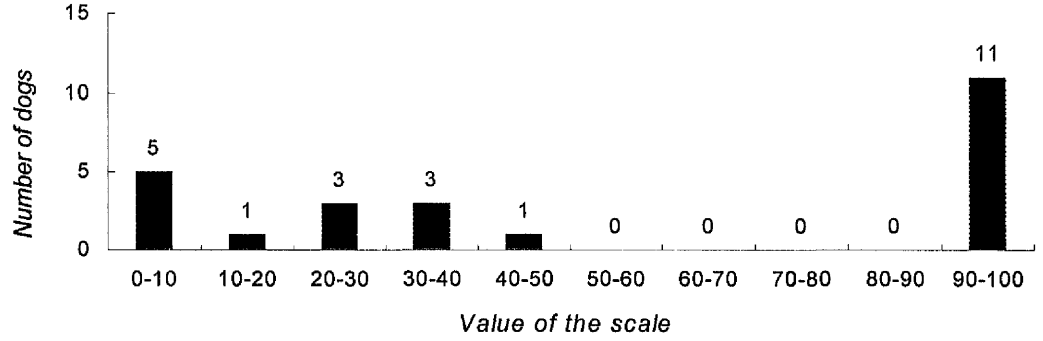
A summary of the responses to the questions (B2-6, B8) is presented in Table 3.9. According to the mean of each factor, "the dog's quality of life" was the most successful factor, followed by "acceptable AED side effect", "concern of the cost of seizure management", and "minimal influence from caring for an epileptic dog on owners' lifestyle". "Adequate seizure frequency" was the least successful factor, with the greatest variation in this section.

In question B2, 13 responses out of 24 had a score of less than 50. According to seizure frequency indicated in question B1, seizure frequency in these dogs varied from one isolated seizure or cluster seizures every 2 weeks to 2 months, except one dog with partial seizure every day. The distribution of values of this factor is presented in Figure 3.6.

Table 3.9 An assessment of seizure management in individual dog of group with AED

Question	Response	Range	Mean	SD±
B2 Adequate seizure frequency	24/25	4-100	55.9	38.5
B3 Acceptable AED side effects	24/25	4-100	74.1	29.1
B4 The dog's quality of life	25/25	5-100	79.9	26.2
B5 Minimal influence from caring for an epileptic dog on the owner's lifestyle	24/25	0-100	65.5	35.2
B6 Concern of the cost of seizure management	24/25	3-100	72.7	28.7
B8 General assessment of seizure management in their dog	25/25	45-100	79.0	19.2

Figure 3.6 Distribution of values for "adequate seizure frequency"



Responses from owners with pets not on AED therapy

A summary of the responses to the questions (B2-6, B8) is presented in Table 3.10. Based on the mean of each factor, "the dog's quality of life" was the most successful factor, followed by "minimal influence from caring for an epileptic dog on owner's lifestyle". "Adequate seizure frequency" scored lowest, which was the same as for the respondents with pets on AED therapy.

Table 3.10 An assessment of seizure management in individual dog of group without AED therapy

Question	Response	Range	Mean	SD±
B2 Adequate seizure frequency	6/7	0-75	42.5	31.1
B4 The dog's quality of life	6/7	94-100	97.8	2.2
B5 Minimal influence from caring for an epileptic dog on the owner's lifestyle	6/7	0-100	80.8	36.2
B6 Concern of the cost of seizure management	6/7	0-100	66.3	43.8
B8 General assessment of seizure management in their dog	5/7	1-89	45.2	37.1

In question B2, 3 responses out of 6 were with the value of the scale less than 50, in which the seizure frequency varied from 5 to 8 partial seizures every day to generalised cluster seizures every 2 to 4 months. In summary, the mean value of general assessment of seizure management was lower than group with AED therapy.

3.2.2.3 Section C: An Assessment of Quality of Life in Epileptic Dogs

Responses from owners with pets on AED therapy

A summary of the responses to questions C1-3 is presented in Table 3.11 (page 91). A minority of respondents (3/23) to question C1 considered their dogs' daily activity had increased compared with the period before the onset of seizure activity. According to further comments, two of these dogs had presented with behavioural changes such as repetitive compulsive behaviour, overactivity, or more attention seeking. In the two responses to question C3 indicating the dog's general quality of life was improved compared to the period before the onset of seizure activity, one related to increased activity and the other was a presumed response as seizures had been present in this dog since adoption.

Table 3.11 Results of assessment of epileptic dogs' quality of life in group with AED

	Question	Response	Response					
			Decreased		*The same*		*Increased*	
C1	Daily activity	23/25	12	(52%)	8	(35%)	3	(13%)
C2	Interaction between the dog and family members	24/25	3	(13%)	16	(67%)	5	(20%)
C3	General assessment of the dog's quality of life	25/25	11	(44%)	12	(48%)	2	(8%)

The respondents (12/25), who indicated that they perceived the dog's quality of life to have deteriorated (question C3), were requested to answer question C4 to indicate the reason. Of the 12 responses to question C4, "side effects of AED" was the largest group, followed by "inadequate control of seizures". Furthermore, "behavioural change" was the commonest additional reason for deteriorating the quality of life of epileptic dogs (3/12, 25%). Responses of question C4 are detailed in Table 3.12.

Table 3.12 Results of question C4 - reasons for the dog's quality of life deteriorating

	Category		Response		Comments
1	Inadequate control of seizures		5/12	42%	None
2	AED side effects		7/12	58%	None
3	Other	- Behavioural changes	3/12	25%	Repetitive compulsively behaviour, over activity, more attention seeking
		- Breathless	1/12	8%	No confirmation as relating to seizure management

Responses from owners with pets not on AED therapy

The majority of respondents indicated the dogs' daily activity, interaction with family members and general quality of life were the same as before seizure started. Detailed results are presented in Table 3.13. Only one respondent considered the dog's general daily life and quality of life decreased. This was due to a perception that there was inadequate control of seizures, with the patient exhibiting approximately 5 to 8 partial seizures daily.

Table 3.13 An assessment of quality of life in dogs of group without AED therapy

	Question	Response	Answers					
			Decreased		*The same*		*Increased*	
C1	Daily activity	6/7	1	(17%)	5	(83%)	0	(0%)
C2	Interaction between the dog and family members	6/7	0	(0%)	5	(83%)	1	(17%)
C3	General assessment of the dog's quality of life	6/7	1	(17%)	5	(83%)	0	(0%)

3.2.2.4 Section D: An Assessment of Work Associated with Caring for Epileptic Dogs

Responses from owners with pets on AED therapy

In the responses to questions D1 and D2, a majority (20/25, 80%) of respondents indicated that family members shared the work associated with caring for the epileptic dog. All respondents were the primary people responsible for caring for the patient.

A summary of the responses of questions D3, D5 and D7 is presented in Table 3.14. In responses to question D3, the majority (18/24, 75%) of respondents scored this factor at less than 10 indicating that they did not consider the administration of the medication as a nuisance. The majority of the 6 respondents (4/6) that identified the administration of medication as a problem indicated the requirement for giving medication at consistent time to be most important. Additional reasons included preparation of medication, difficulty in halving the tablets, and the need of carrying medication at all times, as well as tools for rectal administration of diazepam. Answers of question D4 are detailed in Table 3.15.

Table 3.14 An assessment of work associated with caring for epileptic dogs

	Question	Response	Range	Mean	SD±
D3	Administration of the medication is a nuisance	24/25	0-95	12.4	21.3
D5	Regular veterinary examination and blood sampling to monitor drug serum concentration is a nuisance	21/25	0-95	26.5	28.6
D7	Seeking emergency veterinary attention due to seizures at unexpected time is a nuisance	5/5	0-88	34.2	35.3

Table 3.15 Reasons of administration of medication is a nuisance

	Category	Response	
1	The requirement for giving medication everyday	2/6	33%
2	The requirement for giving medication more than once a day	2/6	33%
3	The requirement for giving medication at consistent time	4/6	67%
4	The need to give more than one drug	2/6	33%
5	Difficulty in administering the drug	0/6	0%
6	Others	3/6	50%

In question D5, approximately 50% of respondents (10/21) did not consider regular veterinary examination and blood sampling for serum drug concentration monitoring as a

nuisance (scoring less than 10). Two of the four owners who did not answer this question commented that repeat veterinary examination and blood sampling for serum drug concentration monitoring were not regularly suggested by the referring veterinarian. Questions D6 and D7 revealed that only five respondents had had to seek emergency veterinary treatment because of seizures following the visit to SAH-UGVS and their opinions on the significance of this event varied greatly.

Responses from owners with pets not on AED therapy

In responses to question D1-2, 4 out of 6 respondents indicated that family members shared the work associated with caring for an epileptic dog. Questions D3 to D5 were inapplicable for this group, and in responses of question D6, no respondent had sought emergency veterinary treatment due to seizure activity since the visit to SAH-UGVS.

3.2.2.5 Section E: An Assessment of AED Side Effects

Responses from owners with pets on AED therapy

A summary of the responses to the questions E3 to E10 is presented in Table 3.16. Polyphagia, polydipsia and polyuria were exhibited by more than half of dogs in the study, in which polydipsia was the largest group but associated with least concern. Lethargy, ataxia and restlessness occurred in approximately 40 to 50 % of patients. Vomiting and/or diarrhoea were the least common AED side effect reported. Of the signs exhibited, ataxia was associated with the greatest degree of concern followed by restlessness.

Table 3.16 AED side effects in all dogs of the study

	Question	Patients exhibiting signs		Degree of owners' concern		
				Range	*Mean*	*SD±*
E3	Increased appetite	16/25	64%	0-100	47.5	32.5
E4	Drinking more	18/25	72%	0-90	39.0	30.9
E5	Urinating more	14/25	56%	5-85	42.3	29.9
E6	Sleeping much more than before	11/25	46%	18-85	46.3	20.9
E7	Ataxia	10/24	42%	40-84	68.1	14.2
E8	Restlessness	12/25	48%	0-88	49.5	29.3
E9	Itchiness	5/25	20%	23-70	48.3	12.9
E10	Vomiting and/or diarrhoea	2/25	8%	6-77	41.6	24.7

Based on the responses to question E1, the responses were divided into three subgroups: phenobarbitone monotherapy (PB), KBr monotherapy; phenobarbitone combined with potassium bromide (PB + KBr) (detailed in Table 3.17).

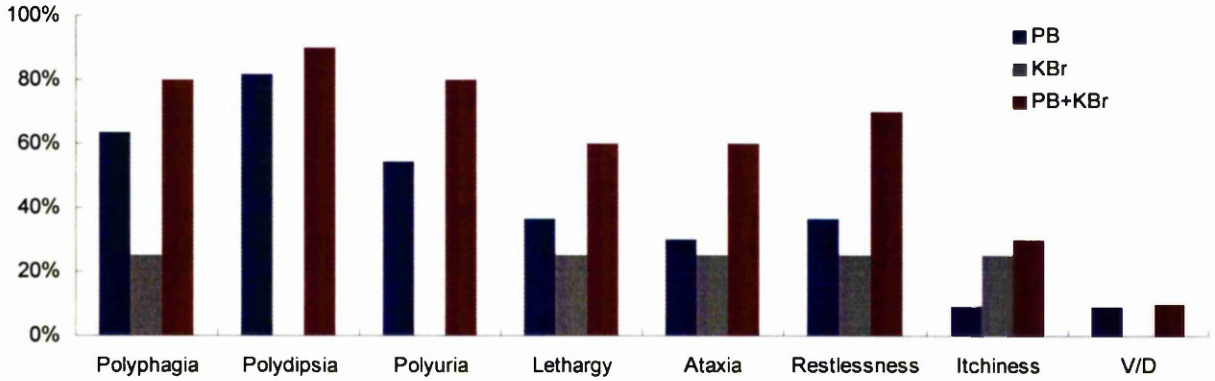
Table 3.17 The occurrence of side effects in patients with AED therapy

Question		Patients exhibiting signs					
		PB		KBr		PB+KBr	
E3	Increased appetite	7/11	64%	1/4	25%	8/10	80%
E4	Drinking more	9/11	82%	0/4	0%	9/10	90%
E5	Urinating more	6/11	55%	0/4	0%	8/10	80%
E6	Sleeping much more than before	4/11	36%	1/4	25%	6/10	60%
E7	Ataxia	3/10	30%	1/4	25%	6/10	60%
E8	Restlessness	4/11	36%	1/4	25%	7/10	70%
E9	Itchiness	1/11	9%	1/4	25%	3/10	30%
E10	Vomiting and/or diarrhoea	1/11	9%	0/4	0%	1/10	10%

PB: phenobarbitone monotherapy; KBr: potassium bromide monotherapy; PB + KBr combination therapy

In the subgroup of dogs on PB monotherapy (11/25), polydipsia remained the most common side effect with polyphagia, polydipsia and polyuria exhibited in more than half of dogs. In the subgroup of dogs on KBr monotherapy (4/25), side effects were only reported in one individual, in which the serum bromide concentration was 2.8 mg/ml. The reported side effects for each subgroup are presented in Figure 3.7.

Figure 3.7 Distribution of side effects in AED subgroups



Results of owners' concern about side effects analysed by different AED therapy are presented in Table 3.18. Ataxia remained owners' highest concern in each group. In general, the degree of owners' concern about AED side effects in polytherapy was higher than phenobarbitone monotherapy.

Table 3.18 The degree of owners' concern in AED subgroups

	Question	PB			PB+KBr			KBr
		Range	*Mean*	*SD±*	*Range*	*Mean*	*SD±*	*Value*
E3	Increased appetite	4-100	32.5	33.9	0-92	55.0	30.0	77
E4	Drinking more	0-90	32.5	36.3	13-88	46. 9	26.5	N/A
E5	Urinating more	5-85	38.6	37.1	8-82	50.4	25.9	N/A
E6	Sleeping much more than before	22-47	37.3	10.9	18-79	41.5	22.4	38
E7	Ataxia	58-84	71.0	13.0	40-79	65.0	15.8	81
E8	Restlessness	0-88	45.0	41.1	15-82	48.3	23.9	79
E9	Itchiness	70	N/A	N/A	44-52	48.0	4.0	52
E10	Vomiting and/or diarrhoea	77	N/A	N/A	49	N/A	N/A	N/A

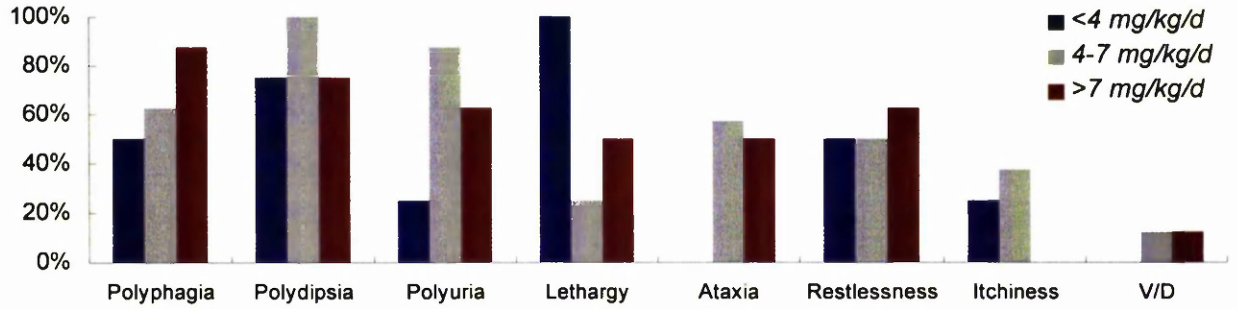
Based on the responses to question E1, dogs on phenobarbitone were divided into three subgroups by dose administered: <4 mg/kg/day (n=4), 4-7 mg/kg/day (n=8), and >7 mg/kg/day (n=8). The results are presented in Table 3.19.

Table 3.19 The occurrence of side effects in dogs with different phenobarbitone dosages

	Question	Patients exhibiting signs					
		PB <4 mg/kg/d		PB 4-7 mg/kg/d		PB >7 mg/kg/d	
E3	Increased appetite	2/4	50%	5/8	63%	7/8	88%
E4	Drinking more	3/4	75%	8/8	100%	6/8	75%
E5	Urinating more	1/4	25%	7/8	88%	5/8	63%
E6	Sleeping much more than before	4/4	100%	2/8	25%	4/8	50%
E7	Ataxia	0/4	0%	4/7	57%	4/8	50%
E8	Restlessness	2/4	50%	4/8	50%	5/8	63%
E9	Itchiness	1/4	25%	3/8	38%	0/8	0%
E10	Vomiting and/or diarrhoea	0/4	0%	1/8	13%	1/8	13%

In general, the occurrence of side effects does not relate to phenobarbitone dosage. In the present study, except ataxia and vomiting/diarrhoea, all signs may exhibit in dogs with phenobarbitone less than 4 mg/kg/day. There was some positive correlation presented between the occurrence of polyphagia and phenobarbitone dosage. Ataxia occurred only in dogs with phenobarbitone dose higher than 4 mg/kg/day. The distribution of occurrence of phenobarbitone side effects in dogs with different range of dosages is presented in Figure 3.8.

Figure 3.8 Distribution of occurrence of phenobarbitone side effects in dogs with different range of dosages



Responses from owners with pets not on AED therapy

Owners of this group of dogs were only requested to answer question E2. A summary of responses of question E2 is presented in Table 3.20. The responses to question E2 indicated the main reason for these dogs not to be on AED therapy was "the seizure interval is longer than one month", followed by "mild seizure severity". Only one dog had been taken off AED due to side effects (the dog exhibiting 5 to 8 partial seizures per day).

Table 3.20 Reasons for dogs currently with no AED therapy

	Category	Response	
1	The severity of seizure activity is mild (only partial seizures)	3/7	43%
2	The seizure interval time is longer than one month	5/7	71%
3	My dog was on medication previously but stopped it due to the side effects	1/7	14%
4	It is difficult to administer the medication	0/7	0%
5	Others	0/7	0%

3.2.2.6 Section F: The Impact of Owning an Epileptic Dog on Owners' Day-to-day Activity

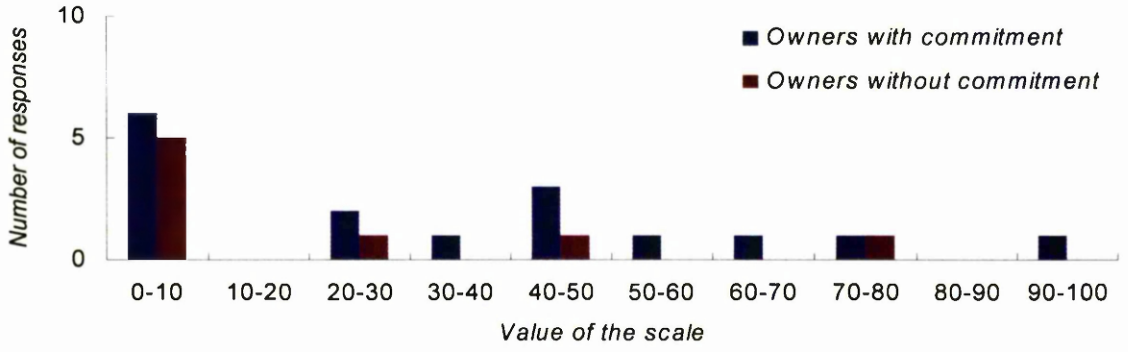
Responses from owners with pets on AED therapy

A summary of responses to question F2 and F4 is presented in Table 3.21 (page 97). The responses to question F2 indicated that 38 % of owners with commitment (6/16, 4 with full-time and 2 with part-time employment) did not consider caring for an epileptic dog had caused them conflicts with their commitments (value of visual analogue scales less than 10). In responses to question F4, 63 % (5/8) of owners, who were not in full-time or part-time employment, did not consider caring for an epileptic dog had caused them conflicts with their commitments. The perceived impact of owning an epileptic dog on respondents' day-to-day activities is presented in Figure 3.9.

Table 3.21 The impact of owning an epileptic dog on owners' day-to-day activity in group with AED therapy

	Question	Response	Range	Mean	SD±
F2	Owners with commitments	16/17	0-100	34.6	28.9
F4	Owners without commitments	8/8	6-76	22.8	24.0

Figure 3.9 Distribution of answers of question F2 and F4



In responses to question F2 and F3, a nonsignificant positive correlation (r_s= 0.48, P>0.05) was presented between the degree of the impact from owners' perspective and the frequency of time off or been late for work due to caring for the epileptic dog. Only one respondent (1/8) to question F5 indicated that caring for an epileptic dog was a factor preventing them from taking up employment.

Responses from owners with pets not on AED therapy

The responses to question F2 indicated that the respondents (4/5, 3 with full-time and 1 with part-time job) did not consider caring for an epileptic dog had caused them conflicts with their work commitments (value of visual analogue scales less than 10). One respondent reported a conflict (full-time employment) with requirements for time-off or being late for work a couple of times in a 6-month period. The only response to question F4 indicated a mild impact on that individual's day-to-day activities (scale value 21). A summary of answers of question F2 and F4 is presented in Table 3.22.

Generally, respondents from the owners of pets on AED therapy indicated a greater impact (higher visual analogue scores) than respondents from the non-treatment group.

Table 3.22 The impact of owning an epileptic dog on owners' day-to-day activity in group without AED therapy

Question	Response	Range	Mean	SD±
F2 People with commitment	5/5	0-100	20.8	39.6
F4 People without commitment	1/2	21	N/A	N/A

3.2.2.7 Section G: The Impact of Owning an Epileptic Dog on Owners' Ability/decision to Stay Away Overnight

Responses from owners with pets on AED therapy

Three of the 25 respondents did not stay away from home overnight. A summary of the responses to questions G1 and G2 are presented in Table 3.23. Compared with the period before the onset of seizure activity, 36 % of respondents (8/22) had changed the way they organised the care of their epileptic dog when they stayed away from home overnight, and more respondents left the dog at home with someone able to care of it.

Table 3.23 How owners organised the care of dogs when they stayed away overnight, in the group with AED therapy

Category	Q G1- before seizures started		Q G2- after seizures started	
	Response		Responses	
1 Take them with you	10/22	46%	9/22	41%
2 Kennel/ boarding	3/22	14%	3/22	14%
3 Ensure that someone is at home to care for them	10/22	46%	13/22	59%
4 Other – leave them relatives or friends	3/22	14%	1/22	5%

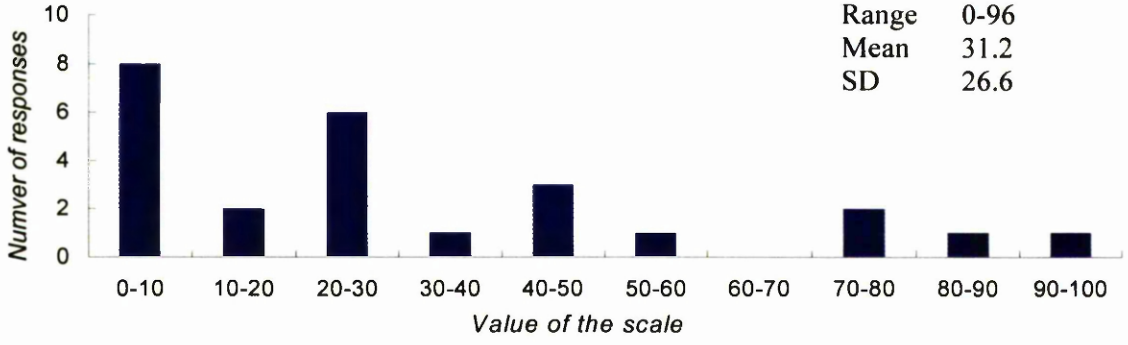
In the responses to question G3, approximately half of respondents (12/22) indicated that their dogs' seizures had affected their ability/decision to stay away overnight, in which the main reason for that was "the owner was too worried to leave the epileptic dog" (9/12), followed by "the owner couldn't find someone able to care for an epileptic dog" (5/12), and "the dog usually has seizures when the owner is away or after return" (3/12). Detailed responses to question G3 are listed in Table 3.24.

Table 3.24 Reasons why seizures in dogs affected their owners' ability/decision to stay away overnight

Category	Response	
I couldn't find someone able to care for an epileptic dog	5/12	42%
I am too worried to leave the dog	9/12	75%
My dog usually has seizures when I am away or after I return	3/12	25%
Other	1/12	8%

A summary of responses to question G5, generally assessing the impact of owning an epileptic dog on owners' free time, is presented in Figure 3.10.

Figure 3.10 The impact of owning an epileptic dog on owners' free time



Responses from owners with pets not on AED therapy

A summary of the responses to questions G1 and G2 are presented in Table 3.25 (page 100). Compared with the period before the onset of seizure activity, only one respondent (1/6, 16%) had changed the way they organised the care of the epileptic dog when they stayed away overnight. One response was inapplicable as the owner had not stayed away overnight since the onset of seizures. Only one respondent to question G3 and G4 (1/5)

indicated that the patient's seizure problem had affected their decision /ability to stay away overnight; this was for two reasons "the owner is too worried to leave the dog" and "the dog usually has seizures when the owner is away or after the return". Apart from this response indicating a mild impact of owning an epileptic dog on the owner's free time (with scale value of 21), the majority of respondents (6/7) reported no impact on their free time (scale value less than 10).

Table 3.25 How owners organised the care of dogs when they stayed away overnight, in the group without AED therapy

Category	Q G1- before seizures started		Q G2- after seizures started	
	Response		Responses	
1 Take them with you	4/7	57%	5/6	83%
2 Kennel/ boarding	0/7	0%	0/6	0%
3 Ensure that someone is at home to care for them	4/7	57%	3/6	50%
4 Other – leave at home	1/7	14%	1/6	16%

3.2.2.8 Section H: Owners' Opinions on Further Investigation of Seizures in their Dogs

Responses from owners with pets on AED therapy

In approximately two-third of cases (17/25), the referral to SAH-UGVS was suggested by the referring veterinary surgeon with the other third of referrals (9/25) being requested by the owner. One response indicated the referral was both suggested by vet and requested by the owner (question H1).

For the majority (23/25), the reasons for referral were to find out whether there was any underlying disease causing seizures, and for approximately 40 % of cases (11/25), referral was due to perceived inadequate seizure management and a desire of a further opinion (question H2). In responses to question H3, the main reason of the previous seizure management being considered unsatisfactory included "seizure frequency was unacceptable", followed by "owner was worried about the dog" and "dog's quality of life was not good" (summarised in Table 3.26, page 101).

Table 3.26 Reasons why the previous seizure management considered unsatisfactory

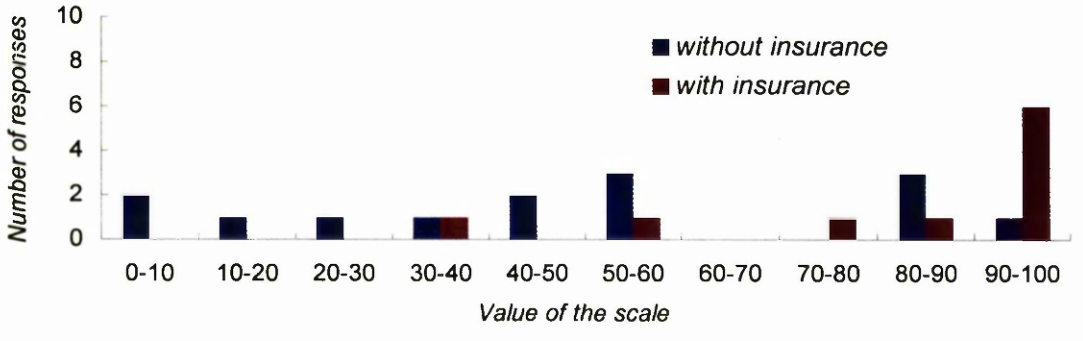
	Category	Response	
1	Seizure frequency was unacceptable	11/12	92%
2	Side effects were unacceptable	2/12	17%
3	The dog's quality of life was not good	6/12	50%
4	The effort associated with caring for the epileptic dog influenced the owner's lifestyle too much	2/12	17%
5	The owner was worried about the dog	9/12	75%
6	Other –worries of long-term side effects of AED	1/12	8%

A summary of the responses to question H4-6 is presented in Table 3.27. Three respondents commented they still did not know the cause of seizures or that their lifestyle had not been changed and did not answer the questions. A summary of the responses to question H6 from the perspective of the influence of pet health insurance (question H7) is presented in Table 3.27 and Figure 3.11.

Table 3.27 Owners' opinions on further investigation of seizure disorder in group with AED

	Question	Response	Range	Mean	SD±
H4	Knowing more about the cause of seizures helped the owner to understand the dog's problem	22/25	10-100	71.6	26.6
H5	Knowing more about the cause of seizures helped the owner accept any lifestyle changes they may have to make.	22/25	9-100	62.0	32.1
H6	The cost of further diagnostic procedures to know more about the cause of seizures is worthwhile	24/25	0-100	62.3	30.8
H6	**Without** pet health care insurance to pay for investigation	14/15	0-99	48.8	29.8
H6	**With** pet health care insurance to pay for investigation	10/10	30-100	81.3	20.7

Figure 3.11 The influence of pet insurance to owners in considering the cost of further investigation is worthwhile in group with AED therapy



Responses from owners with pets not on AED therapy

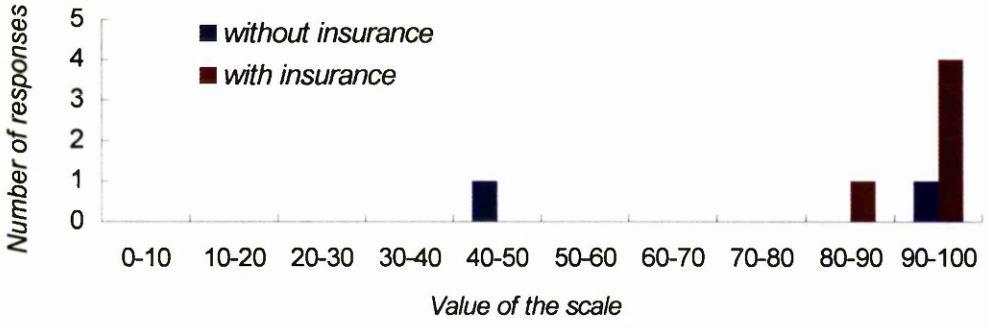
In half of responses (4/7), the referral was suggested by vet and in the other, it was requested by the owner, in which one response indicated the referral was combined both circumstances. In all responses, to question H2, the reason of referral was "to find out whether there was any underlying disease causing seizures". In one response, an additional reason was "seizure management was inadequate and the owner needed another opinion".

A summary of the responses of question H4-6 is presented in Table 3.28. One owner commented he still did not know the cause of seizures and did not answer some questions. A summary of the responses to question H6 from the perspective of the influence of pet health insurance (question H7) is presented in Table 3.28 and Figure 3.12.

Table 3.28 Owners' opinions on further investigation of seizure disorder in group without AED therapy

	Question	Response	Range	Mean	SD±
H4	Knowing more about the cause of seizures helped the owner to understand the dog' problem	6/7	60-100	87.3	14.4
H5	Knowing more about the cause of seizures helped the owner accept any lifestyle changes they may have to make.	5/7	0-99	37.6	45.4
H6	The cost of further diagnostic procedures to know more about the cause of seizures is worthwhile	7/7	46-100	88.3	17.9
H6	**Without** pet health care insurance to pay for investigation	2/2	46-100	73.0	27.0
H6	**With** pet health care insurance to pay for investigation	5/5	85-100	94.4	5.2

Figure 3.12 The influence of pet insurance to owners in considering the cost of further investigation is worthwhile in group without AED therapy



Considering that the responses to question H4-6 should not be influenced by whether the dog was on AED therapy, all responses to the questionnaire were interpreted jointly and summarised in Table 3.29. In considering the responses to question H6 for the cases in which the full investigation protocol was undertaken, the influence of pet health insurance in these cases were also examined (Table 3.30).

Table 3.29 Owners' opinions on further investigation of seizure disorder from all responses of the study

Question	Response	Range	Mean	SD±
H4 Knowing more about the cause of seizures helped the owner to understand the dog' problem	28/32	10-100	74.9	25.3
H5 Knowing more about the cause of seizures helped the owner accept any lifestyle changes they may have to make.	27/32	0-100	57.4	36.2
H6 The cost of further diagnostic procedures to know more about the cause of seizures is worthwhile	31/32	0-100	68.2	30.5
H6 **Without** pet health care insurance to pay for investigation	16/17	0-100	51.8	30.5
H6 **With** pet health care insurance to pay for investigation	15/15	30-100	85.7	18.2

Table 3.30 Responses from cases, on which the full investigation protocol performed

Question	Response	Range	Mean	SD±
H6 The cost of further diagnostic procedures to know more about the cause of seizures is worthwhile	22/23	4-100	77.6	27.5
H6 **Without** pet health care insurance to pay for investigation	9/10	4-100	63.7	32.5
H6 **With** pet health care insurance to pay for investigation	13/13	30-100	87.2	18.0

In order to compare the perception of clinicians and owners in reasons for referral, all responses to the questionnaire were interpreted jointly and categorised by the duration of seizure history when presented (divided into Group One or Group Two). Within these 32 dogs, 13 dogs presented with a duration of seizure activity less than 6 months and 15 dogs greater than 6 months. Detailed results from the perception of owners and clinicians are presented in Table 3. 31 and Table 3. 32 (page 104).

Table 3. 31 The association between the duration of seizure history and reasons for referral from owner's perception

Reasons for referral	Group One Duration of seizure history < 6 mo		Group Two Duration of seizure history > 6 mo	
The desire for further diagnosis	16/17	94%	14/15	93%
Seizure control was inadequent	4/17	24%	8/15	53%
Concern of AED side effects	1/17	6%	0/15	0%

Table 3. 32 The association between the duration of seizure history and reasons for referral from clinician's perception

Reasons for referral	Group One Duration of seizure history < 6 mo		Group Two Duration of seizure history > 6 mo	
The desire for further diagnosis	13/17	76%	4/15	27%
Seizure control was inadequent	2/17	12%	11/15	73%
Concern of AED side effects	2/17	12%	0/15	0%

A summary of the solicited comments owners made on the back cover of questionnaire is presented in Table 3.33 (page 104).

Table 3.33 General comments

Comments	Response
The cost of treatment at UGVS has been a high burden, as the animal was not insured.	2
The reassurance the owner received from both own vet and clinicians at UGVS is important and helped them cope with the lifestyle of caring an epileptic dog.	1
Local follow up should be implemented including blood checks for assessment of medication control. (The owner also indicated they never received any information on serum drug concentration monitoring until 3 months before the questionnaire study was undertaken.	1
The control of seizures is much more important than knowing the cause of seizures.	1
The owner explained the reason for not performing further diagnostic investigation in the dog: further diagnostic procedures might be too stressful to the dog due to its age. In addition, current stress levels were minimal.	1
The study is worthwhile. Also ask some questions related to the genetic aspect in epilepsy.	1
The reason of not performing further diagnostic procedures was due to the risk (CSF tap). The owner is worried about side effects of AED, although blood tests were carried out frequently. The owner also wondered whether the dog was too quickly started on medication to which it soon developed drug tolerance.	1
Behavioural changes were the most severe problem at that moment, and it had changed the owner's lifestyle very much.	1

3.3 QUESTIONNAIRE TWO: BEHAVIOURAL CHANGES IN EPILEPTIC DOGS

3.3.1 The Response

A total of 11 questionnaires were mailed in the study. Nine questionnaires were returned in 3 weeks after the original mail, and two were returned after the follow-up mailing. The response rate of the study was 100 % (Table 3.34).

Table 3.34 The response rate of the study

	Response rate of useable questionnaires	
Original Mailing	9/11	82%
Follow-up	2/11	18%
Total	**11/11**	**100 %**

3.3.2 Detailed Results

3.3.2.1 The Behavioural Change and the Frequency (Q-1, Q-15 and Q-16)

A summary of the responses to question 1 is presented in Table 3.35. The commonest behavioural changes reported were "more attention seeking" and "overactivity and excitability", followed by "excessive vocalisation"; these three features were reported in more than half of dogs in the study. "Repetitive, compulsive behaviour", "destructive behaviour", "aggression" and "inappropriate urination and/or defaecation" presented in smaller populations. An additional behavioural change reported in the "other" category was excessive hunger. One respondent indicated their pet's behaviour had returned to normal after AED therapy was adjusted at SAH-UGVS. A summary of behavioural changes and the frequency in each dog (question 1, 15 and 16) is presented in Table 3.36 (page 106).

Table 3.35 Behavioural changes in epileptic dogs

Category	Response	
1 Attention seeking	7/10	64%
2 Repetitive, compulsive behaviour	2/10	19%
3 Destructive behaviour	2/10	19%
4 Excessive vocalisation (such as barking or whining)	6/10	55%
5 Overactivity and excitability	7/10	64%
6 Aggression	2/10	19%
7 Inappropriate urination and/or defecation	2/10	19%
8 Other- excessive hunger	2/10	19%

Table 3.36 The frequency of the behaviour in each dog (Q-1, Q-15 to 16)

	Behaviour	Frequency
Dog 1	Attention seeking Repetitive, compulsive behaviour Excessive vocalisation Overactivity and excitability Inappropriate urination and defecation	Off and on all the day
Dog 2	Repetitive, compulsive behaviour	Controlled at present
Dog 3	Excessive hunger-licking the floor	Everyday after feeding and lasted for 1 hour
Dog 4	Attention seeking Destructive behaviour Excessive vocalisation Aggression	30 minutes per day
Dog 5	Attention seeking Excessive vocalisation Overactivity and excitability	Up to one hour per day
Dog 6	Attention seeking Excessive vocalisation Overactivity and excitability	After each seizure and lasted for 2-3 days
Dog 7	Attention seeking Excessive vocalisation	All the day
Dog 8	Attention seeking Overactivity and excitability Inappropriate urination and defecation Excessive hunger	Attention seeking and excessive hunger- everyday Inappropriate urination- once per 2 weeks Overactivity- 1 or few hours after a seizure
Dog 9	Attention seeking Repetitive, compulsive behaviour Overactivity and excitability Aggression	Approximately every 6 weeks and lasted for 1 week
Dog 10	Overactivity and excitability	All the day
Dog 11	Destructive behaviour Excessive vocalisation Overactivity and excitability	All the day

3.3.2.2 The Onset of the Behavioural Changes (Q-2 and Q-3)

Questions 2 and 3 were related to the onset of behavioural changes. The majority (7/10) of respondents to question 2 indicated the onset of behavioural changes was after seizure management started (for detail see Table 3.37, page 107).

Question 3 (respondents were asked to describe when the behavioural changes started in detail) was designed to allow cross checking of the responses to question 2 with our clinical records. In five responses (5/9), the onset of behavioural changes was after seizure

activity occurred but before AED were introduced, and in the other four responses (4/9), the onset of behavioural changes was after AED were introduced (Table 3.37, page 107).

Responses to question 2 and 3 were compared for cross checking. Some responses were inapplicable for comparison, as one or other of the questions was not answered. Of the eight paired responses available for cross checking, in 3 responses the information did not correspond.

Table 3.37 The onset of behavioural changes from Q-2 and Q-3

	Category	Response			
		Question 2		Question 3	
1	Within 6 months before the onset of seizures	2/10	20%	0/9	0%
2	After seizures started but before seizure treatment started	1/10	10%	5/9	56 %
3	After seizure treatment started	7/10	70%	4/9	44%

3.3.2.3 Trigger Factors or the Reason of the Certain Behaviour (Q-4 to Q-6)

Behavioural changes and separation anxiety

In the responses to question 4, three owners (3/11, 27%) indicated the described behaviour was related to separation between the dog and family members; one respondent commented that, although the behaviour was also present when the owner were at home, it deteriorated when they were away.

Behavioural changes and exercise

In the responses to question 5, approximately half the patients (5/11, 46%) were having the same amount of exercise as in the period before seizure activity started, with the remaining patients (6/11, 54 %) having less exercise; one owner commented the decreased exercise was related to the dog's age and ability to exercise, not seizures *per se*.

Other factors reported by respondents

Three owners indicated some further factors related to the behavioural changes observed in their dogs, which included (1) a younger dog initiating play behaviour, (2) stress, and (3) when the dog was kept in one room to avoid him chewing the carpet.

3.3.2.4 History of Behavioural Problems (Q-7 to Q-9)

The responses to question 7 revealed that two dogs had had similar behaviour in the past (defined as prior to 6 months before seizures started in the study). In addition, one respondent indicated that the patient had exhibited other behavioural problems in the past, in which the dog repeatedly ran away during exercise but spontaneously returned hours later; this reported behaviour was considered related to the general behaviour of this dog.

3.3.2.5 Behavioural Changes and AED Therapy (Q-10)

A summary of the responses to question 10 is presented in Table 3.38. Forty percent of owners (4/10) did not perceive a relationship between the behavioural changes and seizure management, with the other respondents indicating some relationship between AED therapy and the behavioural changes.

Two thirds (4/6) of the cases, thought to be related to AED therapy, involved phenobarbitone / KBr combination therapy. The monotherapy regimens were represented by one patient each on PB and KBr monotherapy. Details of these 6 patients are presented in Table 3.39 (page 109).

Table 3.38 Behavioural changes and AED therapy

	Category	Response
1	The behaviour started (or worsened) immediately after phenobarbitone was started.	2/10
2	The behaviour started (or worsened) after phenobarbitone dose was increased.	3/10
3	The behaviour started (or worsened) after phenobarbitone dose was decreased.	0/10
4	The behaviour started (or worsened) after phenobarbitone was started, but was not related to the change of dosage.	1/10
5	The behaviour started (or worsened) immediately after KBr was started	1/10
6	The behaviour started (or worsened) after KBr dose was increased.	2/10
7	The behaviour started (or worsened) after KBr dose was decreased.	0/10
8	The behaviour started (or worsened) after KBr was started, but was not related to the change of dosage.	2/10
9	The behaviour started (or worsened) after AED was started, but was not related to the change of drug and dosage.	0/10
10	There is no relationship between the behavioural changes and seizure management.	4/10
11	Other	0/10

Table 3.39 The onset and progress of the behavioural changes

	AED therapy	Dog 5 PB	Dog 2Φ KBr	Dog 7 PB+KBr	Dog 8 PB+KBr	Dog 1 PB+KBr	Dog 11 PB+KBr
1	Immediately after phenobarbitone was started	✓				✓	
2	After phenobarbitone dose was increased	✓	N/A		✓	✓	
3	After phenobarbitone dose was decreased						
4	After phenobarbitone was started, but was not related to the change of dosage						✓
5	Immediately after KBr was started					✓	
6	After KBr dose was increased	N/A		✓		✓	
7	After KBr dose was decreased						
8	After KBr was started, but was not related to the change of dosage		✓				✓

Φ Behavioural changes in the dog responded to a decrease in the potassium bromide dose.

3.3.2.6 Behavioural Changes and Seizure Activity (Q-11 to Q-14)

The purpose of question 11 was to establish if there was evidence that suggested the reported behavioural changes might be analogous to the psychosis reported in epileptic human patients (Kanner 2000). In the 10 responses to question 11, the majority (7/10) indicated that the behavioural changes were not associated with seizure frequency. In 3 dogs, the behavioural changes started or deteriorated when seizure frequency increased.

The purpose of question 12 was to differentiate the behavioural changes from prodrome and post-ictal phase of seizure activity. The responses were summarised in Table 3.40. Four respondents (4/11) indicated the behaviour might be associated with prodrome and 3 respondents indicated it was related to the post-ictal phase of the seizure. Approximately 36% of responses indicated the behavioural was not associated with seizure activity.

Table 3.40 Behaviour and seizure activity

	Category	Response	
1	The behaviour happens few hours to days before a seizure.	4/11	36%
2	The behaviour happens few hours to days after a seizure.	3/11	28%
3	There is no relationship between the behaviour and seizure activity.	4/11	36%

The purpose of questions 13 and 14 was to determine if there is a relationship between the usual time that the patient had seizures and reported behavioural changes. The majority of respondents indicated there was no consistent time for seizure activity (7/11) or the behavioural changes they reported (9/11). Furthermore, in the responses which indicated specific times for both seizures and behavioural disturbance, the two phenomena were not related (for detail see Table 3.41). In summary, the responses did not suggest a relationship between the usual time that patients had seizures and the reported behavioural changes.

Table 3.41 Comparison of certain occurring time of seizure and the behaviour

	Q-13 Occurring time for seizure activity	Seizure frequency	Q-14 Occurring time for the behaviour	Details of behavioural changes
Dog 3	Early morning	Once per month	After feeding	Excessive hunger- licking the floor after feeding, off and on for about 1 hour
Dog 5	Mostly daytime	Cluster seizures every week to every 3 months	Afternoon or evening	Attention seeking, excessive vocalisation, and overactivity up to one hour everyday

3.3.2.7 The Response of the Reported Behaviour (Q-17 and Q-18)

A summary of the responses to question 17 and 18 is presented in Table 3.42. Greater than 50% of owners tried managing the situation by paying more attention (6/10) or ignoring the behaviour (6/10). Other approaches to management included: interrupting the behaviour by introducing other interesting stimuli (4/10) and punishment (4/10). Examining the relationship between these methods and the patients' response suggested that generally, the behaviour was difficult to influence (6/10). Only one patient responded to being ignored and the owner commented that the behavioural changes in this dog were mild and never became a nuisance. No patients responded to punishment.

Table 3.42 Responses of the behaviour

	The way owners used to control the behaviour	Number of owners	Dogs with response
1	Paying more attention	6/10	1/6
2	Try to interrupt the behaviour by introducing other interesting stimuli	5/10	2/5
3	Punishment	4/10	0/4
4	Ignoring the behaviour	6/10	1/6
5	Other	0/10	N/A

3.3.3 Summary of Questionnaire Two

In order to determine the possible cause or pattern of the behavioural changes, the responses of individual patients were reviewed and are summarised in Table 3.43.

Table 3.43 Summary of the responses of individual patient

The possible cause or pattern of the behavioural changes	Responses
The behavioural changes were associated with AED therapy (**AED-related activity**)	7/11
The onset of behavioural changes was the same as seizure activity (**interictal activity**)	1/11
The behavioural problem was related to postictal phase of seizure activity (**postictal activity**)	2/11
The reported behaviour was likely to be related to the general behaviour of the dog	1/11

In the seven patients with AED-related behavioural changes, one patient's behaviour (excessive hunger only) was apparently related to the common side effect of phenobarbitone or phenobarbitone combined with bromide therapy. In the other six patients, the behavioural changes included attention seeking, repetitive and compulsive behaviour, excessive vocalisation, overactivity and excitability and inappropriate urination / defaecation. Details of the relationship between the behavioural changes and AED therapy in these six patients were described in 3.3.2.5 Behavioural Changes and AED Therapy (Q-10) (page 108). Two out of six respondents also indicated the behavioural changes were exhibited during prodrome; one patient's behaviour also deteriorated when the dog was separated from the owner. One respondent also indicated that the behavioural changes were also exhibited during the postictal phase and deteriorated when seizure frequency increased.

In one patient, the onset of behavioural change was the similar to the seizure problem, but without any relationship between the behaviour and seizure frequency or seizure activity; the behaviour was considered as interictal activity. The respondent indicated that even when the seizure frequency was controlled well by AED therapy, the frequency of the behaviour was the same as before.

In the two patients with behavioural changes mainly related to the postictal phase of seizure activity, one patient's behaviour usually lasted for 2 to 3 days and the other for 7 days. The latter respondent commented that when diazepam was administered rectally to control cluster seizures, the postictal behaviour lasted for briefer time. Furthermore, the

same respondent also indicated the behaviour had been exhibited before the onset of seizure disorder but deteriorated after seizures occurred.

In one patient, the behaviour was not related to AED therapy, seizure activity, or seizure frequency. In addition, the onset of behaviour had preceded the onset of seizure activity by more than 6 months. In summary, the reported behaviour of the dog was considered to be associated with the general behaviour of the dog. In this dog, the behavioural changes reported were attention seeking, destructive behaviour, excessive vocalisation and aggression.

CHAPTER FOUR

DISCUSSION

4.1 General Aspect of the Study

The Significance of the Population Surveyed

All owners/patients surveyed for this study were derived from the client base of the Neurology Service of SAH-UGVS and consequently the results obtained pertain to this particular population. As the composition of such a referral population is likely to be affected by a number of factors (including disease severity, proximity to the referral centre, owners' mobility, owners' socioeconomic status, individual practitioner preferences for referral etc) and although the conclusions of the study are thought to be representative of the clinic owner population profile, extrapolation to the general dog owning public is inappropriate.

The highly motivated nature of this client profile may also be significant in responses to this study (see below).

Reflections on the Response Rate to the Questionnaires

High response rates were achieved to both the questionnaires. The initial survey assessing seizure management from owners' perspective had an 86% response rate, with the second survey concerning behavioural changes described by respondents to the survey having a response rate of 100%. Although these response rates are encouraging (see below), there are factors that might contribute to the apparently high response rate.

First, the high response rate may reflect a study of a referral population. Compared with the general dog owning population, owners who have accepted referral to a specialist clinic may also have greater determination to understand their pet's problem, wish to contribute to further studies and have a strong desire to explore avenues that may potentially lead to successful management.

Second, the method of recruiting subjects may affect the response rate. The decision whether to pursue a complete population survey or a sample study is based on the issue under investigation and the nature of the population to be studied. The reported response rates of examples of veterinary sample studies using mailed questionnaires were approximately 30 to 40% (Blackshaw & Day 1994; Leppanen *et al.* 2000a; Leppanen *et al.* 2000b). In the present survey, a complete population study was performed. A professional relationship had been developed between owners and the service clinicians before the

questionnaires were mailed, which is likely to foster greater trust and interest from the subjects approached. In one study of a related issue undertaken by the veterinary teaching hospital of The Ohio State University (owner perception of the care of epileptic dogs on long-term phenobarbitone therapy), a high response rate was also achieved (86%, 19/22) (Lord & Podell 1999). Response rate is also affected by the period of time over which subjects are studied. For example, in a complete population study of owner assessment of the outcome of total hip arthroplasty in dogs, case accrual extended over 15 years and there was a reported response rate of 41%; this lower-than-hoped-for response rate was interpreted as reflecting the importance of the interaction between owners and clinicians (Skurla *et al.* 2000). In this present study, accrual has been over the past two years and the majority of patients had undergone follow-up.

Third, the high response rate may reflect the effort put into the design of the questionnaires, including pretesting the wording and layout to achieve a user friendly presentation with relevance to the interests of the sampled owners (all responses indicated they would like to receive a summary of the results). There was also a carefully timed follow-up of non-respondents to encourage replies, which increased the response rate to the first questionnaire from 59% to 86% (see 3.2.1 The Response, page 86).

The Source of Biases

Non-response bias

Even though the non-response rate of the study was low (14%, 5/37), results must still be interpreted with some caution, as this indicates the possibility for non-response bias. For example, of the five non-respondents, three of the associated patients were on AED therapy. One patient was known to have refractory seizure activity with apparent behavioural change and one was blind following a status epilepticus. It is likely that both these patients would have had an increased care requirement likely to affect the owners' life and a lower degree of satisfaction of seizure management would be suspected (affecting the response to questions of section B, C, F and G in Questionnaire One). Accordingly, the present results could overestimate the success of seizure management from the owners' perspective. However, it was impossible to assess either the presence or magnitude of the bias.

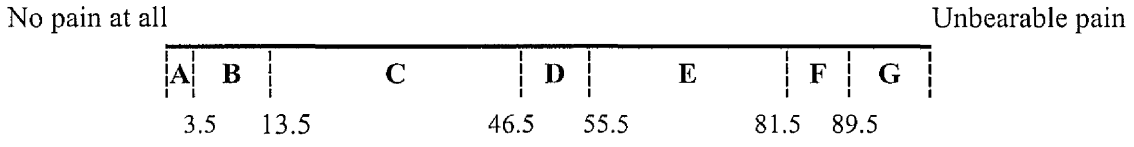
The Use of Visual Analogue Scales

Visual Analogue Scales (VAS) provide a simple technique for quantifying subjective experience (McCormack *et al.* 1988). They have been widely used for repeated measurements on subjects and for comparison between subject studies. The main advantage of VAS is that, unlike numerical scales or verbal rating scales, they provide an unlimited number of possible responses along a single continuum, and have been claimed to offer a high degree of 'sensitivity' i.e., a discriminating capacity superior to that of other scales (Price *et al.* 1994). Ease of construction, use, and versatility are other proposed advantages of VAS (McCormack *et al.* 1988).

Visual analogue scales have been established as valid and reliable in a range of clinical and research applications, such as measuring pain, depression and mood in human patients. The majority of studies have assessed validity by correlating VAS scores with the scores of an appropriate established scale. Some studies have undertaken validation by testing the VAS ability to discriminate between subject groups described by objective criteria, which provides a more objective means of establishing the validity of VAS than correlations with other scales. Test re-test reliability and inter-rater reliability techniques have been used to assess the reliability of VAS (McCormack *et al.* 1988).

However, there is controversy regarding whether the VAS score represents a ratio or is ordinal data. One study of the assessment of pain evaluated the level of order consistency between a VAS and a discrete seven-point scale for the same variable, in which the non-linear properties of VAS assessment were demonstrated (Svensson 2000). The positions of the cut-off points on the VAS that re-scale the continuous analogue recordings to a seven-point discrete scale are presented in Figure 4.1. The distance between the cut-off positions on the VAS is not equidistant. The implication of this non-linear property of the VAS assessment is that a median value of VAS assessments cannot be interpreted or described by words related to the concept of pain intensity. It has been suggested that the lack of a reliable interpretation of the significance of the positions on a VAS means that VAS assessments are not reliable in clinical research.

Figure 4.1 The positions of the cut-off points on the VAS in the bias-eliminated calibration versus the discrete seven-point scale (labelled A to G)



However, another study recording the pain response to graded changes in noxious thermal stimuli suggested the VAS gave a linear scale and implied that the VAS score can be treated as ratio data (Price *et al.* 1994). In another study, patients were requested to consider different amounts of pain and repeated their VAS rating after each consideration. Comparing these VAS scores suggested that VAS is a linear scale and a change in the VAS score represents a relative change in the magnitude of pain sensation (Myles *et al.* 1999).

Some studies report a tri-modal distribution of VAS scores, with clusters at the midpoint and extremes of scales, suggesting that subjects do not always make use of the full potential of the scale or treat it as a continuum (McCormack *et al.* 1988). In the present study, a few respondents apparently exhibited such a phenomenon.

Ease of use is another major advantage of the VAS over other scales. However, some studies point out that the VAS requires an ability to transform a complex subjective experience into a visuo-spatial display, involving perceptual judgement and accuracy. Age and the loss of ability to think abstractly, mental disorganisation and confusion, and perceptual skills and memory have all been suggested as factors which may contribute to response error (McCormack *et al.* 1988).

In summary, the use of VAS is controversial and it is impossible to attribute these factors specifically to response bias and assess their magnitude. However, for some authors, VAS are no weaker than other comparable psychological measures and have many additional advantages (McCormack *et al.* 1988).

Questionnaire Design

Reflection on the responses to the questionnaires revealed unexpected problems related to questionnaire design. In the first questionnaire assessing seizure management from owners' perspective, most errors in completion of the form were in questions associated with AED side effects, in which respondents were asked about which side effects the dog had exhibited and how these specific side effects concerned them (see 3.2.2.5 Section E: An Assessment of AED Side Effects, page 93, Q-E3 to Q-E10). Commonly, respondents indicated no such side effects in their dog whilst stating how the problem worried them, or conversely, they recognised the specific sign in the dog without indicating their degree of concern. Such confusion may stem from the different structure of this particular set of questions compared to other parts of questionnaire and the number of clusters of questions respondents had to review.

In the second survey concerning behavioural changes, major problems were apparent in the responses to questions relating to the onset of reported behavioural changes and its relationship with AED therapy. For some respondents, this may have reflected the chronic seizure history of their dogs leading to problems in recollection. In addition, as the behavioral changes usually developed gradually, the onset of behavioural changes was vague in the respondents' memory. Minor and distant events are more difficult to target in a question and the greater the demands a question places on memory, the less accurate the respondents' answers and the less accurate the survey conclusions derived. Increasing the number of questions about a subject is thought to improve the quality of respondents' recollection in a questionnaire survey. By asking more than one question about events, more time will elapse for the respondents to think (Fowler 1984). However, in cross checking the responses to different questions relating to the same event in this study, some responses did not apparently correspond in the study and revealed the decreased reliability for the answers to certain questions (see 3.3.2.2 The Onset of the Behavioural Changes (Q-2 and Q-3), page 106).

As such internal cross checking of responses in this study was only possible for two questions, it is impossible to assess the reliability in other responses and therefore impossible to assess the magnitude of the potential bias.

4.2 Cases Review

The predisposition to idiopathic epilepsy in certain breeds

In this study, there is a preponderance of three specific breeds exhibiting idiopathic epilepsy: Labrador retriever, Border collie and German shepherd dog. All three breeds have been described as having predisposition to idiopathic epilepsy in the veterinary literature and furthermore, the genetics in Labrador retrievers and German shepherd dog have been studied (see 1.2.2 Genetic Aspect of Idiopathic Epilepsy, page 20). However, the preponderance of specific breeds may also reflect the breed distribution of canine general population in Scotland. In one study of idiopathic epilepsy in 125 dogs undertaken at the University of Berne, Switzerland, a breed predisposition for Labrador retriever (27/125, 21.6%) was represented, with less German shepherd dogs exhibiting idiopathic epilepsy (7/125, 5.6%). The breed distribution in this study may also reflect that of the local canine population.

Comparing clinician's perception of reasons for referral with that of owners

In this study, half of cases were in Group One (epilepsy of less than 6-months duration, see 2.3.1 Categories of Seizure Cases Included in This Study, page 67) and the other half of cases were in Group Two (epilepsy of greater than 6-months). For the majority of patients in Group One, the perception of clinicians and owners was that the underlying reason for referral was the desire for further diagnosis. For the cases in Group Two, clinicians overestimated "inadequate seizure management" as the main reason for referral suggesting this for 73% (11/15) of cases, whilst owners only identified this reason for 53% (8/15) of cases (see Table 3. 31 and Table 3. 32, page 104). This finding, that about half the owners of dogs with long-term history of epilepsy referred for a second opinion may be looking for increased confidence in the diagnosis, suggests that clinicians should discuss further investigation before adjusting the patient's AED therapy. Such an approach, by increasing confidence in the diagnosis, may provide owners with more confidence in AED therapy adjustment and accepting the balance between AED efficacy and side effects.

Factors underlying apparent treatment failure

Phenobarbitone appears to be the first choice AED in primary veterinary clinics that refer cases to SAH-UGVS. However, the dose at the time of accession was relatively low in one-third of patients (see 3.1.6 AED Therapy at the Time of Referral, page 81). The reason for this may due to the different dose ranges quoted in the Veterinary Data Sheet Compendium 1999-2000 (National Office of Animal Health Ltd, Enfield, 1999) and the BSAVA Small Animal Formulary (Tennant ed., British Small Animal Veterinary Association, Cheltenham, 1999), two important sources of dose information for veterinary clinicians, in which the dose range suggested in Veterinary Data Sheet Compendium is lower than that in BSAVA Formulary and the current literature. For more than half of the patients, serum phenobarbitone concentrations at the time of accession were lower than the quoted therapeutic ranges or were within the lower end of the therapeutic range (3.1.6 AED Therapy at the Time of Referral, page 81). In fact, there has been a variation in the therapeutic ranges being reported for the dog in the veterinary literature. Initially, the therapeutic range of phenobarbitone had been extrapolated from humans (15-40 μg/ml) and veterinary clinical trials had confirmed these targets (15-45 μg/ml) (Farnbach 1984b). The low end of therapeutic ranges suggested in both the BSAVA Formulary and Veterinary Data Sheet Compendium is 15 μg/ml. However, the current literature suggested that seizures are better controlled when serum concentrations are above 20

μg/ml and serum concentrations above 35 μg/ml had been reported as the highest correlation with the development of hepatotoxicity (Dayrell-Hart *et al.* 1991). There is an implication for this finding in relation to both undergraduate and post-graduate education suggesting that the value of measuring the serum phenobarbitone concentrations and understanding that the current literature should be emphasised in relation to case management.

Few patients had been treated with potassium bromide prior to referral (6/48, 3.1.6 AED Therapy at the Time of Referral, page 81). Excepting one patient, in which the referring veterinarian had established the standard regimen in use at SAH-UGVS (AED regimen, page 68) through phone consultation, other patients were on a maintenance doses lower than 30 mg/kg, had not been administered a loading dose at the beginning of the therapy and their serum bromide concentrations had not been monitored prior to referral. The initial bromide dose differs according to different protocols from 20 mg/kg to 30-40 mg/kg (Schwartz-Porsche 1992; Podell 1996; Boothe 1998). Some authors also prefer not to use the loading dose; the reason for this is that the majority of their patients had already had serum phenobarbitone concentrations at the top of the therapeutic range and they considered the protocol of potassium bromide at 20 mg/kg, without loading dose, allowed for a gradual adaptation to the cumulative sedative effects of bromide and phenobarbitone (Podell 1996). The initial bromide dose used at SAH-UGVS is 30 mg/kg with a loading dose of 450 mg/kg, targeting a serum bromide concentration of 1 mg/ml (Boothe 1998). In the majority of patients administered this protocol at SAH-UGVS, the steady-state concentration achieved was less than 1 mg/ml(unpublished data). Consequently, the initial dose of 20 mg/kg was considered to be too low to achieve therapeutic serum bromide concentrations. The implication is that potassium bromide remains a relatively new AED to most veterinary surgeons that refer cases to SAH-UGVS. Bromide, due to its efficacy and safety, has become the preferred add-on AED and has been reported to improve seizure control in about 58 to 83% of dogs with idiopathic epilepsy (Schwartz-Porsche 1992; Podell & Fenner 1993; Trepanier *et al.* 1998). Another advantage of bromide is that it is the AED of choice in patients that have developed liver disease (Thomas 2000). Again, there is an implication here for an increased emphasis on the use of this preparation in the management of epilepsy in the dog in the provision of undergraduate and post-graduate veterinary education.

4.3 Assessing Seizure Management from Owners' Perspective

The majority of owners understood that successful therapy might not mean the complete elimination of seizure activity (see 3.2.2.1 Section A: Establishing the Ideals for Assessing the Outcome of Seizure Management, page 86). Only one-third of owners considered decreased cluster seizures to isolated seizures as a reasonable outcome. This may relate to personal experience from the pattern of seizure activity in their dogs. "Quality of life", "adequate seizure frequency" and "acceptable AED side effects" were the three main concepts chosen by owners to use in assessing seizure management; the concepts "concern of the cost of seizure management" and "influence of caring for an epileptic dog on owners' lifestyle" were of less concern.

In general, in their assessment of the seizure management in their own dogs, owners with pets not on AED therapy was less satisfied with circumstances than those owners whose pets were on AED therapy (see 3.2.2.2 Section B: An Assessment of Seizure Management in their Own Dogs, page 89). However, there was a small sample size with great variance in the group of dogs not on AED therapy. In this group, all owners agreed the dogs' qualities of life were good. However, the responses "seizure frequency", "concern of the cost of seizure management", and "caring for an epileptic dog on owners' lifestyle" exhibited great variation (see Responses from owners with pets not on AED therapy, page 90). Additionally, 4 of 6 responses in the section showed tri-modal distribution of VAS scores, which might affect the results dramatically, especially in a small sample size. For the two respondents who expressed low scores for seizure frequency, one patient exhibited five to eight partial seizures daily and the other reported clustered, generalised seizures every two months. Although those owners made the decision not to administer AED therapy, this decision might be questioned for these two patients.

More than half of owners indicated the dogs' general daily activity or quality of life was decreased, which was mainly due to AED side effects (see 3.2.2.3 Section C: An Assessment of Quality of Life in Epileptic Dogs, page 90). It was concluded AEDs with fewer side effects are required. The responses to the section on AED side effects suggested dogs on potassium bromide alone exhibited fewer side effects than dogs on phenobarbitone. However, due to the small sample size, further study of potassium bromide as monotherapy would be required to confirm this.

Dogs on phenobarbitone or bromide exhibiting the side effect of lethargy or sedation, which results in decreasing general activity, are reflecting the main mechanism of the

anticonvulsant action of these drugs- enhancement of inhibitory processes. Antiepileptic drugs in which the main mechanism of action is a reduction of excitatory transmission or modulation of membrane cation conductance, supposedly do not cause sedation or lethargy; this may be an important consideration for choosing AED therapy that maintains the general activity and quality of life as before the onset of seizures. However, such drugs are not currently available for the canine patient.

The majority of the owners did not consider the administration of the medication a nuisance and coped well with medicating more than one time every day (see 3.2.2.4 Section D: An Assessment of Work Associated with Caring for Epileptic Dogs, page 92). However, the requirement of medicating at consistent times was the main concern over medication that was expressed. This may reflect another potential advantage of bromide, in which, due to the long half-life, accurately medicating at consistent times is not critical.

Regular veterinary examination and blood sampling to monitor serum concentration were of greater concern to more owners, even though more than half of owners did not report this as a significant problem (3.2.2.4 Section D: An Assessment of Work Associated with Caring for Epileptic Dogs, page 92). In addition, as mentioned previously, two owners who did not answer the relevant question commented that they could not express an opinion because veterinary examination and serum monitoring were not regularly requested by their practice. Given the positive attitudes expressed by the majority of owners, it is suggested that regular veterinary examination and serum drug concentration monitoring should be suggested more widely to achieve appropriate seizure management.

In general, owning an epileptic dog did not have a major impact on owners' work/day-to-day activities and free time. However, half of owners with dogs on AED therapy indicated epilepsy in their dogs did affect their decision/ability to be away from home, which was mainly a reflection of respondents concern for their dog and difficultly in finding people able to provide care (see 3.2.2.7 Section G: The Impact of Owning an Epileptic Dog on Owners' Ability/decision to Stay Away Overnight, page 98). Seizure frequency recorded in these patients ranged from more than one generalised seizure per month to a seizure-free interval of 18 months. Using the criteria for acceptable seizure control expressed in the literature (discussed in 1.4.1 General Principles of Antiepileptic Drug Therapy, page 31), it is evident that, in the patients cared for by the group of respondents who expressed an inability/unwillingness to be away from home overnight, seizure control was generally less acceptable (6/13, 46%) than amongst those belonging to individuals who felt able to be away from home overnight (13/18, 72%). This implies that, for the majority of owners,

adequate seizure control decreases the impact of owning epileptic dogs on owners' free time, however, for some owners, even if seizures are well controlled, the seizure disorder in their dog still negatively affects their decision/ability to be away from home. This reflects that the self selection bias may exist when interpretating the owner's perception of this topic.

A few owners (4/23, see 3.2.2.8 Section H: Owners' Opinions on Further Investigation of Seizures in their Dogs, page 100) indicated they were still uncertain of the cause of seizures in their pet even if the diagnosis of idiopathic epilepsy was made following the full investigation protocol described (see 2.2 INVESTIGATION PROTOCOL FOR PATIENT WITH EPILEPSY, page 60). This implies the concept of diagnosis of idiopathic epilepsy by exclusion is difficult for some owners to comprehend. However, for the majority of owners, the further diagnostic procedures did help them understand their dog's condition. Furthermore, even for the patients without a pet health insurance plan, after the full investigation protocol was performed, most owners (6/9) agreed the cost of further diagnostic procedures to know more about the cause of seizures was worthwhile (VAS scores greater than 50; see 3.2.2.8 Section H: Owners' Opinions on Further Investigation of Seizures in their Dogs, page 100).

4.4 Behavioural Changes in Epileptic Dogs

In human medicine, "psychosis of epilepsy" is a term applied to a group of psychotic disorders in which potential aetiopathogenic mechanisms are believed to be closely related to those underlying the seizure disorder (Kanner 2000). The term *psychosis* has been used to describe not only psychiatric illnesses but also affective disorders such as depression, mania, hypomania, as well as other states of clouded consciousness. Four time periods need to be considered when psychiatric or behavioural symptoms are evaluated in patients with epilepsy: prodrome (which may not occur in every patient and may precede a seizure by minutes to hours); ictus (including aura and main seizure component); postictal period; the interictal phase (Stagno 2001). The psychoses of epilepsy are further classified as interictal psychosis, postictal psychosis, alternative psychosis (also known as 'forced normalisation') and AED-related psychosis (Kanner 2000).

In the present study, a subgroup of patients exhibited behavioural changes (33%, 16/48), of which 11 patients were available for further study to establish if there was evidence that

suggested the reported behavioural changes might be analogous to the psychosis reported in epileptic human patients. Even though the term 'psychosis' is considered inapplicable to describe behavioural problems in veterinary medicine, it is thought reasonable to evaluate the behavioural changes in epileptic dogs and characterise this as interictal, postictal, forced normalisation or AED-related activity. Behavioural changes related to AED therapy, postictal activity, and interictal activity were recognised in the study (see 3.3.3 Summary of Questionnaire Two, page 111).

In human medicine, phenobarbitone is known to produce hyperactivity, irritability, and belligerence in children or elderly patients. These effects are not related to dose or serum concentrations. Barbiturates also may cause sedation, insomnia, tearfulness, mood shifts, and increased aggressiveness (Stagno 2001). In the veterinary literature, the use of phenobarbitone has infrequently been associated with hyperactivity and restlessness that appears especially during the first few weeks of therapy, is not dose related and resolves within a few weeks of initiating therapy (see Side effects of phenobarbitone, page 41). In the present study, there was some evidence that behaviour may be related to phenobarbitone dose in some patients (see 3.3.2.5 Behavioural Changes and AED Therapy (Q-10), page 108). However, further studies would be required to confirm the finding.

The adverse effects of bromide reported in human medicine are primarily neurological and include phenomena such as headache, vertigo, hallucinations, delirium, ataxia and stupor (see Side effects of bromide, page 47). Abnormal behaviour, such as irritability or restlessness, have been described in the veterinary literature but with limited details (Thomas 2000). In the present study, in the 14 patients on potassium bromide alone or in combination with phenobarbitone, four owners reported behavioural changes related to bromide therapy, which, at 29% of the population, suggests a potentially significant clinical effect of using this preparation. Results of this study suggest the incidence of behavioural change may be dose related (see 3.3.2.5 Behavioural Changes and AED Therapy (Q-10), page 108), which reflects the literature; and may require a reduction in the dose (Thomas 2000).

In human epileptic patients, postictal psychiatric disturbances occur relatively commonly. According to the suggested diagnostic criteria of postictal psychiatric disturbances, symptoms are manifested immediately upon a seizure or within a week of the return to normal mental functioning (i.e., after a lucid interval), and last days, rarely weeks. The event may be characterised by psychosis, depression, mania, hypomania, or anxiety-related symptoms (Stagno 2001). In the veterinary literature, it is known that hyperactivity or

restlessness can occur in the postictal phase and the postictal phase refers to the phase immediately following seizure activity, which lasts from minutes to days. Interestingly, in one of our patients exhibiting postictal behavioural changes, the behaviour sometimes appeared after a lucid interval of few days following a seizure, and lasted for 1 week, which has similarities to the phenomenon described in human literature.

The cause of postictal psychiatric disturbances in human medicine remains unknown, although Todd's phenomenon, a transient disturbance of neurological function has been suggested. Some authors regarded postictal psychoses as similar to other postictal focal neurological deficits. They have suggested that postictal paresis, aphasia, amnesia, emotional changes and psychosis in human patients may all be manifestation of homeostatic phenomena, which are induced by recurrent seizures, to reduce epileptic hyperexcitability, and presumably terminate ictal events, prevent ictal spread and persist to maintain the interictal state (Stagno 2001).

Interictal psychoses can present intermittently or persistently. EEG investigation is necessary to determine whether intermittent or brief psychoses are related to seizure activity. Virtually, all theories that relate emotional or behavioural changes to epilepsy implicate abnormalities of limbic system. A temporal lobe focus appears to raise the incidence of interictal psychosis in epileptic patients, as do partial seizures with secondary generalisation (Stagno 2001). In general, the presence of interictal psychosis suggests the presence of underlying central nervous system pathology, which implies symptomatic or cryptogenic epilepsy in human patients (Kanner 2000).

In this study, behavioural changes in one dog were considered by the owner to represent interictal activity. The patient exhibited partial seizures and the onset of behavioural changes related to seizure disorder. Behavioural changes observed in the patient were an increase in general activity (e.g., restless) and reduced sleep periods as compared to before the onset of seizure activity. Seizure activity was well-controlled by phenobarbitone therapy, but the pattern of behavioural changes remained the same. The diagnosis of idiopathic epilepsy was made by the investigation protocol described previously (see 2.2 INVESTIGATION PROTOCOL FOR PATIENT WITH EPILEPSY, page 60). However, MR imaging may be considered in the patient potentially to refine the diagnosis. In human medicine, some authors suggest, in patients with interictal psychosis, high-resolution MR studies should be performed in search of small, multiple tumours such as gangliogliomas and hamartomas. Such tumours may be difficult to identify on standard MRI studies (Kanner 2000). In summary, instead of idiopathic epilepsy, cryptogenic epilepsy may be a

more appropriate term to describe the problem in this patient but this could only be established by the passage of time and post-mortem.

This study revealed a relatively large proportion of cases exhibiting behavioural changes, which appeared to be AED-related. Once patients exhibit this problem, a dose reduction or discontinuation of the particular AED may be necessary. However, when AED-related behavioural changes have been observed in dogs managed with both phenobarbitone and bromide, seizure management would be difficult to achieve, due to the limited choice of AED for dogs. The demand for further choice of AEDs with well-documented efficacy and tolerance in dogs is suggested.

CHAPTER FIVE

CONCLUSIONS

From a clinician's perspective, the major goals in the management of idiopathic epilepsy have traditionally been thought of as to the reduction of seizure frequency and of the severity of individual seizures, with minimal postictal complications so that the condition does not substantially compromise the quality of life for the dog and family, whilst avoiding serious side effects associated with the use of AED therapy. This study has demonstrated that, from the owners' perception, the "dogs' quality of life", "adequate seizure frequency" and "acceptable AED side effects" were the three main concepts for owners to use in assessing seizure management. The concepts of "concern of the cost of seizure management" and "influence of caring for an epileptic dog on owners' lifestyle" were of less significance.

The study also demonstrated that owning an epileptic dog did not have a major impact on owners' work/day-to-day activities and free time. The majority of owners did not consider the administration of the medication a nuisance and coped well with medicating more than once daily and, for some dogs, with the administration of more than one drug. For more than half of the owners, regular veterinary examination and blood sampling for serum AED concentration monitoring did not cause a significant problem. However, as mentioned previously, the highly motivated nature of the client profile from a referral population may be significant in responses to this study. Further study of non-referral populations would be required to understand owners' attitude in canine seizure management from the general population.

Achieving a confident diagnosis of idiopathic epilepsy is not only the basis of achieving successful seizure management from the clinician's point of view, but also helped most owners to understand their dog's condition and gave them more confidence in AED therapy adjustment and accepting the balance between AED efficacy and side effects. The majority of owners agreed that the cost of further diagnostic procedures was worthwhile.

Given the positive attitude expressed by the majority of owners, regular veterinary examination and serum drug concentration monitoring should be suggested more widely to achieve appropriate seizure management. Furthermore, based on the results of case review in the study, in both undergraduate and post-graduate education the value of measuring AED serum concentrations, as well as the use of bromide in canine epilepsy, should be emphasised. The study also demonstrated that dogs on potassium bromide alone exhibited fewer side effects than dogs on phenobarbitone. However, due to the small sample size, further study of potassium bromide as monotherapy would be required to confirm this.

This study also revealed a relatively large proportion of cases exhibiting behavioural changes, which mainly appeared to be AED-related in our patients. Clinicians should increase the awareness of behavioural changes in epileptic dogs. Determining the pattern of behavioural changes and the potential causes is not straightforward, and detailed, diary recorded seizure and behaviour activities may help to make objective judgement. Once patients exhibit AED-related behavioural changes, a dose reduction or discontinuation of the particular AED may be necessary. Further prospective study would be required to confirm the relationship between dose of specific AED and behavioural changes. A study of a non-referral population would help demonstrate more accurately the prevalence and presentation of behavioural changes in dogs with idiopathic epilepsy.