The structural basis of the epilepsies:  
an MRI and epidemiological study

Dr Alex Daniel Everitt

MB BS, MRCP

A thesis submitted to
The University of London
in 2003
for the degree of PhD

Epilepsy Research Group
Institute of Neurology
University College London
ABSTRACT

Contemporary knowledge of the epidemiology, aetiology and consequences of epilepsy are essential in order to effectively manage this common condition. Brain magnetic resonance imaging (MRI) helps determine the underlying cause in up to 75% of hospital based epilepsy patients, whilst at the population level the aetiology remains cryptogenic in the majority of cases. In particular, the frequency of hippocampal sclerosis (HS), the commonest structural correlate of epilepsy in tertiary referral centres, is unknown in the community. The cause(s) of HS, and whether it is progressive, are also poorly understood.

This thesis consists of a series of community based studies of epilepsy employing high resolution MRI, in addition to a single MRI study of severe intractable epilepsy amongst the inhabitants of a large residential epilepsy centre. The main aim was to characterise the nature, frequency and severity of structural brain abnormalities, especially HS.

A population base of 207,553 persons was established in Buckinghamshire, England. During a 2 year period, 165 adults with newly diagnosed and 279 adults with chronic active epilepsy were prospectively identified. The age-corrected annual incidence of all afebrile seizures was 52.8 per 100,000 (95% CI 42.9-62.6). In a sub-population of 159,388 adults, 279 had chronic active epilepsy (epilepsy of at least 4 years duration, with at least 1 seizure during the year preceding prevalence day), yielding a prevalence of 1.8 per 1000 (95% CI 1.55-1.96).

High resolution MRI was performed in 110/165 (66.7%) of newly diagnosed adults, in 174/279 (62.3%) with chronic active epilepsy, and in 170 neurologically normal control subjects. 130/170 (76.5%) of the control subjects had normal MRI. Small (WML) were the most frequent visible abnormality (18.8%). No control had HS, MCD, or focal cortical brain damage. Patients with newly diagnosed partial onset seizures (37.9%) were significantly more likely to harbour focal brain lesions (focal scars, HS, MCD, cavernomas and neoplastic lesions) detectable by MRI than those with generalised seizures (7.0%) (p=0.0003). Focal brain abnormalities were also found more frequently in those with chronic active partial onset seizures (54.4%) than in those with generalised seizures (4.5%) (p<0.0001). The most frequent abnormalities overall were multiple small white matter
lesions (WML) and focal neocortical damage. HS was an infrequent finding in the newly diagnosed partial seizures group (2.7%), but more common in the chronic active partial cohort (13.6%). However, quantitative hippocampal abnormalities were more frequent and were found in approximately one quarter of patients with newly diagnosed seizures, in one third with chronic active epilepsy, and in only 4.7% of control subjects. It was possible to assign a precise aetiology (including the idiopathic category) in more than three quarters of patients with newly diagnosed seizures, and in nearly two thirds with chronic active epilepsy.

Hippocampal damage, as determined by the group comparisons of mean and smallest corrected hippocampal volumes, and mean and highest hippocampal T2 relaxation time, with control values, was statistically significant only in those with newly diagnosed partial onset seizures and chronic active partial epilepsy. Patients with idiopathic seizures did not have hippocampal damage, although those with non-idiopathic generalised seizures tended to have lower hippocampal volumes and higher hippocampal T2 values.

Of the 263 residential epilepsy centre inhabitants, MRI showed abnormalities of aetiological relevance in 66%: HS/HA without other focal pathology, 26%; focal neocortical brain damage and HS/HA, 16%; isolated focal neocortical brain damage, 14%; malformations of cortical development, 7% (of whom 55% had HS/HA); other, 3%. Quantitative hippocampal abnormalities were present in 47.5%. High resolution MRI revealed previously undetected, aetiologically relevant lesions in 47% of the 203 residents previously scanned. MRI increased the proportion of residents with a definable aetiology from 50% to 68%.

Logistic regression analyses in both the community and residential centre based subjects failed to reveal any significant correlations between the extent of hippocampal damage and the severity of the epilepsy.
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>2</td>
</tr>
<tr>
<td>Table of contents</td>
<td>4</td>
</tr>
<tr>
<td>Chapter 1 contents</td>
<td>5</td>
</tr>
<tr>
<td>Chapter 2 contents</td>
<td>6</td>
</tr>
<tr>
<td>Chapter 3 contents</td>
<td>7</td>
</tr>
<tr>
<td>Chapter 4 contents</td>
<td>8</td>
</tr>
<tr>
<td>Chapter 5 contents</td>
<td>9</td>
</tr>
<tr>
<td>Chapter 6 contents</td>
<td>10</td>
</tr>
<tr>
<td>Chapter 7 contents</td>
<td>11</td>
</tr>
<tr>
<td>Chapter 8 contents</td>
<td>12</td>
</tr>
<tr>
<td>Chapter 9 contents</td>
<td>13</td>
</tr>
<tr>
<td>List of tables</td>
<td>14</td>
</tr>
<tr>
<td>List of figures</td>
<td>16</td>
</tr>
<tr>
<td>Glossary of abbreviations</td>
<td>17</td>
</tr>
<tr>
<td>Statement of originality</td>
<td>19</td>
</tr>
<tr>
<td>Author's contribution</td>
<td>20</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>21</td>
</tr>
<tr>
<td>Dedication</td>
<td>22</td>
</tr>
<tr>
<td>Chapter 1: Introduction</td>
<td>23</td>
</tr>
<tr>
<td>Chapter 2: Study Aims</td>
<td>90</td>
</tr>
<tr>
<td>Chapter 3: Methods</td>
<td>96</td>
</tr>
<tr>
<td>Chapter 4: Prospective incidence and prevalence study (Study 1)</td>
<td>116</td>
</tr>
<tr>
<td>Chapter 5: High resolution MRI in community based neurologically normal control subjects (Study 2)</td>
<td>137</td>
</tr>
<tr>
<td>Chapter 6: The aetiology of epilepsy in adults: a prospective community based study (Study 3)</td>
<td>153</td>
</tr>
<tr>
<td>Chapter 7: The severity of HS in community based adult patients (Study 4)</td>
<td>186</td>
</tr>
<tr>
<td>Chapter 8: High resolution MRI in a residential population (Study 5)</td>
<td>210</td>
</tr>
<tr>
<td>Chapter 9: Summary of results, conclusions and future directions</td>
<td>228</td>
</tr>
<tr>
<td>References</td>
<td>239</td>
</tr>
</tbody>
</table>
# Chapter 1

## Introduction

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Definitions, diagnosis and investigation of epilepsy</td>
<td></td>
</tr>
<tr>
<td>1.1.1 Definitions</td>
<td>23</td>
</tr>
<tr>
<td>1.1.2 Diagnosis</td>
<td>26</td>
</tr>
<tr>
<td>1.1.3 Investigation</td>
<td>27</td>
</tr>
<tr>
<td>1.2 Classification in epileptology</td>
<td></td>
</tr>
<tr>
<td>1.2.1 The International Classification of Epileptic Seizures</td>
<td>32</td>
</tr>
<tr>
<td>1.2.2 The International Classification of the Epilepsies and Epileptic Syndromes</td>
<td>34</td>
</tr>
<tr>
<td>1.2.3 ILAE Commission on Epidemiology and Prognosis Classification</td>
<td>39</td>
</tr>
<tr>
<td>1.3 Epidemiology</td>
<td></td>
</tr>
<tr>
<td>1.3.1 Methodological issues</td>
<td>40</td>
</tr>
<tr>
<td>1.3.2 Incidence, age-specific incidence and secular trends in incidence</td>
<td>45</td>
</tr>
<tr>
<td>1.3.3 Prevalence</td>
<td>47</td>
</tr>
<tr>
<td>1.3.4 Cumulative incidence (lifetime prevalence)</td>
<td>48</td>
</tr>
<tr>
<td>1.3.5 Prognosis</td>
<td>49</td>
</tr>
<tr>
<td>1.4 Aetiology</td>
<td></td>
</tr>
<tr>
<td>1.4.1 Range of aetiologies of epilepsy in developed countries</td>
<td>52</td>
</tr>
<tr>
<td>1.4.2 Population and hospital based studies of epilepsy in developed countries reporting aetiology: a review of the literature</td>
<td>61</td>
</tr>
<tr>
<td>1.5 Hippocampal sclerosis and epilepsy, and the role of MRI</td>
<td></td>
</tr>
<tr>
<td>1.5.1 Functions of the normal hippocampus</td>
<td>69</td>
</tr>
<tr>
<td>1.5.2 Hippocampal anatomy: normal and pathological</td>
<td>69</td>
</tr>
<tr>
<td>1.5.3 Frequency of HS</td>
<td>71</td>
</tr>
<tr>
<td>1.5.4 MRI of hippocampal sclerosis</td>
<td>71</td>
</tr>
<tr>
<td>1.5.5 Epilepsy and the aetiological relevance of HS</td>
<td>76</td>
</tr>
<tr>
<td>1.5.6 The aetiology of HS</td>
<td>77</td>
</tr>
<tr>
<td>1.5.8 Evidence for the progression of HS</td>
<td>82</td>
</tr>
<tr>
<td>1.5.8 Amygdalar sclerosis</td>
<td>88</td>
</tr>
<tr>
<td>1.5.9 Conclusions</td>
<td>89</td>
</tr>
</tbody>
</table>
Chapter 2

Aims of thesis

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Introduction</td>
<td>90</td>
</tr>
<tr>
<td>2.2 Aims</td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>91</td>
</tr>
<tr>
<td>Study 2</td>
<td>91</td>
</tr>
<tr>
<td>Study 3</td>
<td>92</td>
</tr>
<tr>
<td>Study 4</td>
<td>93</td>
</tr>
<tr>
<td>Study 5</td>
<td>94</td>
</tr>
</tbody>
</table>
# Methods: Epidemiological study design and MRI methodology

## 3.1 Introduction

## 3.2 Epidemiological study methodology

- **3.2.1 Study population**
- **3.2.2 Demographic data**
- **3.2.3 Period of study**
- **3.2.4 Inclusion criteria and case definitions**
- **3.2.5 Case ascertainment**
- **3.2.6 Clinical assessment and investigation**
- **3.2.7 Follow up**
- **3.2.8 Case classification**
- **3.2.9 Calculations of standardised incidence, cumulative incidence and prevalence rates**
- **3.2.10 Prevalence of active and inactive epilepsy (using ILAE definitions) and of isolated seizures in a smaller population of adults and children**
- **3.2.11 Recruitment of control subjects for the MRI study**
- **3.2.12 Data storage and analysis**

## 3.3 MRI methodology

- **3.3.1 MRI hardware and image acquisition**
- **3.3.2 Qualitative MRI reporting**
- **3.3.3 Quantitative hippocampal MRI analysis**
- **3.3.4 Intra-rater and inter-rater reliability**
- **3.3.5 Quality assurance: reproducibility of MRI data**
- **3.3.6 Statistical analysis**
- **3.3.7 Ethical approval**
Chapter 4

Study 1:
A prospective population based incidence and prevalence study of epilepsy in Buckinghamshire, UK

4.1 Introduction 116
4.2 Aims and hypotheses 116
4.3 Methods
   4.3.1 Quality control for note audit 117
   4.3.2 Incidence study 117
   4.3.3 Prevalence study of chronic active epilepsy in adults 119
   4.3.4 Prevalence of active and inactive epilepsy (using ILAE definitions) and of isolated seizures 119
4.4 Results
   4.4.1 Quality control of note audit 119
   4.4.2 Incidence and characteristics of incident (newly diagnosed) cases 120
   4.4.3 Prevalence of chronic active epilepsy and characteristics of prevalent cases 125
   4.4.4 Prevalence of active and inactive epilepsy in a population of 127
      12,178 people
4.5 Discussion
   4.5.1 Summary of major findings 128
   4.5.2 Relevance of findings and methodological issues 128
## Chapter 5

### Study 2:
Qualitative and quantitative high resolution cranial MRI in 170 community based, neurologically normal volunteers

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Introduction</td>
<td>137</td>
</tr>
<tr>
<td>5.2 Aims and hypotheses</td>
<td>138</td>
</tr>
<tr>
<td>5.3 Methods</td>
<td></td>
</tr>
<tr>
<td>5.3.1 Subjects</td>
<td>139</td>
</tr>
<tr>
<td>5.3.2 Handedness</td>
<td>139</td>
</tr>
<tr>
<td>5.3.3 MRI methodology</td>
<td>139</td>
</tr>
<tr>
<td>5.3.4 Qualitative MRI reporting</td>
<td>139</td>
</tr>
<tr>
<td>5.3.5 Quantitative hippocampal MRI analysis</td>
<td>140</td>
</tr>
<tr>
<td>5.3.6 Intra-rater and inter-rater reliability</td>
<td>140</td>
</tr>
<tr>
<td>5.3.7 Quality assurance: reproducibility of MRI data</td>
<td>140</td>
</tr>
<tr>
<td>5.3.8 Statistical analysis</td>
<td>140</td>
</tr>
<tr>
<td>5.4 Results</td>
<td></td>
</tr>
<tr>
<td>5.4.1 Handedness</td>
<td>140</td>
</tr>
<tr>
<td>5.4.2 Qualitative MRI findings</td>
<td>140</td>
</tr>
<tr>
<td>5.4.3 Quantitative MRI findings</td>
<td>142</td>
</tr>
<tr>
<td>5.4.4 Intra-rater and inter-rater reliability</td>
<td>147</td>
</tr>
<tr>
<td>5.4.5 Quality assurance</td>
<td>147</td>
</tr>
<tr>
<td>5.5 Discussion</td>
<td></td>
</tr>
<tr>
<td>5.5.1 Summary of major findings</td>
<td>147</td>
</tr>
<tr>
<td>5.5.2 Methodological issues</td>
<td>148</td>
</tr>
<tr>
<td>5.5.3 Significance of asymptomatic cerebral abnormalities</td>
<td>149</td>
</tr>
</tbody>
</table>
Chapter 6

Study 3:
The aetiology of epilepsy in adults: a prospective, population based MRI study

6.1 Introduction 153
6.2 Aims and hypotheses 154
6.3 Methods
  6.3.1 Subjects 155
  6.3.2 Electro-clinical classification 155
  6.3.3 High resolution MRI scanning 157
  6.3.4 Aetiological classification 157
  6.3.5 Statistics 159
6.4 Results
  6.4.1 Extent of investigation 159
  6.4.2 High resolution MRI findings 160
  6.4.3 Standard neuroimaging findings and impact of high resolution MRI 168
  6.4.4 Aetiology of the epilepsies 170
  6.4.5 Age-specific aetiology of the epilepsies 175
6.5 Discussion
  6.5.1 Summary of major findings 178
  6.5.2 Advantages and limitations of study design 178
  6.5.3 MRI findings and relevance to aetiology of seizures 180
Chapter 7

Study 4:
The severity of hippocampal sclerosis in adults with newly diagnosed and chronic active epilepsy: a prospective, cross-sectional, population based quantitative MRI study

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1 Introduction</td>
<td>186</td>
</tr>
<tr>
<td>7.2 Aims and hypotheses</td>
<td>188</td>
</tr>
<tr>
<td>7.3 Methods</td>
<td></td>
</tr>
<tr>
<td>7.3.1 Patients and controls subjects</td>
<td>188</td>
</tr>
<tr>
<td>7.3.2 Classification of seizure type</td>
<td>189</td>
</tr>
<tr>
<td>7.3.3 Age at onset of epilepsy, duration of epilepsy, seizure frequency, lifetime number of seizures, and past history of febrile seizures</td>
<td>190</td>
</tr>
<tr>
<td>7.3.4 Quantitative hippocampal analysis</td>
<td>190</td>
</tr>
<tr>
<td>7.3.5 Statistical analysis of quantitative MRI data and clinico-quantitative MRI correlations</td>
<td>190</td>
</tr>
<tr>
<td>7.4 Results</td>
<td></td>
</tr>
<tr>
<td>7.4.1 Hippocampal volmetric analysis</td>
<td>191</td>
</tr>
<tr>
<td>7.4.2 Hippocampal T2 relaxometry</td>
<td>201</td>
</tr>
<tr>
<td>7.4.3 Logistic regression analyses</td>
<td>201</td>
</tr>
<tr>
<td>7.5 Discussion</td>
<td></td>
</tr>
<tr>
<td>7.5.1 Summary of major findings</td>
<td>206</td>
</tr>
<tr>
<td>7.5.2 Methodological considerations</td>
<td>206</td>
</tr>
<tr>
<td>7.5.3 Biological implications</td>
<td>208</td>
</tr>
</tbody>
</table>
Chapter 8

Study 5:
Qualitative and quantitative MRI findings in severe refractory epilepsy in a residential epilepsy centre

8.1 Introduction 210
8.2 Aims and hypotheses 210
8.3 Methods
  8.3.1 Subjects 211
  8.3.2 Clinical data collection 211
  8.3.3 Extent of previous investigation 213
  8.3.4 High resolution MRI scanning 213
  8.3.5 Statistical analysis 214
8.4 Results
  8.4.1 Seizure classification and epilepsy syndromic classification 214
  8.4.2 High resolution MRI findings 214
  8.4.3 Clinical-MRI correlations 218
  8.4.4 Impact of high resolution MRI upon aetiology 222
8.5 Discussion
  8.5.1 Summary of major findings 222
  8.5.2 Methodological and biological considerations 224
Chapter 9

Summary of results, conclusions and future directions

9.1 Summary of findings
   9.1.1 Study 1
   9.1.2 Study 2
   9.1.3 Study 3
   9.1.4 Study 4
   9.1.5 Study 5

9.2 Conclusions

9.3 Future directions
**LIST OF TABLES**

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Simplified version of the International Classification of Epileptic Seizures (p33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 2</td>
<td>The 1989 International Classification of the Epilepsies and Epileptic Syndromes (p35)</td>
</tr>
<tr>
<td>Table 3</td>
<td>Population based studies of epilepsy utilising the International Classification of the Epilepsies (p38)</td>
</tr>
<tr>
<td>Table 4</td>
<td>Annual incidence and point prevalence rates for epilepsy (p46)</td>
</tr>
<tr>
<td>Table 5</td>
<td>The aetiology of unprovoked and/or provoked seizures in selected community based studies from developed studies (p63)</td>
</tr>
<tr>
<td>Table 6</td>
<td>Magnetic resonance imaging (MRI) abnormalities in hospital based studies of 50 patients or more with epilepsy (p68)</td>
</tr>
<tr>
<td>Table 7</td>
<td>Age and sex structure of incidence study population and also the England and Wales population (Office of Population Census and Surveys data, mid-1996) (p118)</td>
</tr>
<tr>
<td>Table 8</td>
<td>Neurological diagnoses in 355 adults excluded from the incidence study (p121)</td>
</tr>
<tr>
<td>Table 9</td>
<td>Age-specific incidence of newly diagnosed afebrile seizures (p122)</td>
</tr>
<tr>
<td>Table 10</td>
<td>Age-specific incidence of newly diagnosed provoked and unprovoked seizures in adults (subjects of 15 years or over) (p123)</td>
</tr>
<tr>
<td>Table 11</td>
<td>Age- and sex-specific point prevalence rates for chronic active epilepsy in adults (subjects of 15 years or over) (p126)</td>
</tr>
<tr>
<td>Table 12</td>
<td>Point prevalence rates for active epilepsy, epilepsy in remission and isolated unprovoked seizures in a population of 12,178 (p129)</td>
</tr>
<tr>
<td>Table 13</td>
<td>Comparable contemporary incidence studies: inclusion criteria, annual incidence rates and study design (p131)</td>
</tr>
<tr>
<td>Table 14</td>
<td>Qualitative high resolution cranial MRI findings in 170 neurologically normal volunteers (p141)</td>
</tr>
<tr>
<td>Table 15</td>
<td>Corrected hippocampal volumes, hippocampal volume ratios and T2 relaxation times in 170 neurologically normal control subjects (p143)</td>
</tr>
<tr>
<td>Table 16</td>
<td>Classification of seizure types using clinical and EEG data in 444 adult patients (p156)</td>
</tr>
</tbody>
</table>
LIST OF TABLES (continued)

Table 17  EEG findings in patients with newly diagnosed seizures and chronic active epilepsy (p158)

Table 18  Qualitative high-resolution MRI in 110 newly diagnosed and 174 chronic active epilepsy patients, and 170 neurologically normal control subjects (p161)

Table 19  Quantitative hippocampal abnormalities in 22 patients with newly diagnosed unprovoked seizures (p166)

Table 20  Quantitative hippocampal abnormalities in patients and control subjects (p169)

Table 21  The aetiologies of provoked seizures in 39 adult patients (p171)

Table 22  The aetiologies of newly diagnosed unprovoked seizures and chronic active epilepsy (p173)

Table 23  Mean HVc and smallest HVc in newly diagnosed patients with respect to duration and frequency of seizures (p195)

Table 24  Mean HVc and smallest HVc in chronic active patients with respect to duration and frequency of seizures (p198)

Table 25  Demographic and clinical features of the 306 residents (p212)

Table 26  Simplified epilepsy syndromic classification (based on clinical and EEG findings) (p215)

Table 27  Combined qualitative and quantitative MRI findings in 263 residents (p216)

Table 28  Malformations of cortical development in 18 patients (p219)

Table 29  MRI evidence of HS/HA (isolated or dual pathology) in 263 residents and 170 normal control subjects (p220)

Table 30  Impact of MRI upon presumed aetiology of epilepsy (p223)
LIST OF FIGURES

Figure 1 Diagrammatic representation of a simplified epilepsy classification proposed by the ILAE Commission on Epidemiology and Prognosis (p41)

Figure 2 MRI features of hippocampal sclerosis (p72)

Figure 3 Measurement of HV and HT2 (p111)

Figure 4 Scatterplot of HV (uncorrected) versus ICV (p145)

Figure 5 Changes in mean HVc with age (p146)

Figure 6 Examples of MRI findings in newly diagnosed patients (p163)

Figure 7 Age-specific aetiology: newly diagnosed unprovoked seizures (p176)

Figure 8 Age-specific aetiology: chronic active epilepsy (p177)

Figure 9 Group analysis of mean HVc in newly diagnosed patients versus control subjects (p192)

Figure 10 Group analysis of smallest HVc in newly diagnosed patients versus control subjects (p194)

Figure 11 Group analysis of mean HVc in chronic active epilepsy patients versus control subjects (p196)

Figure 12 Group analysis of smallest HVc in patients with chronic active epilepsy versus control subjects (p197)

Figure 13 Group analysis of mean HVc in patients with newly diagnosed versus chronic active partial onset seizures (p199)

Figure 14 Group analysis of mean HVc in patients with newly diagnosed versus chronic active generalised (non-idiopathic) seizures (p200)

Figure 15 Group analysis of mean HT2 in chronic active epilepsy patients versus control subjects (p202)

Figure 16 Group analysis of highest HT2 in chronic active epilepsy patients versus control subjects (p203)

Figure 17 Group analysis of mean HT2 in patients with newly diagnosed versus chronic active partial onset seizures (p204)

Figure 18 Group analysis of mean HT2 in patients with newly diagnosed versus chronic active generalised (non-idiopathic) seizures (p205)

Figure 19 Examples of MRI findings in residential population with epilepsy (p217)
GLOSSARY OF ABBREVIATIONS

AD Alzheimer’s disease
AMPA α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
AED anti-epileptic drug
CI confidence intervals
CNS central nervous system
CPS complex partial seizure(s)
CSF cerebrospinal fluid
CVD cerebrovascular disease
CT computerised tomography
EEG electroencephalography
FLAIR fluid attenuated inversion recovery
GP general practitioner
GTCS generalised tonic-clonic seizure
HS hippocampal sclerosis
HA hippocampal atrophy
HT2 hippocampal T2 relaxation time
HV hippocampal volume
HVc corrected hippocampal volume (hippocampal volume, corrected for intracranial volume)
HVR hippocampal volume ratio (ratio of smaller to larger hippocampus within a patient)
ICEES International Classification of Epilepsies and Epileptic Syndromes
ICES International Classification of Epileptic Seizures
ICV intracranial volume
IGE idiopathic generalised epilepsy
ILAE International League Against Epilepsy
JME juvenile myoclonic epilepsy
MCD malformation(s) of cortical development
MRI magnetic resonance imaging
NMDA N-methyl-D-aspartate
NSE National Society for Epilepsy
OPCS  Office of Population Census and Surveys
SD    standard deviation
SGTCS secondarily generalised tonic-clonic seizure(s)
SPS   simple partial seizure(s)
TLE   temporal lobe epilepsy
>     greater than
≥     equal to or greater than
<     less than
≤     equal to or less than
STATEMENT OF ORIGINALITY

I hereby confirm that the studies contained in this PhD thesis form a distinct contribution to knowledge in the field of epilepsy. All of the work is original, as evidenced by the application of independent critical appraisal of the published literature, and by the discovery of new facts concerning the structural basis of the epilepsies in the general population. This thesis is my account of a series of investigations performed by myself, under the supervision of others.
AUTHOR’S CONTRIBUTION

The methodologies used to examine the hypotheses were designed by the author in conjunction with Professors Simon Shorvon, John Duncan and Ley Sander. I also recruited the 120 general practitioners who participated in this study, and developed the study population base.

All of the patients included in this study were personally reviewed. I collected, recorded and analysed all clinical and MRI data. In addition, I supervised the exhaustive search of primary care medical records performed by the team of approximately fifty medical students, and independently examined the notes of all “positive” cases.

Epileptic seizure and aetiological classification in all patients was carried out by Professors Simon Shorvon, John Duncan and Ley Sander, with the author presenting the clinical details and MRI findings.

The methods used for measuring hippocampal volume, hippocampal T2 relaxation time and intracranial volume were developed and validated by earlier investigators in the Epilepsy Research Group, namely Dr Samantha Free, Dr Mark Cook and Professor John Duncan. The acquisition of all MRI datasets used in this study was performed by radiographers at the National Society of Epilepsy MRI Unit, in particular Ms Kim Bimie and Ms Phillipa Bartlett, with me present. Due to the large number of patients included in this study, some help was required with quantitative hippocampal analysis: I measured the majority of hippocampal and intracranial volumes, with additional help from Kim Bimie, whereas Phillipa Bartlett and Kim Bimie measured all hippocampal T2 relaxation times. Dr Gail Bell helped check all of the data analysis. Statistical analysis was performed by the author with significant help from Dr Gail Bell. The interpretation of the data was originated by the author. This thesis was written entirely and solely by the author.
ACKNOWLEDGEMENTS

I am indebted to Professor Simon Shorvon and Professor John Duncan, my two supervisors, firstly for appointing me as their research fellow, and subsequently for imparting their wisdom and experience, in addition to providing strong encouragement and for exercising considerable patience and kindness during the past 7 years. I am also most grateful to Professor Ley Sander for arranging all things financial in my last research year, but mostly for his advice, vitality and good humour, all of which helped spur me through times of academic adversity. Most importantly, I thank Amit, my beautiful, wonderful wife, for her love and unflinching support, and for continually reminding me of the significance of completing this work, especially during the past two years. She has also blessed us with two beautiful children, Zachary and Saffron, whose very existence has been an inspiration to me in finishing this thesis. In this I was also spurred on by the memory of my beloved grandparents, George Sowter and Frederick and Winifred Everitt, who all wanted so much to see me complete my thesis but, sadly, were unable to do so. I would also like to take advantage of this rare opportunity to thank my parents, for everything. I know how desperately both wanted me to submit my thesis, and I am deliriously happy I have finally been able to realise this for them.

On a more practical note, I would like to thank the following people: Dr Samantha Free for scientific advice and for teaching me how to measure the volume of the human hippocampus; Drs Louis Lemieux and Mark Simms for help with physics and computing problems; Dr Gail Bell for helping me tremendously with statistical analysis and obsessive checking of raw data and results; Kim Birnie and Phillipa Bartlett for scanning patients, help with quantitative hippocampal analysis, MRI data retrieval, and for encouragement throughout; Drs. John Stevens and Brian Kendall for superb MRI reporting; all of the medical students who participated in the exhaustive audit of 175,000 patient records, whom are too numerous to mention individually; the 120 general practitioners who generously and whole-heartedly participated in this project; and all of the staff at the National Society for Epilepsy, particularly in the MRI unit. I am also deeply grateful to The Wellcome Trust and the National Society for Epilepsy for opportunities provided and for generous financial support throughout my time as a research fellow. Finally, I thank all of the patients who made this project possible and whom have taught me so much.
For Amit, Zachary and Saffron
CHAPTER 1

Introduction

Epilepsy is one of the commonest serious neurological conditions, second only to acute cerebrovascular events in terms of annual incidence and lifetime prevalence (MacDonald et al., 2000a). It presents an important global health problem, given its potential to affect any individual, irrespective of age, nationality, race and socioeconomic status, and its liability to become chronic. The economic burden on health services and society as a whole is considerable (Heaney and Sander, 1998), and the psychosocial repercussions of social stigmatisation, loss of employment and poor self-esteem equally detrimental (Morrell and Pedley, 2000). Contemporary knowledge of the epidemiology, aetiology and effects of epilepsy are thus essential in order to effectively manage this condition within a population.

In this introductory chapter the most commonly used terms in epileptology are defined, and the processes of diagnosis, investigation, and classification of epilepsy are discussed. There follows a literature review of studies investigating the epidemiology, prognosis and aetiology of the epilepsies, and the methodological problems encountered in such studies. In particular, the pivotal role of magnetic resonance imaging (MRI) in the assignation of aetiology of the epilepsies and in the quantitation of cerebral, especially hippocampal, damage is considered.

1.1 Definitions, diagnosis and investigation of epilepsy

1.1.1 Definitions

In 1993, the Commission on Epidemiology and Prognosis of the International League Against Epilepsy (ILAE) defined the terms used (and misused) most frequently in the field of epileptology, emphasising the importance of precise case definition in epidemiological studies of the epilepsies (ILAE,1993). The following definitions are adapted from this ILAE report.

EPILEPTIC SEIZURE

A clinical manifestation presumed to result from an abnormal and excessive discharge of
a set of neurones in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena which may include alterations of consciousness, motor, sensory, autonomic, or psychic events, perceived by the patient or an observer. Thus, clinical events caused by non-epileptiform abnormalities of neuronal function, such as ischaemia, and epileptiform discharges occurring in the absence of clinical concomitants, do not constitute epileptic seizures.

ISOLATED (SINGLE) SEIZURE
One or more epileptic seizures occurring in a 24 hour period.

FEBRILE SEIZURE
An epileptic seizure occurring in childhood after one month of age and before age six years, associated with a febrile illness which is not caused by CNS infection. There should be no history of neonatal seizures or previous unprovoked seizures, and an absence of other acute CNS or systemic insults.

PROVOKED (ACUTE SYMPTOMATIC, SITUATION-RELATED) SEIZURE
A seizure occurring in close temporal association (generally defined as within 7 days) with an acute systemic metabolic or toxic insult, or in association with an acute central nervous system (CNS) insult such as infection, stroke, cranial trauma, intracerebral haemorrhage, metabolic derangement, acute alcohol/drug intoxication or withdrawal, or any combination of the above.

UNPROVOKED SEIZURE
Unprovoked seizures, or seizures which do not occur in close temporal association with a CNS or systemic insult, fall into three main categories: (1) remote symptomatic unprovoked seizures refer to seizures occurring as a consequence of an antecedent CNS insult (occurring a minimum of one week prior to the seizure) such as head injury, cerebrovascular disease, CNS infection/infestation, pre- and peri-natal injury, chronic alcohol abuse or post-encephalopathic states (2) symptomatic unprovoked seizures resulting from progressive CNS disorders such as neoplasia, neurodegenerative conditions, autoimmune inflammatory disease and disorders of metabolism (3) unprovoked seizures of unknown aetiology include all seizures for which no clear antecedent aetiology can be
identified, although, as will be seen later, this is highly dependent upon the extent of investigation.

EPILEPSY
A condition characterised by recurrent (two or more) epileptic seizures, unprovoked by any immediate cause. Multiple seizures occurring within a 24 hour period and isolated episodes of status epilepticus are considered as single events and do not constitute epilepsy.

ACTIVE EPILEPSY
A prevalent case of active epilepsy is defined as a person with a correct diagnosis of epilepsy who has had at least one epileptic seizure during a defined period, usually the preceding 5 years, irrespective of anti-epileptic drug (AED) treatment.

INACTIVE EPILEPSY (EPILEPSY IN REMISSION)
A prevalent case of inactive epilepsy is defined as a person who has previously attracted a diagnosis of epilepsy but has experienced no seizures for a defined minimum period of time, most often 5 years. Inactive epilepsy can be further subdivided according to treatment status, into those who are receiving AED treatment and those who are not.

CHRONIC ACTIVE EPILEPSY
For the purposes of this study, chronic active epilepsy was defined as a history of at least 2 unprovoked epileptic seizures occurring over a minimum of 4 years, with at least 1 seizure having occurred during the preceding 12 months (see section 3.2.4).

PREVALENCE (POINT PREVALENCE)
The proportion of patients with epilepsy in a given population at a specified time (usually a specific day, the prevalence day). Inclusion criteria, such as whether the epilepsy is active or inactive, should be reported by the investigator.

POINT PREVALENCE RATE
The ratio of identified cases to the total defined population, usually expressed as the number of cases per 1000 persons.
INCIDENCE
The number of new cases of epilepsy (or isolated seizures, if specified) occurring during a given time interval, usually one year, in a specified population.

INCIDENCE RATE
The ratio of new cases to population at risk, usually expressed as cases per 100,000 persons/year. The criteria for defining an incident case must clearly state whether it is based upon the date of diagnosis (ascertainment) or the date of onset of seizures. Age-specific and gender-specific rates should be provided whenever possible. Comparisons of frequency indexes between different populations require adjustment of the values to a well-defined population (e.g., the United Kingdom (UK) census population) for a specific year.

CUMULATIVE INCIDENCE
An individual's risk of developing epilepsy by a certain time or specified age.

1.1.2 Diagnosis
An accurate diagnosis of epilepsy or isolated epileptic seizure can usually be made on clinical grounds alone and seldom requires more than obtaining a detailed history from the patient and a corroborative eye-witness account (Chadwick, 1990; Nashef 1996). The reliability of the diagnosis is subject to inter-rater variability but can be increased by the use of simple yet explicit diagnostic clinical criteria (Ottman et al., 1993; Kuyk et al., 1997). Complete reliance should not be placed on the history related by the patient alone who may only have limited recall or a “second-hand” version of events. The highly pleomorphic nature of seizures must be considered, although attacks within an individual are often stereotyped. Occasionally, a prolonged period of observation is required in order for attacks to be witnessed by a reliable eye-witness and the diagnosis confirmed. Particular care must be taken to exclude cases of syncope (Zaidi et al., 2000), hypoglycaemia, panic attacks and other types of psychogenic or dissociative episodes, transient ischaemic attacks and migraine, as well as rare conditions such as paroxysmal movement disorders, narcolepsy and transient global amnesia. In hospital based series, the misdiagnosis rate of epilepsy is estimated to be approximately 1 in 4 cases (Smith et al., 1999; Chadwick and Smith, 2002), with incomplete history-taking and misinterpretation of the electroencephalogram (EEG) cited as the main determinants of incorrect diagnosis.
Diagnostic difficulties may arise when potentially epileptogenic events remain unwitnessed or are associated with only some of the classical features of seizures. Consequently, a degree of uncertainty can persist in the early stages of diagnosis and the full clinical picture may emerge only with the passage of time. Non-epileptic attack disorder (non-epileptic seizures, pseudoseizures), for example, is said to account for up to 10-20% of patients referred to specialised epilepsy clinics for management of apparently chronic, intractable seizures (Lesser, 1996), but careful history-taking and/or direct observation commonly facilitate differentiation of these from true epileptic seizures (Lesser, 1996, Kuyk et al., 1997). For the purposes of epidemiological studies, it is therefore preferable to state whether an individual case represents either definite, probable or possible epilepsy since a proportion of such cases are likely to be later re-classified as not having epilepsy when further clinical information becomes available (Sander and Shorvon, 1996).

There is also continued debate as to exactly what constitutes epilepsy (Everitt and Sander, 1999). Some commentators believe that isolated epileptic seizures should be considered as part of the epilepsy spectrum (Wolf, 1997) since studies of prognosis have shown that the risk of recurrence after a single unprovoked seizure is so high (more than 75% of people experience a recurrent seizure within 36 months) (Hart et al., 1990) as to make the historical distinction from epilepsy (two or more seizures) completely arbitrary (Sander, 1993). Most experts are of the opinion, however, that febrile and provoked seizures should be regarded as distinct from epilepsy for the purposes of epidemiological and clinical studies (Sander and Shorvon, 1996).

1.1.3 Investigation

The use of supplementary investigations may facilitate confirmation of the diagnosis of epilepsy (Chadwick, 1990; Nashef, 1996), but their application more often influences epilepsy syndromic classification. Abnormal investigative findings cannot necessarily be considered as being of diagnostic importance or aetiological relevance and must always be interpreted in the context of the clinical setting. The most commonly used supplementary investigative procedures are outlined below:

ELECTROENCEPHALOGRAPHY (EEG)
Epilepsy surgery was pioneered by Sir Victor Horsley in the latter half of the 19th century,
using clinical localisation, yet investigation of epilepsy remained rudimentary until the introduction of EEG by Berger in the late 1920s. The impact of EEG was enormous, providing physicians with the means to both detect epileptogenic activity and to localise its site of origin, and it continues to be a valuable investigative procedure today (Rowan and French, 1988). Although EEG cannot compete with modern neuroimaging in the detection or localisation of small structural lesions, it frequently detects localised aggregates of neuronal dysfunction in patients with epilepsy who have no demonstrable localised structural lesions. A single routine EEG is likely to show an epileptiform abnormality in 35-50% of patients with epilepsy (Ajmone-Marsan and Zivin, 1970), but a normal interictal (and sometimes ictal) EEG does not exclude a diagnosis of epilepsy (Shorvon, 1990) and it is well recognised that epileptiform discharges may be found in approximately 1-2% of a healthy non-epileptic population (Zivin and Ajmone-Marsan, 1968).

EEG is particularly useful in diagnosing certain specific epilepsy syndromes (eg. childhood absence epilepsy) and in determining whether:

• seizures are primarily or secondarily generalised
• epileptiform activity is localised, multifocal or generalised
• certain attacks have an epileptogenic basis or not (if ictal EEG obtained)

The detection of interictal epileptiform EEG abnormalities may be enhanced by longer duration of recording, sleep deprivation or drug-induced sleep, and recording as soon as possible after a seizure. Over the years the usefulness of EEG has also been augmented by the addition of sphenoidal and intracranial electrodes, ambulatory recording and correlation with video monitoring but, overall, EEG technology has remained largely unchanged since its inception. More recently, a new mode of localising the epileptogenic zone, magnetoencephalography (MEG), has been introduced which has been shown to yield information which complements EEG findings (Baumgartner et al., 2000). In the future, combined MEG-EEG recordings may improve the non-invasive evaluation of epilepsy patients, especially those with neocortical epilepsy.

X-RAY COMPUTED TOMOGRAPHY (CT)

The next major advance in the investigation of epilepsy, and the advent of modern
neuroimaging, came with the introduction of X-ray computed tomography (CT) in the 1970s. Cranial CT allowed the first useful in-vivo identification of major structural abnormalities in patients with seizure disorders, but its main drawbacks were poor structural resolution (particularly in the temporal lobes), the ability to acquire images in one plane only, and patient exposure to ionising radiation. At best, cranial CT can detect relevant structural abnormalities in 25% of patients with chronic epilepsy and in even fewer with newly diagnosed seizures (Young et al., 1982). In the late 1980s, the role of cranial CT in the investigation of patients with refractory epilepsy began to be superseded by the introduction of MRI (Jabbari et al., 1986; Latack et al., 1986; Avrahami et al., 1987; Francheschi et al., 1989; Duncan R et al., 1990a). Cranial CT, however, continues to be an important investigation in acute neurology, for example the acute assessment of seizures, particularly when intracranial haemorrhage or neoplasia need to be urgently excluded. CT also remains the neuroimaging investigation of choice for the detection of small intracranial calcified lesions associated with epilepsy, such as those of neurocysticercosis (ILAE, 1997).

MAGNETIC RESONANCE IMAGING (MRI)

MRI offers unparalleled in vivo visualisation of brain structure and permits image acquisition in multiple planes. The application of separate MRI sequences can generate different relative contrasts from the same tissues and thereby improve sensitivity for detecting lesions. The advent of MRI has revolutionised the investigation and management of patients with epilepsy, and cranial MRI is now the neuroimaging investigation of choice in the majority of clinical situations. In 1997, the ILAE published recommendations for neuroimaging of patients with epilepsy (ILAE, 1997). It was suggested that structural MRI should be obtained in all non-acute situations, with the exception of patients with a definite electro-clinical diagnosis of idiopathic generalised epilepsy (IGE) or benign rolandic epilepsy. MRI is particularly indicated in patients with one or more of the following: a history or EEG suggestive of partial onset seizures with onset at any age, onset of unclassified or generalised seizures in adulthood, fixed focal deficits on CNS or neuropsychological examination, difficulty in obtaining control of seizures with first line AED treatment, and loss of control of seizures with AED treatment or a change in seizure pattern that might imply a progressive underlying lesion (ILAE, 1997).
High resolution MRI (employing thin slices and excellent anatomical definition) with relevant scanning protocols enables reliable demonstration of subtle abnormalities associated with epilepsy such as hippocampal sclerosis (HS), foreign tissue lesions and malformations of cortical development (MCD) (Lee et al., 1988; Duncan, 1997). In contrast to the low yield of CT scanning in chronic epilepsy (relevant focal lesions observed in 15-20% of cases (Young et al., 1982)), high resolution MRI demonstrates cerebral lesions in as many as 85% of hospital based subjects with chronic epilepsy (Li et al., 1995). A detailed discussion of the impact of both CT and MRI in determining epilepsy aetiology is presented in section 1.4.2.

Manual and computerised analysis of MRI datasets following image acquisition ("post-processing") can provide further useful information. These methods include quantitative hippocampal measurements (see section 1.5.3), quantitative grey-white matter analysis, fractal analysis of the cortex, and three-dimensional renderings of the cortical surface (Duncan, 1997). All may reveal structural abnormalities which were not detected by visual inspection alone.

A discussion of the potential roles of MR spectroscopy, functional MRI and diffusion-weighted MR imaging in epilepsy investigation (Duncan, 1997) is beyond the scope of this thesis, but all of these techniques are likely to advance our understanding of the structural, physiological and neurochemical basis of seizure generation.

**GENETIC ANALYSIS**
Considerable advances in the field of molecular genetics have led to improved understanding of the biological basis of many of the epilepsies (Delgado Escueta et al., 1994; Leppert and Singh, 1999; Johnson and Sander, 2001). Genetic mapping studies have allowed linkage of certain epileptic syndromes to specific chromosomes, such as that of juvenile myoclonic epilepsy (JME) and chromosomes 6p and 15q (Bate and Gardiner, 1999; Leppert and Singh, 1999). In a few exceptional cases, the specific mechanism of action of the abnormal gene has been determined, as with autosomal dominant nocturnal frontal lobe epilepsy which is associated with a missense mutation of a subunit of neuronal nicotinic acetylcholine receptors (Steinlein et al., 1995 and 1997). At present such investigation is not widely available and genetic testing is currently possible only for a
small number of abnormal genes associated with epilepsy, but it is likely that such testing will play a fundamental role in the investigation and classification of patients with epilepsy in the near future when the full range of genetic polymorphisms is known, when the function of individual genes is known, and with technological advances in genetic analysis. Recently, a new line of genetic research, pharmaco-genetics, has emerged and it has been hypothesised that certain polymorphisms at genetic loci which encode drug-transporter proteins, may be implicated in multi-drug resistant intractable epilepsy (Siddiqui et al., 2003).

OTHER INVESTIGATIONS
There are several other investigative tools at the disposal of the epileptologist which may help characterise an epilepsy syndrome or identify localised functional abnormalities. These include the selective use of haematological, biochemical and immunological blood tests (for metabolic and inflammatory disorders), karyotyping, neuropsychological assessment (which may help localise cortical deficits), non-MRI functional imaging techniques such as positron emission tomography (which may identify regions of localised interictal hypometabolism) and single photon emission computerised tomography (which may show interictal or ictal abnormalities in regional cerebral blood flow) (Cook and Kilpatrick, 1994; Duncan, 1997). Neither method of emission tomography is widely available, and both expose the patient to ionising radiation such that they are generally reserved for research purposes or the evaluation of patients being seriously considered for epilepsy surgery.

1.2 Classification in epileptology
Epilepsy is not a single disease and it has been argued, with some justification, that epilepsy is simply a neurological symptom. It is certainly true that, if one takes its basic definition at face value, epilepsy represents little more than one clinical expression of a plethora of conditions associated with the production of seizures. In some cases, epilepsy is the sole expression of this condition, whilst in others it may be just one of many clinical manifestations (Nashef, 1996). Epilepsy is best considered as a heterogenous disorder with multitudinous subtypes and pathogeneses, each with differing clinical characteristics and prognoses. It is therefore insufficient to make a diagnosis of epilepsy per se and an attempt should be made to classify a case as accurately as possible so that conditions with similar
clinical characteristics, aetiologies, prognoses and response to treatment may be recognised as such, whilst conditions with little in common may be separated. Such practice carries obvious benefits for both patient management and clinical research.

Most epileptologists currently employ two parallel classifications, both of which were devised by representatives of the ILAE. The first, the International Classification of Epileptic Seizures (ICES) was last revised in 1981 (ILAE, 1981) (Table 1), although recently a separate semiological seizure classification, principally for use in tertiary epilepsy units, has also been proposed (Luders et al., 1998). Epileptic seizures are considered to be the symptoms and signs of epileptology, and can be classified according to clinical and EEG phenomenology, but rarely provide clues as to their underlying aetiology. The second classification, the International Classification of the Epilepsies and Epilepsy Syndromes (ICEES), was last revised in 1989 (ILAE, 1989) (Table 2). The epilepsies and epileptic syndromes are broadly defined by their anatomical and electro-clinical characteristics, and sometimes by their aetiology. As such they have the potential to provide more useful information with respect to the successful planning of treatment and the assessment of prognosis (Benbadis and Luders, 1996; Everitt and Sander, 1999).

Individual epilepsy syndromes may be associated with multiple seizure types and, conversely, individual seizure types may be associated with multiple epilepsy syndromes, so that the requirement for separate seizure and syndromic classifications is both valid and helpful to successful clinical management (Benbadis and Luders, 1996).

1.2.1 The International Classification of Epileptic Seizures (ICES) (Table 1)
The ICES is based upon the interpretation of clinical phenomenology and EEG findings. In brief, it categorises seizures into partial (simple, complex, secondarily generalised), generalised (absence, myoclonic, clonic, tonic, tonic-clonic, atonic) or unclassified subgroups.

Unfortunately, the ICES does not specify which EEG findings should be incorporated (if more than one EEG has been performed), the number of EEG recordings required for classification, and whether sleep EEG findings override those of routine EEG. Furthermore, guidelines concerning the significance of EEG slow wave activity in seizure
Table 1  Simplified version of the International Classification of Epileptic Seizures (ILAE, 1981)

<table>
<thead>
<tr>
<th>1. PARTIAL (FOCAL, PARTIAL) SEIZURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Simple partial seizures (consciousness not impaired)</td>
</tr>
<tr>
<td>1.1.1 with motor signs</td>
</tr>
<tr>
<td>1.1.2 with somatosensory or special sensory symptoms</td>
</tr>
<tr>
<td>1.1.3 with autonomic symptoms or signs</td>
</tr>
<tr>
<td>1.1.4 with psychic symptoms</td>
</tr>
<tr>
<td>1.2 Complex partial seizures</td>
</tr>
<tr>
<td>1.2.1 simple partial onset followed by impairment of consciousness</td>
</tr>
<tr>
<td>1.2.2 with impairment of consciousness at onset</td>
</tr>
<tr>
<td>1.3 Partial seizures evolving to secondarily generalised seizures (tonic-clonic, tonic or clonic)</td>
</tr>
<tr>
<td>1.3.1 simple partial seizures evolving to generalised seizures</td>
</tr>
<tr>
<td>1.3.2 complex partial seizures evolving to generalised seizures</td>
</tr>
<tr>
<td>1.3.3 simple partial seizures evolving complex partial, evolving to generalised seizures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. GENERALISED SEIZURES (CONVULSIVE OR NON-CONVULSIVE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1 Absence seizures</td>
</tr>
<tr>
<td>2.1.2 Atypical absence seizures</td>
</tr>
<tr>
<td>2.2 Myoclonic seizures</td>
</tr>
<tr>
<td>2.3 Clonic seizures</td>
</tr>
<tr>
<td>2.4 Tonic seizures</td>
</tr>
<tr>
<td>2.5 Tonic-clonic seizures</td>
</tr>
<tr>
<td>2.6 Atonic (astatic) seizures</td>
</tr>
</tbody>
</table>

| 3. UNCLASSIFIED EPILEPTIC SEIZURES |
classification are vague and precise definitions of EEG epileptiform activity are lacking. Neurologists also encounter difficulties with seizure classification when EEG and clinical data are at variance, or when attempting to accurately define consciousness in order to differentiate simple (consciousness not impaired) from complex (consciousness impaired) partial seizures.

Consequently, it is often difficult to apply the ICES in epidemiological field studies where EEG facilities may be insufficient. For these reasons it has been suggested that a purely clinical seizure classification would be more appropriate (ILAE, 1993; Sander and Shorvon, 1996), particularly since the ICEES also incorporates EEG findings with the effect that the two classifications are currently inextricably linked. In recognition of this conflict, the ILAE has recommended that a future seizure classification be based solely upon seizure semiology (ILAE, 1993), which would also ease application in field studies, although one recent proposal (Luders et al., 1998) is far too cumbersome for this use.

1.2.2 The International Classification of the Epilepsies and Epileptic Syndromes (ICEES) (Table 2)

The ICEES is moulded (on the basis of the presumed location of seizure onset) by a fundamental dichotomy into the two major categories of epilepsy:

- **generalised**
- **localisation related** (partial or focal)

For each of these groups there is further sub-categorisation into:

- **idiopathic** implying an age-related onset, no known structural cause and a suspected genetic basis
- **symptomatic** signifying a known or suspected CNS insult
- **cryptogenic** indicating a putative symptomatic cause but in the absence of evidence of a CNS disorder or lesion

Unfortunately, the term cryptogenic does not allow differentiation of an extensively worked up case from a case which has not been investigated at all.
Table 2 The International Classification of the Epilepsies and Epileptic Syndromes (ILAE, 1989)

<table>
<thead>
<tr>
<th>1</th>
<th>LOCALISATION RELATED EPILEPSIES AND SYNDROMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Idiopathic (with age-related onset)</td>
</tr>
<tr>
<td>1.1.1</td>
<td>Benign childhood epilepsy with centrotemporal spikes</td>
</tr>
<tr>
<td>1.1.2</td>
<td>Childhood epilepsy with occipital paroxysms</td>
</tr>
<tr>
<td>1.1.3</td>
<td>Primary reading epilepsy</td>
</tr>
<tr>
<td>1.2</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>1.2.1</td>
<td>Chronic progressive epilepsy partialis continua of childhood</td>
</tr>
<tr>
<td>1.2.2</td>
<td>Syndromes characterised by seizures with specific modes of precipitation</td>
</tr>
<tr>
<td>1.2.3</td>
<td>Temporal, frontal, parietal and occipital lobe epilepsies</td>
</tr>
<tr>
<td>1.3</td>
<td>Cryptogenic</td>
</tr>
<tr>
<td>1.3.1</td>
<td>Temporal, frontal, parietal and occipital lobe epilepsies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>GENERALISED EPILEPSIES AND SYNDROMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Idiopathic (with age-related onset)</td>
</tr>
<tr>
<td>2.1.1</td>
<td>Benign myoclonic epilepsy in infancy</td>
</tr>
<tr>
<td>2.1.2</td>
<td>Childhood absence epilepsy / juvenile absence epilepsy</td>
</tr>
<tr>
<td>2.1.3</td>
<td>Juvenile myoclonic epilepsy (impulsive petit mal)</td>
</tr>
<tr>
<td>2.1.4</td>
<td>Epilepsy with generalised tonic-clonic seizures on awakening</td>
</tr>
<tr>
<td>2.1.5</td>
<td>Syndromes characterised by seizures with specific modes of precipitation</td>
</tr>
<tr>
<td>2.1.6</td>
<td>Other idiopathic generalised epilepsies</td>
</tr>
<tr>
<td>2.2</td>
<td>Cryptogenic or symptomatic (in order of age)</td>
</tr>
<tr>
<td>2.2.1</td>
<td>West syndrome (infantile spasms)</td>
</tr>
<tr>
<td>2.2.2</td>
<td>Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>2.2.3</td>
<td>Epilepsy with myoclonic-astatic seizures</td>
</tr>
<tr>
<td>2.2.4</td>
<td>Epilepsy with myoclonic absences</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3</th>
<th>SPECIAL SYNDROMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Situation-related epilepsies</td>
</tr>
<tr>
<td>3.1.1</td>
<td>Febrile convulsions</td>
</tr>
<tr>
<td>3.1.2</td>
<td>Isolated seizures or status epilepticus</td>
</tr>
<tr>
<td>3.1.3</td>
<td>Seizures due to an acute toxic or metabolic event</td>
</tr>
</tbody>
</table>
The localisation related symptomatic and cryptogenic categories can be also be divided on
the basis of their presumed lobar (e.g. temporal, frontal) or sub-lobar (e.g. cingulate,
orbitofrontal) site of localisation, although the latter is rarely possible without a detailed
video-EEG evaluation (Manford et al., 1992a).

There are two other ICEES categories:

- epilepsies which remain undetermined as to whether localisation related or
generalised
  epilepsies with features of both focal and generalised epilepsy, or with features of
  neither
- special syndromes
  miscellaneous events including febrile, provoked and isolated unprovoked seizures,
  and status epilepticus

An epileptic syndrome has been defined as “an epileptic disorder characterised by a cluster
of signs and symptoms customarily occurring together” (ILAE, 1989). These symptoms and
signs can be of either a clinical nature (including seizure type, aetiology, anatomy,
precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and
prognosis) or pertain to the findings of ancillary investigations (ILAE, 1989). The EEG in
particular may be crucial in diagnosing the various IGE and idiopathic localisation related
epilepsy syndromes, and this may impact greatly upon treatment selection and
determination of prognosis.

Patients with JME, for example, frequently enter remission following treatment with
sodium valproate, yet attempted withdrawal of valproate subsequently is associated with
a high rate of seizure relapse (Janz, 1989; Sander, 1993). Successful empirical treatment
with valproate, however, in the absence of knowledge of the JME syndrome might lead one
to incorrectly deduce that prolonged remission on treatment will be followed by a high
probability of seizure freedom following AED withdrawal. Most other epilepsy syndromes
are not so neatly linked to an optimum treatment or clear-cut prognosis. In essence, a
syndrome amounts to little more than a constellation of symptoms and signs and, unlike
a disease, “...does not necessarily have a common aetiology or prognosis” (ILAE, 1989).
A syndrome such as frontal lobe epilepsy may therefore be a consequence of mechanisms as diverse as CNS trauma, infarction or infection, malformations of cortical development (MCD), foreign tissue lesions and, rarely, autosomal dominant inheritance (Steinlein et al., 1997). Consequently, many major ICEES categories (especially the localisation related syndromes) do not necessarily represent or group together, clinically and prognostically similar syndromes. Frequently, their only common characteristic is the location of seizure onset.

A major criticism of the ICEES is that the criteria on which the classification is based are ill-defined and it is not clear how to apply them (eg. the number EEG recordings required, the interpretation of discordant data). This makes the classification useless for many research purposes.

Much of the complexity of the current ICEES has resulted from its development in tertiary referral epilepsy centres where patients with intractable epilepsy, well-defined epileptogenic foci, and surgically-implanted depth electrodes were studied with combined video and EEG telemetry (ILAE, 1989). Such patients comprise a small (probably less than 5%) and unrepresentative fraction of all people with epilepsy. To base an epilepsy classification which is intended for use by all physicians, not merely epileptologists, on such an atypical patient group is illogical (Manford et al., 1992b). It is unsurprising, therefore, that the classification precludes diagnostic precision when employed in population based studies (Table 3) where intensive investigation has not, thus far, been feasible (Everitt and Sander, 1999).

Another limitation is that the ICEES attempts to incorporate many schools of thought within the world of epileptology. In reality, it is unrealistic to create a single classification satisfactory to both nosological “lumpers” and “splitters”, a fact recognised by Hughlings-Jackson more than 100 years ago. In his famous analogy with gardeners and botanists, he deemed that an utilitarian approach to classification of the epilepsies (equivalent to the gardener’s classification into border plants, shrubs and suchlike), favourable to the non-specialist or lay person, was of equal validity to a more rigorous and scientifically accurate all-encompassing classification (equivalent to that used by botanists) (Taylor, 1931; Mosewich and So, 1996). Whilst the increasingly complex sub-categorisation of syndromic
Table 3 Population based studies of epilepsy utilising the International Classification of the Epilepsies and Epileptic Syndromes (ILAE, 1989)

<table>
<thead>
<tr>
<th>Study</th>
<th>Localisation-related</th>
<th>Generalised</th>
<th>Undet.</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of case ascertainment:</td>
<td>1.1</td>
<td>1.2</td>
<td>1.3</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Author, Country</strong></td>
<td><strong>n</strong></td>
<td><strong>Alving, Denmark</strong></td>
<td><strong>1508</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Bauer, Austria</strong></td>
<td><strong>2881</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>OREp, Italy</strong></td>
<td><strong>8525 (all)</strong></td>
<td><strong>4.6</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>7332 (def)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. Paediatric tertiary referral epilepsy centre:</strong></td>
<td></td>
<td><strong>Alving, Denmark</strong></td>
<td><strong>402</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Cavazzuti, Italy</strong></td>
<td><strong>178</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Viani, Italy</strong></td>
<td><strong>645</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Eslava-Cobos Colombia</strong></td>
<td><strong>182</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Shah, India</strong></td>
<td><strong>483</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3. EEG department:</strong></td>
<td></td>
<td><strong>Gastaut, France</strong></td>
<td><strong>6562</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Loiseau, France</strong></td>
<td><strong>804 (D)</strong></td>
<td><strong>2.4</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>751 (D365)</strong></td>
<td><strong>2.3</strong></td>
<td></td>
</tr>
<tr>
<td><strong>4. Community based studies, including epidemiological surveys:</strong></td>
<td></td>
<td><strong>Manford, UK</strong></td>
<td><strong>594</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Oka, Japan</strong></td>
<td><strong>2378</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>de la Court Holland</strong></td>
<td><strong>85</strong></td>
<td></td>
</tr>
<tr>
<td><strong>5. Adult neurology clinic:</strong></td>
<td></td>
<td><strong>Joshi, India</strong></td>
<td><strong>1000</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Danesi, Nigeria</strong></td>
<td><strong>945</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Loiseau, France</strong></td>
<td><strong>642 (PP)</strong></td>
<td><strong>10.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>344 (adults)</strong></td>
<td><strong>7</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Eadie, Australia</strong></td>
<td><strong>1902</strong></td>
<td><strong>0.3</strong></td>
</tr>
<tr>
<td><strong>6. Neuropsychiatric clinic:</strong></td>
<td></td>
<td><strong>Kido, Japan</strong></td>
<td><strong>300</strong></td>
<td></td>
</tr>
</tbody>
</table>

Studies employing 1970 or 1985 syndromic classifications have been adapted to comply with the 1989 ICEES categories (denoted by numbers 1.1 through to 4.1; see table 2 for definitions). Febrile seizures have been excluded, so that the total n and % proportions may differ slightly from those reported in the original articles.

n = sample size (after febrile convulsions excluded)  Undet = undetermined whether epilepsy focal or generalised  SS = special syndromes  U = unclassifiable cases  D = day adults = adult cohort  PP = private patient cohort (includes adults and children)  def = definite epilepsy cases only  all = definite and uncertain epilepsy cases  excl = excluded (original study criteria)
groups (especially the IGE syndromes) may have a clear purpose (searching for candidate genes in IGE requires phenotypic homogeneity if it is to be fruitful), the validity of splitting to such an extent remains the subject of fierce debate (Berkovic et al., 1994a). For the majority of doctors attempting to classify their patients' epilepsies, this degree of subcategorisation is both meaningless and unrealistic, and has probably even discouraged use of the ICEES.

A further problem is that even the most recent ICEES makes no specific mention of the extent to which CT and MRI should contribute to epilepsy syndromic classification (ILAE, 1989). High resolution neuroimaging can reliably demonstrate subtle structural abnormalities, but it is presently unclear whether the discovery of focal cerebral abnormalities should dictate that an epilepsy syndrome is classified as localisation related, particularly when EEG findings are discordant.

Finally, much of the ICEES is moulded by the fundamental electro-clinical dichotomy "...which in many types of epilepsy is difficult to justify and presumes an unrealistic understanding of the underlying physiological processes" (Duncan et al., 1995a). Symptomatic generalised and cryptogenic/symptomatic generalised epilepsies, for example, are poorly defined and may be the consequence of either focal, multifocal, or diffuse brain pathologies or encephalopathies, rather than true generalised pathophysiological processes. The neurophysiological basis of IGE is similarly unclear, although the ICEES does not acknowledge this. In such situations, it is unclear whether EEG or neuroimaging findings should take precedence in syndromic classification. This difficulty is likely to be amplified in the future as the resolution of structural neuroimaging improves and functional neuroimaging becomes more widely available (Sisodiya et al., 1995 and 1996; Free et al., 1996a; Duncan, 1997). It is not inconceivable that structural and/or functional cerebral abnormalities will eventually be identifiable in the majority of patients with localisation related, or even generalised, epilepsies. Future classifications of the epilepsies will need to address these issues if they are to remain useful (Everitt and Sander, 1999).

1.2.3 ILAE Commission on Epidemiology and Prognosis Classification

In 1993, in recognition of the incorrect and infrequent use of the ICEES and ICES in
epidemiological studies of epilepsy, the ILAE Commission on Epidemiology and Prognosis (ILAE, 1993) published a simplified classification (Figure 1) which is based predominantly on clinical seizure types, but which is equally applicable to the epilepsies and epileptic syndromes. This scheme is less confusing than other classifications and more practical for population studies of epilepsy (Jallon et al., 1997). In particular, the division of symptomatic epilepsies into those owing to a static or progressive encephalopathy is useful in separating prognostically discrete conditions. In many ways this represents the utilitarian approach to classification since it is more amenable to use by general practitioners and non-epileptologists, in addition to epilepsy specialists and epidemiologists. As such, it should be more frequently used since a practical, reproducible classification of the epilepsies is of major importance if studies of aetiology, treatment or prognosis are to be comparable across different populations.

1.3 Epidemiology

1.3.1 Methodological issues
Before reviewing the published studies of the incidence and prevalence of the epilepsies, it is necessary to first consider the factors which most influence the epidemiology of the epilepsies, since this in turn modifies the interpretation of results. This important subject has been extensively reviewed previously (Sander and Shorvon, 1987 and 1996).

DIAGNOSTIC ACCURACY

The diagnosis of epilepsy is almost entirely dependent on the discretionary judgement of the physician involved. The robustness of this judgement will be affected by both the physician’s clinical skill and experience and also the quality of patient and eye-witness accounts. Some syncopal events, particularly when associated with myoclonic jerks or urinary incontinence, are liable to be misdiagnosed as epileptic seizures by inexperienced physicians (Lempert, 1996; Zaidi et al., 1998) and, if recurrent, may lead to an erroneous diagnosis of chronic refractory epilepsy and unnecessary AED treatment (Zaidi et al., 1998; Smith et al., 1999). In the UK National General Practice Study of Epilepsy (Sander et al., 1990), the “possible epilepsy” cohort comprised one fifth of all cases of newly diagnosed epilepsy, indicating the scale of the problem of achieving diagnostic accuracy. Several studies of “chronic epilepsy” in tertiary referral centres have revealed that up to 25% of treated patients do not have epilepsy (Sander, 1993; Smith et al., 1999), the other principal
Figure 1 Diagrammatic representation of a simplified epilepsy classification proposed by the ILAE Commission on Epidemiology and Prognosis, 1993

- Epileptic seizure (single or recurrent)
  - Provoked seizure(s) (acute symptomatic seizure: insult < 7 days before seizure)
  - Unprovoked seizure (single or recurrent)
    - Symptomatic (remote cause: insult > 7 days before seizure)
      - Owing to a static encephalopathy (e.g., previous CNS infection, trauma, perinatal injury or cerebrovascular disease)
      - Owing to a progressive CNS disorder (e.g., neoplasm, autoimmune or degenerative CNS disease, spongiform encephalopathy, metabolic or mitochondrial disease)
    - Unknown cause (no clear antecedent aetiology)
      - Idiopathic
      - Cryptogenic
source of misdiagnosis being non-epileptic attacks (alternatively known as pseudoseizures or psychogenic seizures). Such diagnostic errors are likely to lead to overestimates of both incidence and prevalence rates, and underestimates of the frequency of relevant abnormalities with investigations such as cranial MRI. This may be partly or completely offset by the number of patients developing or having epilepsy who are not detected by the method of case ascertainment used.

CASE ASCERTAINMENT AND SELECTION BIAS
Selection bias is perhaps the most important confounding factor in epidemiological studies of epilepsy. Firstly, “some patients with seizures never seek medical attention through concealment, denial or ignorance” (Beran et al., 1985; Sander and Shorvon, 1996). Likewise, people with established epilepsy are less likely to report recent seizures to their GP as this may affect their eligibility to drive or engage in various employment or leisure activities (Dalrymple and Appleby, 2000). Field studies will therefore tend to miss a proportion of incident cases and underestimate the prevalence of active epilepsy, unless sensitive and/or anonymous screening techniques are employed. Secondly, the method and location of case ascertainment is critical. The majority of incidence and prevalence studies have involved retrospective analyses of medical records, examining for evidence of seizures, AED prescriptions or epilepsy diagnostic codes. These methods are liable to lead to diagnostic inaccuracy and incomplete ascertainment (Sander and Shorvon, 1996) and significant underestimates of both incidence (Zielinski, 1974) and prevalence rates (Stanhope et al., 1972). Many studies, particularly those of aetiology, have not been community based and have relied upon EEG departments, neurology or epilepsy clinics for case ascertainment, thus tending to under-represent “milder” cases who are not referred for hospital assessment, and over-represent patients with more severe epilepsy.

Community based screening questionnaires and door-to-door surveys (Placencia et al., 1992a; de la Court, 1996) have the advantage that they do not rely upon prior diagnosis for ascertainment of florid clinical events such as tonic-clonic seizures, but such instruments probably lack the sensitivity to detect subtle seizure types (Sander and Shorvon, 1996) and are only suitable for investigation of relatively small populations or samples of populations.

Alternative data sources for epidemiological studies have included (a) special registers set
up for research purposes, such as the Mayo Clinic’s Rochester Project (Hauser and Kurland, 1975; Hauser et al. 1991 and 1993; Annegers et al. 1995) or that of Aarhus in Denmark (Juul Jensen and Foldspang, 1983), though both these systems employed retrospective data analyses and were thus subject to the same biases as reviews of medical records, and (b) computerised databases (Wallace et al., 1998). One such scheme, the GP Research Database, contains complete epidemiological, morbidity and prescription data for more than two million people from nearly 300 computerised general practices in the UK and was the source of a recent retrospective incidence and prevalence study of treated epilepsy (Wallace et al., 1998). Assuming continued high levels of complete data entry, this huge database has the potential to provide readily accessible, high quality prospective epidemiological data for years to come and, in particular, provide information regarding secular trends in the incidence and prevalence of epilepsy.

CASE DEFINITION

In epidemiological studies of epilepsy case definition is vital since it will have a significant bearing on the ability to compare data across different populations (ILAE, 1993; Sander and Shorvon, 1996). In some incidence studies, isolated unprovoked seizures (Loiseau et al., 1990a), and occasionally even provoked seizures (Loiseau et al., 1990a; Sander et al., 1990), are embraced under the rubric “epilepsy”. The inclusion of these events may affect incidence or prevalence data by two- or three-fold (Sander and Shorvon, 1987). If isolated seizures are excluded, the time elapsed since the first episode should be specified since a second seizure may occur several months or even years after the first (Sander and Shorvon, 1987; Sander, 1993). The term “first seizure” can be misleading since it does not necessarily refer to a first, isolated epileptic seizure and may simply be an inaccurate catch-all phrase referring to all patients presenting with seizures for the first time. Descriptive terms such as “new diagnosis” or “first medical attendance” are therefore preferable in incidence studies since minor seizure types (eg. myoclonic jerks, simple partial seizures with psychic phenomena) are frequently only recognised as such by the patient and/or physician following a first ever tonic-clonic seizure, even though they may have been occurring intermittently for months or years.

Case definition has been especially poor in prevalence studies of epilepsy. Even though the majority of patients with epilepsy enter “terminal” remission (see section 1.3.5) (Annegers
et al., 1979; Cockerell et al., 1995a and 1997), a consensus statement as to the duration of remission designating inactive epilepsy (5 years, regardless of treatment status) was published only recently (ILAE, 1993). Prior to this, “active” epilepsy has been variously defined as a lifetime history of epilepsy (“once an epileptic, always an epileptic”) or, more conventionally, as a history of epilepsy and the occurrence of seizures in the preceding 1, 2, 3, or 5 years. Additionally, some authors have considered patients who were in remission, but still receiving AED treatment, as having active epilepsy. In some reports case definitions were not provided at all. The overall effect is that much of the observed variation in prevalence data emerging from epidemiological studies of epilepsy has resulted from a failure to accurately define the activity of the condition (Sander and Shorvon, 1987 and 1996).

CLASSIFICATION CRITERIA

With the exception of the simplified classification proposed in the 1993 ILAE Guidelines for Epidemiologic Studies on Epilepsy (Figure 1) (ILAE, 1993), current classifications of epilepsy are too complicated for use in field studies (Everitt and Sander, 1999) and so vague as to be useless for rigorous scientific analysis. The ICES (ILAE, 1981) is often inapplicable simply because the use of EEG is impractical. Even when extensive EEG and clinical data is available, specialists frequently disagree on seizure classification (Lavy et al., 1972; Duncan et al., 1995a). As previously mentioned, EEG criteria for seizure classification are ill-defined, thus impeding successful application of the ICES. In any case, routine EEG is normal in approximately half of patients with newly diagnosed epilepsy (Ajmone-Marsan and Zivin, 1970), and therefore frequently does not aid seizure classification. The ICEES (ILAE, 1989), already discussed in detail, is also too cumbersome to be of practical utility in population based studies of epilepsy (Everitt and Sander, 1999) and the majority of patients fall into catch-all categories such as the cryptogenic localisation related epilepsies, and epilepsies which remain undetermined as to whether partial or generalised (Manford et al., 1992b). The terminology used in the ICEES is also rather complicated and not always correctly applied in field studies: “idiopathic” has been frequently misused as a term implying “cause unknown” (ie. idiopathic and cryptogenic combined) rather than referring specifically to those epilepsies with an age-related onset, specific electro-clinical features and a presumed genetic basis.
1.3.2 Incidence, age-specific incidence and secular trends in incidence

The majority of incidence studies have been retrospective and carried out in developed countries. To date, few prospective and population based studies of the incidence of epileptic seizures or syndromes have been reported (Sander and Shorvon, 1996; Jallon et al., 1997).

The annual incidence rates of epilepsy (definition variable) have ranged from 11/100,000 in Norway (Krohn, 1961) to 230/100,000 in Ecuador (Placencia et al., 1984), although in most developed countries the rate is approximately 40 to 80/100,000/year (Crombie et al., 1960; Hauser and Kurland, 1975; Goodridge and Shorvon, 1983a; Joensen, 1986; Loiseau et al., 1990a; Hauser et al., 1993; Cockerell et al., 1995b; Olaffson et al., 1996; Forsgren et al., 1996; Jallon et al., 1997; Wallace et al., 1998; Annegers et al., 1999; Zarelli et al., 1999; MacDonald et al., 2000a) (Table 4). In developing countries, however, the figures have been consistently higher and usually over 100/100,000/year (Placencia et al., 1992b; Rwiza et al., 1992). This is likely to result from the higher rates of CNS infection/parasitic infestation and head/birth injury observed in developing countries (Li et al., 1985; Arruda, 1991; de Bittencourt et al., 1996; Bittencourt, 1988; Murthy et al., 1998).

Some early studies reported relatively low incidence rates amongst the elderly (Crombie et al., 1960), but this was probably an artefact of incomplete case ascertainment. It is now recognised that, in developed countries at least, the incidence rate of epilepsy is bimodally distributed: it is highest in the elderly, relatively high in children, and much lower in early and mid-adult life (Hauser et al., 1993; Forsgren et al., 1996; Jallon et al., 1997; Wallace et al., 1998). There is also some evidence that the incidence of epilepsy in children has declined over the past two decades whilst simultaneously increasing amongst the elderly (Hauser et al., 1993; Cockerell et al., 1995b; Everitt and Sander, 1998). Several factors are likely to be involved in these secular trends. The apparent decline in incidence rates in children may have indirectly resulted from improvements in antenatal and peri-natal care coupled with an increased awareness amongst expectant mothers of the necessity to adopt healthier lifestyles. This in turn may have led to a decreased incidence of MCD and birth hypoxia, though this explanation is speculative (Sander and Shorvon, 1996; Everitt and Sander, 1998). The concomitant increased incidence of epilepsy in the elderly may be partly explained by the increased life expectancy which has inevitably led to a larger
<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>First author</th>
<th>Annual incidence per 100 000</th>
<th>Prevalence per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faeroes</td>
<td>1986</td>
<td>Joensen</td>
<td>42</td>
<td>7.6</td>
</tr>
<tr>
<td>Finland</td>
<td>1989</td>
<td>Kerfinsen et al.</td>
<td>24</td>
<td>6.3</td>
</tr>
<tr>
<td>France</td>
<td>1990</td>
<td>Loiseau J et al.</td>
<td>71.3</td>
<td>-</td>
</tr>
<tr>
<td>Iceland</td>
<td>1966</td>
<td>Gudmundsson</td>
<td>26</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>Olafsson et al.</td>
<td>47</td>
<td>36*</td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>Olafsson et al.</td>
<td>-</td>
<td>4.8</td>
</tr>
<tr>
<td>Italy</td>
<td>1983</td>
<td>Granieri et al.</td>
<td>33</td>
<td>6.2</td>
</tr>
<tr>
<td>Norway</td>
<td>1974</td>
<td>de Graaf</td>
<td>33</td>
<td>3.5</td>
</tr>
<tr>
<td>Sweden</td>
<td>1990-92</td>
<td>Forsgren</td>
<td>34</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>Forsgren et al.</td>
<td>56</td>
<td>46*</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1997</td>
<td>Jallon et al.</td>
<td>69.4</td>
<td>-</td>
</tr>
<tr>
<td>UK</td>
<td>1960</td>
<td>Crombie et al.</td>
<td>63</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>1983</td>
<td>Goodridge and Shorvon</td>
<td>52</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>Cockerell et al.</td>
<td>48</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>Wallace et al.</td>
<td>80.8</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>MacDonald et al.</td>
<td>46</td>
<td>4**</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>Wright et al.</td>
<td>-</td>
<td>7.3</td>
</tr>
<tr>
<td>US</td>
<td>1975</td>
<td>Hauser et al.</td>
<td>54</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>1986</td>
<td>Haerer et al.</td>
<td>-</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>1993</td>
<td>Hauser et al.</td>
<td>44</td>
<td>31*</td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>Annegers et al.</td>
<td>35.5 (+ 50.9 IUS)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>Zarrelli et al.</td>
<td>52.3</td>
<td>-</td>
</tr>
<tr>
<td>Brazil</td>
<td>1987</td>
<td>Marino Jr et al. (eds)</td>
<td>-</td>
<td>13*</td>
</tr>
<tr>
<td>Colombia</td>
<td>1978</td>
<td>Gomez et al.</td>
<td>-</td>
<td>19.5*</td>
</tr>
<tr>
<td>Chile</td>
<td>1992</td>
<td>Lavados et al.</td>
<td>113</td>
<td>11.5-17.7</td>
</tr>
<tr>
<td>China</td>
<td>1985</td>
<td>Li et al.</td>
<td>35</td>
<td>4.4</td>
</tr>
<tr>
<td>Ecuador</td>
<td>1992</td>
<td>Placencia et al.</td>
<td>122-190</td>
<td>6.7-8.0</td>
</tr>
<tr>
<td></td>
<td>1984</td>
<td>Placencia et al.</td>
<td>230</td>
<td>9.3</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>1990</td>
<td>Telko-Haimanot et al.</td>
<td>-</td>
<td>5.2</td>
</tr>
<tr>
<td>Guatemala</td>
<td>1996</td>
<td>Mendizabal et al.</td>
<td>-</td>
<td>5.8</td>
</tr>
<tr>
<td>India</td>
<td>1988</td>
<td>Bharucha et al.</td>
<td>-</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>1988</td>
<td>Kou et al.</td>
<td>-</td>
<td>3.6</td>
</tr>
<tr>
<td>Libya</td>
<td>1986</td>
<td>Sridharan et al.</td>
<td>-</td>
<td>2.3</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1987</td>
<td>Onnokun et al.</td>
<td>-</td>
<td>5.3</td>
</tr>
<tr>
<td>Pakistan</td>
<td>1994</td>
<td>Aziz et al.</td>
<td>-</td>
<td>7.4-14.8</td>
</tr>
<tr>
<td>Tanzania</td>
<td>1992</td>
<td>Rwix et al.</td>
<td>73-140</td>
<td>5.1-37.0</td>
</tr>
</tbody>
</table>

* lifetime prevalence (cumulative incidence) **active epilepsy
population at risk of illness, and also a "survivor effect" whereby increasing levels of non-fatal, chronic illnesses, such as epilepsy, accrue. In addition, the elderly are more susceptible to cerebrovascular disease, the commonest identifiable aetiological factor in this age group (see section 1.4.2) (Schold et al., 1977; Luhdorf et al., 1986; Sung and Chu, 1990; Kilpatrick et al., 1991; Hauser et al., 1993; Sander and Shorvon, 1996; Thomas et al., 1997).

The incidence of provoked epileptic seizures has been reported to be between 20 and 40 per 100,000 population/year (Loiseau et al., 1990a; Annegers et al., 1995; Forsgren et al., 1996; Jallon et al., 1997), with slightly higher rates occurring in males (Hauser and Annegers, 1997). Provoked seizures are said to comprise approximately 40% of all incident epileptic seizures (Hauser and Annegers, 1997). Age-specific incidence rates also have a bimodal distribution, with the highest rates being observed in the first year of life and, to a lesser extent, in the elderly (Annegers et al., 1995).

1.3.3 Prevalence

Cross-sectional prevalence data are easier to obtain than incidence data, and consequently there is a wealth of literature pertaining to prevalence studies. Point prevalence rates (Table 4) have varied widely, between approximately 2 and 60 per 1000 people (Sridharan et al., 1986; Gracia et al. 1990), although in most populations, both developed and developing, the range has been from 3 to 10 per 1000 (Crombie et al.; 1960; Brewis et al., 1966; Gudmundsson, 1966; Zielinski, 1974; Hauser and Kurland, 1975; Cavazzuti, 1980; Goodridge and Shorvon, 1983a; Granieri et al., 1983; Li et al., 1985; Haerer et al., 1986; Joensen, 1986; Osuntokun et al., 1987; Bharucha et al., 1988; Koul, 1988; Keranen et al., 1989; Tekle-Haimanot et al., 1990; Rwiza et al., 1992; Placencia et al., 1992b; Aziz et al., 1994; Cockerell, 1995b; Mendizabal and Salguero, 1996; Wallace et al., 1998; Olafsson and Hauser, 1999; Sridharan and Murthy, 1999; MacDonald et al., 2000a; Wright et al., 2000). Once again, much of the observed variation in prevalence has resulted from inconsistency in methods of case ascertainment and definition.

A number of studies from developing countries in Africa and south America have reported the highest prevalence rates, up to 57 per 1000 people (Jilek-Aall, 1965; Gomez, 1978; Jilek-Aall et al., 1979; Osuntokun et al., 1982; Goudsmit et al., 1983; Marino Jr et al., 1997).
1987; Gracia et al., 1990; Fernandez et al., 1992; Lavados et al., 1992), but these studies have mostly been of very small, highly selected and isolated populations which may have had high rates of inherited or rare degenerative diseases or endemic CNS parasitic infestation (Sander and Shorvon, 1996). In two studies from developing countries, of populations comprising mixed urban and rural areas, the prevalence was nearly twice as high in the rural areas as it was in the urban areas (Aziz et al., 1984, Placencia et al., 1992b). Given that case ascertainment methods were identical in the two different areas, it is likely that these geographical variations are underpinned by differences in rates of parasitic infestation or some other, as yet unidentified, socioeconomic factor.

As with incidence studies, the age-specific prevalence of epilepsy is now generally recognised as being greatest in the elderly (Hauser et al., 1991; de la Court et al., 1996; Wallace et al., 1998; Olafsson and Hauser, 1999; Wright et al., 2000). Few studies have specified prevalence rates according to the activity of epilepsy (Goodridge and Shorvon, 1983a; Haerer et al., 1986; Wright et al., 2000). In a study of 6000 patients from a single general practice in southeastern England (Goodridge and Shorvon, 1983a), the prevalence was 5.3/1000 for active epilepsy (defined as a seizure within the previous 2 years) and 10.5/1000 for those with either active epilepsy or an active repeat AED prescription. The lifetime prevalence of all (single as well as recurrent) non-febrile seizures was 17.0/1000.

1.3.4 Cumulative incidence (lifetime prevalence)

The reported cumulative incidence rates of epilepsy are generally much higher than either incidence or point prevalence rates. Several studies have indicated that between 1.5% and 5% of any population will experience non-febrile seizures at some time during their lifetime (Crombie et al., 1960; Gudmundsson, 1966; Hauser and Kurland, 1975; Goodridge and Shorvon, 1983a; Juul Jensen and Foldspang, 1983; Placencia et al., 1992b; Hauser et al., 1993; Sander, 1993; Cockerell et al., 1995b; Forsgren et al., 1996; Olafsson et al., 1996). This finding seems to apply to patients in both the developed and the developing world, even though the incidence rate is higher and the availability of treatment lower in the latter (Sander and Shorvon, 1996). The increased mortality rate associated with epilepsy (Hauser and Hesdorffer, 1990; Kloner et al., 1993; Cockerell et al., 1994), including the small risk of sudden unexpected death (Nashef et al., 1995; Langan et al., 2000; Langan et al., 2002), however, is unlikely to account for a significant proportion of
the difference between lifetime and point prevalence rates (which is more likely to be explained by remission), although the precise effect of mortality has not yet been fully evaluated.

1.3.5 Prognosis

Prognosis can be defined as the chance of recovering from a condition. In the case of epilepsy this denotes the chance of a patient achieving longstanding (for example, 5 years) "terminal" remission following a previously established pattern of recurrent epileptic seizures (Sander, 1993).

Until relatively recently (Sander, 1993), the likelihood of a patient with epilepsy entering remission was considered by many to be very poor (Rodin, 1968), upholding the proclamation by Gowers in 1881 that “the spontaneous cessation of the disease is an event too rare to be reasonably anticipated in any given case” (Gowers, 1881). This misconception also resulted from the fact that such studies were hospital based and thus biased towards a chronic epilepsy population (Shorvon, 1984). Later, epidemiological studies revealed ratios of lifetime prevalence (1.5-5%) to point prevalence of active epilepsy (approximately 0.5%) to be between 3:1 and 10:1 (Crombie et al., 1960; Gudmundsson, 1966; Hauser and Kurland, 1975), suggesting that the majority of patients developing seizures have an excellent prognosis for eventual seizure control. The retrospective community based Rochester Project found that 76% of patients achieved long-term remission (Hauser and Kurland, 1975), and many prospective studies of newly diagnosed epilepsy have confirmed this predominantly good prognosis (Annegers et al., 1979; Shorvon and Reynolds, 1982; Elwes et al., 1984; Shorvon, 1984; Cockerell et al., 1995a). Although the probability of experiencing seizure recurrence following a first episode is high, in the order of 80% (Goodridge and Shorvon, 1983b; Hart et al., 1990; Ramos Lizana et al., 2000), the total number of subsequent seizures suffered by patients is usually small, and the period of active epilepsy short (Goodridge and Shorvon, 1983b). Remission, when it occurs, is usually permanent and the proportion of patients in remission increases with time (Goodridge and Shorvon, 1983b; Shorvon, 1984). It is now generally accepted that as many as 70-80% of patients developing seizures for the first time will enter terminal remission, whilst the remaining 20-30% will experience intractable seizures despite all treatment (Reynolds et al., 1983; Sander, 1993). In most cases, the pattern of
epilepsy becomes established relatively early in its course and it has been suggested that long term prognosis might be predicatable in the early stages following diagnosis (Shorvon, 1984; Kwan and Brodie, 2000). The precise role of AED treatment in this good outcome remains a matter of debate since the natural history of untreated epilepsy is largely unknown (Sander, 1993). Some have suggested that early AED treatment might theoretically prevent the development of chronicity (Reynolds, 1994), but this was partly refuted by a study of AED treatment in hitherto drug-naive patients with intractable epilepsy (Feksi et al., 1991) which suggested that AED efficacy was not influenced by the duration of epilepsy.

Various factors are known to have an adverse effect on prognosis, including partial onset seizure types, symptomatic epilepsy syndromes (with clinical or neuroimaging evidence of cerebral disease), increased number and frequency of seizures prior to commencing AED treatment (MacDonald et al., 2000b), intellectual disability and neurological deficit (Hart et al., 1990; Sander, 1993; Reynolds, 1994; Shinnar et al., 2000), but the precise mechanisms determining intractability are yet to be fully elucidated (Reynolds, 1994). One possible mechanism involves the inheritance of genetic polymorphisms which confer resistance to multiple AEDs (Siddiqui et al., 2003). In vivo equivalents of the experimental phenomenon of kindling (the progressive intensification of local or regional excitability that ultimately leads to the establishment of a permanent epileptic focus and seizure disorder) and the process of secondary epileptogenesis (the development of an independent "mirror" seizure focus, contralateral to the primary focus) have also been postulated (Goddard et al., 1969; Goldensohn, 1984; Moshe and Ludwig, 1988), but these processes have yet to be proven to be directly applicable to epilepsy in humans (Moshe and Ludwig, 1988; Reynolds, 1989; Shinnar and Berg, 1996). The influence of specific aetiological factors and structural brain abnormalities on prognosis and intractability is relatively unknown, but MRI studies are ideal for such an investigation. A hospital based MRI study, which included hippocampal quantitation, of 63 adult patients with newly diagnosed partial seizures found that the 6 (10%) patients with hippocampal sclerosis (HS) had a worse early prognosis (higher number of seizures prior to first MRI and during subsequent follow up) than those with either normal MRI (76%) or other MRI abnormalities (14%) (van Paesschen et al., 1997a). Despite the small number of patients with HS, there was some evidence that the extent of hippocampal damage was related to seizure frequency,
secondary generalisation of seizures and resistance to AED treatment. A much larger French study, using a standardised MRI protocol, examined the relationship between prognosis, epilepsy syndrome, and aetiology in 2200 consecutive adult epilepsy clinic outpatients, of whom 1369 had localisation related epilepsy (66% with temporal lobe epilepsy, TLE) (Semah et al., 1998). Seizure control was best in those with IGE, but most refractory in patients with TLE, particularly those with MRI evidence of either HS or dual pathology (HS associated with a separate neocortical lesion; see section 1.5.6) who had the worst prognosis of all. Amongst patients with localisation related epilepsy, it was concluded that structural brain abnormalities (especially HS or dual pathology), rather than the location of the epileptogenic zone, are a major prognostic factor for epilepsy. Smaller studies, however, indicate that some subjects with HS may still have benign TLE with either seizure remission or good seizure control (Kobayashi et al., 2001). Such data are of vital importance because they suggest that early MRI can provide prognostic information which facilitates optimal patient management at the time of diagnosis, such as the decision to commence an AED, or the consideration of early epilepsy surgery, should AED treatment fail (Engel Jr, 1998 and 1999; Wiebe et al., 2001). Clearly, randomised placebo-controlled AED studies employing MRI would be required to address some of these issues adequately. There is also an obvious need for prospective, population based MRI studies of patients with newly diagnosed epilepsy to provide a more representative picture of prognosis than is possible with hospital based studies (Engel Jr, 1998). These should be of sufficient size to ensure that the whole spectrum of common aetiologies are adequately represented (Sander and Shorvon, 1996).

1.4 Aetiology
The following section describes the range of recognised causes of epilepsy in developed countries, and reviews the epidemiological literature reporting the frequencies of these aetiologies in population and hospital based studies of epilepsy. A full discussion of the aetiologies of epilepsy in the developing world, which are fascinating and quite different from those of developed countries, is beyond the scope of this thesis.

It should be emphasised that the aetiology of epilepsy is sometimes multifactorial, and therefore difficult to assign accurately in some cases. The “multifactorial issue” may in fact be more important than is currently recognised. For example, it may ultimately be revealed
that the presence of certain epilepsy susceptibility genes determines which patients with focal brain damage due to CNS trauma or infection will develop epilepsy, and it has already been suggested that there are genes determining epilepsy intractability (Johnson and Sander, 2001; Siddiqui et al., 2003). A further issue (discussed in section 1.5.6) is that some patients have two or more structural brain pathologies that are likely to be of aetiological relevance (termed dual pathology when one of the pathological abnormalities is HS).

1.4.1 Range of aetiologies of epilepsy in developed countries

HIPPOCAMPAL SCLEROSIS

The association between HS and the aetiology of epilepsy is discussed in detail in section 1.5.

CEREBRAL TUMOURS

Cerebral tumours are responsible for up to 5% of all epilepsy and 10% of late onset epilepsy (Duncan et al., 1995a; Maudgil and Shorvon, 1999). The peak incidence is in middle age. Tumours of the cerebral cortex, especially those of fronto-parietal or temporal lobes, are most likely to cause seizures. Overall, seizures occur as a presenting symptom in 25-50% of patients with cerebral tumours. Tumour histology and rate of growth also affect the likelihood of seizures, with oligodendrogliomas (90%), low grade gliomas (60-90%), anaplastic astrocytomas (70%) and meningiomas (30-60%) being the most, and malignant gliomas (30-35%) the least, epileptogenic. Although metastatic brain tumours have a similar incidence to primary cerebral tumours, seizures are a less common presenting symptom (10-15%), or eventual symptom (25-30%), in the former (Maudgil and Shorvon, 1999).

CEREBROVASCULAR DISEASE

Cerebrovascular disease is an important cause of epilepsy (Roberts R et al., 1988), particularly amongst the elderly (Roberts M et al., 1982; Sander et al., 1990; Everitt and Sander, 1998; Stephen and Brodie, 2000). In three prospective population based studies of acute stroke (So et al., 1996; Burn et al., 1997; Bladin et al., 2000), the risk of early seizures was 2-6% (the majority of which develop in the first 24 hours), the risk of initial late seizures was 5-8%, and of recurrent late seizures was 2.5 to 4%. In comparison to the
general population, the relative risk of late epilepsy was 17 to 35 times higher following stroke. The risk of seizures was highest in survivors of intracerebral haemorrhage, and following severe strokes due to total anterior circulation infarction (So et al., 1996; Burn et al., 1997; Bladin et al., 2000). More than half of all patients with early seizures went on to develop chronic epilepsy (Duncan et al., 1995b; Burn et al., 1997). Epilepsy also develops in 25% of patients surviving aneurysmal subarachnoid haemorrhage, and is more common in those who experienced acute symptomatic seizures or severe neurological deficit (Olafsson, 2000).

Additionally, epilepsy may be the initial or sole manifestation of cerebrovascular disease. In a case-control study of 132 patients with late onset epilepsy, CT evidence of vascular disease was found in 14.5% of patients and in only 1.5% of control subjects (Roberts et al., 1988). In two thirds of patients, only lacunar infarcts were present, and the frequency of atrophy did not differ between the two groups. A small prospective study of 18 patients with seizures and subcortical vascular encephalopathy (as determined by MRI) revealed significantly more subcortical lacunar infarctions than in carefully matched control subjects with an equal severity of subcortical vascular encephalopathy, but no seizures (Schreiner et al., 1995). Conversely, there was no statistical difference between groups in either the extent or distribution of periventricular white matter changes, or the presence of cortical atrophy. Vascular risk factors such as hypercholesterolaemia, hypertension and left ventricular hypertrophy have been shown to be associated with a significantly higher risk of lifetime and late onset epilepsy, even when stroke patients were excluded (Li et al., 1997). Shinton et al. (1987) found a history of previous late onset seizures in 4.5% of cases presenting to a hospital with a first ever stroke, suggesting that early cerebrovascular disease may cause epilepsy in the absence of other neurological dysfunction. Silent lacunar infarcts have also been correlated with more subtle neurological dysfunction in elderly subjects (Longstreth et al., 1998). On the basis of such data, it has been estimated that overt or occult cerebrovascular disease may be responsible for 10-20% of all adult onset, and 50% of late onset, epilepsy (Duncan et al., 1995b). A prospective, population based MRI study could confirm or refute this.

CRANIAL TRAUMA
In population based studies, epilepsy has been attributed to head injury in between 2-4%
of cases (Sander et al., 1990; Annegers et al., 1996). Acute symptomatic (early) seizures occur in the first week after injury in 2-5% admitted to hospital with civilian head injury (Jennett, 1975a; Annegers et al., 1980). In the community based Rochester project, head injuries were categorised as either mild, moderate or severe. Mild injuries were associated with amnesia or loss of consciousness for less than 30 minutes, and no skull fracture. Moderate injuries were those with loss of consciousness or amnesia lasting 30 minutes to 24 hours, and/or skull fracture. Severe injuries involved intracranial haematoma, cerebral contusion, or post-traumatic amnesia/loss of consciousness for more than 24 hours (Annegers et al., 1980). Following mild injury the risk of late seizures was 0.1% and 0.6% at 1 and 5 years, respectively. After moderate injury, late seizures occurred in 0.7% at 1 year, and 1.6% at 5 years. After severe injury, early seizures occurred in 10% in adults and as many as 30% of children, whilst late seizures occurred in 7% and 11% at 1 and 5 years, respectively. A subsequent analysis estimated the standardised incidence ratios for epilepsy after mild, moderate and severe head injuries as 1.5, 2.9 and 17.0, respectively (Annegers et al., 1998).

In series of hospital based studies by Jennett and colleagues (Jennett et al., 1974; Jennett, 1975b, 1979 and 1982), non-penetrating (closed) head injuries led to late epilepsy in 17% of patients with a depressed skull fracture (60% risk if dural tears, focal deficit, early seizures, or prolonged amnesia; 5% risk if none of these features), in 35% with an intracranial haematoma necessitating surgical intervention, and in 25% with early seizures. In the absence of these features, the risk of late epilepsy was less than 2%, even when post-traumatic amnesia exceeded 24 hours. However, if early seizures occurred in the absence of a haematoma or depressed fracture, the risk of late epilepsy was 19%.

Penetrating (open) head injury is associated with a much greater risk (approximately 50%) of developing late epilepsy in the 3 years after injury (Caveness et al., 1979; Salazar et al., 1985). If a patient remains seizure-free beyond this period, the risk is less than 5% (Caveness et al., 1979). The risk is highest when brain damage is extensive, especially if frontal, central and temporal regions are involved, or if there has been secondary infection (Martins da Silva, 1999; Wilmore, 1992).

The relationship between cranial trauma, epilepsy and HS (Swartz et al., 1999; Diaz-
Arrastia et al., 2000) is considered further in section 1.5.5.

The risk of epilepsy following neurosurgery is lower than after penetrating head injury, and depends on the nature and location of surgery, the underlying condition, and the presence or absence of focal brain damage (Duncan et al., 1995b). New epilepsy develops in 22% and 21% following meningioma removal and haematoma evacuation, respectively (Foy et al., 1981), and in 4-25% after craniotomy for ruptured intracerebral aneurysms with the highest risk related to anterior and middle cerebral aneurysms associated with fixed neurological deficit (Jennett et al., 1990). As a rule, the risk of epilepsy is greatly enhanced if seizures occurred pre-operatively.

No data have yet proved the efficacy of AEDs in the prevention of post-traumatic and post-neurosurgical epilepsy (Willmore, 1992; Martins da Silva, 1999).

PRE-NATAL AND PERI-NATAL INJURY

When epilepsy is congenital, learning disability is a relatively frequent association (Duncan et al., 1995b). Conversely, up to 20% of children with learning disability have epilepsy (Airaksinen et al., 2000). It is likely that, in the past, many congenital cases of epilepsy were wrongly attributed to peri-natal disorders because it is now evident that minor peri-natal disturbances rarely lead to epilepsy (Nelson and Ellenberg, 1986). Advances in neuroimaging have allowed dysgenetic lesions to be identified in a proportion of such subjects (see below), whilst additional, some as yet unidentified, factors including genetic defects and exogenous insults (drugs, infections, toxins) are responsible in other cases (Wallace, 1992). In one study, cranial CT revealed cerebral infarction in 14% of 50 cases of neonatal epilepsy, often with an unremarkable obstetric history and with no neurological signs other than lethargy or hypotonia (Levy et al., 1985), suggesting the usefulness of neuroimaging in such cases.

Sturge-Weber syndrome is a rare congenital neurocutaneous condition of unknown aetiology associated with, usually unilateral, leptomeningeal angiomatosis (Kotagal and Rothner, 1993). Partial and/or secondarily generalised seizures affect 70-90% of cases, and usually begin before the age of 2 years (Kotagal and Rothner, 1993). Progressive hemispheric damage follows leading to hemiparesis (30%), hemisensory loss, hemianopia,
and mental retardation (50-60%) (Kotagal and Rothner, 1993). It has been postulated that this deterioration is due to seizure-related hypoxia.

In a population-based study of active epilepsy amongst 299 subjects with mental retardation, factors implicated in the aetiology of both were: pre-natal, 35%, peri-natal, 9.5%, post-natal, 8.8%, multiple, 14.9%, and unknown, 31.5% (Forsgren et al., 1990). CT, however, was only applied in one third of cases and none had MRI.

**IMMUNISATION AND CNS INFECTION**

The risk of epilepsy following childhood immunisation is extremely low. One study found that pertussis vaccination resulted in severe brain damage in one in 310,000 immunisations, but this study has since been criticised methodologically and the figure is likely to be an over-estimate (Bowie, 1990; Gale et al., 1994). The risk of epilepsy due to post-infective encephalopathy of childhood is probably much greater.

CNS infections are a potent cause of epilepsy. Bacterial cerebral abscess may be followed by epilepsy in almost three quarters of survivors (Legg et al., 1973), especially when the infection involves the frontal or temporal lobes. Bacterial meningitis carries a 10% risk of subsequent epilepsy if seizures occur acutely, and a 3% risk if there are no acute seizures (Duncan et al., 1995b). Viral encephalitis, especially when due to herpes simplex virus, leads to chronic epilepsy in one quarter of survivors who had acute seizures, and in 10% who did not (Meyer et al., 1970; Illis and Gostling, 1972; Annegers et al., 1988). Both meningitis and encephalitis have been associated with the development of HS, as highlighted in section 1.5.5.

Human immunodeficiency virus encephalopathy, in addition to opportunistic CNS infections secondary to immunosuppression, may also cause seizures.

**MALFORMATION OF CORTICAL DEVELOPMENT**

Focal dysplasia of the cerebral cortex was originally reported in 1971 as a rare pathological finding in epilepsy surgical specimens (Taylor et al., 1971). With the advent of MRI, MCD are being increasingly recognised as an important cause of epilepsy (Raymond et al., 1995; Kuzniecky, 1998). Seizures may be the only overt clinical sign in subtle cases including
subependymal heterotopias, whilst more severe MCD such as pachgyria, lissencephaly, schizencephaly, diffuse heterotopias, polymicrogyria, macrogyria and agenesis of the corpus callosum may be associated with learning or physical disability (Palmini et al., 1991; Raymond et al., 1995). Dysembryoplastic neuroepithelial tumours (DNET) are also best considered as a type of MCD (Raymond et al., 1995), since they are essentially developmental lesions with some neoplastic features.

There is evidence to suggest that many MCD lesions have intrinsic epileptogenicity (Palmini et al., 1995; Kothare et al., 1998; Sisodiya et al., 1999), yet the results of epilepsy surgery for MCD (with the exception of DNET) are generally disappointing compared to surgery for HS (Wieser et al., 1993; Raymond et al., 1995; Sisodiya, 2000). One possibility is that the extent of dysgenesis is greater than that visualised by MRI (Palmini et al., 1991; Sisodiya, 2000), such that surgical resections are invariably incomplete. Sisodiya et al. (1995) have used quantitative MRI in patients with apparently focal MCD and epilepsy to demonstrate extra-lesional abnormalities in the regional distribution of grey and subcortical white matter volumes. It was suggested that these changes were indicative of widespread abnormalities of connectivity between the lesion and other brain areas, and may partly explain the relative failure of epilepsy surgery.

The mildest form of abnormal neuronal migration, termed microdysgenesis, consists of a largely quantitative alteration of neuronal disposition in cortical and subcortical regions. Meencke and Janz (1984) reported such findings at autopsy in a small number of patients with IGE, and in 38% of 591 with epilepsy compared to 6% of 7374 control subjects (Meencke, 1994). Although controversy exists as to the clinical significance of microdysgenesis (Lyon and Gastaut, 1985; Meencke and Janz, 1985), some corroborative support for their relevance to epilepsy came from a recent quantitative MRI study which found evidence for widespread structural changes in approximately 40% of subjects with IGE and visually normal MRI (Woermann et al., 1998).

A more comprehensive discussion of MCD and epilepsy is, unfortunately, also beyond the scope of this thesis, and several excellent reviews of the subject have recently been published (Kuzniecky and Barkovich, 2001; Porter et al., 2002)
CAVERNOUS HAEMANGIOMAS AND ARTERIOVENOUS MALFORMATIONS

Cavernous haemangiomas (cavernomas) are benign, vascular lesions of unknown aetiology that can occur at any site within the CNS (Moran et al., 1999). They consist of ectatic, endothelium-lined channels whose walls lack muscular and elastic fibres, and may only be demonstrated with MRI. As many as a quarter of all cases are multiple, in which case a genetic cause is likely. Epileptic seizures are the most frequent clinical manifestation of supratentorial cavernomas, occurring in nearly 80% of cases reported in the literature (Moran et al., 1999). Although cavernomas contain no neuronal elements, their epileptogenicity probably derives from gliosis and haemosiderin deposition in surrounding neural parenchyma.

Large arteriovenous malformations cause epilepsy in 40% of cases (Paterson and McKissock, 1956; Kelly et al., 1969), and this was the presenting symptom in 19% of patients in one hospital based series (Crawford et al., 1986). The incidence of these two pathologies in the community is currently unknown as no population based studies have been performed.

GENETIC CAUSES

The idiopathic partial and generalised epilepsy syndromes are, by definition, thought to be genetically determined. Genetic linkage studies have identified a number of loci that appear to be implicated in susceptibility to many of these syndromes, but the actual genes and their role in regulating neuronal excitability have not yet been identified (Berkovic and Scheffer, 1997; Leppert and Singh, 1999; Johnson and Sander, 2001). Exceptions to this include the syndromes of benign familial neonatal convulsions, autosomal dominant nocturnal frontal lobe epilepsy (Scheffer et al., 1995), and generalised epilepsy with febrile seizures plus (Scheffer and Berkovic, 1997), in which both the genes and putative pathogeneses have been described (Leppert and Singh, 1999). Genetic loci and gene products have also been mapped for a number of the diseases causing symptomatic progressive myoclonic epilepsy.

Several simple Mendelian-inherited conditions are also associated with epilepsy. The frequency of epilepsy is between 60-80% in tuberous sclerosis, and 5-10% in neurofibromatosis type 1 (Kotagal and Rothner, 1993). In the former, dysgenetic lesions
including subependymal nodules and cortical tubers, and giant cell astrocytomas, appear to be responsible for seizures (Kotagal and Rothner, 1993; Raymond et al. 1995), whilst in the latter the pathogenesis is less clear.

Genetic susceptibility may also contribute in cases of symptomatic epilepsy (Ottman et al., 1996). One study found a three-fold increase in the risk of epilepsy after mild head injury in subjects with first degree relatives with epilepsy (Majkowski, 1990), although this has not been found in other studies (Jennett, 1975a; Salazar et al., 1985; Ottman et al., 1996). In a study of moderate and severe head injury amongst Korean war soldiers, epilepsy developed in 60% with a positive family history of seizures, and in 30% without (Caveness et al., 1979).

PRIMARY CNS DEGENERATIVE DISEASES
Epilepsy develops in up to one third of cases of Alzheimer’s disease, usually late in the course of the illness. Seizures are often mild, infrequent and easily controlled (Radermecker, 1974). In patients with Down syndrome (trisomy 21), the prevalence of epilepsy increases markedly with age (Johannsen et al., 1996), probably because of coexistent early onset Alzheimer’s disease associated with the amyloid precursor protein gene on chromosome 21 (Murrell et al., 1991). Seizures also occur in approximately 5% of patients with Huntingdon’s disease (Duncan et al., 1995b), and in 10-20% with sporadic Creutzfeldt-Jakob disease (Will and Matthews, 1984; Johnson and Gibbs, 1998).

ALCOHOL AND DRUG MISUSE
Seizures, most often generalised tonic-clonic, may occur acutely in the context of alcohol withdrawal or intoxication (Victor and Brausch, 1967; Edelsberg et al., 1989; Brathen et al., 2000), and are found in approximately 10% of longstanding alcohol abusers (Devetag et al., 1983). Repetitive cranial trauma, subdural haemorrhage, metabolic disturbances, organ failure, and vitamin and nutritional deficiencies may also contribute to causation of seizures. In chronic alcoholics it is also well recognised that seizures occur which are unrelated to withdrawal or any other identifiable cause, and this has been termed alcoholic epilepsy (Devetag et al., 1983; Bartolomei et al., 1997). The effect appears to be dose-dependent (Edelsberg et al., 1989). It has been postulated that chronic alcohol abuse leads to progressive changes in brain function with a lowering of the seizure threshold and an
increase in neuronal excitability, sometimes referred to as alcoholic kindling (Bartolomei et al., 1997). Furthermore, alcohol misuse may exacerbate established epilepsy and has been implicated in 40% of hospital admissions for seizures (Earnest and Yarnell, 1976).

Drug-induced seizures are probably more common than generally appreciated (Duncan et al., 1995b). Recreational drug use, especially involving cocaine, ecstasy, opiates and amphetamine, is an under-reported cause of seizures in young people. Seizures may also be induced by prescribed drugs including anti-depressants, anti-psychotics, anaesthetic agents, sympathomimetics, and certain antibiotics. Withdrawal from benzodiazepines, barbiturates, AEDs, and other psychotropic drugs may also precipitate seizures, particularly in those already predisposed to epilepsy (Duncan, 1988).

For obvious reasons, the frequency of alcohol or drug provoked seizures will differ substantially between defined populations. Another important issue is that the proportion who harbour underlying cerebral structural abnormalities has not yet been ascertained.

INFLAMMATORY CNS DISEASE
Rasmussen's encephalitis is a rare, unilateral focal cortical inflammatory CNS disorder characterised by seizures and progressive hemiparesis (Antel and Rasmussen, 1996). The syndrome typically has its onset in childhood or adolescence, and may have an autoimmune basis since antibodies to the glutamate receptor 3 subunit have been identified in the CSF and serum of some patients (Twyman et al., 1995). It has been hypothesised that these antibodies gain access to the CNS following an initial insult which disrupts the blood-brain barrier, such as trauma or infection, and mediates excitotoxic damage to neurones expressing the target receptor (Twyman et al., 1995), but the pathogenesis ultimately remains a matter of controversy.

Epilepsy also occurs in approximately 3.5% of patients with multiple sclerosis (Kinnunen and Wikstrom, 1986; Ghezzi et al., 1990). Although generally considered to be a disease of white matter, lesions implicated in the causation of seizures are often acute and involve cortical or subcortical areas (Brownell and Hughes, 1962; Thompson et al., 1993). Similarly, epilepsy may also be a sequelae of post-infectious acute disseminated encephalomyelitis. Seizures are a relatively infrequent occurrence in neurosarcoidosis
(Stern et al., 1985), but a common manifestation of cerebral lupus erythematous (Wong et al., 1991).

OTHER NEUROLOGICAL DISORDERS
Virtually any condition affecting the cerebral cortex may result in seizures. In addition to those already mentioned, hydrocephalus, Wilson’s disease, neuroacanthocytosis, dentato-rubro-pallido-luysian atrophy and the many diseases causing progressive myoclonic encephalopathy may also cause epilepsy.

1.4.2 Population and hospital based studies of epilepsy in developed countries reporting aetiology: a review of the literature

METHODOLOGICAL ISSUES
When interpreting studies which address the aetiology of epilepsy, the methodological considerations relevant to epilepsy epidemiology in general (see section 1.3.1) also apply. It is especially important to regard the method(s) of case ascertainment, classification criteria, the interpretation of the relevance of certain risk factors (e.g. the definition of “head trauma”, “birth injury” or “vascular disease”), the proportion of patients investigated, and the extent of investigation.

Studies which have assessed aetiology can be broadly segregated into those which are population based and those which are hospital based. In the former, a more representative picture of epilepsy at the population level emerges, but this may be offset by difficulties in accurately classifying seizures and epileptic syndromes, and the low uptake of advanced investigative procedures. In hospital based studies, however, high levels of patient investigation with EEG and modern neuroimaging are counteracted by selection bias, since the very source of case ascertainment (often tertiary referral neurology or epilepsy centres) dictates that those patients investigated are the most severely affected.

Many studies have restricted the assignment of putative aetiology to those patients with partial onset seizures (Joshi et al., 1977; Danesi, 1985; Li et al., 1985), with the effect that the proportion with cryptogenic seizures was artificially lowered. In some studies employing the ICEES, the aetiologies of generalised and unclassified epilepsies were completely unreported (Joshi et al., 1977; Danesi, 1985; Loiseau et al., 1990a). Only a few
papers have addressed the issue of age-specific aetiology (Forsgren, 1990; Hauser et al., 1993), and none have compared the aetiologies of both newly diagnosed and chronic epilepsy within the same population.

POPULATION BASED STUDIES

Table 5 shows the frequencies of the major causes of epilepsy in published epidemiological studies which have reported aetiological data. Some such studies (Hauser and Kurland, 1975; Goodridge and Shorvon, 1983a; Hauser et al., 1981; Forsgren et al., 1996; Zarelli et al., 1999) have been excluded from analysis because at least some of the cohort had been reported on elsewhere by the same investigators (e.g. the same newly diagnosed patients appearing in separate incidence and prevalence studies). Before reviewing these data, it is worth remarking that, in practical terms, precise aetiological categorisation is occasionally difficult and therefore somewhat artificial. For example, cases of epilepsy associated with vascular dementia could be classified as due to either "vascular" or "degenerative CNS" disease, and those secondary to pre-natal infarcts as either "congenital" or "vascular". Such decisions may be resolved by simply choosing "the best fit" out of the competing categories, or by classifying into a "mixed" or "other" category, though this is unsatisfactory in terms of diagnostic accuracy. There are no defined criteria to aid aetiological classification. For example, it is unclear as to whether the presence of hypertension in a patient with epilepsy and no other risk factors provides sufficient grounds to state that epilepsy was due to cerebrovascular disease.

If one considers those studies which have solely examined patients with unprovoked (isolated and/or recurrent) epileptic seizures (Granieri et al., 1983; Haerer et al., 1986; Forsgren, 1990; Sander et al., 1990; Forsgren, 1992; Hauser et al., 1993; Cockerell et al., 1995b; Olafsson et al., 1996; Jallon et al., 1997; Kurtz et al., 1998; Olafsson and Hauser, 1999; Wright et al., 2000), the proportions of cases with a definable aetiology (approximately one third) and without discernible cause (approximately two thirds) are remarkably consistent. In virtually all of these studies, the major cause of epilepsy (all age groups combined) was cerebrovascular disease (Forsgren, 1990; Sander et al., 1990; Forsgren, 1992; Hauser et al., 1993; Olafsson et al., 1996; Jallon et al., 1997; Cockerell et al., 1995b; Wright et al., 2000), with a frequency of approximately 5-22%. In several studies, however, the evidence for cerebrovascular disease as the cause of epilepsy was
<table>
<thead>
<tr>
<th>Country</th>
<th>First author</th>
<th>Year</th>
<th>n</th>
<th>Case definition</th>
<th>Birth injury (%)</th>
<th>Head trauma (%)</th>
<th>CNS infection (%)</th>
<th>Degenerative (%)</th>
<th>Congenital (%)</th>
<th>Vascular (%)</th>
<th>Tumour (%)</th>
<th>Alcohol or drug related (%)</th>
<th>Other (%)</th>
<th>Unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Loiseau</td>
<td>1990</td>
<td>327*</td>
<td>ND provoked seizures</td>
<td>-</td>
<td>4.9</td>
<td>5.5</td>
<td>5.2</td>
<td></td>
<td>38.2</td>
<td>-</td>
<td>32.7</td>
<td>13.5</td>
<td>0</td>
</tr>
<tr>
<td>Iceland</td>
<td>Olafsson</td>
<td>1996</td>
<td>42</td>
<td>ND epilepsy</td>
<td>-</td>
<td>-</td>
<td>2.4</td>
<td>2.4</td>
<td>4.8</td>
<td>14.3</td>
<td>7.1</td>
<td>-</td>
<td>-</td>
<td>69.0</td>
</tr>
<tr>
<td></td>
<td>Olafsson</td>
<td>1999</td>
<td>428</td>
<td>Prevalent epilepsy</td>
<td>-</td>
<td>4.4</td>
<td>3.0</td>
<td>4.2</td>
<td>15.0*</td>
<td>8.4</td>
<td>2.8</td>
<td>-</td>
<td>0.2</td>
<td>61.9</td>
</tr>
<tr>
<td>Italy</td>
<td>Granieri</td>
<td>1983</td>
<td>278</td>
<td>Prevalent epilepsy</td>
<td>23.7</td>
<td>6.8</td>
<td>3.7</td>
<td>-</td>
<td>1.1</td>
<td>2.9</td>
<td>1.4</td>
<td>-</td>
<td>-</td>
<td>60.4</td>
</tr>
<tr>
<td>Sweden</td>
<td>Forsgren</td>
<td>1992</td>
<td>685</td>
<td>Prevalent epilepsy</td>
<td>3.8</td>
<td>7.2</td>
<td>3.5</td>
<td>-</td>
<td>4.2</td>
<td>11.8</td>
<td>4.7</td>
<td>-</td>
<td>-</td>
<td>64.8</td>
</tr>
<tr>
<td></td>
<td>Forsgren</td>
<td>1990</td>
<td>107</td>
<td>ND unprovoked seizures</td>
<td>0.9</td>
<td>6.5</td>
<td>0.9</td>
<td>0.9</td>
<td></td>
<td>21.5</td>
<td>11.2</td>
<td>-</td>
<td>6.5</td>
<td>51.4</td>
</tr>
<tr>
<td></td>
<td>Jallon</td>
<td>1997</td>
<td>176</td>
<td>ND unprovoked seizures</td>
<td>5.7</td>
<td>5.1</td>
<td>9.7**</td>
<td>2.3</td>
<td>3.4</td>
<td>16.5</td>
<td>4.5</td>
<td>5.1</td>
<td>2.3</td>
<td>45.5</td>
</tr>
<tr>
<td></td>
<td>Forsgren</td>
<td>1990</td>
<td>34</td>
<td>ND provoked seizures</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>5.9</td>
<td>88.2</td>
<td>5.9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jallon</td>
<td>1997</td>
<td>97</td>
<td>ND provoked seizures</td>
<td>-</td>
<td>4.1</td>
<td>6.2</td>
<td>-</td>
<td></td>
<td>18.6</td>
<td>10.3</td>
<td>50.5</td>
<td>10.3</td>
<td>0</td>
</tr>
<tr>
<td>UK</td>
<td>Sander</td>
<td>1990</td>
<td>564†</td>
<td>Cohort with ND seizures</td>
<td>-</td>
<td>2.5</td>
<td>1.6</td>
<td>-</td>
<td>(2.8)</td>
<td>15.4††</td>
<td>6.0</td>
<td>6.2</td>
<td>6.9</td>
<td>61.3</td>
</tr>
<tr>
<td></td>
<td>Kurtz</td>
<td>1998</td>
<td>124</td>
<td>Young adult cohort with prevalent epilepsy</td>
<td>2.4</td>
<td>8.9</td>
<td>5.6</td>
<td>-</td>
<td>8.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>74.2</td>
</tr>
<tr>
<td>USA</td>
<td>Haerer</td>
<td>1986</td>
<td>246</td>
<td>Prevalent epilepsy</td>
<td>-</td>
<td>10.6</td>
<td>6.9</td>
<td>-</td>
<td>-</td>
<td>6.5</td>
<td>1.6</td>
<td>2.8</td>
<td>8.1</td>
<td>63.4</td>
</tr>
<tr>
<td></td>
<td>Hauser</td>
<td>1993</td>
<td>880</td>
<td>ND epilepsy 1935-1984</td>
<td>-</td>
<td>5.5</td>
<td>2.5</td>
<td>3.5</td>
<td>8.0</td>
<td>10.9</td>
<td>4.1</td>
<td>-</td>
<td>-</td>
<td>65.5</td>
</tr>
<tr>
<td></td>
<td>Annegers</td>
<td>1995</td>
<td>696</td>
<td>ND provoked seizures 1935-1984</td>
<td>-</td>
<td>16</td>
<td>15</td>
<td>-</td>
<td>16</td>
<td>8</td>
<td>20</td>
<td>26†††</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** Ref=reference number  ND=newly diagnosed (incident)  n=number of patients with aetiological classification
* of the original 804 cases, aetiology is only stated in 327 with acute symptomatic seizures
† these 564 patients with definite epilepsy/seizures include 83 with provoked seizures
†† including 2.8% (see adjacent column) with "congenital neurological deficit"
††† including 9% metabolic, 5% encephalopathy and 2% eclampsia

**Includes 10 (5.7%) with HIV infection**
circumstantial. In the absence of a history or neuroimaging evidence of a large vessel stroke, classification of epilepsy due to vascular disease may often be inaccurate. For example, some patients with epilepsy and “cardiac disease, hypertension or atheromatous disease elsewhere in the body” have been classified as having a vascular aetiology (Sander et al., 1990). In addition, where neuroimaging has been performed, interpretation of the significance of small, presumed vascular lesions can be difficult, since small vascular lesions are frequently observed in neurological patients without epilepsy (Roberts et al., 1988; Schreiner et al., 1995) and in neurologically normal control subjects (de Leeuw et al. 2001) (also see section 1.4.1). Large case-controlled MRI studies are required to address this issue.

Frequencies of the other important aetiological categories have varied from study to study. To summarise, epilepsy or isolated unprovoked seizures were caused by: cerebral tumours in 1-11%, birth injury in 1-6%, head trauma in 2-9%, CNS infection in 1-6%, CNS degenerative disease in 0-5%, congenital factors in 1-9% and “other” factors in less than 10%. There have been some notable exceptions. One Swiss study found that nearly 10% of unprovoked seizures were caused by CNS infection (Jallon et al., 1997), of which two thirds were due to human immunodeficiency virus, thus indicating significant selection bias. An Italian study found that nearly one quarter of 238 patients had epilepsy caused by peri-natal injury (birth trauma, hypoxic encephalopathy, kernicterus, neonatal haemorrhagic encephalopathy or prematurity) (Granieri et al., 1983), far in excess of the proportion in other studies (Forsgren, 1990; Forsgren, 1992; Jallon et al., 1997; Kurtz et al., 1998). It is highly probable that this represents an artefact of case ascertainment, because the reported incidence and prevalence figures indicate a significant bias towards paediatric cases and a marked underdetection of late onset cases.

No reported population based study in adults has specifically incorporated modern neuroimaging into the methodological design in order to improve the precision of aetiological classification (Berg et al., 2000). In two adult studies, CT findings were available in 97% and 67% of cases, and standard MRI findings in 42% and 20%, respectively (Forsgren, 1990; Jallon, 1997). There was some suggestion that this resulted in improved aetiological classification, since these two studies have the lowest frequencies of unknown aetiologies (approximately 45-50%) in all the published literature. Yet,
because the neuroimaging employed was of low resolution, and the aetiological categories broad, the frequency of specific, subtle aetiological factors such as HS and MCD remain entirely unknown at the population level.

Standard MRI was performed in 388 (63%) of 613 children with newly diagnosed epilepsy in a recent observational, multicentre community based study from the United States (Berg et al., 2000). A variety of “aetiologically relevant” lesions were found in 12% overall, mainly those with symptomatic localisation related or cryptogenic/symptomatic generalised epilepsies. None had HS, but two (0.5%) had hippocampal atrophy which was not considered aetiologically significant by the authors. It is likely, however, that the MRI used in this study was of insufficient quality to reliably detect HS.

Age-specific aetiology has been addressed in three incidence studies (Forsgren, 1990; Hauser et al., 1993; Forsgren et al., 1996). The proportion with an “unknown cause” (cryptogenic and idiopathic categories combined) declined with the transition from childhood to old age, although aetiology remained obscure in a significant fraction (up to 50%) of elderly patients with newly diagnosed seizures. Broadly speaking, epilepsy due to birth or head injury tended to present in childhood or young adulthood, whereas CNS tumours, head injury and cerebrovascular disease were the most important aetiologies in middle life (Hauser et al., 1993; Forsgren et al., 1996). In studies of epilepsy confined to the elderly (Schold et al., 1977; Ahuja and Mohanta, 1982; Loiseau et al., 1990b; Sander et al., 1990; Sung and Chu, 1990; Kilpatrick et al., 1991; Schreiner and Pohlmann-Eden, 1996; Thomas et al., 1997), cerebrovascular disease was by far the commonest cause, accounting for up to 50% of cases. Less frequent causes of epilepsy in later life included CNS tumours, head injury, and primary CNS degenerative disease. The frequency of cryptogenic epilepsy amongst the elderly was generally lower than for other age groups, but varied from 10-75% (Ahuja and Mohanta, 1982; Loiseau et al., 1990b), according to the extent of investigation.

The frequencies of the common causes of provoked seizures have been much more prone to variation from case ascertainment bias than studies of unprovoked seizures. In most incidence studies, adult provoked seizures were related to alcohol/drug withdrawal or intoxication (20-88%), or related to an acute cerebrovascular event (6-40%) (Forsgren,
1990; Loiseau et al., 1990a; Forsgren et al., 1996; Jallon et al., 1997). The Rochester study, however, which retrospectively analysed 696 cases from 1934 to 1985, found that the frequencies of provoked seizures due to either head trauma, CNS infection, cerebrovascular disease or alcohol/drug misuse were similar at 15-20% each (Annegers et al., 1995). Provoked seizures occurring in the first year of life were more often associated with metabolic, infectious or encephalopathic causes (Hauser and Annegers, 1997).

HOSPITAL BASED STUDIES: THE IMPACT OF MODERN NEUROIMAGING

A few large hospital based studies examining the utility of the ICEES in large epilepsy patient populations have reported aetiological data (Loiseau et al., 1991; Bauer, 1994; OREP, 1996), but the proportion of patients in each study undergoing MRI was small, and the reported data restricted to those with symptomatic localisation related epilepsies (Bauer, 1994; OREP, 1996). Peri-natal injury, head trauma, vascular disease and tumours (in that order) were the most commonly identified causes, but the small size of these studies precludes a more detailed analysis.

The usefulness of CT in the investigation of epilepsy has been evaluated in several studies (Gastaut and Gastaut, 1976; Young et al., 1982; Ramirez-Lassepas et al., 1984; Hay et al., 1995). An investigation using cranial CT in patients presenting to emergency departments with a first generalised tonic-clonic seizure (Hay et al., 1995) found no abnormality in 40-45%, generalised atrophy in 25% (mainly subjects with alcohol- or dementia-related seizures), and focal abnormalities of possible aetiological relevance in 30-35%. The commonest focal lesions were tumours, vascular events, traumatic brain damage and vascular malformations (Hay et al., 1995), with the frequencies of each varying considerably from study to study. Unsurprisingly, such lesions were more likely to be found (in up to 50%) when there was evidence of focal neurological deficit, focal seizures or focal EEG findings, whereas CT was normal in over 90% without such features (Young et al., 1992). The yield of CT in detecting relevant focal lesions in chronic epilepsy is approximately 15-20% for all epilepsies, and 20-40% for localisation related epilepsies (Young et al., 1992).

The advantages of MRI over CT in the investigation of late onset epilepsy have been well documented (Kilpatrick et al., 1991; Thomas, 1997; Stephen and Brodie, 2000), and the
inability of CT to detect subtle lesions, particularly in the temporal lobe (eg. HS, MCD, cavernomas) has been shown (Jabbari et al., 1986; Latack et al., 1986; Avrahami et al., 1987; Franceschi et al., 1989; Duncan R et al., 1990a). Table 6 presents data from hospital based MRI and histopathological studies which have addressed the aetiology of epilepsy in 50 or more patients. The key methodological limitation affecting such studies is selection bias, particularly in those series describing patients undergoing epilepsy surgery or pre-surgical evaluation (Li et al., 1995; Lehericy et al., 1997; McBride et al., 1998). There has also been inconsistency in the definition of dual pathology. An additional problem is that most of these studies referred to MRI findings and not aetiology (Li et al., 1995; Lehericy et al., 1997), with occasional exceptions (Semah et al., 1998). This reflects the difficulty in the interpretation of certain MRI findings, particularly as to whether an abnormality is coincidental to, associated with, or synonymous with, the epileptogenic lesion. Many studies have ignored supposedly "non-aetiologically relevant" findings such as small ischaemic lesions, and cerebral or cerebellar atrophy, such that their frequencies, even in tertiary referral centres, remains unknown. The frequency of HS has varied considerably. The lowest frequencies (1.3% and 9.5%) were observed in two studies of newly diagnosed seizures (van Paesschen et al., 1997a; King et al., 1998), whereas studies of chronic localisation related or temporal lobe epilepsy have found much higher proportions of HS (20-57%) using either MRI (Li et al., 1995; Lehericy et al., 1997; McBride et al., 1998; Semah et al., 1998) or histological assessment (Falconer et al., 1964). In contrast, the proportions with dual pathology (<5.0%), MCD (<8.5%), vascular malformations (<7.6%) and cortical scars (<14.1%) were subject to minimal inter-study variation (Li et al., 1995; Lehericy et al., 1997; King et al., 1998; McBride et al., 1998; Semah et al., 1998). The frequency of tumours (3.2-10.3%) has also been relatively consistent (Li et al., 1995; Lehericy et al., 1997; King et al., 1998; Semah et al., 1998), the exceptions being surgical (McBride et al., 1998) and histopathological (Falconer et al., 1964) series of temporal lobectomy patients in which neoplastic lesions have been found in 15% and 23.5%, respectively.

CONCLUSIONS
In summary, population based studies have revealed the aetiology of epilepsy in approximately one third of all cases, leaving the cause unknown in two thirds, principally as a consequence of retrospective case ascertainment and limited uptake of modern
<table>
<thead>
<tr>
<th>Country</th>
<th>First author</th>
<th>Year</th>
<th>n</th>
<th>Case definition and MRI methodology</th>
<th>HS/HA</th>
<th>MCD</th>
<th>HS + other (dual pathology)</th>
<th>Tumour</th>
<th>Vascular malformation</th>
<th>Infarct or contusion</th>
<th>Small ischaemic lesions</th>
<th>Diffuse atrophy</th>
<th>Other</th>
<th>NAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>King</td>
<td>1998</td>
<td>300</td>
<td>Newly diagnosed seizures. Visual MRI analysis in 88%</td>
<td>1.3%</td>
<td>2.3%</td>
<td>0.3%*</td>
<td>5.7%</td>
<td>0.3%*</td>
<td>2%</td>
<td>N/S</td>
<td>N/S</td>
<td>0.6%*</td>
<td>N/S</td>
</tr>
<tr>
<td>France</td>
<td>Lehericy</td>
<td>1997</td>
<td>222</td>
<td>TLE</td>
<td>55.0%</td>
<td>7.2%</td>
<td>N/S</td>
<td>6.8%</td>
<td>4.5%***</td>
<td>0%</td>
<td>N/S</td>
<td>N/S</td>
<td>3.6%</td>
<td>18.0%</td>
</tr>
<tr>
<td></td>
<td>Semah</td>
<td>1998</td>
<td>1148</td>
<td>Localisation related epilepsy</td>
<td>20.7%</td>
<td>8.4%</td>
<td>3.8%</td>
<td>5.3%</td>
<td>5.7%</td>
<td>14.1%</td>
<td>N/S</td>
<td>N/S</td>
<td>12.8%</td>
<td>29.1%</td>
</tr>
<tr>
<td>UK</td>
<td>Li</td>
<td>1995</td>
<td>341</td>
<td>Localisation related epilepsy. Visual MRI analysis</td>
<td>27.0%</td>
<td>8.5%</td>
<td>5.0%</td>
<td>10.3%</td>
<td>7.6%</td>
<td>3.5%</td>
<td>7.9%</td>
<td>2.1%</td>
<td>2.6%†</td>
<td>25.5%</td>
</tr>
<tr>
<td></td>
<td>Van Paesschen</td>
<td>1997</td>
<td>63</td>
<td>Newly diagnosed partial seizures. Quantitative hippocampal analysis</td>
<td>9.5%</td>
<td>0%</td>
<td>0%</td>
<td>3.2%</td>
<td>3.2%††</td>
<td>1.6%</td>
<td>1.6%</td>
<td>0%</td>
<td>4.8%†††</td>
<td>76.2%</td>
</tr>
<tr>
<td>USA</td>
<td>McBride</td>
<td>1998</td>
<td>51</td>
<td>Temporal lobectomy patients with intractable TLE. Visual MRI analysis and pathological confirmation</td>
<td>56.9%</td>
<td>3.9%</td>
<td>N/S</td>
<td>23.5%</td>
<td>3.9%</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
<td>7.8%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

**Abbreviations:** n=number  HS/HA=hippocampal sclerosis or atrophy  MCD=malformation of cortical development  NAD=no abnormality demonstrated  N/S=not specified  TLE=temporal lobe epilepsy

*2 cavernomas: 1 isolated, 1 associated with HS  **1 with hydrocephalus and bilateral HA  ***all 10 had cavernomas  †includes 5 with mixed pathologies (2 MCD and tumour; 2 tumour and infarct; 1 MCD and vascular malformation)  ††1 cavernoma, 1 arterio-venous malformation  †††1 giant aneurysm, 1 arachnoid or epidermoid cyst, 1 hippocampal oedema (post-status epilepticus)
neuroimaging techniques. Conversely, hospital based studies provide improved access to CT and MRI and have led to higher proportions with a definable aetiology and lower proportions with cryptogenic epilepsies. However, this has been at the expense of introducing significant bias in patient selection. Furthermore, the introduction of high resolution neuroimaging has revealed that abnormal findings of questionable aetiological significance are frequently present. In conclusion, there is a clear need for prospective, population based studies of the aetiology of epilepsy which employ high resolution MRI and a large age-matched control group for comparison, in order to demonstrate the range of pathological findings and aetiologies of epilepsy at the population level.

1.5 Hippocampal sclerosis and epilepsy, and the role of MRI

1.5.1 Functions of the normal hippocampus

The functions of the hippocampi are somewhat controversial (Duvernoy, 1988), but it is generally acknowledged that, along with other mesial temporal lobe structures, they are vitally important in memory processing, especially short-term memory.Broadly speaking, the dominant hemisphere hippocampus participates in verbal memory, whilst the non-dominant hippocampus has a critical role in non-verbal, particularly spatial, memory. Other putative roles of the hippocampus include motor learning, vigilance, hypothalamo-hypophysial interaction and the regulation of vegetative brain functions (Duvernoy, 1988).

1.5.2 Hippocampal anatomy: normal and pathological

The hippocampus is a 4 cm long, sea-horse shaped grey matter structure located in the medial temporal lobe where it bulges into the temporal horn of the lateral ventricle (Duvernoy 1988). In simple anatomical terms it is divisible into a head (anterior segment) which is adjacent to the amygdala, a body (middle segment) and a tail (posterior segment). In embryological terms it comprises two distinct, interlocking parts, the hippocampus proper (cornu ammonis or Ammon’s horn) and the dentate gyrus (gyrus dentatus). The hippocampus forms part of the archaeocortex (or allocortex), a three-layered structure which is simpler than the complex six-layered neocortex. The hippocampus proper is connected to the neocortex by the subiculum and entorhinal cortex, which represent a transitional cortical zone. Lorente de Nó described 4 fields within the hippocampus proper, according to their sensitivity to hypoxia (Lorente de Nó, 1934). Progressing from the subiculum to the dentate gyrus, these are designated CA1 (cornu ammonis 1) through to
CA4. CA1 is the most vulnerable sector, CA4 is of medium vulnerability, and CA2 and CA3 represent the sectors most resistant to hypoxia.

The major input to the hippocampal formation is the entorhinal cortex, which receives converging pathways from the neocortex, and other subcortical, limbic, and brainstem structures. Neurones of the entorhinal cortex project via the perforant path to granule cells of the dentate gyrus. Pyramidal neurones in CA3 project to other pyramidal neurones in CA1. The major outputs from the hippocampus are through the fimbria-fornix, and the subiculum, that in turn projects back to entorhinal cortex and other limbic structures. In addition to these major pathways, there is an extensive system of ipsilateral associational pathways, and commissural pathways to analogous structures of the contralateral hippocampus. Excitatory amino acids are thought to be the major neurotransmitters in these pathways (Sutula, 1991).

HS was first described in 1825 by Bouchet and Cazauvieilh (1825), though not associated with epilepsy until more than half a century later (Taylor, 1931). Since HS is frequently associated with ipsilateral sclerosis of another important mesial temporal structure, the amygdala, (see section 1.5.8), the term mesial temporal sclerosis is sometimes used synonymously with HS (O'Brien et al., 1996). HS was not specifically associated with mesial TLE until Stauder's autopsy studies in the 1930s (Mathern et al., 1997). Classical HS is characterised by severe neuronal loss and reactive gliosis, particularly in the CA1 and, to a lesser extent, the CA4 and CA3 regions of the hippocampus proper (Margerison and Corsellis, 1966; Bruton, 1988). A similar pattern of hippocampal neuronal loss is seen in hippocampal damage induced by hypoxia and status epilepticus (Meldrum, 1991; Sutula, 1991). There is also synaptic reorganisation including mossy fibre (dentate granule cell axons) sprouting within the dentate gyrus of the hippocampus (Sutula et al., 1989; Babb et al., 1991; Mathern et al., 1995a; Parent and Lowenstein, 1997). Mossy fibres project to neurones in the hilus of the dentate gyrus, and to pyramidal neurones in CA3. Focal anterior and diffuse unilateral HS have been described pathologically, and autopsy studies have reported that classical HS is bilateral in 18-60% of cases of TLE (Sano and Malamud, 1953; Margerison and Corsellis, 1966; Meencke and Veith, 1991). Occasionally, HS is confined to the dentate gyrus or endfolium (Sano and Malamud, 1953; Margerison and Corsellis, 1966; Bruton, 1988).
It is now also well recognised that hippocampal atrophy (without the gliosis that accompanies HS) is the major pathological substrate to the memory loss which accompanies Alzheimer’s disease.

1.5.3 The frequency of HS
Although the frequency of HS has been studied in highly selected hospital based patients (see section 1.4.2), the incidence and prevalence of HS amongst community based epilepsy patients is entirely unknown. Furthermore, there are no estimates of its frequency in unselected populations of neurologically normal subjects. One retrospective study of high resolution MRI in 207 patients investigated for hearing loss found hippocampal abnormalities consistent with HS in only 2 (1%) subjects, both of whom were subsequently identified as having previously diagnosed epilepsy (Moore et al., 1999). There does not appear to be any gender difference in the frequency of HS in epilepsy patients (Briellmann et al., 1999), although it has recently been postulated that males with TLE may be more vulnerable to generalised brain atrophy than females (Briellmann et al., 2000).

1.5.4 MRI of hippocampal sclerosis
QUALITATIVE ASSESSMENT
Early MRI could not reliably identify HS (Sperling et al., 1986; Brooks et al., 1990). Subsequent improvements in scanning techniques have permitted reliable detection of HS on visual inspection of MR images (Kuzniecky et al., 1987; Jackson et al., 1990; Berkovic et al., 1991; Lee et al., 1998). These advances include better MRI instrumentation, acquisition of images perpendicular to the long axis of the hippocampus, the use of thin (1-3 mm) slices to reduce partial volume effects, and inversion recovery (IR) T1-weighted sequences which increase grey/white matter contrast and facilitate easier differentiation of the hippocampus from the amygdala (Duncan, 1997). The principal MRI features of HS are: hippocampal atrophy (HA), hypodensity on T1-weighted images, increased signal on T2-weighted images (Figure 2) and disruption of the internal structure (Jackson et al., 1990; Jackson et al., 1993a; Bronen, 1998). Increased T2-weighted signal is a relatively non-specific finding which can result from foreign tissue lesions or from pixels containing partial volumes of CSF (the partial volume effect). Therefore, the finding of increased signal in the hippocampus on T2-weighted imaging should always be interpreted in the light of high resolution T1-weighted anatomical imaging (Duncan, 1997).
Figure 2 MRI features of hippocampal sclerosis

Volume loss on T1-weighted images
(left hippocampal atrophy shown)

High signal on T2-weighted or fast FLAIR images
(bilateral HS shown, worse on the left)
QUANTITATIVE ASSESSMENT

Hippocampal volumetry

Hippocampal volumetry, the most commonly used MRI based method of hippocampal quantitation, was first reported to improve the detection of HA in 1990 (Jack Jr et al., 1990). The principle of this technique is to measure hippocampal cross-sectional area along the length of the hippocampus using a manually-driven cursor, and to obtain a volume by multiplying the sum of these areas by the image slice thickness. The main source of measurement error occurs anteriorly where disarticulation of the hippocampal head from the amygdala may be difficult. The method is time-consuming and takes a trained observer up to 30 minutes per patient, and accurate, fully automated methods of measurement have not yet been developed.

Preliminary studies tended to measure hippocampal volume (HV) using thick (eg. 5mm), non-contiguous slices and did not measure the full length of the hippocampus (Jack Jr et al., 1989; Cascino et al., 1991). These biases were initially considered responsible for an apparent physiological asymmetry (right larger than left) of normal hippocampal size (Jack Jr et al., 1989; Watson et al., 1992), but this finding has not been reproduced in several subsequent studies using thin (1.5-3 mm), contiguous slices and measurement along the entire hippocampal length (Cook et al., 1992; Free et al., 1995; Bigler et al., 1997). Initial studies were also restricted to an assessment of HV ratio (HVR) or right-left difference (Jack Jr et al., 1990; Watson et al., 1992; Adam et al., 1994), though these were suboptimal in the detection of bilateral HA because of the wide normal range of absolute HV (Jack Jr et al., 1995; King et al., 1995; van Paesschen et al., 1995). In addition, head size and HV are greater in males than in females (Jack Jr et al., 1989 and 1995; Free et al., 1995). Correction (normalisation) of HV for total intracranial volume has obviated this limitation and facilitated easier detection of bilateral HA (Cendes et al., 1993a; Free et al., 1995; Jack Jr et al., 1995; van Paesschen et al., 1995 and 1997b). In clinical practice, hippocampal asymmetry of more than 20% is reliably visually apparent to skilled neuroradiologists (Reutens et al., 1996; Cheon et al.; 1998), but lesser degrees of asymmetry can only be detected with quantitation (van Paesschen et al., 1995; Watson et al., 1997).

HA defined by MRI has been correlated pathologically with a reduction of neuronal density in most hippocampal sub-regions (Bronen et al., 1991; Lencz et al., 1992; Lee et al., 1995;
van Paesschen et al, 1997c; Watson et al., 1997). Furthermore, HA detected by MRI compared favourably with other non-invasive means of seizure localisation in a study using ictal intracranial EEG as a gold standard (Spencer et al., 1993). Significant pre-operative abnormalities of HVR or right-left differences in HV have been correlated with the presence and severity of HS on the smaller side, using post-operative neuropathological confirmation (Cascino et al., 1991; Lencz et al., 1992; Cendes et al., 1993b; Watson et al., 1997). Several studies have also shown that ipsilateral HA is a good prognostic factor for seizure control following anterior temporal lobectomy (Berkovic et al., 1991; Jack Jr et al., 1992; Grattan Smith et al., 1993; Berkovic et al., 1994b; Garcia et al., 1994; Watson et al., 1997; Lee et al., 1998). The relevance of HA in extratemporal or generalised epilepsies has been a source of divided opinion with the authors of various MRI studies concluding either that it does not occur at all (Cook et al., 1992; Watson et al., 1996a; Watson et al., 1996b), or that it is present infrequently (Adam et al., 1994) or frequently (Lawson et al., 1997).

Based on these findings, the optimal MR based protocol for hippocampal volumetric analysis should include acquisition of thin, contiguous, high resolution images, measurement of hippocampal cross-sectional area along the entire length of the hippocampus, and subsequent correction for intracranial volume.

**Hippocampal T2 relaxometry**

A visually evident increase in hippocampal T2-weighted signal intensity has been reported in up to 60% of cases of HS (Duncan, 1997). Measurement of hippocampal T2 relaxation time (HT2) increases the sensitivity and objectivity of assessing pathological hippocampal signal change on T2-weighted images (Jackson et al., 1993b). Data from control subjects indicate that there is a narrow range of normal HT2 (Duncan, 1997). The main source of measurement error is from partial volume effect, which can be considerable in a very shrunken hippocampus.

HT2 maps have been reproducibly estimated from 16 images obtained at a range of echo times (usually 22 to 262 milliseconds) and generated by fitting single exponentials to the image data of corresponding pixels from these 16 echoes (Jackson et al., 1993b; Grunewald et al., 1994). In these early studies, HT2 measurements were presented as a useful identifier of hippocampal pathology, with marked elevations being associated with
HS (Jackson et al., 1993b; Grunewald et al., 1994; Namer et al., 1994). Intermediate HT2 values were seen in some patients without qualitative MRI evidence of HS, and in one third of hippocampi contralateral to HS, suggesting possible bilaterality of HS. Subsequent studies using the same technique with neuropathological confirmation showed that, although HS is usually associated with elevated HT2, some patients with definite HS have normal HT2 (van Paesschen et al., 1997a). An inverse relationship exists between HT2 and the ratio of neuronal to glial density in the hippocampus, and HT2 is closely correlated with the severity of hippocampal volume loss, particularly in CA1 (van Paesschen et al., 1997c). It has been postulated that elevations in HT2 have a different neuropathological basis than reductions in HV, such that these two methods of quantitation provide complementary information (van Paesschen et al., 1997c), but the significance of isolated HT2 abnormalities remains unclear and should not generally be considered as indicative of HS.

A limitation of the 16 echo method of measuring HT2 is that only a single value can be obtained from within the body of the hippocampus, such that focal anterior HS could be missed. It has been suggested that this is the likely explanation for HS associated with normal HT2 values (Duncan, 1997). Duncan and colleagues have since developed a reproducible dual echo technique of HT2 mapping which allows the acquisition of multiple HT2 measurements along the entire length of the hippocampus (Duncan et al., 1996; Woermann et al., 1998).

**CONCLUSIONS**

High resolution MRI is a sensitive and specific means of diagnosing HS in vivo. HS is characterised by hippocampal atrophy (HA) on T1-weighted images and increased hippocampal signal return on T2-weighted images. Quantitative hippocampal volumetry and T2 relaxometry further increase the sensitivity of MRI, permitting detection of subtle or bilateral HS. Hippocampal volumetry, however, is the more sensitive of the two methods for detecting HS.

Although HA (usually bilateral) without HT2 signal change may be seen in Alzheimer’s disease as well as in epilepsy, MRI-defined “textbook” HS (ie. hippocampal volume loss with increased signal return) is relatively specific to epilepsy, as will be discussed in the
1.5.5 Epilepsy and the aetiological relevance of HS

Since it was first described in patients with epilepsy, there has been considerable debate as to whether HS is of aetiological importance, a manifestation of seizure-induced damage, or a combination of the two. Much evidence points to a causative role, especially in TLE. Firstly, there is a strong association between HS and intractable TLE (Mathern et al., 1997; Margerison et al., 1966) which does not exist between HS and other common epilepsy syndromes (Cook et al., 1992; Watson et al., 1996a), although HS has been described in the relatively uncommon symptomatic generalised epilepsies (such as West’s syndrome) (Meencke et al., 1996). HS is also associated with a worse prognosis than other putative causes of epilepsy (Semah et al., 1998). Secondly, and perhaps most convincingly, anterior temporal lobectomy for ipsilateral HS produces remission of seizures in more than two thirds of cases (Babb et al., 1987; Bruton, 1988; Airaksinen et al., 2000). Thirdly, several studies assessing pre-surgical intracranial EEG have documented mesial temporal seizure onset ipsilateral to a sclerosed hippocampus (as well as seizure onset elsewhere in the ipsilateral limbic system), (Quesney, 1986; Wieser, 1988; Spencer et al., 1993; Williamson et al., 1993; Baulac et al., 1994). Furthermore, patients with focal anterior HS and depth-EEG proven anterior hippocampal seizure onset had a better surgical outcome than those with more diffuse HS and seizures which were shown to have simultaneous anterior and posterior hippocampal onset electrographically (Babb, 1984). It was postulated that the patients with diffuse HS did less well because the seizure focus extended beyond the resection boundaries. Other surgical failures in patients with definite HS may be due to dual pathology (Raymond et al., 1994; Sisodiya, 2000) or microdysgenesis, which is undetectable by conventional structural MRI but indirectly demonstrable with grey/white matter volumetric analysis (Sisodiya et al., 1997; Sisodiya, 2000), and do not militate against the theory that HS has a causative role in TLE. Interestingly, bilateral hippocampal damage (a relatively common finding) is not necessarily associated with a poor surgical outcome (Bronen et al., 1991; Jack et al., 1992), although the outcome is better when bilateral HA is asymmetrical (Bronen et al., 1991) rather than symmetrical (Jack et al., 1992 and 1995).

Despite these observations, a fundamental question remains unanswered. Is HS and its
associated neuronal damage necessary for the production of mesial temporal lobe seizures? Experimental work has revealed a marked dissociation between hippocampal damage and epileptogenesis, such that severe hippocampal damage may not be associated with seizures (Jefferys, 1999; Milward et al., 1999) whilst, conversely, minimal hippocampal damage may be associated with intractable seizures (Mellanby et al., 1977; Jefferys et al., 1992; Jefferys, 1999). This latter experimental finding is echoed by the clinical observation that a significant proportion of patients with mesial TLE lack HS. In the relatively small number of patients with apparently normal hippocampi on high resolution MRI who have a temporal lobectomy for intractable epilepsy, histopathological analysis sometimes uncovers endfolium sclerosis (van Paesschen et al., 1997b), suggesting that modern neuroimaging still lacks the sensitivity to detect very subtle hippocampal and extra-hippocampal pathology. In the majority of other “MRI negative” cases, however, excised tissue contains no histological evidence for HS and its associated neuronal damage. Overall, neurological outcome appears to be independent of the severity of the underlying mesial temporal damage and it has therefore been postulated that the relationship between epilepsy severity and hippocampal morphology is more dependent on the amount and nature of synaptic reorganisation and specifically targeted cell death (apoptosis) (Bengzon et al., 1997; Parent et al., 1997).

In summary, there is some clinical evidence supporting the theory that HS can cause TLE, yet experimental animal research suggesting that the presence of HS is not absolutely necessary for temporal lobe epileptogenesis. Evidence indicating that hippocampal damage is a progressive consequence of epilepsy is discussed in section 1.5.7.

1.5.6 The aetiology of HS

Several factors have been implicated in the aetiology of HS. It seems likely that there is a common pathogenetic mechanism, irrespective of the underlying cause. In particular, glutamate neurotoxicity probably contributes to hippocampal neuronal death but does not explain the equally important process of synaptic reorganisation within the hippocampus.

Glutamate acts on three classes of ligand-gated ion channels, namely N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), and kainate receptors, as well as on metabotropic receptors. These excitatory amino acid receptors have
different anatomical distributions within the hippocampus, as do the distribution of protective calcium-binding proteins, which may explain the selective vulnerability of certain hippocampal subregions (especially CA1 and CA4) to pathogenic agents (Monaghan et al., 1983; Munoz, 1990).

Sustained complex partial seizure activity in adult animals, whether induced by kainic acid or perforant path stimulation, consistently results in HS if allowed to continue for more than 1 hour (Olney et al., 1974; Nadler et al., 1978; Ben-Ari, 1985; Bouilleret et al., 1999; Sloviter, 1987). A recent longitudinal MRI study in a mouse model of mesial TLE employing intrahippocampal kainic acid injection concluded, perhaps rather simplistically, that HS develops in two stages (Bouilleret et al., 2000). Firstly, an early, transient hyperintense T2-weighted signal appeared in the injected hippocampus and ipsilateral amygdala, and was associated with total cell loss in the dentate gyrus, and early cell death in CA1. This early signal hyperintensity was interpreted as reflecting cytotoxic oedema occurring in relation to the excitotoxic consequences of kainic acid and seizure activity. Secondly, from 15 days onwards, a persistent hyperintense T2-weighted signal was detected in the ipsilateral hippocampus, most probably indicating reactive gliosis. At this stage, extensive degeneration of CA1 was also noted.

Pro-inflammatory cytokines including interleukins may also be involved in modulating the effects of neurotransmitters and the development of glial scars at the sites of CNS injury (Kanemoto et al., 2000), and it seems likely that many other, as yet, unidentified factors are also involved in the pathogenesis of HS.

More recently, apoptotic cell death and proliferation of dentate gyrus neurones has also been implicated in the early development of hippocampal pathology following brief epileptic seizures (Bengzon et al., 1997). It has been hypothesised that repeated seizures over several years could lead via this mechanism to severe pathological changes, possibly including HS (Bengzon et al., 1997). This research is discussed further in section 1.5.7.

Those factors which have hitherto been implicated in the aetiology of HS are discussed below:
PROLONGED FEBRILE SEIZURES AND/OR STATUS EPILEPTICUS

Although only 1.5-6% of children with febrile seizures eventually develop epilepsy (Nelson et al., 1976; Annegers et al., 1979; Berkovic et al., 1998; MacDonald et al., 1999), it has long been recognised from retrospective neuropathological and MRI studies that up to 50-80% of patients with unilateral HS have a history of prolonged early childhood convulsive seizures, especially febrile seizures (Cavanagh et al., 1956; Falconer et al., 1964; Falconer, 1974; Bruton, 1988; Annegers et al., 1987; Sagar et al., 1987; Cendes et al., 1993c; Kuks et al., 1993; Holthausen, 1994; Maher et al., 1995; Mathern et al., 1995b; Shinnar, 1998). Very prolonged (approximately 100 minutes) febrile seizures appear to confer the greatest risk of subsequent HS (Maher et al., 1995; VanLandingham et al., 1998). Acute pathological changes of oedema and pyramidal cell necrosis in CA1 (typical of HS) have been reported in patients dying in tonic-clonic status epilepticus (Spielmeyer, 1927; Corsellis et al., 1983; DeGiorgio et al., 1992), with chronic changes consisting of HA, gliosis and mossy fibre sprouting. This progression has been documented with MRI in six paediatric cases with tonic-clonic status epilepticus (Nohria et al., 1994; Jackson et al., 1995), although only two subsequently developed complex partial seizures. Recently, acute hippocampal changes consistent with oedema were observed on MRI in 6 of 15 children with prolonged, focal febrile tonic-clonic seizures (VanLandingham et al., 1998). The majority of infants, and a further 12 with generalised febrile seizures, had normal MRI. In 2 of the 6 focal cases, follow up MRI revealed the development of HA, suggesting a causal connection (Shinnar, 1998). Interestingly, however, 2 of the 6 patients had HA on their acute MRI which was likely to be a pre-existing abnormality (both had peri-natal insults) and possibly the focus of the febrile seizures. Scott et al. (2002) have also recently reported MRI changes consistent with hippocampal oedema in infants scanned within 5 days of prolonged febrile status epilepticus, but not in those with afebrile status epilepticus. Several other authors have suggested that pre-existing hippocampal abnormalities such as subtle developmental malformations might predispose to complex febrile seizures and subsequent HS (Kuks et al., 1993; Fernandez et al., 1998; Sloviter et al., 1998; Roulet et al., 2000). Additionally, experimentally-induced neuronal migration defects in immature rats cause a lower threshold to hyperthermia-induced seizures and an increased susceptibility to irreversible hippocampal damage (Germano et al., 1996). A recent quantitative MRI study found that febrile seizures do not cause more severe HA than is seen in HS patients without a history of febrile seizures, which is also consistent with the
hypothesis that HS is a pre-existing abnormality (Bower et al., 2000).

DOMOIC ACID INTOXICATION
Domoic acid is a naturally-occurring excitotoxin which may be ingested by mussels, and in turn cause poisoning in humans. It is structurally related to glutamate and analogous to kainic acid, a substance capable of chemically inducing kindling in animals (see section 1.5.7). Domoic acid intoxication has been reported to cause complex partial status epileptics and tonic-clonic seizures with subsequent memory impairment in 4 patients who died a few months later, with bilateral HS documented at autopsy (Teitelbaum et al., 1990). Cendes et al. (1995a) described a patient who developed intractable TLE due to bilateral HS, one year after domoic acid intoxication with a silent intervening period. These observations are consistent with the animal model of kainic acid-induced TLE in which HS has been shown to be a direct effect of prolonged seizures rather than due to the neurotoxic effects of kainic acid (Olney et al., 1974; Nalder et al., 1978).

CNS INFECTION
Both meningitis and encephalitis have been associated with unilateral or bilateral HS (Ounsted et al., 1985; Marks et al., 1992; Gambardella et al., 1993; Free et al., 1996b), but the mechanism of this relationship is unclear, particularly since encephalitis frequently causes acute seizures with fever, and tonic-clonic status epilepticus, both of which have been independently linked with HS (see above).

HEAD TRAUMA
In humans, there is frequently a silent period between cranial trauma and the development of epilepsy, although the precise relationship between trauma and HS is unclear. French et al. (1993) found a history of cranial trauma as the sole risk factor in 7.5% of 67 patients with TLE, most of whom had HS, and a retrospective study by Mathern et al. (1995) found a similar history in 16% of 162 TLE patients. A recent retrospective study found a prior history of cranial trauma in 18% of 200 neuropathologically-proven HS cases, although the trauma was major in only half of these (Swartz et al., 1999). There was no correlation between the age of trauma (median, 21 years) and the latency to seizure onset and no correlation between the severity of HS and the duration of the latent period. A further retrospective study of 247 patients with TLE found a history of moderate to severe head
trauma in 32 (13%) (Diaz-Arrastia et al., 2000). Of these, 23 had suffered head trauma after the age of 10 years (8 with mesial TLE and HS, and 15 with neocortical TLE and other MRI findings). A recent quantitative MRI study found that 94 patients with traumatic brain injury ranging from mild to severe showed “significant yet modest” bilateral hippocampal atrophy when compared to age-matched control subjects (Bigler et al., 1997), though it was not stated whether any of the patients had experienced seizures. The authors did not correlate HV with the severity of head injury.

In rats, experimental traumatic brain injury (fluid percussion injury) is associated with the development of hippocampal cell loss, particularly within the dentate hilus (Lowenstein et al., 1992). One week after momentary trauma there was a dramatic reduction in the number of hilar neurones ipsilateral to the impact, and a milder but significant decrease in neurones on the contralateral side. This was accompanied by functional change since abnormal dentate granule cell hyperexcitability occurred following perforant path stimulation. A subsequent study of percussion injury in rats confirmed these findings and also demonstrated enhanced limbic epileptogenesis (kindling) in hippocampal-entorhinal cortical slices prepared 1 week after injury (Coulter et al., 1996). Such findings provide a potential mechanistic link between human head trauma and the subsequent development of HS and TLE.

GENETIC FACTORS
Research in animals has targeted numerous genes, some of which have been associated with limbic and hippocampal seizures in mice (Noebels, 1996). Human familial TLE has also been recognised, but the genetic basis has not been discovered. Subjects were initially described as having normal MRI (Berkovic et al., 1996) although a more recent study of familial mesial TLE reported HS to be present in approximately 50% of cases (Kobayashi et al., 2000). Febrile seizures also have a significant genetic basis (Rich et al., 1987; Maher et al., 1995; Scheffer et al., 1997; Berkovic et al., 1998), so that some patients with HS will have a positive family history of febrile seizures (see above). HS has also been reported in identical twins (Everitt et al., 1996; Jackson et al., 1998) and hippocampal developmental malformations have been associated with familial febrile seizures (Fernandez et al., 1998). It is possible therefore that some subjects harbour either minor developmental anomalies (which may have a genetic basis) or other genetic susceptibility factors that predispose to
the development of hippocampal damage. Such damage could theoretically be triggered by an initial precipitating injury (such as a prolonged febrile seizure or major head injury), or by repeated epileptic seizures (Berkovic et al., 2000). This genetic susceptibility theory is supported by a recent study which found that temporal lobe epilepsy patients with HS carry interleukin gene polymorphisms which are absent from those without HS (Kanemoto et al., 2000).

DUAL PATHOLOGY

HS frequently occurs in association with a second, neocortical lesion, in particular MCD (Babb et al., 1987; Levesque et al., 1991; Rush and Morrell, 1993; Cendes et al., 1995b; Raymond et al., 1994 and 1995). Rush and Morrell (1993) reported 4 patients with MCD and HS who developed a new seizure type 1-15 years following the onset of epilepsy, and postulated that this clinical development was the consequence of HS being a secondary lesion induced by kindling from a primary extrahippocampal MCD focus. A recent kindling study in immature rats suggested that seizure-induced hippocampal neuronal damage occurs more readily if experimentally-induced neuronal migration disorders are also present (Germano et al., 1998). In contrast to these findings, Cendes et al. (1995b) found HS in 25% of patients with MCD and in only 2% with tumours, arguing that kindling is an unlikely mechanism for dual pathology. A common pathogenic mechanism during early development is perhaps a more plausible explanation (Cook et al., 1995; Lawn et al., 2000).

1.5.7 Evidence for the progression of HS

HUMAN STUDIES

It is presently unclear whether HS is present from the time of onset of habitual epilepsy, is the result of repeated seizures, or is a lesion which progresses as a consequence of repeated seizures.

Approximately 15-30% of patients with epilepsy have seizures intractable to medical therapy (Sander, 1993). Clinical studies have revealed that seizures in some TLE patients become progressively worse with time (Gowers, 1881; Glaser, 1987; French et al., 1993), and that the interval between successive seizures declines in patients presenting with between 2 and 5 secondarily generalised tonic-clonic seizures (Elwes et al., 1984; Elwes
et al., 1988), suggesting an escalating process. These studies, however, have not implicated progressive hippocampal pathology in this process.

Typically, mesial TLE has its onset towards the end of the first decade of life, several years after an early childhood precipitating event. The intervening period is sometimes referred to as the “silent period”. Many authors have postulated that HS, along with epileptogenicity, slowly develops during this childhood silent period as a consequence of progressive neuronal reorganisation (Bragin et al., 2000). Two lines of evidence undermine this theory. Firstly, HS has been reported in infants as young as 9 months of age (Risse et al., 1999), suggesting either a congenital basis or that HS can develop extremely rapidly. Secondly, HS or HA was found on standard MRI in only 0.5% of 388 children (up to 15 years old) in a recent community based study of newly diagnosed epilepsy, the majority of whom had localisation related epilepsy (Berg et al., 2000). This latter observation, coupled with the fact that a much higher frequency of HS occurs in hospital based adults with epilepsy, tempts one to postulate that HS can develop in adulthood, but the validity of these observations is countered by the lack of high resolution MRI in this community based childhood study, and the inherent selection bias in hospital based adult studies. Indeed, the possibility of adult onset HS occurring without any history of preceding neurological insult is supported only by isolated case reports (Jackson et al., 1999, Briellmann et al., 2001, Worrell et al., 2002).

Other MRI based case reports have described the progression of hippocampal damage in patients with partial onset seizures following status epilepticus (Nohria et al., 1994, Wieshmann et al., 1997), and a number of hospital based cross-sectional studies have tackled the issue of whether HS is progressive. Quantitative hippocampal analysis is particularly well suited to such research by allowing in vivo assessment. An early retrospective quantitative MRI study found no relationship between the degree of HA and the duration of epilepsy (Trenerry et al., 1993). Similarly, Cendes et al. (1993d) found no correlation between HV and duration of epilepsy, estimated seizure frequency, or age at onset of epilepsy. One small, retrospective cross-sectional MRI study found that patients with both newly diagnosed and chronic refractory cryptogenic TLE had smaller hippocampi than control subjects, but that HVs were smaller in the chronic group (Saukkonen et al., 1994). The authors suggested that mild structural hippocampal damage
was already present at the time of diagnosis of TLE, but progressed thereafter as a result of recurrent seizures. A later study by this Finnish group failed to reproduce evidence of hippocampal damage in patients with newly diagnosed TLE, and only a small subgroup with longstanding (>21 years) childhood onset epilepsy and frequent seizures had HV reduction ipsilateral to a surface EEG epileptic focus (Salmenpera et al., 1998). The suggestion that these findings were an effect of selection bias and methodological limitations (Sisodiya et al., 1998) was refuted by the authors (Salmenpera et al., 1998). The Finnish group also reported a separate analysis in a subgroup of the same cryptogenic TLE patients and found that those with drug-resistant seizures had a significantly smaller (14-18%) HV and higher HT2 ipsilateral to the seizure focus than did control subjects or patients with newly diagnosed or chronic, well-controlled seizures (Kalviainen et al., 1998). There were also correlations between the estimated lifetime number of partial and secondarily generalised seizures and both hippocampal quantitative parameters. The conclusion that their findings supported the theory of seizure-induced hippocampal damage (Kalviainen et al., 1998) was strongly contested because the drug-resistant group had a significantly earlier age of onset (approximately 10 years) than the well-controlled group, with the implication that the latter group had neocortical temporal rather than mesial temporal lobe epilepsy and therefore a lower likelihood of having hippocampal damage (Janszky et al., 1999). A subsequent re-analysis confirmed that a young age of onset of TLE was a more important predictor of HA than was seizure number or frequency (Janszky et al., 1999). A recent combined MR spectroscopy/hippocampal volumetry study of 82 presurgical, intractable TLE patients found significant correlations of (1) bilateral N-acetylaspartate/creatine ratios (a marker of neuronal dysfunction/loss) and (2) HV ipsilateral to the seizure focus, with both duration of epilepsy and history of frequent secondarily generalised tonic-clonic seizures (Tasch et al., 1999). The findings were considered to be due to the combination of an early insult causing asymmetrical hippocampal damage, and subsequent progressive neuronal dysfunction/loss secondary to frequent secondarily generalised tonic-clonic seizures (Sutula and Hermann, 1999; Tasch et al., 1999). A cross-sectional volumetric MRI and pathological study of 46 unilateral HS patients found that earlier seizure onset and a longer duration of epilepsy were associated with more severe HS, greater hippocampal volume asymmetry and worse performance on neuropsychological measures (Fuerst et al., 2001). It was suggested that these data also indicate that HS may be a progressive disorder associated with increasing cognitive
dysfunction. A number of other studies in humans have found that intractable TLE is associated with worsening memory function, with progressive hippocampal pathology postulated as the underlying cause (Fuerst et al., 2001; Helmstaedter, 2002; Hermann et al., 2002; Jokeit and Ebner, 2002; Stefan and Pauli, 2002).

Although two small neuropathological studies have suggested that severe seizures may cause hippocampal neuronal damage (Mouritzen Dam, 1980; DeGiorgio et al., 1992), others have suggested that HS results primarily from an initial cerebral injury or medical illness and progresses little, or not at all, thereafter (Sagar and Oxbury, 1987; Mathern et al., 1995b). In general, however, there is a stark deficiency of histopathological data (autopsy material) to assess the degree of hippocampal neuronal damage in patients who have only had a one or a few seizures and, as a consequence, there has been little possibility of using autopsy material to test the hypothesis that seizures induce hippocampal damage. This may change, however, with the increased focus on sudden unexpected death in epilepsy (Nashef et al., 1995; Langan et al, 2000; Langan et al., 2002), which occasionally affects people during their index seizure, and which necessitates post mortem examination.

It is likely that the retrospective design of these studies precluded accurate estimation of seizure frequency, the total lifetime number of seizures, and possibly even the age of onset of epilepsy. Prospective, longitudinal studies using quantitative MRI are better suited to determining the precise relationship between seizures and HS, and to establishing whether this is a pathology restricted to patients with TLE. A recent hospital based study by van Paesschen et al. (1998) included follow up MRI in 36 of 63 patients scanned one year previously because of newly diagnosed seizures. One of the 4 subjects originally found to have HS (a female with bilateral HA and normal HT2) had significantly increased HT2 without further HV loss when re-scanned. It was argued that this probably represented pathological change rather than hippocampal oedema. The patient had experienced almost daily secondarily generalised tonic-clonic seizures in the period between the 2 scans. Two additional subjects (5.6%) showed hippocampal changes between scans, probably relating to resolution of oedema following control of seizures, but no other subjects had quantitative hippocampal changes. A more recent longitudinal hospital based MRI study by Fuerst et al. (2003) of 12 patients with mostly refractory TLE involved serial brain MRI
performed a mean of 3.4 years apart. Three seizure-free patients showed no change in HV, whereas those with continuing seizures had a reduction in HV ipsilateral to the seizure focus that correlated with seizure frequency. Only 1 patient with very frequent GTC seizures (2.5 per month) had additional contralateral HA. No correlation was found between the amount of HV loss and the duration between scans, contradicting other cross-sectional hospital based studies reporting a linear relationship between HV and epilepsy duration. Liu et al. (2002) performed serial MRI brain scans 3.5 years apart in 68 adult patients with newly diagnosed seizures, of whom 50% had experienced recurrent unprovoked seizures between baseline and follow-up scans. One patient with pre-existing HS did not develop progressive hippocampal damage, and the group analyses found no difference in change in hippocampal and neocortical measures between patients and controls, or between patients with and without recurrent seizures. It is likely that much larger studies with a longer period of follow up, and/or serial MRI co-registration (to accurately assess small volume change), are required to replicate these progressive changes, if they occur.

In a series of studies by DeGiorgio and colleagues, levels of serum neuron-specific enolase have been shown to be elevated acutely following convulsive and non-convulsive status epilepticus in humans (DeGiorgio et al., 1995, 1996, and 1999), and that the highest levels are significantly correlated with a longer duration of status epilepticus and poor neurological outcome (DeGiorgio et al., 1995). The same group have also reported an increase in CSF neuron-specific enolase following cryptogenic and remote symptomatic convulsive status epilepticus (Correale et al., 1998). Such elevations do not occur after recent isolated tonic-clonic seizures (Palmio et al., 2001). Neuron-specific enolase is considered to be a sensitive marker of acute neuronal injury and elevations have also previously been described following stroke, global brain ischemia and coma. However, the anatomical distribution of neuron-specific enolase elevation following status epilepticus has not been addressed, although it seems likely from the neuropathological and neuroimaging studies described above that a significant proportion is of hippocampal origin.

ANIMAL STUDIES
The concept that neuronal damage induced by seizures may be progressive has emerged
from three lines of animal research.

Firstly, the kindling model of epilepsy has shown that an increasing number of seizures is associated with increased neuronal damage (Sutula, 1993). Kindling is the process by which periodic subthreshold (subconvulsive) electrical or chemical (e.g., tetanus toxin) stimulation of neural pathways progressively leads to a permanent state of spontaneous electrographic and behavioural seizures resulting from the same stimuli (Goddard et al., 1969). The hippocampus has been implicated as an important structure for kindling-induced epileptogenesis (Feldblum and Ackermann, 1987). Kindling studies in animals have provided evidence of progressive, yet very mild, hippocampal neuronal loss (Sutula et al., 1989; Lynch et al., 1996) and more substantial mossy fibre sprouting (Anderson et al., 1999; Sankar et al., 2000). Although a similar pattern of mossy fibre synaptic reorganisation has been observed in the resected human hippocampi of patients with TLE and HS (Sutula et al., 1989; Babb et al., 1991; Mathern et al., 1995b; Lehmann et al., 2000), the relevance of the animal kindling model to human TLE has still not been established, and the role that mossy fibre sprouting plays in the genesis of chronic epilepsy remains a subject of debate (Berg and Shinnar, 1997; Parent and Lowenstein, 1997). Furthermore, in immature animals, attempted kindling does not seem to induce either HS or unprovoked seizures in adulthood (Fisher et al., 1998).

Secondly, continuous or repeated prolonged tonic-clonic seizure activity in animal models consistently causes increasing hippocampal neuronal loss in a pattern mimicking that of humans (Sperk, 1994). This seizure-induced cell death has traditionally been attributed to the mechanism of excitotoxicity-induced necrosis (Wasterlain et al., 1993) which deletes clusters of cells and includes loss of membrane integrity, cellular swelling and lysis, as well as activation of brain microglia and astrocytes.

A third and more recent line of research has shown that apoptosis (programmed cell death) also contributes to the hippocampal neuronal degeneration which follows prolonged limbic status epilepticus in rats (Pollard et al., 1994; Weiss et al., 1996). Apoptosis involves specific deletion of single cells and is characterised by cell shrinkage, plasma and nuclear membrane blebbing and budding off of fragments known as apoptotic bodies, chromatin condensation, and endonuclease-mediated DNA cleavage (Bengzon et al., 1997). Bengzon
et al., using a kindling model and highly sensitive DNA fragmentation analysis, recently found that single and intermittent brief limbic seizures induce neuronal apoptosis and neurogenesis in the rat dentate gyrus (Bengzon et al., 1997). The degeneration was correlated with the severity and duration of epileptic activity. The authors hypothesised that these processes, occurring early in epileptogenesis, are primary events in the development of hippocampal pathology in animals, and may also be highly relevant in humans with TLE.

1.5.8 Amygdalar sclerosis

In experimental animal studies, the amygdala kindles more readily than the hippocampus (Goddard et al., 1969; Moshe and Ludwig, 1988; Garant and Moshe, 1994). Several authors have postulated that the amygdala, another important mesial temporal structure, might be an important structure for human epileptogenesis (Falconer et al., 1964; Gloor, 1980; Wieser, 1988; Feindel and Rasmussen, 1991). In pathological and MRI studies, the amygdala is gliotic ipsilateral to HS in half to three quarters of cases (Sano and Malamud, 1953; Falconer et al., 1964; Margerison and Corsellis, 1966; Bruton, 1988; Cendes et al., 1993b; van Paesschen et al., 1996). Depth EEG studies in patients with mesiobasal limbic epilepsy have demonstrated focal amygdalar ictal onset in 10% of cases, focal hippocampal onset in 25%, and regional amygdalo-hippocampal onset in 65% (Quesney, 1986; Wieser, 1988; So et al., 1989).

However, the amygdala is technically more difficult to measure volumetrically by MRI in humans than is the hippocampus (Watson et al., 1992 and 1997), and isolated amygdalar sclerosis is much less frequent than HS or combined amygdalo-hippocampal sclerosis (Bruton, 1988; van Paesschen et al., 1995). Amygdalar T2 measurements may be a more sensitive method for detecting amygdalar sclerosis (van Paesschen et al., 1996). In a cross-sectional quantitative MRI study, amygdalar volumes in newly diagnosed and chronic refractory TLE patients were no different from those of control subjects (Saukkonen et al., 1994). A subsequent study by the same group found that amygdalar damage, as evidenced by volume loss or abnormal elevation in T2 values, were observed in 20% of patients with TLE, most of whom had chronic epilepsy (Kalviainen et al., 1997). There was also a correlation between the severity of amygdalar damage (as evidenced by MRI) and the total lifetime number of seizures.
Overall though, quantitative amygdalar assessment is a far less useful means of assessing mesial temporal lobe damage than is hippocampal quantitative analysis and, for this reason, is not considered further in this thesis.

1.5.9 Conclusions
Several factors have been implicated in the aetiology of HS, although there may be a final common mechanism. From the available evidence, it seems likely that HS has an important role in the causation of seizures originating in the temporal lobe. There is also evidence from humans and animals suggesting that HS may be progressive, most likely as a consequence of intractable seizures.

High resolution MRI is a sensitive and specific means of diagnosing HS in vivo. Given these properties, prospective, community based, cross-sectional MRI studies should establish the frequency and severity of HS at the population level in neurologically normal subjects and in epilepsy patients with differing durations and types of epilepsy. Additional longitudinal MRI studies will help determine when HS first becomes manifest, whether HS is definitely progressive and, if so, the rapidity of, and the reasons for, progression.
CHAPTER 2

Aims of thesis

2.1 Introduction
In chapter 1, several important deficiencies of knowledge concerning the epidemiology of epilepsy were highlighted, as was the controversy surrounding the pathogenesis of HS. These areas of interest are summarised below.

There is a dearth of prospective population based incidence and prevalence studies of epilepsy with the majority of previous studies having been retrospective in design. In particular, the possibility that there has been an increase in the incidence of epilepsy in the elderly over recent decades has not been fully substantiated. The vast proportion of patients seen at tertiary referral epilepsy clinics have chronic intractable epilepsy, yet its prevalence at the population level is largely unknown. In addition the importance of better understanding the aetiology of epilepsy in the general population was discussed. In epidemiological studies performed to date, the aetiology of epilepsy has defied investigators in approximately two thirds of all cases, a reflection of retrospective case ascertainment and limited access to the EEG and neuroimaging. In stark contrast to this, the introduction of high resolution MRI has greatly advanced our knowledge of the causes of epilepsy amongst hospital based patients by facilitating the identification of subtle pathologies including MCD and HS. It is currently unclear whether these aetiologies are equally important in the general population or whether they represent an artefact of case selection bias in tertiary referral centres. The studies of epilepsy which comprise this thesis are the first to use MRI in a community based population.

The vital importance of HS in epilepsy, especially TLE, has been emphasised. The central issues are whether HS is a cause or consequence of epilepsy, the timing of its development, and whether it is progressive. A multitude of hospital based studies have unsuccessfully or incompletely addressed these questions, largely because of retrospective design and/or because the subjects investigated were highly selected and often studied long after the onset of their epilepsy. It will be shown that the population based studies contained in this thesis are ideally suited to scrutinise these controversies.
The following five studies were performed in order to achieve the aims of this thesis. Studies 1, 2, 3 and 4 were carried out in the same community based population. Study 5 was performed in a residential epilepsy centre.

2.2 Aims

Study 1:
A prospective population based incidence and prevalence study of epilepsy in Buckinghamshire, UK

Aim
To define the age-specific incidence (in adults and children) and prevalence (in adults alone) of epilepsy, including chronic active epilepsy, in a community based population of approximately 200,000 people by means of prospective case ascertainment. The cohorts of patients identified in this study will subsequently be investigated in studies 3, 4 and 5, and compared with the cohort of control subjects identified in study 2.

Hypotheses
1. The incidence of epilepsy is now greater in the elderly than it is amongst children.

2. The prevalence of chronic active epilepsy, as defined by a history of at least 2 unprovoked seizures over a minimum of 4 years (with at least 1 seizure during the preceding 12 months), will be substantially less than the prevalence of active epilepsy (using standard ILAE criteria), as defined by a correct diagnosis of epilepsy and a history of at least 1 seizure during the preceding 5 years (irrespective of AED treatment status).

Study 2:
Qualitative and quantitative high resolution cranial MRI in 170 community based, neurologically normal volunteers

Aims
1. To employ a high resolution MRI "epilepsy protocol" in order to establish the range and frequency of intracranial MRI abnormalities in a large group of neurologically normal subjects, and to better understand the relevance and significance of a variety of cerebral structural abnormalities in patients with epilepsy.
2. To establish normative ranges for MRI based HV and HT2 measurements in a large community based population of neurologically normal subjects, so that values from patient cohorts can subsequently be compared to these.

Hypotheses
1. Non-specific cerebral abnormalities such as small white matter lesions are likely to be found infrequently amongst healthy volunteers whereas abnormalities traditionally associated with epilepsy, such as HS, MCD and foreign tissue lesions, are likely to be absent altogether.

2. Normative ranges for HV and HT2 can be successfully founded from a large group of community based neurologically normal subjects, but these hippocampal parameters are likely to be affected by age, gender and, possibly, laterality.

Study 3:
The aetiology of epilepsy in adults: a prospective, population based MRI study

Aims
1. To describe the range and frequency of intracranial MRI abnormalities in community based adults with epilepsy in order to determine whether there are significant differences compared to healthy volunteers ascertained from the same population base, or from previous reports of hospital based epilepsy patients.

2. To describe the range and frequency of intracranial MRI abnormalities in community based cohorts of adults with newly diagnosed and chronic active epilepsy in order to see whether there are significant differences between these two groups.

3. To describe the aetiology of incident and prevalent cases in a community, using investigation with high resolution MRI. This allows the frequency of HS and MCD at a population level to be defined, and also enables an estimation of the proportion of cases with an MRI diagnosis in whom previous investigation did not reveal the underlying aetiology.

4. To compare the age-specific distributions of specific aetiologies of epilepsy amongst
adults with newly diagnosed and chronic active epilepsy.

Hypotheses

1. The frequency of cerebral structural abnormalities including HS, MCD and foreign tissue lesions in patients with epilepsy will be much greater than in age-matched neurologically normal control subjects, but less than has been reported in previous hospital based studies of epilepsy because of the elimination of selection bias.

2. HS will be more frequent in patients with chronic active epilepsy than in those with newly diagnosed epilepsy, suggesting that it is a slowly progressive abnormality which predisposes to medical intractability, whereas other cerebral structural abnormalities are less likely to differ significantly in frequency between these two groups.

3. High resolution MRI will allow the aetiology of epilepsy to be identified in a significant number of subjects in whom previous investigation failed to reveal the cause. A proportion of patients, however, will still have an unknown aetiology, but this will be much less than in previously reported epidemiological studies of epilepsy which have not employed MRI.

4. Cerebrovascular disease is likely to be the commonest cause of newly diagnosed epilepsy amongst the middle aged and elderly, whilst chronic active epilepsies are more likely to be associated with HS or caused by cranial trauma, CNS infection, perinatal injury, MCD or idiopathic epilepsy.

Study 4:
The severity of hippocampal sclerosis in adults with newly diagnosed and chronic active epilepsy: a prospective, cross-sectional, population based quantitative MRI study

Aims

1. To determine the severity of hippocampal structural damage in patients with newly diagnosed and chronic active epilepsy, as determined by MRI measurements of HV and HT2, by comparison with normative data from the cohort of neurologically normal volunteers.
2. To compare the extent of hippocampal damage in patients with partial onset seizures with those having generalised seizures, in both newly diagnosed and chronic epilepsy.

3. To correlate the extent of hippocampal damage in epilepsy patients with relevant clinical variables, including age of onset, duration of epilepsy, seizure frequency, and the total lifetime number of seizures.

Hypotheses
1. Patients with chronic active epilepsy have more severe hippocampal damage (as evidenced by quantitative hippocampal MRI) than do those with newly diagnosed epilepsy, since HS is probably a progressive pathology which predisposes to intractability.

2. Hippocampal damage is likely to be more severe in patients with partial onset epilepsy compared to those with generalised epilepsy, irrespective of whether the epilepsy is newly diagnosed or chronic and active.

3. The severity of hippocampal damage is likely to be correlated with the age of onset of epilepsy, the duration of epilepsy, the frequency of seizures and an estimate of the total lifetime number of seizures.

Study 5:
A quantitative MRI study of severe intractable epilepsy in an adult residential epilepsy centre
Aims
1. To perform a descriptive analysis of the range and frequency of qualitative and quantitative MRI abnormalities (including HS and HA) amongst inhabitants of a large residential epilepsy centre with severe, intractable epilepsy.

2. To determine the effect of MRI upon epilepsy syndromic classification, by determining the proportion in whom MRI led to the discovery of a new aetiology.

3. To see whether there is a correlation between the severity of epilepsy and the extent of hippocampal damage.
Hypothesis

1. Epilepsy centre residents are likely to have a much higher prevalence of identifiable cerebral structural abnormalities on MRI than amongst the community based epilepsy population because the average severity of epilepsy will be greater, and the frequency of brain injury resulting from seizure-related cerebral hypoxia and head trauma will be higher.

2. MRI data will permit the identification of the cause of epilepsy in a significant number of subjects in whom aetiology was not previously known.
CHAPTER 3

Methods:
Epidemiological study design and MRI methodology

3.1 Introduction

Well designed community based epidemiological studies can yield important information concerning the characteristics of a condition at the population level. Case ascertainment should be prospective, complete, and from a large representative population, with a high level of investigation applied to all identified subjects. Epilepsy, one of the commonest serious neurological disorders (MacDonald et al., 2000a), warrants particular epidemiological consideration. Contemporary knowledge of the age-specific incidence, prevalence, aetiology and prognosis of the epilepsies are vital for effective planning of health care.

The unique structure of the UK primary health care system makes it ideally suited to the devison of a rigorous community based study of epilepsy. Each general practitioner (GP) is responsible for the long-term primary medical care of approximately 2000 patients, including all community based prescribing (Wallace et al., 1998). In the event of developing a new symptom such as an epileptic seizure, a patient usually seeks the advice of his GP who decides whether to refer the patient for a specialist opinion or to instigate appropriate investigations/treatment himself. Alternatively, a patient may attend a casualty department directly following a seizure, or suffer a seizure whilst hospitalised for an unrelated condition. The centralisation of that patient’s medical history with his GP, however, ensures that the GP is subsequently informed of any such hospital contact via a letter or discharge summary. It is therefore relatively easy to obtain accurate, up-to-date information concerning a patient’s clinical history through review of their primary care medical records.

The aims of this thesis necessitated a methodological design permitting (a) the development of cohorts of unselected patients with newly diagnosed seizures and chronic active epilepsy, and a cohort of age-matched neurologically normal control subjects, and (b) the acquisition of high resolution cranial magnetic resonance imaging (MRI) data in
all three cohorts. This chapter details the epidemiological study design and MRI methodology used to fulfil these objectives.

3.2 Epidemiological study methodology

3.2.1 Study population

The study took place in an area approximately 30 km to the west of London. In April 1995, following written invitation to 30 GP group practices in this area, 112 GPs from 21 GP health centres agreed to participate in the study. Visits to each health centre were then arranged in order to explain the purpose and logistics of the study. All 21 health centres were located within a 20 km radius of Chalfont St. Peter, where the National Society for Epilepsy (NSE) operates a research MRI scanner. This is a mixed locality, consisting of relatively affluent rural and suburban areas, and also some deprived urban areas.

Two important prerequisites for health centre inclusion in the study were that (a) all GPs from that centre should participate in order to minimise bias in individual GP referral patterns and (b) that computerised demographic data were easily accessible.

The incidence study population comprised all 207,553 persons who were fully and permanently registered with these 21 health centres during the period of study. For the prevalence study, a subset (159,388 persons) of the incidence study population was used, for two reasons. Firstly, the prevalence study was confined to persons aged 15 years and over (hereafter referred to as adults) and, secondly, one health centre with responsibility for the medical care of a large residential epilepsy centre was excluded in order to avoid selection bias.

3.2.2 Demographic data

Six monthly age-sex registers with groupings into 10 year age bands (5-14, 15-24 years etc.) were acquired for all patients permanently registered with the 21 participating health centres. These data were used to generate a mean study population age-sex register for the duration of the study which was compared with the Office of Population Census and Surveys (OPCS) population data for England and Wales (1996). This method of calculation made negligible the effects of migration and death within the study population during the period of study, factors which are more likely to have a significant effect in studies where demographic data is obtained at the mid-point of the study only.
3.2.3 Period of study and prevalence day
Registration of incident cases continued for 24 months (1 June 1995 to 31 May 1997 inclusive). Patients were only included if the seizure precipitating first medical attendance (Sander et al., 1990) occurred on or between these two dates. In order to minimise the possibility of missed cases, active surveillance (see section 3.2.5) continued through until the end of October 1997.

The prevalence day was the midpoint of the study, 1 June 1996. This was the day for calculating demographics, but prevalent cases were collected in the 6 month period following this.

3.2.4 Inclusion criteria and case definitions
NEWLY DIAGNOSED (INCIDENT) CASES:
Newly diagnosed (incident) cases were those who had a first seizure during the period of study, and others who had not previously attracted a diagnosis of epilepsy, such as those presenting with a first generalised tonic-clonic seizure and a hitherto unreported history of minor seizures eg. myoclonic jerks and simple partial seizures.

Incident febrile seizures were first epileptic seizures occurring in an infant of 3 months to 6 years of age, associated with a clearly documented febrile illness, but without evidence of intracranial infection (NIH consensus statement, 1980). Fever-associated seizures occurring in children who had previously suffered a non-febrile seizure were not considered as febrile seizures (NIH consensus statement, 1980).

CHRONIC ACTIVE EPILEPSY:
Patients with chronic active epilepsy were those whom, on the prevalence day (see above), had a 4 or more year history of at least 2 unprovoked epileptic seizures, with a minimum of 1 seizure during the preceding 12 months. Current antiepileptic drug treatment (AED) status did not affect this definition.

3.2.5 Case ascertainment
All case ascertainment was prospective. Several methods were employed to ensure complete case ascertainment:
FAST TRACK CLINIC

GPs were strongly encouraged to refer all adult patients (15 years or over) with a history suggestive of newly diagnosed seizures to a fast-track clinic at the NSE, established specifically for this study. This enabled a detailed clinical assessment (see section 3.2.6) within 10 days of referral. A simple proforma referral form was provided to encourage rapid referral. GPs were advised to have a low threshold of clinical suspicion of seizures.

IN VolvEMMENT OF LOCAL NEUROLOGICAL SERVICES

All consultant neurologists practising within the study catchment area were informed of the study, provided with a list of the participating health centres, and invited to refer any suspected new seizure or chronic active epilepsy patients (NHS or private) from these health centres for further investigation.

ACTIVE SURVEILLANCE

A system of active surveillance (Sander et al., 1990) was prospectively employed throughout the period of study, to minimise the possibility of newly diagnosed cases going undetected. A variety of methods were used. The same methods were used to help determine which adult patients fulfilled the criteria for chronic active epilepsy.

A. monthly reminder/notification cards and regular newsletters

Each collaborating GP was sent a monthly notification card with which to notify the principal investigator of any new case of febrile or afebrile seizures, continuing until October 1997. GPs were asked to always return these pre-addressed, postage pre-paid cards, even in the absence of any new cases. The cards did not compromise patient anonymity. New case notifications were followed up by means of a telephone call to the relevant GP to establish patient details. The medical records of any definite new cases were then examined at a later date. In addition, a regular newsletter was sent to all collaborators, with updates on case ascertainment for each practice and reminders of the importance of new case notification.

B. computerised patient database searches

Until October 1997, frequent systematic searches were made of each health centre’s computerised patient database, checking for newly commenced AED prescriptions and
recently documented blackouts or seizures. This effective method was recently used by Wallace et al. in an incidence and prevalence study of epilepsy (Wallace et al., 1998). The full computerised medical history and primary care records were then scrutinised for all patients picked up in this way, in order to exclude false positive diagnoses such as patients receiving an AED for the treatment of neuropathic pain or an affective disorder.

C. inspection of GP referral letters to consultant neurologists
Every month, the principal investigator reviewed all referral letters sent from each health centre to local consultant neurologists, again examining for cases of newly diagnosed seizures.

D. monitoring of the rate of new case diagnosis
Close monitoring of the rate at which new seizures were diagnosed, with comparison to an expected incidence rate (based upon data from previous incidence studies), permitted an estimation of the frequency of missed cases. An indication as to their likely source was revealed by a regular assessment of the number of new diagnoses in each of the 21 health centres.

E. large scale audit of primary care records
Following a successful pilot study of 40,000 case records in September 1996 in which 12 new adult cases were ascertained, a detailed manual search (audit) of patient records held in GP health centres, nursing, and residential homes was carried out in 19 of 21 health centres (approximately 175,000 case records, or 85% of the entire study population). Only 2 of 21 health centres (a total of about 32,500 registered patients) denied permission to perform the audit, perceiving that the process would be too disruptive to the running of the practice. One of these, however, had an exceptionally well-organised computerised database which was regularly updated, obviating the need for a manual note search.

For this audit, a team of 55 London medical students was instructed to scrutinise medical records for mention of relevant CNS symptoms, neurological diagnoses or new AED prescriptions after 1 June 1995 inclusive. The principal investigator then reviewed the records of more than 2000 cases detected in this way, in order to assign a diagnosis and exclude false positives. In many cases, such patients had been seen by other neurologists
practising in the region, and a reliable neurological diagnosis had already been made. Because of the magnitude of this task and the limited availability of the medical students, the audit was performed in 3 stages at 16 months (14 health centres; approximately 125,000 records), 19 months (3 centres; 25,000 records), and 24 months (2 centres; 33,000 records) into the study period, respectively.

In order to check the sensitivity of the audit, all medical records in one health centre with 2896 registered patients (1.4% of the study population) were re-examined three months later by a second team of medical students. The false negative rate for case detection was calculated by establishing the number of newly diagnosed and chronic active cases missed in the first audit, but detected in the second, and using the total number of registered patients as the denominator.

3.2.6 Clinical assessment and investigation

As much of the following information as possible was recorded for all patients: NHS number (to facilitate future patient tracking), demographic data, past medical history, family history, seizure description, circumstances of seizure, provoking factors, age at onset, duration of seizure history, results of previous medical assessments/investigations (particularly neuroimaging), relevant aetiological factors (including history of head injury, febrile seizures and meningo-encephalitis), and AED treatment. Age at onset was defined as either age at the time of an isolated seizure, or age at onset of habitual seizures in a patient with a history of recurrent seizures. Duration of epilepsy was defined as the length of time between the age at onset of habitual seizures and the prevalence day (see 3.2.3) in the case of those with chronic active epilepsy, or between the age at onset and the date of case ascertainment in those with newly diagnosed seizures. In patients who had high resolution MRI, the frequencies and estimated total lifetime numbers of tonic-clonic (primary or secondary generalised) and other non-tonic-clonic seizure types (partial, absence or myoclonic seizures), respectively, were obtained.

All patients seen in the fast-track clinic had a full neurological examination, blood tests (full blood count, erythrocyte sedimentation rate, urea, electrolytes, liver function tests, serum calcium), routine electroencephalography (EEG), and high resolution cranial MRI. Sleep, ambulatory or video/EEG studies were carried out to assist diagnosis or
classification as necessary. All EEG studies were reported by an experienced neurophysiologist. EEGs carried out elsewhere were not usually repeated.

Following consultation with their GPs, and where appropriate, all newly diagnosed adult patients not initially referred to the fast-track clinic, and all adults (≥15 years) with chronic active epilepsy, were invited by means of a standard letter to attend the NSE for high resolution cranial MRI. Repeat invitations were issued whenever necessary. We did not attempt to investigate children under the age of 14 years.

3.2.7 Follow up
All adults referred to the fast-track clinic were kept under clinical review whenever a definite new seizure diagnosis was made or if there was initial diagnostic uncertainty. This allowed time for a clear diagnosis to emerge in the majority of cases. Those under the sole care of their GP or neurologist were followed up from information obtained from their primary care medical records.

3.2.8 Case classification
Between 1 September 1997 and 15 November 1997, a study panel comprising 3 experienced consultant neurologists with an interest in epilepsy (Professors Simon Shorvon, John Duncan and Josemir Sander) convened in order to classify all suspected adult newly diagnosed and chronic active epilepsy patients according to likelihood of diagnosis, seizure type(s) and aetiology.

Cases were categorised as either “definite”, “probable” or “unlikely” on the basis of clinical findings. Definite cases had witnessed seizures. Probable cases included those with witnessed or unwitnessed episodes very suggestive of seizures. Unlikely cases had undiagnosed episodes which were not strongly suggestive of seizures eg. loss of consciousness without warning and fast recovery, or loss of consciousness preceded by a pre-syncopal aura, but with prolonged recovery. Patients classified as unlikely were excluded from further analysis at this stage.

Seizure type(s) and aetiology were also classified, using the 1993 ILAE Guidelines for Epidemiological Studies (ILAE, 1993). In accordance with this, seizure type classification
took into account clinical features only, and was blind to the results of EEG and neuroimaging. Partial onset seizures were those in which there was evidence of a clinical partial (focal) onset. Generalised seizures included absence and myoclonic seizures, as well as tonic-clonic seizures without clinical symptomatology or signs to indicate an anatomical localisation or focal onset (i.e. generalised seizures were not necessarily primarily generalised seizures). On rare occasions, seizure type was unclassifiable due to the lack of adequate clinical information.

Aetiological classification was based upon clinical, EEG and neuroimaging findings (ILAE, 1993), and is detailed below. In newly diagnosed adults, seizures were additionally categorised as being either provoked or unprovoked, depending on whether a precipitating (provoking) CNS insult had occurred during the 7 days preceding the seizure.

As no children were assessed clinically by the study team, further categorisation into provoked and unprovoked seizures was not possible, with the exception of febrile seizures which were usually clearly recorded as such in the medical records.

SCHEME AND DEFINITIONS USED FOR CLASSIFICATION OF AETIOLOGY:
This classification was first described in the 1993 ILAE Guidelines for Epidemiological Studies (ILAE, 1993).

1. Provoked (acute symptomatic) seizures
This category encompassed all seizures occurring within 7 days of an acute systemic metabolic or toxic insult, cranial trauma (head injury or post-craniotomy), cerebrovascular accident, or acute CNS infection. In addition, seizures occurring in association with acute alcohol/drug intoxication or withdrawal, as the presenting symptom of a CNS tumour, or due to any combination of the above were included.

2. Unprovoked (remote symptomatic) seizures
A seizure or epilepsy occurring as a consequence of a variety of static or progressive neurological conditions, or some unknown aetiology. The following is a list of the commonest recognised aetiologies of seizures, accompanied by a brief working definition.
A. Static neurologic conditions
The following aetiologies are best considered as essentially static (non-progressive), although this is somewhat contentious in the case of both small vessel cerebrovascular disease and HS, where there is some evidence that progression may occur slowly.

HEAD TRAUMA
Seizures occurring more than one week after head injury were only attributed to head trauma when one or more of the following criteria were satisfied:

- open head injury, including neurosurgery
- closed head injury with intracranial haematoma, haemorrhagic contusion or focal neurological deficit
- depressed skull fracture
- unconsciousness or post-traumatic amnesia lasting more than 30 minutes
- neuroimaging evidence of brain damage

CEREBROVASCULAR DISEASE
Seizures were attributed to this aetiology when they occurred more than one week after a clinically identified cerebral infarction or intracranial haemorrhage, or when there was neuroimaging evidence of cerebrovascular disease in conjunction with a late onset of seizures and/or appropriate risk factors, such as hypertension, ischaemic heart disease and diabetes mellitus.

CNS INFECTION
Seizures occurring as a sequela of meningitis, encephalitis or cerebral abscess.

PRENATAL AND PERINATAL RISK FACTORS
Seizures occurring in subjects with either:

- a history of severe neonatal encephalopathy and residual motor disorder and/or mental retardation
- MRI evidence of a malformation of cortical development (MCD)

POST-METABOLIC ENCEPHALOPATHY AND ALCOHOLIC EPILEPSY
Seizures occurring in subjects with a history of:
• toxic or metabolic encephalopathy
• a clinical diagnosis of chronic alcohol abuse, but without evidence of acute alcohol withdrawal or intoxication, or other remote symptomatic causes of seizures

HIPPOCAMPAL SCLEROSIS/ATROPHY
Seizures associated with qualitative or quantitative MRI evidence of HS or HA. Isolated elevations of HT2 were not considered as indicative of HS.

OTHER
Seizures associated with miscellaneous static lesions including cavernomas, and lesions of uncertain nature.

B. Progressive neurological conditions
Individuals with epilepsy or unprovoked seizures secondary to progressive neurological conditions frequently experience recurrent seizures, but the underlying condition is characterised by a pathophysiology which is in evolution. In such a situation, it is often unclear whether seizures occur in relation to abnormalities associated with existing damage (akin to remote symptomatic seizures) or to the evolving pathological process (akin to acute symptomatic seizures). As such, these conditions are best considered separately from relatively static neurological conditions.

CNS NEOPLASMS
Seizures due to CNS tumours, including incompletely or unsuccessfully removed neoplasms, but excluding dysembryoplastic tumours which were considered as part of the spectrum of MCD.

PROGRESSIVE CNS INFECTIONS
Conditions including Creutzfeldt-Jacob disease and human immunodeficiency virus infection.

INFLAMMATORY AUTOIMMUNE CNS DISORDERS
Seizures due to CNS-specific autoimmune disease such as multiple sclerosis, or to systemic autoimmune/inflammatory disease which has been demonstrated to involve the
CNS, such as neurosarcoidosis or cerebral lupus.

NEUROMETABOLIC CONDITIONS
Diseases affecting the CNS and associated with identified errors of metabolism, such as phenylketonuria.

PRIMARY CNS DEGENERATIVE DISORDERS
Miscellaneous neurodegenerative conditions including Alzheimer’s disease, Huntington’s disease, diffuse Lewy body disease, and multiple system atrophy.

C. Unknown aetiology
Cases of unprovoked seizures for which no antecedent aetiology could be identified were classified into one of the following two groups.

IDIOPATHIC
Patients with particular clinical and EEG features suggesting one of the idiopathic epilepsy syndromes, as defined by the ILAE (ILAE, 1989).

CRYPTOGENIC
Patients with unprovoked partial or generalised seizures of unknown aetiology who did not conform to criteria for any of the symptomatic or idiopathic categories. These patients were sub-categorised according to whether or not high resolution MRI had been performed.

3.2.9 Calculations of standardised incidence, cumulative incidence and prevalence rates
Standardised age-specific incidence rates (Rothman, 1986; Olafsson et al., 1996) were calculated using the incidence study population age-sex register as the denominator, and corrected for OPCS population data for England and Wales from 1996. As previously mentioned in section 3.2.5, the note audits in 17 of the health centres were performed 5 to 8 months before the completion of the incidence study period. For this reason, the incidence rates calculated using these data were considered to be an estimate of minimum incidence. Therefore, the incidence data derived from the audits in each of these health centres was extrapolated in order to estimate the total number of newly diagnosed adults that would have been ascertained had the entire note audit been performed at the
conclusion of the study period. This figure was used to yield an additional estimate of the maximum annual incidence rate for adult newly diagnosed seizures amongst the (approximately) 175,000 subjects whose medical records were audited. These incidence rates were expressed as the number of cases per 100,000 persons per annum.

Children were not clinically assessed by the principal investigator, and further categorisation into provoked and unprovoked seizures was therefore not possible, with the exception of febrile seizures which were usually clearly recorded as such in medical records. As a consequence, separate incidence rates for provoked and unprovoked seizures, and prevalence rates of chronic active epilepsy, were not calculated in children of 14 years and under. Although febrile seizures were defined as fever-associated seizures in infants aged 3 months to 6 years, the incidence rate could only be calculated for those aged 0-4 years, because the available demographic data dictated that the 0-4 years age band had to be used as the denominator (the 5-14 years age band could not be further sub-divided).

Cumulative incidence was determined by the following method. Firstly, the incidence rate in each 10 year age band was calculated using all ascertained cases and the known denominators. Each age band incidence rate was then multiplied by the number of years in that age group (ie. x 10), to find the contribution of each age group. The contributions of each age group were then added, and the cumulative sum expressed as a percentage (Rothman, 1986; Olafsson et al., 1996). Therefore, this calculation took into account the fact that the population at risk (the denominator) declines with increasing age.

Age-specific prevalence rates were determined using the prevalence study population age-sex register as the denominator, and corrected for OPCS data as before. All prevalence rates were expressed as the number of cases per 1000 of population.

Confidence limits (95%) for incidence and prevalence rates were calculated using the standard error of a proportion, providing the numbers were large enough.

3.2.10 Prevalence of active and epilepsy in remission and of isolated seizures in a smaller population of adults and children (ILAE 1993):

In order to investigate the proportion of patients in remission, a second analysis of
prevalence was performed in study 2 using alternative ILAE definitions of epilepsy (ILAE, 1993) in a smaller population of 12,178 adults and children registered with one large health centre. A detailed audit of their medical records was performed on 1.12.96, and all patients with a lifetime history of at least one seizure were ascertained. Point prevalence rates (per 1000) for active epilepsy (two or more unprovoked seizures with at least one seizure during the preceding 5 years) and epilepsy in remission (inactive epilepsy: the absence of seizures for 5 or more years in a patient with a history of two or more unprovoked seizures) were determined, with additional sub-categorisation according to AED treatment status. Age-specific prevalence rates and frequencies of different seizure types were not calculated in this analysis due to the relatively small number of patients in each 10 year age band.

3.2.11 Recruitment of control subjects for the MRI study

Neurologically normal subjects were prospectively recruited from the study population base of 207,553 persons in order to create a control group for the MRI study. These subjects were either unrelated partners or friends of patients who had been ascertained as part of the study, or responders to advertisements placed in community locations. The control group was broadly age-matched and sex-matched with the chronic active patient group. The same group of control subjects was used for studies 2, 3, 4 and 5.

Subjects were excluded if they had a history of any of the following: febrile or afebrile seizures; unexplained blackouts; a positive family history of seizures or dementia; head injury associated with loss of consciousness, skull fracture, neurological deficit or post-traumatic amnesia; birth injury; encephalitis; meningitis; stroke; transient ischaemic attack; psychosis; other important psychiatric morbidity; a diagnosis of learning disability; any significant current or previous neurological symptomatology not covered by the above, specifically: frequent headache, memory impairment, motor or sensory symptoms, dysequilibrium, or visual symptoms. Subjects without any of the above, but with a history of cardiovascular or peripheral vascular disease, or risk factors for vascular disease were not excluded.

All volunteers were examined neurologically, and any with abnormal findings were excluded from the study. Handedness was determined using a standard, validated 13-point questionnaire (Chapman and Chapman, 1987).
3.2.12 Data storage and analysis

Each patient and control subject was assigned a code number to facilitate anonymous data storage and analysis. Clinical and demographic data was stored in a database and spreadsheet (Borland Paradox and Quattro Pro for Windows, respectively). Statistical analysis was performed using both Quattro Pro for Windows and SPSS 8.0 for Windows.

3.3 MRI methodology

3.3.1 MRI hardware and image acquisition

All volunteers were imaged between 1.6.95 and 1.3.98 in a 1.5 T Signa Horizon scanner (GE Medical Systems, Milwaukee, USA). A standardised imaging protocol taking approximately 30 minutes to acquire was applied:

SAGITTAL T1 SPIN ECHO:
Echo time (TE)/recovery time (TR)/number of slices/matrix/field of view (FOV)/
number of excitations (NEX)/slice thickness/spacing/imaging time:
14ms/620ms/17/256 x 256/240mm/1/5mm/2.5mm/2mins 47secs.

CORONAL INVERSION RECOVERY-PREPARED FAST SPOiled GRADIENT ECHO
(IRFSPGR):
TE/TR/Inversion time (TI)/flip angle/number of slices/bandwidth/matrix/FOV/NEX/
slice thickness/spacing/ imaging time:
4.2ms/15.5ms/450ms/20/124/10.7kHz/256x192/240mm/1/1.5mm/0mm/6mins 56secs.

DUAL ECHO CONVENTIONAL SPIN ECHO (CSE):
TE/TR/number of slices/band width/matrix/FOV/NEX/slice thickness/spacing/imaging time:
30ms +120ms/2000ms/28/15.6 kHz +12.5kHz/256 x 192/240mm/1/5mm/0mm/10 mins 24secs.

FAST FLUID ATTENUATED INVERSION RECOVERY (FAST FLAIR) (Wiesmann et al., 1996):
TE/TR/TI/number of slices/band width/matrix/FOV/NEX/slice thickness/spacing/echo
train length (ETL)/imaging time:
The CSE and fast FLAIR sequences were acquired in the coronal oblique plane, with slices arranged orthogonal to the long axis of the hippocampus.

3.3.2 Qualitative MRI reporting
All images were visually assessed by two experienced neuroradiologists (Dr John Stevens and Dr Brian Kendall) who were blinded as to whether the subject was a patient or a neurologically normal volunteer. No clinical details were provided. Lesions were classified according to position and presumed pathology, and a judgement was made as to whether visible cerebral and/or cerebellar atrophy were present.

3.3.3 Quantitative hippocampal MRI analysis
MEASUREMENT OF HIPPOCAMPAL VOLUME
All hippocampal volume (HV) measurements were made by one of two raters (Alex Everitt, Kim Birnie) who were blinded as to subject status. Both raters had spent approximately 3 months learning and perfecting the technique of HV measurement, with instruction from a physicist, Dr Samantha Free, who had helped prove the method’s accuracy and reproducibility a year or two earlier. Each rater practiced measuring the hippocampi of a bank of 20 epilepsy patients, until their results were consistent with those produced by the “gold standard”, Dr Free. Only then did each rater commence measurement of HV for the purposes of studies 2 to 5.

IRFSPGR images (124 slices per dataset) were transferred from the scanner to a remote workstation (Advantage Windows 1.2, GE Medical Systems, Milwaukee, USA). Pre-set window widths and levels were selected to provide optimal visualisation of the grey/white matter interface. At x 4 magnification, the cross-sectional area of each hippocampus was outlined manually in all slices where it was visible, using a mouse-driven cursor (Figure 3).

Measurement commenced at the posterior limit of the hippocampus, defined anatomically as the slice showing the greatest length of the fornix. The mesial limit of the hippocampus was defined by the open end of the hippocampal fissure in its posterior and middle
Figure 3 Measurement of hippocampal T2 relaxation time and volume

1. Measurement of hippocampal T2 (HT2):
   - Region of interest
   - 88 milliseconds

2. Measurement of hippocampal volume (HV):
   - Cross-sectional area
   - 45 mm²
   - Posterior
   - Anterior
portions, and the uncal fissure more anteriorly. The uncus was included up to the point where cerebro-spinal fluid (CSF) was visible superiorly, separating the amygdala from the hippocampus. The alveus, fimbria, subiculum, and choroid plexus were all included in the measurements, but the white matter of the parahippocampal gyrus was excluded inferiorly. The hippocampal head was tracked by moving infero-laterally, until it could no longer be distinguished from the amygdala. This method, and the anatomical landmarks employed, has been previously described by Cook et al. (1992).

HV was calculated by multiplying the slice thickness (1.5mm) by the sum of all hippocampal cross-sectional areas on each side (Cavalieri’s principle) (Gunderson and Jensen, 1987). A hippocampal volume ratio (HVR) was obtained in each subject by dividing the smaller HV by the larger HV.

MEASUREMENT OF INTRACRANIAL VOLUME

Intracranial volume (ICV) was measured in the same session as HV measurement, by the same raters, using the following method. Cross-sectional intracranial areas were manually outlined in 9 slices (every tenth slice) of the IRFSPGR sequence, and the sum of these cross-sectional areas was multiplied by the distance between the measured slices (15mm) to yield a value approximating to the ICV.

CORRECTION OF HIPPOCAMPAL VOLUME FOR INTRACRANIAL SIZE

HV was corrected for ICV (termed HVc) using a covariance method, as described previously by Free et al. (1995). In Free’s study, correction of HV via ICV produced the most consistent reduction in standard deviation for HV, compared to other correction measures such as cerebral volume or single slice cranial area. The method derives a corrected hippocampal volume via the following equation:

\[ HV_c = HV - \text{Grad} \times (ICV_i - ICV_{\text{mean}}) \]

where:

- \( HV_c \) = corrected hippocampal volume
- \( HV \) = uncorrected (measured) hippocampal volume
- \( \text{Grad} \) = gradient of the regression line between HV and ICV (control data)
ICV<sub>s</sub> = ICV in the subject
ICV<sub>mean</sub> = mean ICV (in 170 control subjects)

For correction of HV in this study, Grad and mean ICV were determined from all 170 neurologically normal control subjects.

MEASUREMENT OF HIPPOCAMPAL T2 RELAXATION TIME

All hippocampal T2 relaxation time (HT2) measurements were made by one of two raters (Kim Birnie, Phillipa Bartlett) who were unaware of the clinical status of the individual subject being assessed.

A dual echo method of measuring HT2 was used, as described and validated previously by Duncan et al. (1996), using the same scanner and post-processing workstation as employed in Duncan et al.'s study. Firstly, dual echo CSE images were transferred to a remote workstation (Sun SPARC workstation, Sun Microsystems, CA, USA). An in-house software programme, "Signa2unc" (Dr Gareth Barker, Institute of Neurology), was then used to convert the images into a file which could be viewed in the UNC format. A second in-house software programme, "calcT2" (Dr Gareth Barker, Institute of Neurology), took the paired images of the dual echo conventional spin echo sequence and, via the equation below, yielded an integer value of signal intensity per pixel (Duncan et al., 1996):

\[
T2 = \frac{(TE_2 - TE_1)}{\ln(S_1/S_2)}
\]

where:
- \( T2 \) = value of T2 signal intensity
- \( TE_1 \) = early echo TE
- \( TE_2 \) = late echo TE
- \( S_1 \) = signal intensity in the early echo image
- \( S_2 \) = signal intensity in the late echo image
- ln = natural log

The T2 calculation format UNC images were then viewed using the "display UNC" software programme (UCL Department of Medical Physics and Bioengineering, London), utilising preset window width and levels to provide optimal grey/white matter contrast. An
elliptical region of interest of approximately 20mm$^2$ was placed within the hippocampus on all sequential 5mm slices in which the hippocampi were visible (usually 5 or 6 slices, depending on hippocampal length), and the T2 signal average within each region of interest was recorded (Figure 3). Care was taken to avoid hippocampal boundaries and partial volume effect from CSF. Mean HT2 values for the entire length of each hippocampus were later calculated for each subject from these data.

3.3.4 Intra-rater and inter-rater reliability

1. The intra-class correlation coefficient (ICC) for reproducibility of HV measurement was calculated using the MRI datasets of 10 control subjects which were measured on 3 separate occasions over a 2 year period (0 months, 12 months and 24 months) by both HV raters.

2. The ICC for reproducibility of HT2 measurement was calculated using the MRI datasets of 20 control subjects which were measured twice by both HT2 raters, at 12 months and 18 months into the study period, respectively.

The ICC was calculated using the formula below:

$$ICC = \frac{S_b^2 - S_w^2}{S_b^2 + (N-1)S_w^2}$$

where:
- $S_b^2$ = mean square of between subject variation
- $S_w^2$ = mean square of within subject variation
- $N$ = number of raters

3.3.5 Quality assurance: reproducibility of MRI data

Quality assurance for the scanning hardware and software was performed regularly throughout the duration of image acquisition.

In order to monitor subtle fluctuations in voxel size, a standard phantom was scanned weekly using the IRFSPGR volumetric acquisition. Each dataset was co-registered to the baseline scan using an in-house software programme, “MRreg” (Lemieux and Barker,
1998), which adjusted, by iteration, 9 parameters defining the relative position, orientation and scaling factors between the baseline and matched scans.

A range of standard (Eurospin II MR quality assessment) gels with pre-defined T2 values (range 73-183 milliseconds, median 136.5 ms at 19°C) similar to intracranial structures were also scanned weekly, using the dual echo CSE sequence. These gels were kept in a constant environment to negate any potential effect of temperature upon T2 relaxation (Duncan et al., 1996).

3.3.6 Statistical analysis
All statistical analysis was performed using SPSS for Windows, version 8.0 (SPSS Inc., Chicago, IL). For analysis of normally-distributed data, unpaired and paired T-tests were used, and for non-parametric data, Kruskal-Wallis and Mann-Whitney U tests were used. Pearson’s correlation coefficient (r) was used where indicated.

3.3.7 Ethical approval
Ethical approval for this study was granted by the Joint Ethical Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. Permission to perform high resolution MRI was only requested for subjects of 14 years or over.

All 5 studies were generously funded by the Wellcome Trust.
CHAPTER 4
Study 1:
A prospective population based incidence and prevalence study of epilepsy in Buckinghamshire, UK

4.1 Introduction
Contemporary knowledge of the age-specific incidence and prevalence of the epilepsies is vital for effective planning of health care, particularly with respect to newly diagnosed and chronic active epilepsy, epilepsy in remission, and febrile seizures. As discussed in chapters 1 and 2, these epidemiological data are best obtained through prospective studies of large unselected populations which apply rigorous case ascertainment and high levels of investigation in all patients (Sander and Shorvon, 1996).

In this study, the advantages of the structure of the UK primary health care system were utilised in order to prospectively identify unselected cohorts of (1) adults with newly diagnosed seizures (2) adults with chronic active epilepsy (3) adults and children with active epilepsy and epilepsy in remission and (4) children with febrile seizures. The age-specific incidence and prevalence rates, and cumulative incidence rates are presented, as are the demographic and clinical characteristics of the adult incident and prevalent patient populations.

4.2 Aims and hypotheses

Aim
To define the age-specific incidence (in adults and children) and prevalence (in adults alone) of epilepsy, including chronic active epilepsy, in a community based population of approximately 200,000 people by means of prospective case ascertainment. The cohorts of patients identified in this study will subsequently be investigated in studies 3, 4 and 5, and compared with the cohort of control subjects identified in study 2.

Hypotheses
1. The incidence of epilepsy is now greater in the elderly than it is amongst children.

2. The prevalence of chronic active epilepsy, as defined by a history of at least 2
unprovoked seizures over a minimum of 4 years (with at least 1 seizure during the preceding 12 months), will be substantially less than the prevalence of active epilepsy (using standard ILAE criteria), as defined by a correct diagnosis of epilepsy and a history of at least 1 seizure during the preceding 5 years (irrespective of AED treatment status).

4.3 Methods
The methodology for this study is as described in detail in Chapter 2, and is only outlined below.

4.3.1 Quality control for note audit
In order to check the sensitivity of the detailed note audit, the case records in one health centre (2896 registered patients; 1.4% of the study population) were re-examined three months later by a second team of medical students. The principal investigator reviewed all records on each occasion so as to determine the false negative rates for case detection of newly diagnosed and chronic active epilepsy patients.

4.3.2 Incidence study
The population base comprised 207,553 persons (Table 7). The age profile of this population was almost identical to that of the 1996 England and Wales population. Ascertainment of incident (newly diagnosed) cases continued for 24 months (1.6.95 to 31.5.97 inclusive). In children, seizures were categorised as either febrile or afebrile. In adults, a decision was made as to whether seizures were provoked or unprovoked (ILAE, 1993). Age-specific incidence rates, corrected for the 1996 England and Wales population, and cumulative incidence rates, were determined. As a consequence of the detailed note audit being performed up to 8 months before the completion of the incidence study period in 17 of the health centres, the number of adult incident cases detected solely by this method of ascertainment was extrapolated to yield an additional, maximal annual incidence rate for adult newly diagnosed seizures amongst the 175,000 population whose notes were searched.

The median age at diagnosis, median duration of seizures and classification of seizure types were obtained in all adult patients with newly diagnosed seizures.
Table 7  Age and sex structure of incidence study population and also the England and Wales population (OPCS\(^\dagger\) data, mid-1996)

<table>
<thead>
<tr>
<th>Age group/years</th>
<th>Incidence study population</th>
<th>England and Wales population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0-4</td>
<td>6,276</td>
<td>5921</td>
</tr>
<tr>
<td>5-14</td>
<td>12,636</td>
<td>12,138</td>
</tr>
<tr>
<td>15-24</td>
<td>11,949</td>
<td>12,189</td>
</tr>
<tr>
<td>25-34</td>
<td>16,257</td>
<td>15,829</td>
</tr>
<tr>
<td>35-44</td>
<td>15,443</td>
<td>14,889</td>
</tr>
<tr>
<td>45-54</td>
<td>15,699</td>
<td>15,069</td>
</tr>
<tr>
<td>55-64</td>
<td>11,340</td>
<td>10,688</td>
</tr>
<tr>
<td>65-74</td>
<td>7,909</td>
<td>8,902</td>
</tr>
<tr>
<td>75+</td>
<td>5,104</td>
<td>9,313</td>
</tr>
<tr>
<td>Total</td>
<td>102,614</td>
<td>104,938</td>
</tr>
</tbody>
</table>

\(^\dagger\)OPCS  Office of Population Census and Surveys
4.3.3 Prevalence study of chronic active epilepsy in adults

A subset (159,388 adults) of the incidence study population was used to determine the prevalence of chronic active epilepsy (see section 3.2.1). This was defined as a four or more year history on prevalence day (1.6.96) of at least 2 unprovoked epileptic seizures, with a minimum of one seizure having occurred during the preceding 12 months. Age-specific prevalence rates were determined. The prevalence of chronic active epilepsy in children (14 years and under) was not calculated.

The median age at diagnosis, median duration of seizures and classification of seizure types were obtained in all adult patients with chronic active epilepsy. The total number of lifetime seizures and the average frequency of seizures in the 2 years prior to assessment were estimated in those patients with chronic active epilepsy who attended for high resolution MRI.

4.3.4 Prevalence of active and epilepsy in remission (using ILAE definitions) and of isolated seizures in a population of 12,178 adults and children (ILAE, 1993):

To investigate the effect of the duration of remission on point prevalence in a smaller population of 12,178 adults and children, a second analysis of the prevalence of active epilepsy (two or more unprovoked seizures with at least one during the preceding 5 years) and epilepsy in remission (inactive epilepsy: the absence of seizures for 5 or more years) was performed using standard ILAE definitions (ILAE, 1993). An additional subcategorisation according to AED treatment status was made.

4.4 Results

4.4.1 Quality control for notes audit

One additional newly diagnosed patient, undetected by the first note search, was ascertained in the re-examination of 2896 case records 3 months later (see section 3.2.5, active surveillance, part E). Two extra patients fulfilling the criteria for chronic active epilepsy were also detected in this way. One subject with chronic active epilepsy who was ascertained in the first note search was missed by the second. Overall, this yielded false negative rates of less than 0.1% for the detection of both newly diagnosed and chronic active epilepsy cases.
4.4.2 Incidence and characteristics of incident (newly diagnosed) cases

Between 1.6.95 and 31.5.97, 98 infants with incident febrile seizures, and 219 adults and children with newly diagnosed afebrile seizures were ascertained.

165 adults (144 definite, 21 probable; 89 males) had newly diagnosed seizures: 39 provoked (23.6%, 27 males) and 126 unprovoked (76.4%, 62 males). 89 patients were directly referred to the NSE and 30 were ascertained by computer searches. The note search disclosed the remaining 46 patients, and confirmed all cases ascertained by referral or computer searches. The notes of a further 355 possible patients were examined and found not to indicate epilepsy or isolated seizures. The diagnosis in these cases is listed in Table 8.

INCIDENCE RATES

A. Febrile seizures

The crude annual incidence of febrile seizures (NIH consensus statement 1980) was 402/100,000 in all 0-4 year olds (95% confidence intervals 289-514), 446/100,000 (95% CI 281-611) in males and 355/100,000 (95% CI 203-506) in females.

B. Afebrile seizures

The figures for age-specific, sex-specific and cumulative incidence of newly diagnosed afebrile seizures (children and adults) are shown in Table 9. The crude annual incidence was 52.8/100,000 (95% CI 42.9-62.6). For males and females, rates were 57.5/100,000 (95% CI 42.8-72.2) and 48.1/100,000 (95% CI 34.9-61.4), respectively. The standardised, age-corrected incidence was 53.6/100,000. The cumulative incidence of afebrile seizures in males and females was 5.7% by 75+ years (males 6.5%, females 5.1%). The age-specific and sex-specific incidence rates of provoked and unprovoked seizures for adults from the whole study population (207,553 persons) are shown in Table 10. The crude annual incidence rates of provoked and unprovoked seizures in adults were 11.4/100,000 (males 16.1/100,000, females 6.9/100,000) and 36.9/100,000 (no significant gender difference), respectively (see Table 9 for 95% CI). The annual incidence of all (provoked and unprovoked) newly diagnosed seizures in adults alone was 48.4/100,000 (males 53.2/100,000, females 43.7/100,000).
Table 8 Neurological diagnoses in 355 adults excluded from the incidence study

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Investigators' assessment</th>
<th>Ascertainment via note audit</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope †</td>
<td>42</td>
<td>54</td>
<td>96</td>
</tr>
<tr>
<td>Unknown loss of consciousness ‡</td>
<td>23</td>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td>Panic attack or hyperventilation syndrome</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>First seizure diagnosed previously (prior to study start date)</td>
<td>6</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>Other psychiatric disorder</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Transient global amnesia</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Vestibular disorder</td>
<td>1</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Severe alcohol intoxication</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rigor</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Oculogyric crisis</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Photomyoclonus</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anticonvulsant for disorders other than epilepsy *</td>
<td>0</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Miscellaneous +</td>
<td>0</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Post-neurosurgery anticonvulsant (seizure prophylaxis)</td>
<td>0</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>258</td>
<td>355</td>
</tr>
</tbody>
</table>

* The patients were examined by the study team. They had a full clinical assessment with blood tests and some/all of the following investigations: electrocardiography (ECG), electroencephalographic (EEG) studies and MRI

** All subjects ascertained via note audit, but assessed and investigated by other physicians

† Includes pre-syncope, syncope and syncope with clonic jerking

• New anticonvulsant prescription for neuralgia or neuropathy (44), bipolar disorder (17)

‡ Loss of consciousness of unknown cause, but seizures considered unlikely following full investigation

+ Miscellaneous conditions including: dementia (7), transient ischaemic attacks (4), migraine (3), others (25)
Table 9  Age-specific incidence of newly diagnosed afebrile seizures

<table>
<thead>
<tr>
<th>Age group/years</th>
<th>Population size</th>
<th>n</th>
<th>Incidence rate</th>
<th>Cumulative incidence (%)</th>
<th>Population size</th>
<th>n</th>
<th>Incidence rate</th>
<th>Cumulative incidence (%)</th>
<th>Population size</th>
<th>n</th>
<th>Incidence rate</th>
<th>Cumulative incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>12197</td>
<td>22</td>
<td>90.2</td>
<td>0.5</td>
<td>6276</td>
<td>12</td>
<td>95.6</td>
<td>0.5</td>
<td>5921</td>
<td>10</td>
<td>84.4</td>
<td>0.4</td>
</tr>
<tr>
<td>5-14</td>
<td>24775</td>
<td>32</td>
<td>64.6</td>
<td>1.1</td>
<td>12636</td>
<td>17</td>
<td>67.3</td>
<td>1.2</td>
<td>12138</td>
<td>15</td>
<td>61.8</td>
<td>1.0</td>
</tr>
<tr>
<td>15-24</td>
<td>24138</td>
<td>25</td>
<td>51.8</td>
<td>1.6</td>
<td>11949</td>
<td>9</td>
<td>37.7</td>
<td>1.5</td>
<td>12189</td>
<td>16</td>
<td>65.6</td>
<td>1.7</td>
</tr>
<tr>
<td>25-34</td>
<td>32086</td>
<td>30</td>
<td>46.8</td>
<td>2.1</td>
<td>16257</td>
<td>19</td>
<td>58.4</td>
<td>2.1</td>
<td>15829</td>
<td>11</td>
<td>34.8</td>
<td>2.0</td>
</tr>
<tr>
<td>35-44</td>
<td>30332</td>
<td>18</td>
<td>29.7</td>
<td>2.4</td>
<td>15443</td>
<td>13</td>
<td>42.1</td>
<td>2.5</td>
<td>14889</td>
<td>5</td>
<td>16.8</td>
<td>2.2</td>
</tr>
<tr>
<td>45-54</td>
<td>30768</td>
<td>25</td>
<td>40.6</td>
<td>2.8</td>
<td>15699</td>
<td>12</td>
<td>38.2</td>
<td>2.9</td>
<td>15069</td>
<td>13</td>
<td>43.1</td>
<td>2.6</td>
</tr>
<tr>
<td>55-64</td>
<td>22029</td>
<td>21</td>
<td>47.7</td>
<td>3.3</td>
<td>11340</td>
<td>13</td>
<td>57.3</td>
<td>3.5</td>
<td>10688</td>
<td>8</td>
<td>37.4</td>
<td>3.0</td>
</tr>
<tr>
<td>65-74</td>
<td>16811</td>
<td>19</td>
<td>56.5</td>
<td>3.8</td>
<td>7909</td>
<td>11</td>
<td>69.5</td>
<td>4.2</td>
<td>8902</td>
<td>8</td>
<td>44.9</td>
<td>3.5</td>
</tr>
<tr>
<td>75+</td>
<td>14417</td>
<td>27</td>
<td>93.6</td>
<td>5.7</td>
<td>5104</td>
<td>12</td>
<td>117.6</td>
<td>6.5</td>
<td>9313</td>
<td>15</td>
<td>80.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Total</td>
<td>207,553</td>
<td>219</td>
<td>52.8 (95% CI 42.9 - 62.6)</td>
<td></td>
<td>102,614</td>
<td>118</td>
<td>57.5 (95% CI 42.8 - 72.2)</td>
<td></td>
<td>104,938</td>
<td>101</td>
<td>48.1 (95% CI 34.9 - 61.4)</td>
<td></td>
</tr>
</tbody>
</table>

Incidence figures are mean annual incidence rates (per 100,000), calculated using the number of incident cases (n) ascertained over a 2 year study period (1.6.95 - 31.5.97).

95% CI  95% confidence intervals
Table 10  Age-specific incidence of newly diagnosed provoked and unprovoked seizures in adults (subjects of 15 years or over)

| Age group/years | Provoked seizures | | | | Unprovoked seizures | | | |
|-----------------|-------------------|---|---|---|-------------------|---|---|
|                 | n  | Annual incidence rate/100,000 | | | n  | Annual incidence rate/100,000 | | |
|                 | All | Male | Female | | All | Male | Female | |
| 15-24           | 5   | 10.4 | 8.4    | 12.3 | 20  | 41.4 | 29.3    | 53.3 |
| 25-34           | 7   | 10.9 | 18.5   | 3.2  | 23  | 35.8 | 40.0    | 31.6 |
| 35-44           | 6   | 9.9  | 19.4   | 0    | 12  | 19.8 | 22.7    | 16.8 |
| 45-54           | 9   | 14.6 | 12.7   | 16.6 | 16  | 26.0 | 25.5    | 26.6 |
| 55-64           | 6   | 13.6 | 22.1   | 4.7  | 15  | 34.1 | 35.3    | 32.8 |
| 65-74           | 4   | 11.9 | 19.0   | 5.6  | 15  | 44.6 | 50.6    | 39.3 |
| 75+             | 2   | 6.9  | 9.8    | 5.4  | 25  | 86.7 | 107.8   | 75.2 |
| Total           | 39  | 11.4 | 16.1   | 6.9  | 126 | 36.9 | 37.0    | 36.8 |
| 95% CI          | 6.4 - 16.5 | 7.5 - 24.7 | 1.4 - 12.4 | 27.8 - 46.1 | 24.0 - 50.1 | 24.1 - 49.6 |

n  number of incident cases during 2 year study period

95% CI  95% confidence intervals
By extrapolating the note audit data (see sections 3.2.5 and 4.3.2), a maximum annual incidence of 52.8/100,000 was calculated from the estimate that an additional 15 newly diagnosed adults might have been ascertained had the entire note search been performed at the conclusion of the study period. This incidence rate was coincidentally identical to the crude annual incidence of afebrile seizures in all adults and children, as recorded above. The incidence data shown in Figures 9 and 10, and all subsequent calculations, use the “raw” incidence data and do not use or include any of these extrapolated figures.

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE ADULT INCIDENT CASES

A. Age at ascertainment
Of all 219 subjects (median age 35 years, range 0.1-91 years) with afebrile seizures, 54 (24.7%) were children (≤14 years), and 165 (75.3%) were adults. 46 (27.9%) of the adults were elderly (≥65 years).

In adult patients, the median age at presentation (ascertainment) was 49 years (range 15-91 years). The age at presentation was very similar for provoked (median 48 years, range 17-91 years) and unprovoked (median 50.5 years, range 15-90 years) seizures.

B. Number of seizures at presentation
110/165 adults (66.6%, 65 males) presented with an isolated seizure. The median duration of follow up from ascertainment to classification was 14 months (range 0-27 months). At classification, 41/110 (37.3%) patients with an initially isolated seizure had experienced at least one further seizure.

55 (33.3%) adults presented with a history of two or more seizures. Of these, 17 (30.9%, 7 males) had a history of previously unsuspected seizures lasting at least one year. In one subject, hitherto unrecognized simple partial seizures had been present for approximately 18 years. Diagnosis usually followed the occurrence of a first ever generalized tonic-clonic seizure (GTCS). The median age at diagnosis in these 17 patients was 34 years (range 17-69 years). 13 had experienced simple partial seizures (SPS) or complex partial seizures (CPS), and 4 had myoclonic jerks (MJ) or absences, for more than 1 year.
C. Duration and number of seizures at time of MRI

The median duration of seizures at the time of MRI was 0.2 years (range 0-18 years) for the 110 adult incident cases (median age 40 years, range 15-71 years) who had high resolution MRI. The median numbers of GTC and non-GTC seizures per patient were 1 (range 0-8) and 0 (range 0-1500), respectively.

D. Seizure types

Seizures were classified as partial onset in 97/165 adults (58.8%, 85 unprovoked, 12 provoked), generalised in 65 (39.4%, 39 unprovoked, 26 provoked) and unclassifiable in 2 (1.2%, 1 unprovoked, 1 provoked). One (0.6%, unprovoked) had mixed partial and generalised seizure types (SPS, secondarily generalised tonic-clonic seizures (SGTCS) and MJ).

Amongst the patients with generalised seizures, 61 had GTCS alone, and 4 had GTCS with another seizure type. In those with partial onset seizures, 67 had one seizure type (40 secondarily generalised tonic-clonic seizures (SGTCS); 22 CPS; 5 SPS) and 30 had at least 2 seizure types (27 SGTCS with CPS and/or SPS; 3 SPS with CPS).

4.4.3 Prevalence of chronic active epilepsy in adults and characteristics of prevalent cases

279 adults (131 males) had chronic active epilepsy on the prevalence day, 1.6.96. All were ascertained through the computerised database searches and/or the notes search.

PREVALENCE RATES

The crude prevalence for chronic active epilepsy in adults was 1.8/1000 (95% CI 1.6-2.0/1000). Table 11 shows age-specific and sex-specific prevalence rates.

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE ADULT PREVALENT CASES

A. Age at ascertainment

The median age at ascertainment was 38 years (range 15-93 years). 48 (17.2%) were aged over 65 years.

B. Number of seizures in lifetime and seizure frequency in those who had MRI
<table>
<thead>
<tr>
<th>Age group/years</th>
<th>Population size</th>
<th>n</th>
<th>Prevalence/1000</th>
<th>95% CI</th>
<th>Population size</th>
<th>n</th>
<th>Prevalence/1000</th>
<th>95% CI</th>
<th>Population size</th>
<th>n</th>
<th>Prevalence/1000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>22170</td>
<td>49</td>
<td>2.2</td>
<td>1.6 - 2.8</td>
<td>11008</td>
<td>20</td>
<td>1.8</td>
<td>1.0 - 2.6</td>
<td>11162</td>
<td>29</td>
<td>2.6</td>
<td>1.7 - 3.5</td>
</tr>
<tr>
<td>25-34</td>
<td>30396</td>
<td>68</td>
<td>2.2</td>
<td>1.7 - 2.8</td>
<td>15361</td>
<td>31</td>
<td>2.0</td>
<td>1.3 - 2.7</td>
<td>15036</td>
<td>37</td>
<td>2.5</td>
<td>1.7 - 3.2</td>
</tr>
<tr>
<td>35-44</td>
<td>28571</td>
<td>46</td>
<td>1.6</td>
<td>1.2 - 2.1</td>
<td>14530</td>
<td>24</td>
<td>1.7</td>
<td>1.0 - 2.3</td>
<td>14042</td>
<td>22</td>
<td>1.6</td>
<td>0.9 - 2.2</td>
</tr>
<tr>
<td>45-54</td>
<td>28699</td>
<td>34</td>
<td>1.2</td>
<td>0.8 - 1.6</td>
<td>14647</td>
<td>18</td>
<td>1.2</td>
<td>0.7 - 1.8</td>
<td>14052</td>
<td>16</td>
<td>1.1</td>
<td>0.6 - 1.7</td>
</tr>
<tr>
<td>55-64</td>
<td>20394</td>
<td>34</td>
<td>1.7</td>
<td>1.1 - 2.2</td>
<td>10507</td>
<td>17</td>
<td>1.6</td>
<td>0.9 - 2.4</td>
<td>9887</td>
<td>17</td>
<td>1.7</td>
<td>0.9 - 2.5</td>
</tr>
<tr>
<td>65-74</td>
<td>15595</td>
<td>28</td>
<td>1.8</td>
<td>1.1 - 2.5</td>
<td>7307</td>
<td>16</td>
<td>2.2</td>
<td>1.1 - 3.3</td>
<td>8288</td>
<td>12</td>
<td>1.5</td>
<td>0.6 - 2.3</td>
</tr>
<tr>
<td>75+</td>
<td>13563</td>
<td>20</td>
<td>1.5</td>
<td>0.8 - 2.1</td>
<td>4780</td>
<td>5</td>
<td>1.1</td>
<td>0.1 - 2.0</td>
<td>8783</td>
<td>15</td>
<td>1.7</td>
<td>0.8 - 2.6</td>
</tr>
<tr>
<td>Total</td>
<td>159,388</td>
<td>279</td>
<td>1.8</td>
<td>1.6 - 2.0</td>
<td>78,139</td>
<td>131</td>
<td>1.7</td>
<td>1.4 - 2.0</td>
<td>81,249</td>
<td>148</td>
<td>1.8</td>
<td>1.5 - 2.1</td>
</tr>
</tbody>
</table>

*Study definition for chronic active epilepsy: 4 or more year history of epilepsy (at least 2 unprovoked seizures) and at least 1 seizure during preceding 12 months, on prevalence day, 1.6.96.

95% CI  95% confidence intervals
In the 175 adult patients who had high resolution MRI (see chapter 5), the median estimated lifetime number of tonic-clonic (primary or secondary generalised) seizures was 12 (range 0-1500), and the median estimated lifetime number of non-tonic-clonic (partial, absence or myoclonic) seizures was 100 (range 0-160,000).

The estimated frequencies of generalised tonic-clonic seizures over the preceding 2 years were: >1/week (0%), 1/week-1/month (10.9%), 1/month-1/year (39.4%), <1/year (40.6%) and none (9.1%), and the estimated frequencies all other seizure types (combined) were: >1/week (22.3%), 1/week-1/month (22.3%), 1/month-1/year (29.1%), <1/year (8.0%) and none (18.3%).

C. Age at diagnosis and duration of epilepsy
The median age at diagnosis of epilepsy was 15.5 years (range 0-84 years). The median duration of epilepsy was 19.5 years (range 4-73 years).

D. Number of AEDs
Subjects with chronic active epilepsy were taking a median of one AED (range 0-4).

E. Seizure types
176/279 (63.1%) had partial onset, 65 (23.3%) had generalised, 8 (2.9%) had mixed, and 30 (10.8%) had unclassifiable seizures.

In patients with generalised seizures, 35 had GTCS alone, 28 had GTCS and another seizure type, and 2 had other generalised seizures alone. In those with partial onset seizures, 50 had a single seizure type (32 SGTCS; 17 CPS; 1 SPS) and 126 had at least 2 seizure types (119 SGTCS with CPS and/or SPS; 7 SPS with CPS). In the 8 with mixed seizure types, various combinations of partial and generalised seizures were seen.

4.4.4 Prevalence of active and inactive epilepsy in a population of 12,178
The search of 12,178 patient records led to the ascertainment of 199 patients with a lifetime history of afebrile seizures, including 152 adults and 9 children with epilepsy (a history of at least 2 unprovoked seizures). The prevalence rates of active and inactive epilepsy (ILAE 1993) were 5.6/1000 (95% CI 4.3-6.9) and 7.6/1000 (95% CI 6.1-9.2),
respectively (Table 12). The point prevalence of epilepsy, as defined by at least 2 unprovoked seizures and either the occurrence of a seizure within the preceding 5 years or an active AED prescription (Hauser and Kurland, 1975; Granieri et al., 1983; Maremmani et al., 1991; Forsgren, 1992), was 9.7/1000. The proportion receiving AEDs is also shown in Table 12.

4.5 Discussion

4.5.1 Summary of major findings

The age-corrected incidence of all newly diagnosed afebrile seizures was 52.8/100,000 per year, with a cumulative incidence of 5.7% by 75+ years of age. Provoked and unprovoked seizures comprised a quarter and three quarters of all adult newly diagnosed afebrile seizures, respectively. Incidence rates were greatest in children and in the elderly, and higher in males than in females. The incidence rate of first febrile seizures was 0.4% of 0-4 year olds.

The age-corrected prevalence of adult chronic active epilepsy (median duration of 19.5 years), using the study definition, was 1.8/1000, whereas the rates of active and inactive epilepsy, using standard ILAE definitions, were 5.6/1000 and 7.6/1000, respectively. There was no significant gender difference in prevalence rates, irrespective of the definition used.

Two thirds of all adults with newly diagnosed unprovoked seizures and chronic active epilepsy had partial onset seizures, but those with newly diagnosed provoked seizures were twice as likely to have had seizures classified clinically as of generalised onset. Two thirds of all adults with newly diagnosed seizures presented with an isolated seizure, although a third of these experienced further seizures by the time of study classification (a median time of 14 months later).

4.5.2 Relevance of findings and related methodological issues

Meticulous active surveillance (Hart et al., 1989; Cockerell et al., 1993; MacDonald et al., 2000a) permitted high levels of case ascertainment, although no method alone provided absolute ascertainment. The search of 175,000 patient records formed the gold standard of case ascertainment, particularly in newly diagnosed adults, 28% of whom were picked up by this method alone. The quality control results indicate the high degree of accuracy.
Table 12  Point prevalence rates for active epilepsy, epilepsy in remission and isolated unprovoked seizures in a population of 12,178

<table>
<thead>
<tr>
<th>Patient category</th>
<th>All</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Prevalence per 1000</td>
<td>95% CI</td>
</tr>
<tr>
<td>Active epilepsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receiving AED</td>
<td>61</td>
<td>5.0</td>
<td>3.8 - 6.3</td>
</tr>
<tr>
<td>Not receiving AED</td>
<td>7</td>
<td>0.6</td>
<td>0.1 - 1.0</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>5.6</td>
<td>4.3 - 6.9</td>
</tr>
<tr>
<td>Epilepsy in remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receiving AED</td>
<td>50</td>
<td>4.1</td>
<td>3.0 - 5.2</td>
</tr>
<tr>
<td>Not receiving AED</td>
<td>43</td>
<td>3.5</td>
<td>2.5 - 4.6</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>7.6</td>
<td>6.1 - 9.2</td>
</tr>
<tr>
<td>Isolated unprovoked seizure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>1.7</td>
<td>1.0 - 2.5</td>
</tr>
<tr>
<td>Provoked seizure(s) without subsequent unprovoked seizures</td>
<td>17</td>
<td>1.4</td>
<td>0.7 - 2.1</td>
</tr>
</tbody>
</table>

Prevalence data calculated from the detailed audit of a single GP health centre (n = 12,178 persons) on prevalence day 1.12.96. Definitions from the 1993 ILAE Guidelines for Epidemiological Studies:

**Active epilepsy:**
- history of epilepsy (at least 2 unprovoked seizures) and at least 1 seizure during preceding 5 years

**Epilepsy in remission:**
- history of epilepsy, with remission of seizures for 5 or more years

**AED**
- antiepileptic drug

**95% CI**
- 95% confidence intervals (* indicates insufficient patient numbers to yield confidence intervals)
of this method. The false negative rate was extremely low, and the possibility of false positive pick-ups was eliminated as far as possible by the assessments of all cases by the principal investigator and study team. The possibility of false positive cases, particularly amongst the incident patients referred for investigation, should also be considered. Such patients may have been more likely to receive a new diagnosis of seizures or epilepsy than those, for example, whose notes were reviewed in the note audit and not personally seen. Classification of all patients seen by the principal investigator, however, and a decision as to whether they should be included in the study, was made by a panel of three very experienced epileptologists and, for this reason, the likelihood of false positive cases was considered to be small.

Isolated searches of computerised medical records were insufficient in detecting these patients for three reasons. Firstly, GPs did not reliably enter computer-coded epilepsy diagnoses and/or indications for AED prescriptions onto these databases. Secondly, GPs sometimes did not assign epilepsy diagnostic codes in patients with isolated seizures and, thirdly, isolated seizures are not often treated with AEDs in the UK, precluding detection through new AED prescriptions, usually a reliable and comprehensive method (Wallace et al., 1998).

INCIDENCE
The age-corrected annual incidence of newly diagnosed afebrile seizures was 52.8/100,000, marginally lower than the rates reported in two recent studies (Loiseau et al., 1990a; Jallon et al., 1997) using comparable inclusion criteria (Table 13). The age-corrected rate was highest in males, as observed in several previous incidence studies (Keranen et al., 1989; Forsgren, 1990; Hauser et al., 1993; Olafsson et al., 1996; Jallon et al., 1997). Age-specific incidence showed a bimodal distribution with the highest rates in children and in the elderly, confirming other reports (Hauser et al., 1993; Olafsson et al., 1996; Jallon et al., 1997; Wallace et al., 1998). The cumulative incidence of afebrile seizures increased from 1.1% by 14 years to 3.3% by 64 years, and to 5.7% by 75+ years. Given the background of an expanding elderly population, these data, as well as reports which have suggested an increasing incidence of seizures in the elderly with a concomitant decrease in children (Hauser et al., 1993; Cockerell et al., 1995b; Everitt and Sander, 1998), support the view that more medical resources need to be made available for the management of seizures in
<table>
<thead>
<tr>
<th>First author Country, year</th>
<th>Inclusion criteria</th>
<th>Age-corrected annual incidence of unprovoked seizures per 100,000 person years</th>
<th>Age-corrected annual incidence of provoked seizures per 100,000 person years</th>
<th>Comments about study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forsgren Sweden, 1990</td>
<td>Adults (≥17 years) with newly diagnosed seizures.</td>
<td>34 (95% 25-42)</td>
<td>Not quoted</td>
<td>Prospective. Case ascertainment from referrals and EEG department.</td>
</tr>
<tr>
<td>Loiseau France, 1990</td>
<td>All adults and children with newly diagnosed seizures.</td>
<td>42 (95% CI not provided)</td>
<td>29 (95% CI not provided)</td>
<td>Prospective with complementary retrospective survey.</td>
</tr>
<tr>
<td>Hauser USA, 1993</td>
<td>1. Newly diagnosed unprovoked seizures. 2. Newly diagnosed epilepsy All age groups included.</td>
<td>61 (95% CI not provided)</td>
<td>N/A</td>
<td>Retrospective study of data from 1935-1984.</td>
</tr>
<tr>
<td>Hauser USA, 1995</td>
<td>All adults and children with provoked seizures.</td>
<td>N/A</td>
<td>35 (95% CI not provided): 45 in males, 27 in females</td>
<td>Retrospective study of data from 1935-1984.</td>
</tr>
<tr>
<td>Forsgren Sweden, 1996</td>
<td>Adults (≥17 years) with newly diagnosed seizures.</td>
<td>56 (95% CI 59-93)</td>
<td>20 (95% CI 11-29)</td>
<td>Prospective. Case ascertainment principally hospital-based.</td>
</tr>
<tr>
<td>Olafsson Iceland, 1996</td>
<td>All subjects with newly diagnosed epilepsy (≥2 unprovoked seizures).</td>
<td>47 (95% CI not provided)</td>
<td>N/A</td>
<td>Retrospective. Very small number of patients.</td>
</tr>
<tr>
<td>Jallon Switzerland, 1997</td>
<td>All adults and children with &quot;first seizures&quot;. No precise case definition.</td>
<td>46 (95% CI not provided)</td>
<td>25 (95% CI not provided)</td>
<td>Retrospective. Case ascertainment primarily via an EEG department.</td>
</tr>
<tr>
<td>Wallace UK, 1998</td>
<td>All subjects aged ≥5 years who commenced AED treatment for newly diagnosed epilepsy.</td>
<td>81 (95% CI 77-85)</td>
<td></td>
<td>Data obtained from a computerised database of an unselected population of 2,052,922 persons.</td>
</tr>
<tr>
<td>MacDonald UK, 2000</td>
<td>All subjects with newly diagnosed epilepsy (≥2 unprovoked seizures).</td>
<td>46 (95% CI 36-60)</td>
<td>11 (95% CI 7-18)</td>
<td>Prospective. Large unselected urban population.</td>
</tr>
<tr>
<td>Everitt UK, 2003</td>
<td>Adults (≥15 years) with newly diagnosed seizures.</td>
<td>37 (95% CI 24-50)</td>
<td>11 (95% CI 6-17)</td>
<td>Prospective. Large unselected community-based population.</td>
</tr>
</tbody>
</table>

**Abbreviations:** 95% CI 95% confidence intervals  N/A not applicable EEG electroencephalography AED anti-epileptic drug
the elderly (Tallis et al., 1991; Wallace et al., 1998). The incidence rates observed amongst
the elderly population in this study, however, were not quite as high as have been recently
reported (Loiseau et al., 1990b; Tallis et al., 1991; Hauser et al., 1993; Jallon et al., 1997;
Wallace et al., 1998). This may relate in part to differences in methodology, with most
other studies utilising retrospective case ascertainment via either manual medical record
reviews/surveys (Loiseau et al., 1990b; Hauser et al., 1993; Jallon et al., 1997) or searches
of computerised databases (Tallis et al., 1991; Wallace et al., 1998), both of which may
result in a proportion of incorrectly diagnosed cases (Sander and Shorvon, 1996). In the
current study, diagnostic accuracy was maximal because patients and/or their medical
records were personally assessed by the study team at, or soon after, presentation with the
result that unproven or equivocal new cases were excluded, even when other physicians
had initiated AED treatment.

The annual incidence of newly diagnosed unprovoked seizures in adults (36.9/100,000)
was close to that found by Forsgren (1990) using very similar inclusion criteria, but
somewhat lower than his subsequent study (Forsgren et al., 1996) in which ascertainment
of elderly cases was more complete. It is likely, however, that selection bias influenced
incidence rates in these two studies because both study populations included a large
university hospital, with many newly diagnosed patients ascertained from clinics, wards
or the EEG department.

The age-corrected annual incidence for provoked seizures in adults (11.4/100,000) was
lower than in previous reports (Loiseau et al., 1990a; Annegers et al., 1995; Forsgren et al.,
1996; Jallon et al., 1997) and significantly lower than that for unprovoked seizures. The
incidence was highest in males, as noted elsewhere (Annegers et al., 1995; Jallon et al.,
1997). In the large Rochester study, Annegers and colleagues attributed this to gender
differences in the incidence of alcohol withdrawal and head trauma (Annegers et al., 1995;
Hauser and Annegers, 1997). In contrast to the Rochester study (Hauser and Annegers,
1997), the age-specific rates of incidence of provoked seizures were relatively constant in
this study. Furthermore, provoked seizures comprised approximately 25% of all newly
diagnosed seizures in the current study, whereas Hauser and Annegers estimated the same
proportion to be in the order of 50-80% (Hauser and Annegers, 1997). The putative reasons
for these differences are three-fold. Firstly, in the current study, all childhood data were
excluded from calculations of incidence of provoked seizures. In the Rochester study, age-
specific incidence of afebrile provoked seizures was very high in 0-4 year olds (Annegers
et al., 1995), thus increasing the overall age-corrected rate. Forsgren’s investigation of
provoked seizures in a purely adult population (Forsgren et al., 1996), however, found an
incidence rate much closer to the figure reported in the current study than in the Rochester
study. Secondly, it is theoretically possible that some patients with newly diagnosed
provoked seizures escaped identification, but this seems unlikely considering the thorough
screening methods employed. Finally, the current study was performed in a population
consisting mainly of subjects of high socioeconomic status. It has long been recognised that
epilepsy is associated with markers of social and economic disadvantage, including poor
academic achievement, unemployment, and low income, although the direction of causality
cannot be established by prevalence studies alone. A subsequent and recently published
satellite study investigated the relationship between the incidence of epilepsy and
socioeconomic deprivation in a population comprising the current study population, and
a smaller urban population from central London (Heaney et al., 2002). This was a
retrospective analysis of two separate prospective incidence studies. A strong association
with deprivation was demonstrated, with the age- and sex-adjusted incidence of epilepsy
being \( x = 2.33 \) greater (95% CI 1.46-3.72; \( p=0.001 \)) in the most deprived fifth of the
population than in the least deprived fifth. The strength of the association was weakened
to \( x = 1.62 \) (95% CI 0.91-2.88; \( p=0.12 \)), however, when the figures were adjusted for area
(London versus outside London), suggesting another factor affecting incidence or, less
likely given the rigorous methods, case ascertainment. The impact of social deprivation
upon the incidence of provoked seizures is currently unknown, yet may be even more
significant. An additional UK hospital-based study also found a strong correlation between
the prevalence of epilepsy and social deprivation (Morgan et al., 2000) which was largely
independent of the presence of psychiatric comorbidity. The potential importance of this
variable should therefore not be underestimated, but further prospective incidence studies
are required to verify the association, and to determine the direction of causality.

The annual incidence of first febrile seizures was approximately 400/100,000 (0.4%) of 0-4
year olds, yielding a cumulative incidence of roughly 2% by 5 years which compares
favourably with several paediatric studies (van den Berg and Yerushalmy, 1969; Hauser
and Kurland, 1975; Ross et al., 1980; Verity et al. 1985).
PREVALENCE

The detailed search of 12,178 patient records using standard ILAE definitions for active epilepsy and epilepsy in remission (ILAE, 1993) yielded prevalence rates (Table 12) similar to those from previous studies performed in developed countries (Crombie et al., 1960; de Graaf, 1974; Hauser and Kurland, 1975; Granieri et al., 1983; Keranen et al., 1989; Hauser et al., 1991; Maremmani et al., 1991; Forsgren, 1992; Wallace et al., 1998).

There are no comparable figures for the observed prevalence (1.8/1000) of chronic active epilepsy in adults ascertained from the larger sub-population of 159,388 (Table 11). This diagnostic category was applied because subjects with chronic active epilepsy form the most important epilepsy sub-group with respect to adult health service provision, given their specific medical, and sometimes surgical, service requirements. Because of the definition used, the prevalence of chronic active epilepsy was much lower than the prevalence of active epilepsy (ILAE definition) since the majority of patients with epilepsy enter remission shortly after commencing treatment (Sander, 1993). No significant gender differences in the prevalence of epilepsy were observed in either of the sub-populations studied. Furthermore, unlike age-specific incidence rates, a high prevalence was not observed in elderly subjects, probably indicating that most elderly patients have relatively benign epilepsy (Stephen and Brodie, 2000). It is also possible, however, that fewer patients with chronic epilepsy survive into late life because of the combined effect of the known increased mortality rate associated with both epilepsy (Klenerman et al., 1993; Cockerell et al., 1994) and old age.

CLINICAL CHARACTERISTICS OF THE ADULT INCIDENT AND PREVALENT PATIENT POPULATIONS

The prospective study design, fast-track clinic and active surveillance ensured that ascertainment of newly diagnosed adults often coincided with or shortly post-dated the presenting seizure. Consequently, a higher proportion (two thirds) had isolated seizures at ascertainment than has been previously reported (Loiseau et al., 1990a; MacDonald et al., 2000a), although one third of these had experienced at least one further seizure by the time of case classification, a median of 14 months later. This low recurrence rate (37.3%) was surprisingly low. Several other population based studies have recorded recurrence rates in the order of 70-80% (Goodridge and Shorvon, 1983b; Hart et al., 1990; Ramos Lizana et
al., 2000). There was no reason to suspect under-reporting of seizures as the explanation for this low figure, and it may simply be an artefact of the relatively small number of incident cases (n=110) who were followed up, as compared to the large epidemiological studies cited above. A subgroup of newly diagnosed patients emerged in whom there was a prolonged history of seizures prior to ascertainment, varying from more than 1 year to as long as 18 years. In nearly all such cases, the new onset of GTC seizures led to the retrospective recognition of longstanding minor seizures. The most accurate data regarding the median number and duration of seizures was only available for those patients who attended for high resolution MRI and were assessed personally by the principal investigator. Seizure frequency could not be reliably calculated in the newly diagnosed cohort because the duration of follow up was highly variable and, in many cases, only one seizure had occurred.

In adults with chronic active epilepsy, the median duration of epilepsy was prolonged at almost 20 years, even though the minimal duration required by the inclusion criteria was just 4 years. This was due in part to the skew effect of a small number of subjects with an extremely long (up to 73 years) duration of epilepsy, rather than indicating a population with unusually intractable epilepsy. This high figure will also have been strongly influenced by the exclusion of children from the chronic active epilepsy cohort, in whom the average duration of active epilepsy is likely to be considerably shorter than in adults. The observed variation in figures for the estimated numbers of seizures experienced in a lifetime, seizure frequencies and number of prescribed AEDs, however, indicate that the chronic active epilepsy cohort was heterogenous and representative of the general epilepsy population, with some subjects having relatively benign epilepsies, and others more severe intractable epilepsies.

Two thirds of adults with newly diagnosed unprovoked seizures and chronic active epilepsy had partial onset seizures, as in previous studies (Keranen et al., 1988; Hauser et al., 1991; Forsgren et al., 1996) This figure was probably an underestimate, however, since the seizure classification employed (ILAE, 1993) dictated that seizures without clinical symptomatology suggesting partial onset should be considered to be of generalised onset. Thus, some patients with rapid secondary generalisation may have been inadvertently classified as having generalised seizures. In the adults with newly diagnosed unprovoked
seizures, generalised seizure types other than GTCS (especially absences) were infrequent, a consequence of the exclusion of children from this part of the study. In adults with provoked seizures two thirds of all seizures were generalised, probably because of the high proportion with seizures induced by alcohol withdrawal.

In total, approximately two thirds of all incident and prevalent cases were scanned with high resolution MRI at the NSE. These findings, and their impact on the assignation of aetiology, are presented in chapter 6.
CHAPTER 5

Study 2:
Qualitative and quantitative high resolution cranial MRI in
170 community based, neurologically normal volunteers

5.1 Introduction
High resolution MRI can reveal structural brain abnormalities such as hippocampal sclerosis (HS) and malformations of cortical development (MCD) in up to 80% of hospital based patients with localisation related epilepsy (Li et al., 1995; Lehericy et al., 1997). Over recent years, the sensitivity and specificity of MRI in the detection of HS has been further enhanced by the use of MRI based quantitative hippocampal analysis (Jackson et al., 1990; Cook et al., 1992; Jackson et al., 1993a; van Paesschen et al., 1997b; Woermann et al., 1998), yet the frequency of HS and other cerebral structural abnormalities relevant to epilepsy remains unknown amongst the general population. Such knowledge is of great importance when judging the aetiological significance of structural lesions revealed by MRI in the investigation of patients with epilepsy.

In previous qualitative MRI studies of epilepsy, control populations have either been small (McLachlan et al., 1985; Wieshmann et al., 1996) or non-existent (Latack et al., 1986; Young et al., 1992; Li et al., 1995; Lehericy et al., 1997). Only in the field of vascular neurology has MRI been applied to large groups of healthy volunteers, but in many instances neuroimaging has been restricted to an elderly population (Manolio et al., 1994; Kasahara et al., 1995; Longstreth et al., 1998; de Leeuw et al., 2001). In MRI studies of epilepsy which have employed quantitative hippocampal analysis, a significant bias has been that control groups have comprised young adult volunteers (Adam et al., 1994; van Paesschen et al., 1997b), despite the knowledge that epilepsy commonly affects patients in later life (Loiseau et al., 1990b; Tallis et al., 1991; Everitt and Sander, 1998; Wallace et al., 1998; Stephen and Brodie, 2000), and that HA may also occur as a consequence of both normal ageing and Alzheimer's disease (AD) (Golomb et al., 1993; Fox et al., 1996a; Bigler et al., 1997; Jack Jr et al., 1997; Mori et al., 1997). Thus, measurement of HV in elderly subjects has not been attempted in many previous studies of epilepsy. In studies using hippocampal volumetric analysis, it is possible that HA may have been overestimated.
because of comparisons against normative ranges established from young control subjects. One important, but as yet undetermined, issue is the age at which hippocampal volume loss begins (Jack Jr et al., 1997), since quantitative MRI studies have either been confined to young or middle-aged adults (where there is usually no volume loss with increasing age) (Jack Jr et al., 1989; Free et al., 1995), or to the elderly (where a linear volume loss is found) (Jack Jr et al., 1997; Mueller et al., 1998). Because of this, it has been assumed that hippocampal volume begins to decline as one approaches old age, although this has not yet been proven. Furthermore, little is known about the effects of age, gender and hemisphere laterality on HT2 as no large study has been performed on healthy community based subjects.

This is the first prospective high resolution MRI study of a large cohort of neurologically normal control subjects, which sets out to examine the frequency of potentially epileptogenic lesions across a wide age range, and to recruit from the same population base from which epilepsy patients were also ascertained.

5.2 Aims and hypotheses

Aims

1. To employ a high resolution MRI “epilepsy protocol” in order to establish the range and frequency of intracranial MRI abnormalities in a large group of neurologically normal subjects, and to better understand the relevance and significance of a variety of cerebral structural abnormalities in patients with epilepsy.

2. To establish normative ranges for MRI based HV and HT2 measurements in a large community based population of neurologically normal subjects, so that values from patient cohorts can subsequently be compared to these.

Hypotheses

1. Non-specific cerebral abnormalities such as small white matter lesions are likely to be found infrequently amongst healthy volunteers whereas abnormalities traditionally associated with epilepsy, such as HS, MCD and foreign tissue lesions, are likely to be absent altogether.
2. Normative ranges for HV and HT2 can be successfully founded from a large group of community based neurologically normal subjects, but these hippocampal parameters are likely to be affected by age, gender and, possibly, laterality.

5.3 **Methods**

5.3.1 **Subjects**

170 neurologically normal control subjects (86 males, median age 37.5 years, range 14-78 years) were prospectively recruited from the study population base of 207,553 persons. All subjects were either unrelated partners or friends of patients with epilepsy ascertained in the study, or responders to advertisements placed in community locations. The criteria for selection of control subjects have been detailed in section 3.2.11. In brief, subjects were only included if, on detailed questioning, there was no history of neurological insult or active neurological symptomatology, and when examination of the nervous system was normal. Subjects with risk factors for vascular disease were not excluded. Informed consent was obtained from all subjects, and from at least one parent of those aged 14-15 years.

5.3.2 **Handedness**

Handedness was determined using a standard, validated 13-point questionnaire (Chapman and Chapman, 1987).

5.3.3 **MRI methodology**

All volunteers were imaged between 1.6.95 and 1.3.98 in a 1.5 T Signa Horizon scanner using a standardised imaging protocol:

1. Sagittal T1 spin echo
2. Coronal inversion recovery-prepared fast spoiled gradient echo (IRFSPGR)
3. Dual echo conventional spin echo (CSE)
4. Fast fluid attenuated inversion recovery (Fast FLAIR)

5.3.4 **Qualitative MRI reporting**

All images were visually assessed by two experienced neuroradiologists who viewed the scans without knowledge of whether the subject was a patient with epilepsy or a neurologically normal volunteer. Lesions were classified according to position and
presumed pathology. Small WML were interpreted as abnormal only when they numbered three or more.

5.3.5 Quantitative hippocampal MRI analysis
All HV and HT2 measurements were made by one of 3 raters (HV: Alex Everitt, Kim Birnie; HT2: Kim Birnie, Phillipa Bartlett). All raters were blinded as to subject status. Hippocampal volume ratio (HVR) was also calculated, and HV was corrected for intracranial volume (ICV) and expressed as HV\(^c\). These methods have all been described in detail in section 3.3.3.

5.3.6 Intra-rater and inter-rater reliability
The calculation of intra-class correlation coefficient (ICC) for reproducibility of HV and HT2 measurements has been detailed in section 3.3.4.

5.3.7 Quality assurance: reproducibility of MRI data
Quality assurance for the scanning hardware and software was performed regularly throughout the duration of image acquisition, as outlined in section 3.3.5.

5.3.8 Statistical analysis
All statistical analysis was performed using SPSS for Windows, version 8.0 (SPSS Inc., Chicago, IL). For analysis of normally-distributed data, unpaired and paired T-tests were used, and for non-parametric data, the Mann-Whitney U test was used. Pearson’s correlation coefficient (r) was used for examination of the relationships between both HV and HT2, and age, gender, handedness and laterality. Statistical significance was set at below the level of 0.05.

5.4 Results
5.4.1 Handedness
150 (88%) were right handed, 18 (11%) were left handed and 2 (1%) were ambidextrous.

5.4.2 Qualitative MRI findings
MRI in 130/170 (76.5%) subjects showed no visible structural pathology (Table 14). None had HS, MCD, or focal brain damage. Thirty-two normal volunteers (18.8%; median age
Table 14 Qualitative high resolution cranial MRI findings in 170 neurologically normal volunteers

<table>
<thead>
<tr>
<th>Principal MRI finding</th>
<th>n</th>
<th>%</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No structural abnormality</td>
<td>130*</td>
<td>76.5</td>
<td>Includes only subjects with no, one or two small WML.</td>
</tr>
<tr>
<td>Small WML</td>
<td>29†</td>
<td>17.1</td>
<td>Median age 59 years; range 33-78 years</td>
</tr>
</tbody>
</table>
| Lesions of uncertain aetiology             | 3     | 1.8  | Male, 41 years: left frontal linear focus of high signal on T2-weighted images only  
                                             |       |     | Female, 25 years: single conspicuous right frontal deep white matter lesion, and a pineal cyst 
                                             |       |     | Male, 25 years: two areas of possible haemosiderin deposition in right frontal lobe and right thalamus |
| Arachnoid cyst and small WML               | 1     | 0.6  | Male, 66 years                                                           |
| Meningioma, hypothalamic tumour and small WML | 1     | 0.6  | Male, 72 years                                                           |
| Diffuse brain atrophy and small WML        | 1     | 0.6  | Male, 58 years                                                           |
| Pituitary enlargement                      | 1     | 0.6  | Female, 68 years                                                         |
| Isolated pineal cyst                       | 1     | 0.6  | Male, 42 years                                                           |
| Minimal cerebellar ectopia                 | 1     | 0.6  | Female, 30 years                                                         |
| Empty sella turcica                        | 1     | 0.6  | Female, 46 years                                                         |
| Probable cavernous haemangioma             | 1     | 0.6  | Male, 45 years                                                           |
| Total                                      | 170   | 100% | Males, 86; median age 37.5 years; range 14-78 years                     |

**Abbreviations:**
- MRI  magnetic resonance imaging
- WML  white matter lesions, of presumed ischaemic aetiology
* including 6 males (all under 50 years of age) with quantitative hippocampal abnormalities
† including 2 elderly females with quantitative hippocampal abnormalities
59 years; range 33-78 years) had 3 or more small WML. In 18 such volunteers, the small WML were few in number. In the remaining 14, small WML were more numerous, including 4 volunteers with confluent periventricular WML. These small WML were considered to be of probable ischaemic origin, although a positive history of cardio- or peripheral vascular disease, or risk factors thereof (diabetes mellitus, hypertension, hypercholesterolaemia, or a strong family history of vascular disease) was present in 7/32 (21.9%) subjects only. Five volunteers with risk factors for vascular disease did not have small WML on their MRI scans. Details regarding smoking history were not sought. Three elderly males with small WML had additional cerebral lesions: small left middle cranial fossa arachnoid cyst, 1; diffuse brain atrophy, 1; hypothalamic enlargement and small parietal parasagittal meningioma, 1. Repeat MRI after 1 year in the latter subject revealed no visible change in any lesion; he remained asymptomatic and without neurological deficit. One 60 year old male with small WML was subsequently diagnosed as having a malignant glioma 2 years after his baseline MRI, following a 6 week history of progressive neurological symptoms. Review of his baseline MRI confirmed that the lesion had not been present at that time.

Other lesions were observed in 8 (4.7%) subjects (Table 14): isolated pituitary enlargement, 1 (female, 68 years); probable, small temporal lobe cavernous haemangioma, 1 (male, 45 years; repeat MRI one year later showed no change); isolated small pineal cyst, 1; empty sella turcica, 1; minimal cerebellar ectopia, 1; lesions of uncertain nature, 3. The latter group included a 41 year old male with a linear area of increased signal in the left frontal lobe, a 25 year old female with a single conspicuous frontal white matter lesion and a small pineal cyst, and a 25 year old male with two small areas of possible haemosiderin deposition.

5.4.3 Quantitative MRI findings

ANALYSIS OF CONTROL POPULATION SUBGROUPS AND DEVELOPMENT OF NORMATIVE RANGES

A. Hippocampal volumetry

Data for HV, ICV and HVc (Table 15) were normally distributed. The ratio of left to right HV was fairly normally distributed, although HVR (the ratio of the smaller to the larger uncorrected HV) was not.
Table 15 Corrected hippocampal volumes, hippocampal volume ratios and T2 relaxation times in 170 neurologically normal control subjects

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Mean corrected hippocampal volumes (cubic millimetres)</th>
<th>Mean hippocampal volume ratios</th>
<th>Mean hippocampal T2 relaxation times (milliseconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RHV&lt;sub&gt;c&lt;/sub&gt; ± SD</td>
<td>LHV&lt;sub&gt;c&lt;/sub&gt; ± SD</td>
<td>HVR ± SD</td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>Male</td>
<td>2970 ± 336</td>
<td>2937 ± 291</td>
<td>0.95 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2951 ± 280</td>
<td>2894 ± 287</td>
<td>0.96 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>2961 ± 308</td>
<td>2916 ± 289</td>
<td>0.95 ± 0.03</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>Male</td>
<td>2937 ± 310</td>
<td>2871 ± 289</td>
<td>0.95 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2790 ± 345</td>
<td>2743 ± 338</td>
<td>0.96 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>2866 ± 332</td>
<td>2810 ± 317</td>
<td>0.96 ± 0.03</td>
</tr>
</tbody>
</table>

**Abbreviations:**

- RHV<sub>c</sub> right hippocampal volume, corrected for intracranial volume
- LHV<sub>c</sub> left hippocampal volume, corrected for intracranial volume
- HVR hippocampal volume ratio (ratio of smaller to larger uncorrected hippocampal volume)
- RHT2 right hippocampal T2 relaxation time
- LHT2 left hippocampal T2 relaxation time
- SD standard deviation
Mean uncorrected RHV was slightly, but significantly, greater than mean uncorrected LHV in subjects under 50 years of age (mean difference 45 mm$^3$ or 1.5%; p=0.003) and in subjects of 50 years or over (mean difference 57 mm$^3$ or 2.0%; p=0.009). Consequently, separate correction factors were required when correcting RHV and LHV for ICV. In total, RHV (corrected or uncorrected) was greater than LHV in 62.4% of volunteers. This difference became more significant when right-handed persons were considered separately (mean difference 53 mm$^3$ or 1.8%, p=0.001). In the 18 left handed volunteers, the mean difference between RHV and LHV (-11 mm$^3$ or 0.4%) was not significant (p=0.76).

Figure 4 shows the correlation between mean uncorrected HV and ICV. This correlation was closer in the younger group (r=0.55) than in the older group (r=0.44). Furthermore, mean HV$_C$ was significantly smaller in subjects aged 50 years or over compared to those under 50 years of age (p<0.05). For these reasons, two separate normative ranges for HV$_C$ were defined for subjects under and over the age of 50 years. There was a trend towards a decline in HV$_C$ that was most apparent in subjects of 60 years or over (Figure 5).

No significant gender difference in mean HV$_C$ was observed (males 2939 mm$^3$, females 2880 mm$^3$, p=0.20), principally because the correction for ICV reduced gender differences in uncorrected HV by correcting for head size, a parameter typically greater in males than in females.

B. Hippocampal T2 relaxometry

HT2 data (Table 15) were normally distributed with a range (± 2 SD) which was considerably narrower than the distribution of mean HV$_C$. There were no statistically significant gender or side-to-side differences in HT2, although there was a slight trend for mean HT2 to decline with increasing age, although this was by less than 1 millisecond (approximately 1%).

HIPPOCAMPAL QUANTITATIVE ANALYSIS IN INDIVIDUAL SUBJECTS

A. Hippocampal volumetry

Individual values for HV$_C$ and HVR were considered abnormal when more than 2 standard deviations (SD) below the mean values of the 170 control subjects. HVR was therefore deemed to be abnormal when lower than 0.89. Four subjects had a reduction of HV$_C$
Figure 4  Mean uncorrected hippocampal volume in the 170 control subjects
Figure 5 Changes in mean corrected hippocampal volume (HVc) with age

95% CI for mean HVc (mm³)

<table>
<thead>
<tr>
<th>Age in 10 year age bands</th>
<th>n = 14</th>
<th>n = 41</th>
<th>n = 34</th>
<th>n = 33</th>
<th>n = 25</th>
<th>n = 15</th>
<th>n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(unilateral, 2; bilateral, 2) and one had a borderline low HVR, giving a total of 5 (2.9%) with abnormal hippocampal volumetry.

B. Hippocampal T2 relaxometry
Individual HT2 values were considered abnormal when more than 2 SD above the control mean (more than 90ms). Three (1.8%) volunteers had minimal unilateral elevations in HT2, not associated with volumetric abnormalities.

5.4.4 Inter-rater reliability
The ICC was 0.76 for left HV (LHV) and 0.77 for right HV (RHV).
The ICC for both right and left HT2 was 0.98.

5.4.5 Quality assurance
Changes in voxel dimensions were found to be less than 1% along any axis during the period of study, insufficient to affect HV and ICV measurements significantly. Similarly, quality assurance found a less than 1% (not significant) change in phantom T2 values.

5.5 Discussion
5.5.1 Summary of major findings
MRI was qualitatively normal in approximately three quarters of 170 neurologically normal volunteers. Small WML were seen in 18.8% and were the most frequent abnormality. Lesions typically associated with epilepsy were very infrequent. No volunteer had HS, MCD or focal brain damage. Other potentially epileptogenic lesions were rare: one volunteer had a probable cavernous haemangioma, whilst another had a small meningioma.

Minor quantitative abnormalities of a single hippocampal parameter were found in 4.7%. Mean uncorrected RHV was slightly, but significantly, greater than mean uncorrected LHV (by 1.5% to 2.0%) in right handed persons and in the sample as a whole, but not in left handers. Mean HVc was significantly reduced in older subjects, such that separate normative ranges were required for those under and above the age of 50 years. There were no significant gender differences in HVc and no significant gender, age-related or side-to-side differences in HT2.
5.5.2 Methodological issues

Image acquisition took place in an everyday clinical scanning environment over nearly 3 years, and quantitative hippocampal analysis involved more than one rater. Consequently, the inter- and intra-rater reliability of HV and HT2 measurements, and the stability of scanning hardware and software, were extremely important factors. The results presented represent a highly acceptable degree of consistency, demonstrating both stability of image acquisition, and the robust nature of data analysis.

The study was population based with the majority of control subjects being recruited on the same day as a relative or partner with epilepsy was being scanned. A small proportion were drafted by local advertising, introducing the possibility that some did so because of an ulterior motive which was withheld. To take a hypothetical example, a subject whose first degree relative had died from a CNS tumour might have denied such a family history in order to obtain an MRI brain scan for reassurance that he or she did not also have a CNS tumour. It seems, however, that the thorough screening and neurological examination made this possibility highly unlikely, given the paucity of important MRI abnormalities found in the study.

It could be argued that a control group for patients with epilepsy should have comprised subjects without a history of seizures, but with exposure to a similar array of neurological insults (e.g. head injury, febrile seizures, encephalitis) as is observed in epilepsy patients. This was hotly debated, but it was finally considered important to exclude control subjects who might have been at an increased risk of developing seizures in the future. Had this occurred, the control group would have become contaminated, probably without the principal investigator’s knowledge. It was also important to apply strict exclusion criteria ensuring the absence of risk factors including the above neurological insults, since these may have adversely affected the development of normative ranges for hippocampal quantitation, although it is likely that this action may have slightly reduced the frequency of significant qualitative MRI abnormalities.

Relatively few (13.5%) control subjects over 60 years of age were scanned, in keeping with the proportion of epilepsy patients in this age band who were imaged. Whilst this may have reduced the prevalence of small WML in neurologically normal subjects, it was important
to have a control group with demographic features comparable to that of the patient group. This relatively small elderly sample size may have contributed to a wider normative range for HVc in aged subjects, although the findings appear to be consistent with those reported in other studies including measurements of HV in the elderly (Jack Jr et al., 1997; Mueller et al., 1998), suggesting that the sample was representative of the elderly population as a whole.

5.5.3 Significance of asymptomatic cerebral abnormalities

Small WML, the most frequent abnormality on MRI (18.8%), were principally found in middle-aged and elderly volunteers. These lesions were considered most likely to be ischaemic in origin, signifying asymptomatic small vessel cerebrovascular disease, but the remote possibility that they represented small foci of gliosis, heterotopic grey matter, or demyelination cannot be completely excluded. The majority of subjects with these lesions had no risk factors for, or past history of, vascular disease, although a detailed smoking history was not obtained. Subjects with small vessel cerebrovascular disease may remain asymptomatic, or develop a variety of neurological symptoms including cognitive impairment or epilepsy. Factors important in the determination of epileptogenicity are likely to include the anatomical position of lesions (e.g., a subcortical rather than deep white matter location), the total lesion load, and the seizure threshold within an individual. This will be discussed further in Chapter 6, when the MRI findings in patients with epilepsy are presented.

The virtual absence of lesions traditionally associated with epilepsy was the most important finding in this study. No control subject had HS, MCD or focal brain damage, reinforcing the clinical impression that these lesions, when present in patients with epilepsy, are highly likely to be aetiologically relevant (Raymond et al., 1995; Mathern et al., 1997). One (0.6%) male had a small temporal lobe lesion with MRI features suggestive of a cavernoma. The prevalence of cavernomas in the general population is unknown, and can only be determined accurately through a much larger prospective MRI study. Although cavernomas present most commonly with seizures (Tagle et al., 1986; Curling et al., 1991; Labauge et al., 1998), and have been estimated to carry an annual risk of symptomatic haemorrhage of approximately 0.25-0.5% (Curling et al., 1991; Aiba et al., 1995), they remain asymptomatic in a significant proportion of subjects (Curling et al., 1991; Aiba et
al., 1995; Labauge et al., 1998), as in this case. One (0.6%) elderly male had a small meningioma. Incidental asymptomatic meningiomas are not uncommonly demonstrated in the elderly by neuroimaging performed for other indications, but most remain asymptomatic over time and show little or no enlargement with repeat imaging (Go et al., 1998).

Quantitative hippocampal analysis revealed that 8 (4.7%) volunteers had a single hippocampal parameter just outside of the 2nd standard deviation. None of these "anomalies" were detected visually. This number approximates to the value one would expect to observe by chance at the level of 2 SD in a sample of this size. As has already been stated, factors which have been reported to be associated with HS (Cendes et al., 1993c; Kuks et al., 1993; Cendes et al., 1995a; Free et al., 1996b; Corey Bloom et al., 1997) or HA (Bigler et al., 1997; Jack Jr et al., 1997; Mori et al., 1997; Nelson et al., 1998) were excluded at enrolment. The pathological significance of the minor quantitative hippocampal abnormalities observed in these healthy volunteers therefore remains uncertain. Likewise, the prevalence of HS in a neurologically normal population appears to be very small, certainly less than 0.6% (estimated CI 0.01-3.23% using "exact probabilities of the binomial distribution"), but a more accurate estimation would require a much larger community based study. In a histopathological study of post-mortem epilepsy patient specimens by Meencke and Veith (1991), HS was reported to be present in 10% of 153 control subjects, but this control group was defined as "patients without epilepsy", and detailed exclusion criteria were not provided such that some control subjects may have had other CNS disorders which affect the hippocampus. Histopathology is a much more sensitive method (the "gold standard") of detecting HS, and this is an additional explanation for Meencke and Veith's figure. A recent retrospective review of high resolution MRI scans in 207 patients investigated for hearing loss revealed normal hippocampi in all but two (1%) subjects who had HS (Moore et al., 1999). Both subjects were subsequently discovered to have previously diagnosed epilepsy, confirming the validity of using a neurologically normal control group in the current study.

In accordance with previous studies (Jack Jr et al., 1989; van Paesschen et al., 1997b), no gender difference in mean HV\textsubscript{c} was found, suggesting that the gender difference in uncorrected HV is predominantly attributable to a difference in head size. Mean
uncorrected RHV, however, was significantly greater (by between 1.5% and 2.0%) than mean uncorrected LHV. Similar findings have been reported in a group of young, healthy control subjects (Jack Jr et al., 1989) and in a cohort of healthy aged adults (Coffey et al., 1992), whilst other authors have found no, or statistically insignificant, side-to-side differences (Ashtari et al., 1991; Cook et al., 1992; Watson et al., 1992; Cendes et al., 1993a). This lack of consensus has probably resulted from small sample sizes and differences in study methodology (Jack Jr et al., 1995), but the current large study appears to verify a small, but definite, right-left difference in HV. The difference was slightly more significant in right-handed persons, but absent in left handers, suggesting that structural asymmetry may relate to functional asymmetry. Functional imaging studies have reported asymmetrical activation of the right hippocampus in taxi drivers asked to “exercise” their spatial memory (Maguire et al., 1997), and a recent quantitative MRI study of these same subjects suggests that this asymmetry has a structural correlate (Maguire et al., 2000). The current study, however, implies that such findings may not be restricted to these with a well-developed spatial memory.

Mean HVc was found to be significantly reduced in subjects of 50 years or over, compared to those under 50 years. The reduction in mean HVc was most pronounced in subjects of 60 years or over (Figure 5). This is one of the first studies to perform quantitative hippocampal MRI across such a wide age range and to document when this reduction first becomes apparent. HA has been reported to occur with normal ageing from approximately 50 years onwards, but is of a significantly lesser degree than that observed in Alzheimer’s disease (AD), regardless of its severity (Jack Jr et al., 1997; Fox et al., 1996a). Age-related HA appears to occur in proportion to a slow, diffuse involutional process affecting some elderly subjects (Mueller et al., 1998; Coffey et al., 1992), in contrast to the rapid hippocampal and generalised atrophy observed in patients with AD (Fox et al., 1996a and 1996b). Mesial temporal lobe limbic structures are central to the integrity of declarative memory function, and are involved earliest and most extensively in the pathogenesis of AD (Jack Jr et al., 1997). Furthermore, the neurodegenerative processes associated with normal ageing and with AD appear to be qualitatively different, such that AD is distinct from accelerated ageing (West et al., 1994). It is presently unknown whether mild HA is a consequence of normal ageing (Golomb et al., 1993), or perhaps the result of presymptomatic dementia (Fox et al., 1996a; Kaye et al., 1997), since the latter also becomes
more prevalent with advancing age. For these reasons, it is conceivable that the female volunteer in this study with bilateral HA had pre-symptomatic AD since atrophy of the mesial temporal structures has been reported in this context (Fox et al., 1996a; Kaye et al., 1997). Clinical and neuroimaging follow up will reveal this individual’s fate, but longitudinal MRI studies, some already underway (Jack Jr et al., 1997; Mueller et al., 1998), are required to resolve the overall temporal relationship between normal ageing and hippocampal volume loss. Ideally, such studies should be followed by autopsy, enabling correlation of HV with hippocampal cell counts and other degenerative changes (Harding et al., 1998). Even without such studies, it is evident from this cross-sectional study that hippocampal volume measurements in elderly patients with epilepsy should be compared with normative values derived from an elderly, neurologically normal control population, and not with values derived solely from young adults.

Finally, no previous study has performed HT2 relaxometry in a control group which comprises so many subjects and is representative of the entire age spectrum. Despite this, HT2 values showed no significant correlation with either age, sex or HV_q indicating either that the method lacks sensitivity or, more likely, that HT2 remains relatively constant in health, thereby suggesting that the parameter is useful in terms of detecting hippocampal damage.
CHAPTER 6

Study 3:

The aetiology of epilepsy in adults:
a prospective, population based MRI study

6.1 Introduction

MRI has revolutionised the investigation and management of patients with epilepsy by providing a sensitive, non-invasive method of detecting aetiologically-relevant and subtle abnormalities, such as HS, which were invisible to earlier neuroimaging techniques (Duncan, 1997). In hospital based MRI studies, HS and other focal abnormalities, including MCD, cavernomas and low grade tumours, have been found in up to three quarters of patients with epilepsy (Li et al., 1995; Lehericy et al., 1997; Semah et al., 1998). These studies, however, have targeted highly-selected patient populations such as those with chronic localisation related (partial onset) epilepsy who attend tertiary referral centres for assessment of suitability for epilepsy surgery.

In contrast, the causes of epilepsy in the general population are largely unknown, with the majority of epidemiological studies having failed to demonstrate the cause of epilepsy in approximately two thirds of patients (Hauser et al., 1975; Goodridge and Shorvon, 1983b; Granieri et al., 1983; Forsgren, 1990; Sander et al., 1990; Hauser et al., 1991; Forsgren, 1992; Hauser et al., 1993; Cockerell et al., 1995b), a consequence of retrospective case ascertainment and sub-optimal patient investigation (Sander and Shorvon, 1996). The frequency of HS and subtle foreign tissue lesions in unselected populations is quite unknown and their relative importance in newly diagnosed and chronic epilepsy, respectively, has not been investigated.

This is the first prospective population based MRI study of epilepsy. A combination of expert qualitative assessment of high resolution MR images and quantitative hippocampal analysis was applied to permit detailed aetiological classification of newly diagnosed and chronic epilepsies, including the proportions with idiopathic epilepsies (those with a presumed genetic origin, and no structural cerebral abnormalities) and cryptogenic epilepsies (those with no demonstrable cause).
6.2 Aims and hypotheses

1. To describe the range and frequency of intracranial MRI abnormalities in community based adults with epilepsy in order to determine whether there are significant differences compared to healthy volunteers ascertained from the same population base, or from previous reports of hospital based epilepsy patients.

2. To describe the range and frequency of intracranial MRI abnormalities in community based cohorts of adults with newly diagnosed and chronic active epilepsy in order to see whether there are significant differences between these two groups.

3. To describe the aetiology of incident and prevalent cases in a community, using investigation with high resolution MRI. This allows the frequency of HS and MCD at a population level to be defined, and also enables an estimation of the proportion of cases with an MRI diagnosis in whom previous investigation did not reveal the underlying aetiology.

4. To compare the age-specific distributions of specific aetiologies of epilepsy amongst adults with newly diagnosed and chronic active epilepsy.

Hypotheses

1. The frequency of cerebral structural abnormalities including HS, MCD and foreign tissue lesions in patients with epilepsy will be much greater than in age-matched neurologically normal control subjects, but less than has been reported in previous hospital based studies of epilepsy because of the elimination of selection bias.

2. HS will be more frequent in patients with chronic active epilepsy than in those with newly diagnosed epilepsy, suggesting that it is a slowly progressive abnormality which predisposes to medical intractability, whereas other cerebral structural abnormalities are less likely to differ significantly in frequency between these two groups.

3. High resolution MRI will allow the aetiology of epilepsy to be identified in a significant number of subjects in whom previous investigation failed to reveal the cause. A proportion of patients, however, will still have an unknown aetiology, but this will be much less than
in previously reported epidemiological studies of epilepsy which have not employed MRI.

4. Cerebrovascular disease is likely to be the commonest cause of newly diagnosed epilepsy amongst the middle aged and elderly, whilst chronic active epilepsies are more likely to be associated with HS or caused by cranial trauma, CNS infection, perinatal injury, MCD or idiopathic epilepsy.

6.3 Methods
The study methodology, which is only summarised here, has been described in detail in chapter 3.

6.3.1 Subjects
Between 1.6.95 and 31.5.97 inclusive, 165 adults (89 males; median age 48 years, range 15-91 years) with newly diagnosed seizures were prospectively ascertained from the study population. During the 6 months following the prevalence day (1.6.96), 279 adults (131 males; median age 38 years, range 15-92 years; median duration of epilepsy 19.5 years, range 4-73 years) with chronic active epilepsy were identified from the same population base. 170 neurologically normal and roughly age-matched control subjects were recruited through means already described in section 3.2.11.

6.3.2 Electro-clinical classification
A detailed seizure, past medical and family history were taken, and the details of previous investigations and suspected aetiology were recorded in all subjects, not just those with high resolution MRI. Most newly diagnosed patients underwent routine EEG which was reported by an experienced neurophysiologist (Professor David Fish and Dr Shelagh Smith). In accordance with the scheme used for seizure classification (ILAE, 1993), seizures without aura or localising electro-clinical features were classified as generalised. Newly diagnosed seizures were also sub-categorised as either provoked (39 patients) if they occurred within 7 days of a clearcut CNS insult, or unprovoked (126 patients) if there were no acute precipitants (ILAE, 1993). The same classification scheme considers seizures which occur as the presenting symptom of a tumour, and do not recur thereafter, as provoked. Table 16 shows the seizure type classification in all patients.
### Table 16  Classification of seizure types using clinical and EEG data in 444 adult patients

<table>
<thead>
<tr>
<th></th>
<th>Newly diagnosed seizures</th>
<th>Chronic active epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Provoked</td>
<td>Unprovoked</td>
</tr>
<tr>
<td><strong>Seizure type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>generalised</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>partial onset</td>
<td>12</td>
<td>85</td>
</tr>
<tr>
<td>unclassifiable</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>mixed</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total number of patients</strong></td>
<td>39</td>
<td>126</td>
</tr>
<tr>
<td><strong>Number with high resolution MRI</strong></td>
<td>22 (56.4%)</td>
<td>88 (69.8%)</td>
</tr>
</tbody>
</table>

### Simplified definitions:

- **Provoked** seizure occurring within 7 days of an identifiable CNS or metabolic insult
- **Unprovoked** seizure with no acute precipitants
- **Generalised** includes definite primary generalised seizures and generalised tonic-clonic seizures without electroclinical features indicating partial onset
- **Partial onset** seizures with a partial (focal) onset based on electroclinical data
- **Unclassifiable** insufficient clinical information to classify seizure type
- **Mixed** patients with generalised (eg. myoclonic jerks) and partial onset seizures
6.3.3 High resolution MRI scanning

High resolution cranial MRI was performed in:

- 110 (59 males; provoked 22, unprovoked 88, median age 40 years, range 15-86 years) of the 165 adults with newly diagnosed seizures
- 174 (81 males; median age 37 years, range 15-73 years) of the 279 with chronic active epilepsy
- 170 neurologically normal control subjects (86 males; median age 37.5 years, range 14-78 years).

The scanning protocol included coronal oblique dual echo (conventional spin echo), proton density/T2-weighted and fast FLAIR acquisitions, and a coronal T1-weighted volumetric acquisition. Images were assessed qualitatively by two experienced neuroradiologists (Drs John Stevens and Dr Brian Kendall) who were unaware of each subject’s status, age, sex or clinical details. The presence of multiple small white matter lesions (WML) was considered abnormal when 3 or more lesions were present. The following quantitative measurements were performed by 1 of 3 blinded raters (Alex Everitt, Kim Birnie, and Phillipa Bartlett) using previously validated methods (Cook et al., 1992; Duncan et al., 1996; Free et al., 1995):

- hippocampal volume (HV), corrected for intracranial volume (HV_c)
- smaller to greater hippocampal volume ratio (HVR) and
- hippocampal T2 relaxation time (HT2)

Normative ranges for HV, HVR and HT2 were derived from values from the 170 control subjects (see section 5.4.3). HA was defined as an HV_c and/or HVR greater than 2 standard deviations (SD) below the control mean. HS was considered to be present when HA was associated with an ipsilateral HT2 greater than 2 SD above the control mean.

6.3.4 Aetiological classification

A panel of 3 experienced neurologists with a specialist interest in epilepsy (Professors Simon Shorvon, John Duncan and Josemir Sander) used all available MRI, EEG (Table 17) and clinical data to assign an aetiology, or aetiologies, for each patient. In patients with
### Table 17 EEG findings in patients with newly diagnosed seizures and chronic active epilepsy

<table>
<thead>
<tr>
<th>EEG finding</th>
<th>Newly diagnosed seizures</th>
<th>Chronic active epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Provoked n (% with EEG)</td>
<td>Unprovoked n (% with EEG)</td>
</tr>
<tr>
<td>Normal</td>
<td>13 (72)</td>
<td>33 (41)</td>
</tr>
<tr>
<td>Focal epileptiform only</td>
<td>0</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Focal non-epileptiform activity</td>
<td>2 (11)</td>
<td>27 (34)</td>
</tr>
<tr>
<td>Multifocal epileptiform activity</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Isolated GSW</td>
<td>0</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Focal epileptiform and GSW</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diffuse non-specific</td>
<td>2 (11)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>EEG performed</td>
<td>18 (100%)</td>
<td>80 (100%)</td>
</tr>
<tr>
<td>Not performed/result untraceable</td>
<td>21</td>
<td>46</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>39</strong></td>
<td><strong>126</strong></td>
</tr>
</tbody>
</table>

NB. % refers to the proportion with that particular EEG finding amongst the patients in each category who had EEG, not the percentage of all patients within each category.

**Abbreviations:**
- EEG electroencephalogram
- GSW generalised spike-wave

**Definitions:**
- Focal spikes, generalised spikes and spike-wave activity were all considered as epileptiform findings. Focal sharp or slow waves were considered as non-epileptiform. Generalised slow or fast wave activity was considered a diffuse, non-specific EEG finding.
seizures of late onset (45 years or over), and when no other cause was identified, conspicuous or numerous small WML in cortical or sub-cortical locations were considered to be of probable aetiological relevance, particularly when associated with risk factors for cerebrovascular disease (see section 5.5.3). For the purposes of this study, isolated HS and HA were considered to be aetiologically relevant.

6.3.5 Statistics
All statistical analysis was performed using SPSS for Windows, version 8.0 (SPSS Inc., Chicago, IL). Parametric data was analysed using unpaired and paired T-tests, and non-parametric data was analysed using Kruskal-Wallis and Mann-Whitney U tests. Statistical significance was set at the level of 0.05. The calculation of the approximate incidence of HS and of other quantitative hippocampal abnormalities involved taking the frequency (in percent) of these MRI abnormalities in the adult patients with newly diagnosed seizures who had high resolution MRI (n=110) and extrapolating to yield a figure for the entire newly diagnosed cohort (n=165). Since the latter figure represented the total number of newly diagnosed adults identified from the adult incident population base (n=170,581) during the 2 year study period, a simple calculation enabled conversion into an annual incidence figure per 100,000 population. An equivalent extrapolation and calculation was performed to produce prevalence figures for HS and other quantitative hippocampal abnormalities in the total adult population prevalent population (n=159,388).

6.4 Results
6.4.1 Extent of investigation
EEG
Incident (newly diagnosed) cases
98/165 (59.4%) had EEG. Epileptiform abnormalities (as defined in Table 17) were observed in 16 (16.3%; unprovoked, 15) of these 98 patients (Table 17). The median age of the 67 patients (40.6%) without EEG was 62 years (range 17-91 years).

Prevalent (chronic active epilepsy) cases
EEG data were available in 194/279 (69.5%), of whom 85 (43.8%) had true epileptiform features (Table 17).
NEUROIMAGING

Incident (newly diagnosed) cases
147/165 (89.1%) had neuroimaging: CT alone, 25; standard MRI alone, 7; standard MRI plus CT, 5; high resolution MRI, 110 (22 provoked; 88 unprovoked seizures). Of these 110 patients, supplementary standard neuroimaging had already been performed in 52 (CT, 41; standard MRI, 4; both, 7). 55/165 (33.3%) did not have high resolution MRI because of contraindications to MRI, frailty, failure to respond to repeated invitations, or refusal.

Prevalent (chronic active epilepsy) cases
221/279 (79.2%) had neuroimaging: CT alone, 35; standard MRI alone, 2; standard MRI plus CT, 10; high resolution MRI, 174 (including 89 with prior CT, 2 with standard MRI, and 29 with both). 58/279 (20.8%) patients were not neuroimaged, of whom 3 had electroclinical evidence of IGE.

6.4.2 High resolution MRI findings
High resolution MRI findings in all 454 adult subjects are presented in Table 18, and subgrouped according to seizure type. Some subjects had more than one MRI abnormality, so that the total number of findings exceeds the total number of patients. The MRI findings in the control subjects is described in more detail in section 5.4.2.

CONTROL SUBJECTS
Qualitative high resolution brain MRI
133/170 (78.2%) control subjects had normal MRI. The most frequent abnormalities were multiple small WML (32/170; 18.8%). None had HS or MCD. One 46 year old male had a probable small temporal lobe cavernoma. One elderly female had asymptomatic pituitary enlargement, and another had diffuse brain atrophy. One elderly male had a small parietal parasagittal menigioma with a coexistent hypothalamic tumour and several small white matter lesions. Three subjects had lesions of uncertain nature (see Table 18).

Quantitative hippocampal analysis
8/170 (4.7%) control subjects had a quantitative hippocampal measure outside 2 SD of the mean. Two such subjects also had small WML. Only one subject had more than one abnormal hippocampal parameter, an elderly female with bilateral HA. All others had
Table 18 Qualitative high resolution MRI in 110 newly diagnosed and 174 chronic active epilepsy patients, and 170 neurologically normal control subjects

<table>
<thead>
<tr>
<th>MRI finding</th>
<th>Patients with newly diagnosed seizures</th>
<th>Patients with chronic active epilepsy</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seizure type</td>
<td>Seizure type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial onset</td>
<td>Generalised</td>
<td>Mixed</td>
</tr>
<tr>
<td></td>
<td>Number with finding (% of n scanned)</td>
<td>Number with finding (% of n scanned)</td>
<td>Number with finding (% of n scanned)</td>
</tr>
<tr>
<td>No structural abnormality</td>
<td>21 (31.8)</td>
<td>27 (62.8)</td>
<td>0</td>
</tr>
<tr>
<td>Multiple small WML</td>
<td>26 (39.4)</td>
<td>8 (18.6)</td>
<td>0</td>
</tr>
<tr>
<td>Focal neocortical damage</td>
<td>13 (19.7)</td>
<td>3 (7.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>2 (3.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MCD</td>
<td>2 (3.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tumour</td>
<td>7 (10.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diffuse brain atrophy</td>
<td>5 (7.6)</td>
<td>1 (2.3)</td>
<td>0</td>
</tr>
<tr>
<td>Cerebellar atrophy</td>
<td>0</td>
<td>3 (7.0)</td>
<td>0</td>
</tr>
<tr>
<td>Cavernous haemangioma</td>
<td>1 (1.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other*</td>
<td>5 (7.6)</td>
<td>4 (9.3)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Total number of findings</td>
<td>82</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>66 (100%)</td>
<td>43 (100%)</td>
<td>1 (100%)</td>
</tr>
</tbody>
</table>

WML = small white matter lesions (at least 3)  
MCD = malformation of cortical development  
† includes 2 subjects with dysembryoplastic neuroepithelial tumours (DNET)  
Other* NEWLY DIAGNOSED: partial onset: amygdalar lesion of uncertain nature, 1; giant aneurysm, 1; right striatal lesions, 1; demyelinating lesions, 1; left insular lesion (?)scar, 1; generalised: multiple small lipomas, 1; Arnold Chiari malformation, 1; right caudate infarct, 1; single conspicuous right temporal WML, 1; mixed: focal insular lesion (?)MCD, 1  
CHRONIC ACTIVE: partial onset: bifrontal white matter signal abnormality, 1; dentate/lentiform nucleus calcification, 1; optic nerve glioma, 1; cavernous sinus mass, 1; Arnold Chiari malformation, 1; possible left frontal dysplastic lesion, 1; generalised: small right superior frontal gyrus lesion (?)scar, 1; three lesions of uncertain aetiology, 1; small left frontal lesion (?)heterotopic nodule, 1;  
CONTROLS: see Table 14 for detailed description of “other” findings
minimal unilateral HA or HT2 elevation.

INCIDENT (NEWLY DIAGNOSED) CASES

Qualitative high resolution brain MRI

a. Comparison of patients with partial onset versus generalised seizures

MRI was qualitatively normal in 27/43 (62.8%) with generalised seizures, as compared to 21/66 (31.8%) with partial onset seizures ($\chi^2 = 10.13$ with 1 degree of freedom, $p = 0.0015$) (Table 18). In contrast, structural abnormalities considered to have definite aetiological relevance (focal cortical brain damage, HS, MCD, cavernomas, and neoplastic lesions) were significantly more frequent in patients with partial onset seizures (25/66, 37.9%) than in those with generalised seizures (3/43, 7.0%) ($\chi^2 = 13.02$ with 1 degree of freedom, $p = 0.0003$). Multiple small WML were significantly more common in patients with partial onset seizures (39.4%) than in control subjects (18.8%) and patients with generalised seizures (18.6%) ($\chi^2 = 11.86$ with 2 degrees of freedom, $p = 0.0027$). Furthermore, many patients with newly diagnosed seizures and multiple WML had relatively large and/or subcortically-placed WML (Figure 6) which were absent in the majority of control subjects or generalised seizure patients with WML, emphasising their probable aetiological relevance. In total, 9 newly diagnosed patients had cerebral and/or cerebellar atrophy noted on MRI reporting, including 4 in whom this was the sole abnormality.

b. Comparison of patients with provoked versus unprovoked seizures

In the 22 patients with provoked seizures, the high resolution MRI findings (with the assigned aetiology of seizures in parentheses) were:

- normal, 12 (alcohol-related or illicit/prescribed drug-related seizures, 9; hypoglycaemia-induced seizure, 1; viral encephalitis, 1; head injury, 1)
- multiple small WML, 3 (alcohol-related seizures, 3)
- venous infarct/saggital sinus thrombosis, 1 (cerebrovascular disease)
- parasagittal frontal meningioma and multiple WML, 1 (CNS neoplasia)
- diffuse brain atrophy, 1 (alcohol-related seizure)
- old haemorrhagic infarct, 1 (alcohol-related seizure: see section 6.4.4. for explanation)
- large single non-specific WML, 1 (alcohol-related seizure)
Figure 6  Examples of MRI findings in newly diagnosed patients

Cerebrovascular disease  Bilateral HS  Malignant glioma

Sub-ependymal heterotopia  Focal cortical scar  Parasagittal meningioma
• non-specific small lesion in right caudate nucleus, 1 (alcohol-related seizure)
• cerebellar atrophy (acute hydrocephalus 3 months earlier, following foramen magnum decompression for an Arnold-Chiari malformation)

In the 88 patients with unprovoked seizures, the following abnormalities were seen on cranial MRI (note that some patients had more than one lesion):

• no abnormality, 36
• multiple small WML, 30
• focal neocortical brain damage, 14 (including 2 with previous meningioma excisions and no evidence of residual tumour)
• cerebral and/or cerebellar atrophy, 7
• neoplastic lesions, 6
• HS, 2 (bilateral, 1; unilateral, 1)
• MCD, 2
• cavernous haemangioma, 1
• widespread periventricular WML and a large subcortical frontal lobe plaque, 1 (patient subsequently confirmed as having multiple sclerosis)
• area of focal neocortical damage and prominent meningeal gadolinium enhancement, 1 (patient with neurosarcoidosis complicating known pulmonary sarcoidosis)
• giant anterior cerebral artery aneurysm, 1
• lesions of uncertain aetiology, 2 (one patient had a small, possibly dysgenetic, lesion in the left insula. The other had a lesion centred upon and slightly expanding the left amygdala and uncus which was initially thought to represent a neoplastic lesion, but serial imaging following seizure remission showed spontaneous resolution of the lesion).

Examples of these MRI findings are shown in Figure 6.

Quantitative hippocampal analysis
a. Patients with provoked seizures
3/22 (13.6%; unilateral, 2; bilateral, 1) had HA. All were considered to have had alcohol
withdrawal seizures on a background of chronic alcoholism.

b. Patients with unprovoked seizures

Quantitative hippocampal abnormalities were found in 22 (25.0%; partial onset, 15; generalised, 7) of 88 patients (Table 19). Notable clinical features and additional neuroimaging findings are in parentheses:

- unilateral HS, 2
  (previous ipsilateral depressed skull fracture and associated frontal lobe haematoma, 1; EEG photosensitivity and a positive family history of idiopathic generalised epilepsy, 1)

- bilateral HS, 1
  (prematurity with recurrent febrile seizures from 12 months and subsequent bacterial meningitis at 18 months)

- unilateral HA, 12 (without associated HT2 abnormalities)
  (congenital hemiparesis and frontal lobe infarct ipsilateral to the HA, 1; mild learning disability, 1; severe closed head injury with prolonged loss of consciousness, 2; large ipsilateral temporal lobe menigioma causing mass effect and oedema, 1; previous transient ischaemic attack, 1; mild prematurity, 1; bipolar affective disorder, 1; history of alcohol abuse, 1; ipsilateral MCD, 1; clinically probable juvenile myoclonic epilepsy with history of early childhood viral meningitis, 1; no relevant history/findings, 1)

- bilateral HA, 2 (without associated HT2 abnormalities)
  (severe closed head injury causing prolonged loss of consciousness at 16 years, 1; no relevant history/findings, 1)

- unilateral HT2 elevation, 3 (without associated HA)
  (ipsilateral temporal lobe menigioma causing mass effect and oedema, 1; Huntingdon’s disease, 1; insulin-dependent diabetes mellitus with frequent hypoglycaemic episodes, 1)

- bilateral HT2 elevation, 1 (without associated HA)
  (multifocal primary CNS lymphoma involving both mesial temporal lobes)
Table 19 Quantitative hippocampal abnormalities in 22 patients with newly diagnosed unprovoked seizures (continued on next page)

<table>
<thead>
<tr>
<th>Sex/age/seizure category</th>
<th>Seizure types</th>
<th>Hippocampal abnormality</th>
<th>Clinical details</th>
<th>Qualitative MRI report</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/15/P</td>
<td>SGTC</td>
<td>R HA (ratio 0.89)</td>
<td>Mild learning disability. EEG L frontal polyspikes + high frequency spikes, raising possibility of cortical dysgenesis</td>
<td>Normal</td>
</tr>
<tr>
<td>F/24/P</td>
<td>CPS + SGTC</td>
<td>Bilateral (R&gt;L) HA</td>
<td>Severe closed head injury aged 16 years with LOC and cerebral oedema requiring intubation/ventilation. Mesial temporal seizures</td>
<td>Normal</td>
</tr>
<tr>
<td>F/29/P</td>
<td>SGTC</td>
<td>R HA (ratio 0.88)</td>
<td>&quot;Cerebral palsy&quot; with congenital L hemiparesis</td>
<td>R frontal infarct with dysplastic features and focal atrophy</td>
</tr>
<tr>
<td>F/30/P</td>
<td>SGTC</td>
<td>L HA (ratio 0.85)</td>
<td>No previous CNS insults. Normal intelligence/examination</td>
<td>L hemisphere SEH + possible L frontal gyral abnormality</td>
</tr>
<tr>
<td>M/30/P</td>
<td>SPS + SGTC</td>
<td>L HS (L HA + L HT2 elevation)</td>
<td>Depressed skull fracture aged 30 years; L frontal intracerebral haematoma evacuated shortly afterwards</td>
<td>L frontal neocortical brain damage</td>
</tr>
<tr>
<td>M/31/P</td>
<td>CPS</td>
<td>Bilateral HA</td>
<td>No history of CNS insults</td>
<td>Normal</td>
</tr>
<tr>
<td>F/33/P</td>
<td>CPS</td>
<td>L HA (ratio 0.83)</td>
<td>No history of CNS insults</td>
<td>Normal</td>
</tr>
<tr>
<td>F/36/P</td>
<td>CPS</td>
<td>Bilateral HS (bilateral HA + HT2 elevation)</td>
<td>Premature 30/40. Several febrile seizures from 12 months. Severe meningitis aged 18 months. Learning disability thereafter</td>
<td>Bilateral HS</td>
</tr>
<tr>
<td>M/36/P</td>
<td>SPS + SGTC</td>
<td>R HA</td>
<td>Severe closed head injury with LOC aged 17 years. Poor visual memory. Mesial temporal lobe seizures</td>
<td>Possibility of RHS</td>
</tr>
<tr>
<td>F/38/P</td>
<td>SPS, CPS + SGTC</td>
<td>Enlarged L hippocampus/amygdala causing abnormal HVR</td>
<td>No history of CNS insults. Initially very frequent seizures with aura of fear; later achieved seizure remission with lamotrigine monotherapy</td>
<td>Swelling + increased signal in L uncus and L amygdala which was absent on MRI following remission of seizures</td>
</tr>
<tr>
<td>F/52/P</td>
<td>SPS</td>
<td>L HA</td>
<td>Focal motor seizures, R sided pyramidal and temporoparietal lobe signs</td>
<td>Large L temporal meningeoma causing mass effect and oedema</td>
</tr>
<tr>
<td>M/57/P</td>
<td>CPS</td>
<td>Bilateral HT2 elevation</td>
<td>Presented with typical mesial temporal seizures</td>
<td>Multifocal neoplasia (lymphoma) with infiltration of R mesial temporal lobe, L hippocampus, and L neocortex</td>
</tr>
<tr>
<td>F/58/P</td>
<td>SPS + SGTC</td>
<td>L HT2 elevation</td>
<td>Mesial temporal seizures. Tumour inoperable due to close relationship with internal carotid artery</td>
<td>Medial L temporal meningeoma with mass effect and oedema and small vessel cerebrovascular disease</td>
</tr>
<tr>
<td>Sex/age/seizure category</td>
<td>Seizure types</td>
<td>Hippocampal abnormality</td>
<td>Clinical details</td>
<td>Qualitative MRI report</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>F/63/P</td>
<td>SGTC</td>
<td>Unilateral R HT2 elevation</td>
<td>Huntington's disease diagnosed 9 months before seizure onset</td>
<td>General atrophy, including hippocampi (but hippocampal size within normal limits on quantitative analysis)</td>
</tr>
<tr>
<td>F/75/P</td>
<td>CPS + SGTC</td>
<td>L HA</td>
<td>Bipolar affective disorder. Pseudobulbar palsy</td>
<td>Generalised atrophy + small vessel cerebrovascular disease</td>
</tr>
<tr>
<td>F/18/G</td>
<td>GTC + MJ</td>
<td>R HA (ratio 0.87)</td>
<td>Clinically probable juvenile myoclonic epilepsy. No CNS insults</td>
<td>Normal</td>
</tr>
<tr>
<td>F/18/G</td>
<td>AA</td>
<td>R HS (RHA + RT2 elevation)</td>
<td>No history of CNS insults. Mother with childhood absence epilepsy. EEG type 4 photosensitivity. Attacks lasting 30-40 seconds, with some post-ictal drowsiness</td>
<td>Normal</td>
</tr>
<tr>
<td>M/19/G</td>
<td>GTC</td>
<td>L HA</td>
<td>Premature 35/40. Minor birth injury (cord round neck). Early morning GTC</td>
<td>Normal</td>
</tr>
<tr>
<td>M/22/G</td>
<td>GTC</td>
<td>R HT2 elevation</td>
<td>Insulin-dependent diabetic with history of several hypoglycaemic episodes, and additional unprovoked epileptic seizures</td>
<td>Normal</td>
</tr>
<tr>
<td>M/35/G</td>
<td>GTC</td>
<td>L HA (ratio 0.88)</td>
<td>Closed head injury with LOC aged 14 years with transient ?L hemiparesis</td>
<td>Normal</td>
</tr>
<tr>
<td>M/55/G</td>
<td>GTC</td>
<td>L HA (ratio 0.83)</td>
<td>Single unprovoked seizure; history of excessive alcohol intake</td>
<td>Small vessel cerebrovascular disease</td>
</tr>
<tr>
<td>M/61/G</td>
<td>GTC</td>
<td>R HA (ratio 0.84)</td>
<td>Past history of bi-hemispheric transient ischaemic attacks</td>
<td>Small vessel cerebrovascular disease</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- F=female  M=male  R=right  L=left
- EEG=electroencephalogram  CNS=central nervous system  LOC=loss of consciousness  SEH=subependymal heterotopia
- P=partial onset  G=generalised  MJ=myoclonic jerk  SGTC=secondarily generalised tonic clonic seizure  SPS=simple partial seizure  CPS=complex partial seizure
- AA=atypical absence  GTC=generalised tonic clonic seizure  HS=hippocampal sclerosis  HA=hippocampal atrophy  HT2=hippocampal T2 relaxation time
• abnormal HVR with HT2 elevation on side of larger hippocampus, 1
(probable mesial temporal oedema (follow-up imaging revealed almost complete
resolution of the lesion with no treatment other than lamotrigine for partial seizures)

In total, 3 subjects (excluding the 3 with CNS tumours involving or distorting the mesial
temporal region) had dual pathology (ie. HS or HA combined with an additional focal
neocortical lesion).

The approximate incidence rates of HS and of all other quantitative hippocampal
abnormalities were calculated at 1.3/100,000/year and 9.8/100,000/year, respectively.

PREVALENT (CHRONIC ACTIVE EPILEPSY) CASES

Qualitative high resolution brain MRI
The MRI findings are shown in Table 18. Patients with generalised seizures were
significantly more likely to have normal high resolution MRI (33/44, 75.0%) than those
with partial onset seizures (38/125, 30.4%) ($\chi^2 = 26.57$ with 1 degree of freedom,
p<0.0001). There was also a highly significant difference in the combined frequency of the
most aetio logically relevant abnormalities (focal neocortical brain damage, HS, MCD and
neoplastic lesions) between these two groups: 68 such lesions were seen on 125 MRI scans
(54.4%) in the partial onset group, compared to 2 lesions on 44 scans (4.5%) from the
generalised group ($\chi^2 = 33.34$ with 1 degree of freedom, p<0.0001). Although multiple
small WML were more common in patients with partial onset (20.0%) compared to
generalised (6.8%) seizures, they were not significantly more frequent than in control
subjects (18.8%) ($\chi^2 = 4.18$ with 2 degrees of freedom, p=0.124).

In total, 25 (14.3%) patients with chronic active epilepsy had visible cerebral and/or
cerebellar atrophy, including 14 in whom this was the sole abnormality.

Quantitative hippocampal analysis
Quantitative hippocampal abnormalities (including those which were also apparent
qualitatively) were found in 53/125 (42.4%) patients with partial onset and in 8/44 (18.1%)
with generalised seizures ($\chi^2 = 8.28$ with 1 degree of freedom, p=0.004). Such
abnormalities were also seen in 2/5 (40.0%) who had both generalised and partial onset

167
Overall, the prevalence rates of HS and of all other quantitative hippocampal abnormalities approximated to 0.2/1000 and to 0.44/1000, respectively.

A history of early febrile seizures was present in just 9 of these 53 subjects (17.0%; HS, 7; HA, 2) with partial onset seizures and abnormal hippocampi, and in 1/2 (50.0%; HS, 1) with mixed seizure types. The frequency of other potential HS risk factors obtained from history-taking in the 53 classified as having partial onset seizures was: CNS infection, 3 (5.7%), severe CNS trauma, 6 (11.3%) and pre-/peri-natal injury, 9 (17.0%). None of the remaining 35 subjects with quantitative hippocampal abnormalities had recognised risk factors for the development of HS.

20 patients (31.7%; partial onset, 19; mixed, 1) with quantitative hippocampal abnormalities had dual MRI pathology. All had foci of brain damage and none had associated MCD.

6.4.3 Standard neuroimaging findings and impact of high resolution MRI

PATIENTS WHO HAD STANDARD NEUROIMAGING ALONE

In the 37 newly diagnosed patients who had CT and/or standard MRI, but not high resolution MRI, the findings were: normal, 14; cerebral infarcts or haemorrhages, 11; cerebral atrophy, 6; tumours, 4; hydrocephalus, 1, cavernoma, 1.

In the 47 chronic active epilepsy patients who had standard neuroimaging, but not high resolution MRI, the findings were: normal, 27; focal brain damage (including infarcts), 10; atrophy, 5; tumours, 4; hydrocephalus, 1.

OVERALL USEFULNESS OF HIGH RESOLUTION MRI COMPARED TO STANDARD NEUROIMAGING

High resolution MRI uncovered previously unknown structural abnormalities of probable aetiological relevance in 39/110 (35.5%) patients with newly diagnosed seizures, including 20 who had normal CT and/or standard MRI. Although multiple WML indicating small vessel cerebrovascular disease were the commonest lesions to have been missed on CT,
Table 20 Quantitative hippocampal abnormalities in patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Newly diagnosed</th>
<th>Chronic active epilepsy</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Partial onset</td>
<td>Generalised</td>
<td>Partial onset</td>
</tr>
<tr>
<td>HS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unilateral HS unilateral</td>
<td>1</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>bilateral HS</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>unilateral with contralateral HA</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>unilateral with contralateral HT2 elevation</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unilateral HA</td>
<td>8</td>
<td>7</td>
<td>21 *</td>
</tr>
<tr>
<td>bilateral HA</td>
<td>2</td>
<td>1</td>
<td>4 †</td>
</tr>
<tr>
<td>HT2 elevation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unilateral HT2 elevation</td>
<td>2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>bilateral HT2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Discordant HA + HT2 elevation</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Temporal lobectomy + contralateral elevated HT2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total with hippocampal abnormalities</td>
<td>15 (22.7%)</td>
<td>10 (23.3%)</td>
<td>53 (42.4%)</td>
</tr>
<tr>
<td>Total number scanned</td>
<td>66 (100%)</td>
<td>43 (100%)</td>
<td>125 (100%)</td>
</tr>
</tbody>
</table>

**HS** hippocampal sclerosis (HA with ipsilateral elevation of HT2)

**HA** hippocampal atrophy (HVR < 0.89 and/or corrected hippocampal volume < 2 SD below control mean)

**HT2** hippocampal T2 relaxation time (elevated if > 2 SD above control mean)

* includes one subject without HT2 data

† includes two subjects without HT2 data
2 cases of post-traumatic brain damage, 2 brain tumours (meningioma, 1; glioma, 1), and single cases of MCD, HS and cavernoma, respectively, had also been missed by conventional neuroimaging. In 12 patients, high resolution MRI confirmed the presence of relevant lesions detected previously on standard imaging, and also revealed coexistent quantitative hippocampal abnormalities in 5 of them. Isolated HA and/or HT2 abnormalities were found in 12 (10.9%) patients, half of whom had previous standard imaging which was reported as normal. Another 5 patients had lesions identified which were of uncertain aetiological relevance. High resolution MRI revealed no abnormalities of aetiological significance in 42/110 (38.2%) cases.

In 174 patients with chronic active epilepsy, high resolution MRI identified hitherto unknown, but probably aetiologically relevant, cerebral lesions in 35 (20.1%) patients (19 with normal CT, 2 with normal standard MRI, and 14 with no prior imaging), isolated HA or HT2 abnormalities in 21 patients (8 with normal CT, 3 with normal standard MRI, and 10 with no prior imaging), and lesions of possible aetiological significance in 4 patients (2 with normal CT, and 2 with normal standard CT and MRI). The most frequent qualitative lesions to have been missed on standard neuroimaging were HS and focal neocortical brain damage. Lesions previously identified on CT were confirmed in 17 patients, with additional HS or HA being discovered in 9 of these. Lesions previously detected on standard MRI were confirmed in 14, of whom 3 also had coexistent HS or HA identified. In 2 subjects with lesions previously considered on standard MRI to be an infarction and low grade glioma, respectively, high resolution MRI led to revised radiological diagnoses of probable dysembryoplastic neuroepithelial tumours. One subject previously thought to have standard MRI evidence of unilateral HS had entirely normal high resolution MRI, including quantitative hippocampal analysis. MRI added no information regarding the cause of epilepsy in 78 (44.8%) patients (CT normal/atrophy only, 43; standard MRI normal/atrophy, 9; no prior neuroimaging, 26).

6.4.4 Aetiology of the epilepsies

INCIDENT (NEWLY DIAGNOSED) CASES

Provoked seizures

The range of causes of provoked seizures in 39 patients is shown in Table 21. It should be noted that 3 patients with CNS tumours were classified as having provoked seizures
Table 21 The aetiologies of provoked seizures in 39 adult patients

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Number of patients</th>
<th>No neuroimaging or standard neuroimaging only</th>
<th>High resolution MRI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol and/or drug-related</td>
<td>7</td>
<td>16 *</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5</td>
<td>1</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>CNS tumour (presenting symptom)</td>
<td>2 †</td>
<td>1 ††</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Cranial trauma</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Viral encephalitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Metabolic (hypoglycaemia)</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>1</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17</td>
<td>22</td>
<td></td>
<td>39</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- CNS: central nervous system
- MRI: magnetic resonance imaging

**Definitions:**
Epileptic seizures are termed provoked (synonyms: acute symptomatic or situation-related) if they occur within 7 days of an acute metabolic or CNS insult. In accordance with the International League Against Epilepsy Guidelines for Epidemiological Studies (232), seizures associated with CNS tumours are also classified as provoked if they are the presenting symptom of the tumour, and do not recur thereafter.

**Notes:**
- * 3 had coexistent multiple small white matter lesions, and 4 had various other lesions (see text) which may have been relevant but were probably longstanding, and were found in the context of definite alcohol withdrawal, illicit drug misuse, or recent prescription of a drug with known pro-convulsant properties. 3 additional patients with alcohol-related seizures had evidence of hippocampal atrophy (unilateral, 2; bilateral, 1) on hippocampal quantitative analysis.
- † both cerebral gliomas found on scans elsewhere, and confirmed following biopsy
- †† patient had both a meningioma and multiple white matter lesions on MRI
because their seizures were the presenting symptom of the tumour and had not recurred by the time of aetiological classification (ILAE, 1993). The majority of alcohol/drug-related seizures were provoked by alcohol withdrawal, with a small proportion being related to either illicit or prescribed (tricyclic antidepressant, anti-psychotic or anti-malarial) drug use. A number of subjects with alcohol withdrawal seizures who underwent high resolution MRI had structural abnormalities including multiple small WML, an old haemorrhagic infarct, diffuse brain atrophy, and isolated HA. Although these structural abnormalities may have contributed to epileptogenesis, the clear temporal association with alcohol misuse in each case led to these seizures being considered as due to alcohol withdrawal per se.

Unprovoked seizures

Prior to high resolution MRI, the cause of seizures was known or surmised in 52/126 (41.3%) patients with newly diagnosed unprovoked seizures. The aetiologies following high resolution MRI are presented in Table 22. Some patients had more than one factor which was considered aetiologicaly relevant, so that the total sum of aetiologies exceeds the number of patients. Overall, by far the most important cause of unprovoked seizures was cerebrovascular disease (31.7%), both small and large vessel. In many instances, the presence and extent of cerebrovascular disease was only revealed by MRI. The majority had partial onset seizures. CNS tumours (7.9%; gliomas, 3; meningiomas, 5; primary CNS lymphoma, 1; cerebral metastases from bronchial carcinoma, 1) and CNS trauma (7.9%) were other important causes, presenting almost exclusively with partial onset seizures. Of note, HS was found in only 3 (2.4%) patients, one of whom also had post-traumatic brain damage, whilst HA, either in isolation or in association with other lesions, was of possible aetiological relevance in an additional 10.3%. Degenerative CNS conditions (8.7%), including Alzheimer’s disease, were the other main identifiable cause of seizures, particularly generalised seizures.

8 patients (6.3%) had electro-clinical data in keeping with IGE. Interestingly, one of these had clearcut unilateral HS on hippocampal quantitative analysis. Her EEG had shown type IV photosensitivity, but clinically she had attacks which were probably complex partial seizures rather than absence attacks (episodes of prolonged vacant staring without automatisms and very brief post-ictal confusion). Another female with classical juvenile
Table 22 The aetiologies of newly diagnosed unprovoked seizures and chronic active epilepsy

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Newly diagnosed</th>
<th>Chronic active</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seizure type classification</td>
<td>Seizure type classification</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>Gen</td>
</tr>
<tr>
<td>STATIC OR NON-PROGRESSIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS trauma (major HI or craniotomy)</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>CNS infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Perinatal or pre-natal injury (excl. MCD)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MCD</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Post-toxic/metabolic encephalopathy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>HA</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Cavernoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lesions of uncertain aetiology</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PROGRESSIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS tumours</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Autoimmune/inflammatory CNS disease</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Degenerative CNS diseases</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Cryptogenic: high resolution MRI normal</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Cryptogenic: without high resolution MRI</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Total number of aetiologies</td>
<td>95</td>
<td>44</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>84</td>
<td>40</td>
</tr>
</tbody>
</table>

Total (%) column indicates the percentage of patients with that aetiology. Since many patients had more than one aetiological diagnosis, the total sum of the percentages exceeds 100%.

Abbreviations:
- Gen = generalised seizures
- HS = hippocampal sclerosis
- CNS = central nervous system
- HA = hippocampal atrophy
- excl. = excluding
- other = mixed and unclassifiable seizures
- MRI = magnetic resonance imaging
- HI = head injury
- MCD = malformation of cortical development (includes dysmorphic/loplastic neuroepithelial tumours)
- ♦ includes 3 patients with craniotomy performed for post-subarachnoid haemorrhage aneurysmal clipping (2), excision of meningioma (1), and evacuation of cavernoma-associated haematoma
- ♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
- ♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦♦ includes patients with post-chronic alcoholism epilepsy
myoclonic epilepsy had minimal unilateral HA of uncertain significance, although she had also had early childhood viral meningitis. All others with IGE had entirely normal high resolution MRI.

A further 21 patients, two thirds of whom had partial onset seizures, persisted in having a cryptogenic aetiology despite high resolution MRI. Of the 38 unprovoked seizure patients who did not have high resolution MRI, an aetiology could still be assigned using other data in all but 11 (8.7%).

PREVALENT (CHRONIC ACTIVE EPILEPSY) CASES
Of the 105 chronic epilepsy patients (47 with prior CT and/or standard MRI) who did not have high resolution MRI, 10 had idiopathic epilepsies on the basis of electro-clinical data, and 51 had a cryptogenic aetiology. In the remaining 44, epilepsy was caused by cerebrovascular disease (n=13), pre-/peri-natal insults (n=8), a previous encephalopathy (including chronic alcoholism without withdrawal seizures) (n=8), CNS trauma (n=4), CNS infections (n=3) and miscellaneous other aetiologies (n=8).

Amongst the entire cohort of 279 adults with chronic active epilepsy, only 8 subjects were known to have HS or HA prior to this study. The cause of epilepsy was known or surmised in just 95/279 (34.1%) patients. Following high resolution MRI, 8.2% were found to have HS, and a further 11.5% to have HA without associated HT2 elevations. Some had aetiological factors in addition to HS or HA present. Approximately 90% of the patients with HS or HA were classified as having partial onset seizures. The full range of aetiologies is shown in Table 22. Cerebrovascular disease (9.7%), pre-/peri-natal insults (8.2%) and CNS trauma (9.0%) were the other main causes of chronic epilepsy, particularly in those with partial onset seizures. Of note, MCD, cavernomas and CNS tumours were infrequent causes of chronic epilepsy. A significant proportion (16.1%) had chronic active idiopathic epilepsies, particularly the IGE syndromes. 105/279 (37.6%) persisted in having no known cause, including 54 (19.4%; partial onset seizures, 42; generalised, 9; mixed seizure types, 3) with unremarkable high resolution MRI. Although several patients with chronic active epilepsy had multiple small WML on MRI, these were not felt to be aetiologically relevant in the cases in whom epilepsy had started in childhood or early adult life, or where other obvious aetiological factors were present.
6.4.5 Age-specific aetiology of the epilepsies

Figure 7 and Figure 8 show the age-specific aetiologies of all newly diagnosed seizures and chronic active epilepsy, respectively (including those without high resolution MRI). For the purpose of simplification, the newly diagnosed group in this figure comprises both provoked and unprovoked seizures.

INCIDENT CASES

It can be seen that nearly all cases of seizures associated with HS, HA, pre-/peri-natal injury, MCD and cavernoma presented in early adult life (15-34 years). Half of the patients with seizures caused in whole or in part by major CNS trauma also presented at 15-34 years, with the other half presenting between 35-64 years. Furthermore, all idiopathic epilepsies, and a significant proportion of the high resolution MRI-negative patients had their seizures diagnosed between ages 15-34 years.

In middle life (35-64 years), the dominant causes of newly diagnosed seizures were cerebrovascular disease, alcohol/drug misuse, CNS tumours and, to a lesser extent, degenerative and autoimmune/inflammatory (eg. multiple sclerosis, systemic lupus erythematosus) CNS diseases.

In later life (65 years and over), cerebrovascular disease was by far the most important cause, with CNS degenerative diseases (mainly primary dementias) being less common, and CNS tumours a relatively rare cause.

PREVALENT CASES

Idiopathic epilepsies were most prevalent in early adult life, and to a lesser extent in middle life. HS and HA were equally prevalent in young and middle aged adults with epilepsy. A similar pattern was seen amongst those with epilepsies secondary to pre-/peri-natal injury, although the number affected was fewer. Likewise, major CNS trauma was as important a cause of chronic active epilepsy in patients of 15-34 years as it was amongst those of 35-65 years of age. Cerebrovascular disease was observed as a cause of chronic active epilepsy predominantly amongst patients in late life. The proportion with no identifiable cause on high resolution MRI was greatest amongst patients in middle life, less common in early adult life, and infrequent in the elderly.
Figure 7 Age-specific aetiology in 165 patients with newly diagnosed seizures (provoked and unprovoked)
Figure 8  Age-specific aetiology in 279 patients with chronic active epilepsy

<table>
<thead>
<tr>
<th>Age band / years</th>
<th>Cranial trauma</th>
<th>Other*</th>
<th>CVD</th>
<th>Pre/perinatal</th>
<th>HS</th>
<th>Idiopathic</th>
<th>Cryogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 - 34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>35 - 64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CNS tumours n = 5
6.5 Discussion

6.5.1 Summary of major findings

Patients with partial onset seizures were significantly more likely to harbour focal brain abnormalities detectable by MRI than those with generalised seizures, irrespective of whether seizures were of recent onset or longstanding. The most frequent abnormalities were multiple small WML, and focal neocortical damage (resulting from CNS trauma, infection, inflammation or stroke). HS was an infrequent finding in patients with newly diagnosed partial seizures, but considerably more common in patients with chronic active partial epilepsy. However, other quantitative hippocampal abnormalities (HA without HT2 elevation, or vice versa) were more frequent and were found in approximately one fifth of patients with newly diagnosed seizures and in one quarter with chronic active epilepsy. HA was more likely to be associated with dual MRI pathology (focal brain damage in every case) in the chronic active epilepsy patients, suggesting that hippocampal damage might represent the secondary lesion in this subgroup. In contrast to published hospital based studies, MCD, vascular malformations and CNS tumours were all uncommon causes of chronic active epilepsy, whereas CNS tumours caused approximately 6% of newly diagnosed seizures. There was also a trend for cerebellar and/or cerebral atrophy to be more common in the chronic active epilepsy patients than amongst those with newly diagnosed seizures.

By incorporating all the available MRI and electro-clinical data, it was possible to assign a probable aetiology (including the idiopathic category) in more than three quarters of patients with newly diagnosed seizures, and in nearly two thirds with chronic active epilepsy, considerably more than in previous population based studies. The frequency of the most important aetiological categories varied according to age, with epilepsy due to HS, pre-/peri-natal injury and head trauma being more common in young adults. Epilepsies due to CNS tumours, cerebrovascular disease and alcoholism were most evident in middle life whilst, in late life, cerebrovascular disease caused the majority of epilepsies, with dementias implicated in a smaller number of patients.

6.5.2 Advantages and limitations of study design

The primary aim of this prospective community based study was to perform high resolution MRI in all patients with newly diagnosed and chronic active epilepsy. Ultimately, this was
achieved in approximately two thirds of all 165 newly diagnosed and 279 chronic active epilepsy patients, with the majority of other patients having data available from previous standard neuroimaging.

An MRI protocol customised for the investigation of epilepsy, in addition to quantitative hippocampal assessment, were applied to maximise the detection of HS, HA and other subtle lesions (Duncan, 1997). This enabled frequency data to be derived for these, and other, pathologies in unselected patients with newly diagnosed and chronic epilepsy, and significantly reduced the proportion of subjects with cryptogenic epilepsies compared to previous epidemiological studies. In order to assess the aetiological relevance of these findings, comparisons were made with the frequencies of similar lesions in a large cohort of control subjects recruited from the same population base and investigated with an identical MRI protocol (see chapter 5).

Unfortunately, it was not possible to obtain high resolution MRI in every patient. In some cases, frailty, or associated learning/physical disability precluded MRI scanning for obvious reasons whilst, in others, the reasons were failure to reply to repeated invitations to attend for MRI, or refusal to attend. This is in keeping with response rates in epidemiological studies employing questionnaires, and probably reflects the stigma, denial or embarrassment which may be associated with epilepsy (Morrell and Pedley, 2000). In addition, MRI investigation of children with epilepsy was beyond the scope of this study because the principal investigator has had no paediatric training, and also because there would have have been considerable difficulties with MRI acquisition may necessitate general anaesthesia in very young children. As a consequence, epilepsies with aetiologies peculiar to childhood may have been missed. However, it does not appear that the exclusion of children significantly altered the proportion of newly diagnosed patients with HS or HA, since a recent community based study of children with newly diagnosed epilepsy found MRI evidence of hippocampal damage in only 0.5% (Berg et al., 2000).

EEG data was also lacking in a large number of patients, yet in those who did have EEG, the findings were rarely diagnostic of a particular syndrome, or of localising/lateralising value. This may have been partly related to the timing of EEG which was not usually in the immediate aftermath of a seizure. The classifications of seizure type and aetiology were
based upon the 1993 ILAE Classification for Epidemiological Studies (ILAE, 1993), rather than upon the over-complicated International Classifications of epileptic seizures and epilepsy syndromes (ILAE, 1981 and 1989) which are too cumbersome and contain too many catch-all categories to be helpful in such a study. The classification employed in this study separates seizure types on the basis of clinical findings alone, and does not take into account the results of either EEG or neuroimaging. Tonic-clonic seizures without localising features were thus classified as generalised, although this term is clearly not synonymous with "primary generalised". As a consequence, some of the patients classified as having generalised seizures were found to have focal abnormalities on MRI, highlighting the additional inadequacies of simplified classifications. This situation was more likely to occur in those with newly diagnosed seizures than in those with chronic active epilepsy, since many of the former group had only experienced isolated seizures and a clear seizure history had not yet emerged.

6.5.3 MRI findings and relevance to aetiology of seizures

Prior to this study, only 15% of the patients with chronic active epilepsy had been investigated with MRI, and only 34% had a known or suspected aetiology. A little over 40% with newly diagnosed unprovoked seizures had a known or suspected cause. In this study, however, MRI revealed qualitative structural abnormalities in 56% of all patients with newly diagnosed seizures and in 58% with chronic active epilepsy. These proportions were significantly greater in patients classified as having partial onset seizures, in whom the MRI abnormalities were also more frequently considered to be of aetiological relevance.

For the purposes of this study, HS was considered as being of aetiological significance, although there is considerable controversy as to whether it is a cause or consequence of epilepsy, or both (Mathern et al., 1997; Jefferys, 1999). One of the main grounds for the supposition that HS is aetiologically important is that temporal lobectomy for intractable temporal lobe epilepsy associated with ipsilateral HS produces remission of seizures in up to two thirds of patients (Babb and Brown, 1987; Bruton, 1988; Salanova et al., 1999). Despite the potentially curative effect of this procedure, the suspicion is that it remains a vastly under-used treatment performed in only a small number of centres in the UK (Elwes, 2002). Determination of the incidence and prevalence of HS in an unselected population
is therefore of major importance since this permits an estimation of the total number of adults in the UK who might benefit from temporal lobectomy. If one takes the current adult (defined as aged 15 years or above) population of the UK as being approximately 48 million, the figures from this study suggest that approximately 600 new adult cases of HS arise in the UK each year. In addition, at any one time, approximately 9500 adults in the UK have HS and chronic active epilepsy. Even if one assumes that many subjects with HS do not require, or are deemed unsuitable for, temporal lobectomy (eg. if MRI and EEG data discordant), these data confirm that potentially curable epilepsy surgery is currently being offered to only a fraction of all subjects in the UK with HS and epilepsy. These data have potentially important implications for the planning of future epilepsy care provision in the UK.

Two important observations regarding the frequency of HS at the population level can be made from this study. Firstly, HS is not as prevalent as has been previously reported in hospital based studies of chronic epilepsy (Li et al., 1995; Mcbride et al., 1998), presumably because the study population was not subject to the selection bias inherent in studies which have recruited patients from epilepsy clinics or pre-surgical assessment programs. This same factor accounts for the relative infrequency of cavemomas and MCD in this study. Secondly, HS was far less frequent in those with newly diagnosed seizures than in those with chronic active epilepsy. There are several possible explanations for this and, unfortunately, this study cannot determine which is the most important. One explanation is that the presence of HS predisposes to the development of intractable epilepsy, so that its prevalence is greater amongst subjects with chronic active epilepsy than in those with newly diagnosed seizures. Another is that HS is a slowly progressive lesion, possibly developing as a result of, and also contributing to, the intractability of seizures in certain patients (Saukkonen et al., 1994; Kalviainen et al., 1998; Sutula and Hermann, 1999). A third possibility is that the majority of cases of HS develop in childhood, with the implication that this study of adults may theoretically have been biased against finding HS in newly diagnosed cases. As mentioned above, this theory appears to have been partly disproved by a recent community based study of newly diagnosed epilepsy in children which found HS in only 0.5% (Berg et al., 2000), with the proviso that the study in question did not employ either high resolution MRI or quantitative hippocampal analysis and may therefore have missed some cases of HS. TLE associated with HS can certainly
begin in late childhood, often several years after an early cerebral insult, particularly prolonged febrile seizures (Bragin et al., 2000). In fact, several authors have reported that as many as 50-80% of patients with unilateral HS have such a history (Falconer et al., 1964; Falconer, 1974; Annegers et al., 1987; Sagar and Oxbury, 1987; Bruton, 1988; Cendes et al., 1993c; Kuks et al., 1993; Holthausen, 1994; Maher and McLachlan, 1995; Mathern et al., 1995b; Shinnar, 1998). Interestingly, in the current study, amongst subjects with qualitatively or quantitatively abnormal hippocampi, only 17% with chronic active epilepsy and 4.5% with newly diagnosed seizures had a history of febrile seizures. Similarly small proportions had experienced other CNS insults. Although it is possible that these low proportions were partly an effect of the study having being confined to an adult population, many of the chronic active epilepsy patients with HS or HA had suffered epilepsy since childhood, suggesting that the high proportion in hospital based studies with HS and a history of febrile seizures is again a result of selection bias. This theory is supported by other, more recent, studies (Tarkka et al., 2003).

The aetiological relevance of HA without associated HT2 elevation, or isolated abnormalities of HT2, are less certain. Such abnormalities, which were not visible in the majority of cases, were found in 22 (20.0%) of the patients with newly diagnosed seizures. In 3 such patients, the abnormalities resulted from anatomical distortion in the mesial temporal lobe caused by large tumours or neighbouring oedema, and were unlikely to represent true HS/dual pathology. Three others (2.7%) had isolated HT2 elevation (compared with 3/170 or 1.8% of control subjects), whilst all other newly diagnosed patients had isolated abnormalities of HVc or HVR. The latter group included one patient with HA and ipsilateral MCD, and another with HA, an ipsilateral atrophic frontal lobe infarct (with dysplastic features) and a history of congenital hemiparesis. Quantitative hippocampal abnormalities (excluding definite cases of HS) were slightly more frequent in those with chronic active epilepsy (25.3%), particularly in those with partial onset seizures (28.8%). The majority had HA as opposed to isolated HT2 elevation, and approximately one third had associated focal brain damage. In these subjects, it is postulated that “isolated” HA is likely to represent a consequence rather than the primary cause of seizures. On the other hand, there is some evidence emerging in the literature which suggests that hippocampal abnormalities seen on MRI in patients with associated MCD (as in at least one of the newly diagnosed patients) may be due either to hippocampal
developmental malformations per se, or to the occurrence of HS in a hippocampus congenitally predisposed to seizure-induced damage (Fernandez et al., 1998; Grunewald et al., 2001; Blumcke et al., 2002). It seems likely from past MRI-neuropathological correlative studies that HA signifies early or mild HS (Cascino et al., 1991; van Paesschen et al., 1997c; Watson et al., 1997), and it was therefore valid to have considered it as having aetiological relevance in this study, especially in subjects without additional, potentially epileptogenic, structural lesions. Conversely, isolated HT2 elevation was not considered as an aetiological factor, since it appears to be a less sensitive predictor of HS (van Paesschen et al., 1997c).

CNS tumours were an important cause of newly diagnosed seizures. A large proportion were primary brain tumours, both benign and malignant, and only one case with CNS metastases was found. This difference may be partly explained by the fact that some patients with CNS metastases may have developed seizures very late in the course of their illness, possibly during a hospital admission precipitated by the underlying malignancy or some non-seizure manifestation of the CNS metastasis. In such a situation, it is theoretically possible that seizures may not have been mentioned specifically in hospital correspondence to the GP, thus precluding detection by the surveillance methods employed in the study, but this possibility seems most unlikely. In contrast, very few chronic active epilepsy patients were classified as having CNS tumours, although 2 with suspected dysembryoplastic neuroepithelial tumours were artificially excluded through classification as MCD. Patients with malignant glioma do not survive to develop chronic epilepsy (Maudgil and Shorvon, 1999), and no patients with low grade gliomas were seen in this study. Furthermore, a few chronic epilepsy patients developed seizures following craniotomy and excision of a meningioma. MRI indicated post-surgical neocortical damage, without residual tumour, and the focal damage was taken to be the prime aetiological factor.

The MRI finding of focal neocortical brain damage was nearly always considered to be of aetiological relevance because, in virtually every case, there was a coexistent history of major head trauma, pre- or peri-natal birth injury, CNS infection or stroke. Sometimes, particularly in the case of head trauma, the lesions were small and had been missed by CT. It is more difficult to judge the aetiological significance of head trauma in patients with
epilepsy when high resolution brain MRI is normal. Interestingly, in this study, three patients with newly diagnosed seizures and a history of severe head injury had quantitative evidence of hippocampal pathology, one fulfilling criteria for HS, the other two with HA. Head trauma is an increasingly well-recognised risk factor for the development of HS (French et al., 1993; Swartz et al., 1999; Diaz-Arrastia et al., 2000). MRI thus permits more accurate assignation of head trauma as an aetiological factor than does history alone, since focal brain damage may be reliably demonstrated.

Overall, multiple small WML were by far the most frequent MRI abnormality, and cerebrovascular disease the commonest putative cause of seizures, especially amongst the elderly. The significance of multiple small WML to the aetiology of seizures warrants further discussion. It is likely that, in the majority of middle aged or elderly subjects, these lesions represent ischaemic small vessel cerebrovascular disease (De Leeuw et al., 2001). In Study 2 (Chapter 5), small WML were shown to be relatively common (18.8%) in similarly-aged, neurologically normal control subjects recruited from the same population base. However, they were considerably more frequent (39.4%) amongst patients with newly diagnosed partial onset seizures, in whom they were often judged to have been of aetiological importance. This decision was based upon a number of factors, including age of onset of seizures (usually in middle or late life), the absence of other aetiological factors, evidence of other vascular disease (angina, peripheral vascular disease, transient ischaemic attacks), risk factors for vascular disease (hypertension, smoking, diabetes, hypercholesterolaemia), and a qualitative assessment of lesion size and position (often comprising subcortical lesions rather than the slightly deeper WML seen in most of the abnormal control subjects). It is of interest that these abnormalities were the most commonly missed lesions on CT. Multiple small WML were also relatively common in patients with newly diagnosed generalised seizures, and in those with chronic active epilepsy, though no more frequent than in control subjects, and were rarely thought to be of aetiological significance. The exceptions were those patients with chronic active epilepsy who had suitable risk factors, and who had developed epilepsy in middle or late life.

Cerebral and/or cerebellar atrophy were moderately common findings on qualitative MRI reporting. There was a tendency for such atrophy to be more common in patients with
chronic active compared to newly diagnosed epilepsy, and for diffuse atrophy to be more frequent in patients with chronic partial onset epilepsy, but the numbers were insufficient to draw firm conclusions. A subsequent published analysis of cerebellar volumes in some of these newly diagnosed and chronic patients with visually normal scans, found no significant cerebellar atrophy and no correlation between cerebellar volume and either seizure frequency, duration of epilepsy, and exposure to multiple AEDs (Hagemann et al., 2002). In addition, two recent studies have reported ipsilateral hemispheric (Lawson et al., 2000) and extrahippocampal temporal lobe atrophy (Moran et al., 2001) in some patients with HS-associated TLE, and Liu et al. (2003) have recently found evidence of neocortical atrophy in a longitudinal voxel-based MRI study of patients with epilepsy.

This study differentiated idiopathic from cryptogenic epilepsies. In many previous epidemiological studies of epilepsy, the term idiopathic was used synonymously with “cause unknown”, with the effect that epilepsies with a probable genetic basis were grouped together with those which were cryptogenic (commonly patients with either non-contributory investigation, or no investigation at all). Electro-clinical and neuroimaging evidence in keeping with idiopathic epilepsy was found in some 6% of newly diagnosed and 16% of chronic active epilepsy patients, including nearly two thirds of those with chronic generalised epilepsy A small number with EEG findings in keeping with IGE also harboured quantitative hippocampal abnormalities and it is possible that, in this minority, idiopathic and symptomatic epilepsies coexist. Yet, despite the application of high resolution MRI and quantitative hippocampal analysis, a significant proportion of patients, especially those with partial onset seizures, continue to have no definable aetiology. There are several potential reasons for this. If one assumes that the majority of epilepsies have a structural basis, then it is possible that the application of other post-processing techniques such as diffusion tensor imaging (Rugg-Gunn et al., 2001), magnetisation transfer imaging (Rugg-Gunn et al., 2003), amygdalar volumetric analysis and relaxometry (Cendes et al., 1993b; van Paesschen et al., 1996; Kalviainen et al., 1997), grey-matter segmentation (Sisodiya et al., 1995), and 3-D cortical surface reconstructions (Sisodiya et al., 1996) may have further increased the yield of MRI in this study (Duncan, 1997). It is also likely that a smaller proportion of patients have epilepsies caused by functional abnormalities such as ion channelopathies or neurotransmitter/receptor deficits (Steinlein et al., 1995) which are, at present, undetectable even by functional neuroimaging techniques.
CHAPTER 7

Study 4:
The severity of hippocampal sclerosis in adults with newly diagnosed and chronic active epilepsy:
a prospective, cross-sectional, population based quantitative MRI study

7.1 Introduction
Hospital based pathological and MRI studies have revealed that HS is the most frequent abnormality associated with the commonest localisation related epilepsy syndrome, TLE. (Margerison and Corsellis, 1966; Bruton, 1988; Li et al., 1995; Lehericy et al., 1997; Mouritzen and Meencke et al., 1999). Despite its obvious importance, the pathogenesis and aetiological significance of HS is a matter of intense debate, as discussed in section 1.5. The fundamental question is whether HS is a cause or consequence of intractable TLE (Cendes et al., 1993d; Kalviainen et al., 1998; Jefferys, 1999; Sutula and Pitkanen, 2001), with the second theory implying progressive damage secondary to uncontrolled epileptic seizures (Nohria et al., 1994; Wiesmann et al., 1997; O’Brien et al., 1999; Sutula and Hermann, 1999; Fuerst et al. 2001 and 2003; Briellmann et al., 2002; Worrell et al., 2002). This issue has important ramifications relating to the degree of urgency that the physician should have in attempting to render the patient seizure-free, either with AEDs, or with epilepsy surgery (Wiebe et al., 2001).

Study 3 (chapter 6) revealed that qualitative or quantitatively-proven HS was present in 19/174 (10.9%) of unselected, community based adults with chronic active epilepsy (including 17/125, or 13.6%, of those with partial onset seizures), but in only 3/110 (2.7%) with newly diagnosed seizures. Other quantitative hippocampal abnormalities (including HA without HT2 change, isolated abnormalities of HVR, and isolated HT2 elevations) were relatively common in both newly diagnosed unprovoked seizure patients (22/110, 20%) and in those with chronic active epilepsy (44/174, 25.2%), although it was suggested that some of the abnormalities demonstrated in the former group were secondary to tumour-related oedema or temporal lobe distortion, and were unlikely to represent true
epilepsy-related hippocampal pathology. Although tantalising, these data do not, for reasons already discussed in section 6.5.3, allow one to deduce that chronic epilepsy leads to progressive hippocampal damage.

It is apparent from a number of cross-sectional hospital based studies that HS is not an all-or-nothing phenomenon, but a pathology with a spectrum of severity. Van Paesschen et al. (1997b), in a quantitative MRI study of TLE, found that bilateral and diffuse hippocampal damage was correlated with an earlier age at onset of epilepsy, and a higher lifetime number of secondarily GTC seizures. Several other quantitative MRI and histopathological studies have also shown a correlation between the severity of epilepsy and the degree of HS (Mouritzen Dam, 1980; Saukkonen et al., 1994; Mathern et al., 1995b; Kalviainen et al., 1998; Fuerst et al., 2001) but these studies have, without exception, targeted highly selected patients from tertiary epilepsy centres, many of whom were being considered for epilepsy surgery. Despite this, there are other hospital based, cross-sectional quantitative MRI studies which have failed to demonstrate such an association (Sagar and Oxbury, 1987; Cendes et al., 1993d; Salmenpera et al., 1998). This finding may have been influenced by the retrospective design of these studies which could have impeded an accurate estimation of seizure frequency and total lifetime number of GTC seizures. An alternative explanation is that the degree of HS in the majority of patients with TLE is effectively determined by the time of onset of habitual epilepsy, with only minimal progression thereafter as a result of repeated seizures. The studies which have found an inverse relationship between hippocampal volume and epilepsy severity might simply relate to selection bias from an unrepresentative subgroup with unusually severe epilepsy. A prospective, population based, quantitative MRI study might help to eliminate some of these confounding factors.

In the course of Study 3, “all-or-nothing” MRI data (qualitative and quantitative) relating to the frequency of HS and HA were produced. In Study 4, a more detailed analysis of HS will be performed. The severity of hippocampal damage, as evidenced by an assessment of HV and HT2, will be compared across groups of unselected epilepsy patients and control subjects, and the relationship between these parameters and a variety of clinical variables (such as the age of onset seizure frequency, duration of epilepsy) will be examined in order to investigate further the theory that chronic epilepsy is associated with
more severe hippocampal damage than is seen in patients with newly diagnosed seizures.

7.2 Aims and hypotheses

Aims
1. To determine the severity of hippocampal structural damage in patients with newly diagnosed and chronic active epilepsy, as determined by MRI measurements of HV and HT2, by comparison with normative data from the cohort of neurologically normal volunteers.

2. To compare the extent of hippocampal damage in patients with partial onset seizures with those having generalised seizures, in both newly diagnosed and chronic epilepsy.

3. To correlate the extent of hippocampal damage in epilepsy patients with relevant clinical variables, including age of onset, duration of epilepsy, seizure frequency, and the total lifetime number of seizures.

Hypotheses (as per Chapter 6: Study 3)
1. Patients with chronic active epilepsy have more severe hippocampal damage (as evidenced by quantitative hippocampal MRI) than do those with newly diagnosed epilepsy, since HS is probably a progressive pathology which predisposes to intractability.

2. Hippocampal damage is likely to be more severe in patients with partial onset epilepsy compared to those with generalised epilepsy, irrespective of whether the epilepsy is newly diagnosed or chronic and active.

3. The severity of hippocampal damage is likely to be correlated with the age of onset of epilepsy, the duration of epilepsy, the frequency of seizures and an estimate of the total lifetime number of seizures.

7.3 Methods

7.3.1 Patients and control subjects
All adult patients and control subjects were prospectively ascertained during the 2 year study period (1.6.95 - 31.5.97 inclusive) using the methods described in detail in chapters
4, 5 and 6:

- 110 with newly diagnosed seizures (59 males; median age 40 years; range 15-86 years)
- 174 with chronic active epilepsy (81 males; median age 37 years; range 15-73 years)
- 170 neurologically normal control subjects (males 86; median age 37.5 years, range 14-78 years)

Patient exclusions

NEWLY DIAGNOSED
All analyses of newly diagnosed patients were after the exclusion of 4 patients whose MRI data would have artificially biased the sample. These were 3 subjects with temporal lobe tumours that were causing oedema and/or distortion of the mesial temporal lobe structures, and 1 patient with a lesion expanding the amygdala and ipsilateral hippocampus which subsequently dimished in size on a follow-up scan.

CHRONIC ACTIVE EPILEPSY
All analyses were performed after the exclusion of 4 subjects whose MRI data may have skewed the sample. These were 3 with previous temporal lobectomies, and 1 with severe hydrocephalus in whom gross generalised cerebral and hippocampal atrophy was present.

A small number of subjects did not have both HT2 and HV quantitative data, but were still included in the relevant analyses.

7.3.2 Classification of seizure type
Seizures were classified clinically as either partial onset, generalised (including an idiopathic sub-category) or as mixed (with both partial onset and generalised seizures), using the 1993 ILAE International League Against Epilepsy Guidelines for Epidemiological Studies (ILAE, 1993). EEG data were generally insufficient to lateralise or localise the epileptogenic focus, but a proportion of subjects with electro-clinical features diagnostic or strongly suggestive of IGE were considered separately from others with non-idiopathic generalised seizures.
7.3.3 Age at onset of epilepsy, duration of epilepsy, seizure frequency, lifetime number of seizures, and past history of febrile seizures

Age at onset was defined as the age at onset of habitual seizure(s). Duration was subdivided into: ≤ 1 year, >1 year to ≤ 10 years, >10 to ≤ 20 years, > 20 years. Patients who experienced seizures (combined GTC and non-GTC) more than once per month were classified as having frequent seizures, whereas those with seizures occurring less frequently than this considered to have rare seizures. The estimated lifetime number of GTC and non-GTC seizures was also obtained. The presence or absence of a past history of febrile seizures was also recorded.

7.3.4 Quantitative hippocampal analysis

Blinded measurements of HV and HT2 were made for all subjects, as described in section 3.3.3. Normative data for HV and HT2 were also derived from the 170 control subjects, as described in section 5.3. HV was normalised for ICV and expressed as HVc.

Smallest HVc was defined as the smaller of the two HVc values within an individual patient. Highest HT2 was defined as the highest of the two HT2 values within an individual patient. Mean HVc (and mean HT2) were calculated by summing the two HVc (or HT2) values in each patient, and dividing by 2.

7.3.5 Statistical analyses of quantitative MRI data and clinico-quantitative MRI correlations

HVc

The Kruskal Wallis test was used to compare (a) smallest HVc and (b) mean HVc ((right + left HVc)/2) between groups of control subjects, patients with newly diagnosed seizures (subdivided into partial onset, generalised non-idiopathic, and idiopathic) and patients with chronic active epilepsy (subdivided into partial onset, generalised non-idiopathic, and idiopathic), following the patient exclusions described in section 7.3.1.

Mann-Whitney tests were used in “head-to-head” comparisons of mean HVc between (a) newly diagnosed and chronic partial seizures and (b) patients with newly diagnosed and chronic non-idiopathic generalised seizures.
Logistic regression analysis was used to detect possible predictors of hippocampal atrophy, including sex, age at onset of habitual seizures, duration of seizures, and history of rare or frequent seizures, in the newly diagnosed and chronic seizure cohorts.

**HT2**

Using the Kruskal Wallis test, comparisons of (a) highest HT2 and (b) mean HT2 ((right + left HT2)/2) were made between groups of control subjects, patients with newly diagnosed seizures (subdivided into partial onset, generalised non-idiopathic, and idiopathic) and patients with chronic active epilepsy (subdivided into partial onset, generalised non-idiopathic, and idiopathic), following the patient exclusions described in section 7.3.1.

Mann-Whitney tests were used in “head-to-head” comparisons of mean HT2 between (a) newly diagnosed and chronic partial seizures and (b) patients with newly diagnosed and chronic non-idiopathic generalised seizures.

Logistic regression analysis was used to detect possible predictors of HT2 elevation, including sex, age at onset of habitual seizures, duration of seizures, and history of rare or frequent seizures, in the newly diagnosed and chronic seizure cohorts.

All analyses were performed using SPSS for Windows 8.0. The level of statistical significance was set at less than 0.05.

**7.4 Results**

7.4.1 Hippocampal volumetric analysis

GROUP COMPARISONS OF MEAN HVc AND SMALLEST HVc

Data for those with mixed seizure types are not included in the following figures, because patient numbers were small (newly diagnosed, 1; chronic, 6).

Patients with newly diagnosed seizures versus control subjects

Figure 9 shows mean HVc in the different subgroups with newly diagnosed seizures and compares to that of control subjects. Compared to controls, mean HVc was 4.9% smaller (p=0.001) in those with newly diagnosed partial onset seizures, 4.8% smaller (p=0.005) in
Figure 9  Group analysis of mean corrected hippocampal volume ($HV_c$) in patients with newly diagnosed seizures versus control subjects

Kruskal Wallis $p=0.001$
those with newly diagnosed generalised (non-idiopathic) seizures, and 1% larger (p=0.81) in those with newly diagnosed idiopathic seizures (Kruskal Wallis p=0.001).

**Figure 10** shows smallest \(HV_c\) versus the above subgroups, and also shows a highly significant reduction in \(HV_c\) amongst those with newly diagnosed non-idiopathic generalised seizures (5.5% smaller than controls; \(p=0.002\)) and partial onset seizures (6.1% smaller; \(p<0.001\)). Patients with newly diagnosed idiopathic seizures had \(HV_c\) which were not significantly smaller (0.36%; \(p=0.8\)) than in controls (overall Kruskal Wallis \(p<0.001\)).

**Table 23** presents the mean \(HV_c\) and smallest \(HV_c\) findings in newly diagnosed patients with respect to duration and frequency of seizures. There was a non-significant trend towards a greater amount of hippocampal volume loss (% difference from control subjects) in those with a longer duration of seizures, and in those with more frequent seizures.

**Patients with chronic active epilepsy versus control subjects**

**Figure 11** shows the same comparison in subgroups with chronic active epilepsy. Compared to control subjects, mean \(HV_c\) was 10.3% smaller (\(p<0.001\)) in patients with chronic partial onset seizures, slightly smaller (3.2%; \(p=0.47\)) in those with non-idiopathic generalised seizures, but was not significantly different (1.1%; \(p=0.35\)) in those with chronic idiopathic seizures (Kruskal Wallis \(p<0.001\)).

**Figure 12** shows that, compared to control subjects, smallest \(HV_c\) was 13.4% smaller (\(p<0.001\)) in patients with chronic partial onset seizures, 5.8% smaller (\(p=0.22\)) in those with non-idiopathic generalised seizures, and only 1.4% smaller (\(p=0.28\)) in the idiopathic group (Kruskal Wallis \(p<0.001\)).

**Table 24** presents the mean \(HV_c\) and smallest \(HV_c\) findings in chronic active patients with respect to duration and frequency of seizures. Once again, there was a trend towards greater hippocampal volume loss (% difference from control subjects) in those with more frequent seizures, and a longer duration of epilepsy.

**Newly diagnosed versus chronic active epilepsy**

**Figure 13** indicates that there was a non-significant trend (\(p=0.129\)) for mean \(HV_c\) to be
Figure 10  Group analysis of smallest corrected hippocampal volume \( (HV_c) \) in patients with newly diagnosed seizures versus control subjects

Kruskal Wallis \( p < 0.001 \)

95\% CI
smallest
\( HV_c \)
\( (mm^3) \)

controls
ND "generalised"
ND partial onset
ND idiopathic

n=170
n=61
n=34
n=10
Table 23 Group analysis of corrected hippocampal volumes in newly diagnosed seizure patients with respect to frequency and duration of seizures

<table>
<thead>
<tr>
<th>Seizure frequency</th>
<th>Smaller HV&lt;sub&gt;C&lt;/sub&gt;</th>
<th>Mean HV&lt;sub&gt;C&lt;/sub&gt;</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HV&lt;sub&gt;C&lt;/sub&gt; (mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>% difference from control group smaller HV&lt;sub&gt;C&lt;/sub&gt; (2842mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>HV&lt;sub&gt;C&lt;/sub&gt; (mm&lt;sup&gt;3&lt;/sup&gt;)</td>
</tr>
<tr>
<td>&gt;1/month</td>
<td>2548</td>
<td>-10.3%</td>
<td>2641</td>
</tr>
<tr>
<td>1/month to 1/year</td>
<td>2722</td>
<td>-4.2%</td>
<td>2813</td>
</tr>
<tr>
<td>&lt;1/year</td>
<td>2704</td>
<td>-5.0%</td>
<td>2792</td>
</tr>
</tbody>
</table>

**Duration of epilepsy**

<table>
<thead>
<tr>
<th>Seizure frequency</th>
<th>Rare</th>
<th>Frequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to ≤ 10 years</td>
<td>3231</td>
<td>2482</td>
</tr>
<tr>
<td></td>
<td>+13.7%</td>
<td>-12.7%</td>
</tr>
<tr>
<td></td>
<td>3318</td>
<td>2573</td>
</tr>
<tr>
<td></td>
<td>+14.0%</td>
<td>-11.6%</td>
</tr>
<tr>
<td>11 to 20 years</td>
<td>1895</td>
<td>2362</td>
</tr>
<tr>
<td></td>
<td>-33.3%</td>
<td>-18.8%</td>
</tr>
</tbody>
</table>

HV<sub>C</sub> Corrected hippocampal volume (corrected for intracranial volume)

mm<sup>3</sup> cubic millimetres

Rare Seizures (GTC or non-GTC) occurring < 1/month

Frequent Seizures (GTC or non-GTC) occurring ≥ 1/month
Figure 11  Group analysis of mean corrected hippocampal volume ($HV_c$) in patients with chronic active epilepsy versus control subjects.

Kruskal Wallis $p < 0.001$

95% CI

Mean $HV_c$ (mm$^3$)

controls

chronic "generalised"

chronic partial onset

chronic idiopathic

$n=170$

$n=13$

$n=29$

$n=122$
Figure 12  Group analysis of smallest corrected hippocampal volume ($HV_c$) in patients with chronic active epilepsy versus control subjects.
Table 24 Group analysis of corrected hippocampal volumes in chronic active epilepsy patients with respect to frequency and duration of seizures

<table>
<thead>
<tr>
<th>Seizure frequency</th>
<th>Smaller HVc (mm³)</th>
<th>% difference from control group smaller HVc (2842mm³)</th>
<th>Mean HVc (mm³)</th>
<th>% difference from control group mean HVc (2910mm³)</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1/month</td>
<td>2498</td>
<td>-12.1%</td>
<td>2665</td>
<td>-8.4%</td>
<td>78</td>
</tr>
<tr>
<td>1/month to 1/year</td>
<td>2547</td>
<td>-10.4%</td>
<td>2694</td>
<td>-7.4%</td>
<td>70</td>
</tr>
<tr>
<td>&lt;1/year</td>
<td>2653</td>
<td>-6.7%</td>
<td>2779</td>
<td>-4.5%</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of epilepsy</th>
<th>Seizure frequency</th>
<th>Rare</th>
<th>% difference</th>
<th>Frequent</th>
<th>% difference</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 to ≤10 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rare</td>
<td>2550</td>
<td>-10.3%</td>
<td>2700</td>
<td>-7.2%</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>frequent</td>
<td>2556</td>
<td>-10.1%</td>
<td>1676</td>
<td>-8.0%</td>
<td>15</td>
</tr>
<tr>
<td>11 to 20 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rare</td>
<td>2607</td>
<td>-8.3%</td>
<td>2729</td>
<td>-6.2%</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>frequent</td>
<td>2610</td>
<td>-8.2%</td>
<td>2727</td>
<td>-6.3%</td>
<td>27</td>
</tr>
<tr>
<td>&gt;20 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rare</td>
<td>2554</td>
<td>-10.1%</td>
<td>2708</td>
<td>-6.9%</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>frequent</td>
<td>2400</td>
<td>-15.6%</td>
<td>2619</td>
<td>-10.0%</td>
<td>39</td>
</tr>
</tbody>
</table>

HVc: Corrected hippocampal volume (corrected for intracranial volume)

- mm³: cubic millimetres
- Rare: Seizures (GTC or non-GTC) occurring < 1/month
- Frequent: Seizures (GTC or non-GTC) occurring ≥ 1/month
Figure 13 Group analysis of mean $HV_C$ in patients with newly diagnosed versus chronic active partial seizures

Mann Whitney $p=0.129$

Newly diagnosed seizures

Chronic active epilepsy
Figure 14 Group analysis of mean $HV_C$ in patients with newly diagnosed versus chronic active generalised (non-idiopathic) seizures

Mann Whitney
$p=0.366$
smaller in the patients with chronic active partial epilepsy compared to the group with newly diagnosed partial onset seizures. There was no significant difference in mean HVc between the groups with newly diagnosed and chronic active non-idiopathic generalised seizures (p=0.366) (Figure 14).

7.4.2 Hippocampal T2 relaxometry

GROUP COMPARISONS OF MEAN HT2 AND HIGHEST HT2

Patients with newly diagnosed seizures versus control subjects

Compared to control subjects, mean or highest HT2 were not significantly elevated in any of the newly diagnosed subgroups (Kruskal Wallis p=0.16 and 0.17, respectively), although there was a trend towards higher mean and highest HT2 in the newly diagnosed partial onset patients (not shown).

Patients with chronic active epilepsy versus control subjects

Compared to control subjects, mean HT2 was significantly higher in the chronic active epilepsy patients classified as having partial onset seizures (2.2%; p<0.001), slightly higher in the non-idiopathic generalised subgroup (1.6%; p=0.04), but not in the idiopathic group (0.4%; p=0.26) (Kruskal Wallis p<0.001) (Figure 15).

The pattern was similar when comparing highest HT2, in that values were significantly higher compared to controls in the chronic partial subgroup (3.4%; p<0.001), but not in the chronic non-idiopathic (1.8%; p=0.12), or in the idiopathic (0.3%; p=0.53) generalised subgroups (Kruskal Wallis p<0.001) (Figure 16).

Patients with newly diagnosed versus chronic active epilepsy

Figure 17 shows that mean HT2 was significantly greater (p=0.048) in the group with chronic active partial epilepsy compared to the group with newly diagnosed partial seizures. There was no significant difference (p=0.278) in mean HT2 between the 2 groups with non-idiopathic generalised seizures (Figure 18).

7.4.3 Logistic regression analyses

HVc

None of the clinical variables, including age of onset, number of lifetime seizures (total,
Figure 15 Group analysis of mean hippocampal relaxation time (HT2) in patients with chronic active epilepsy versus control subjects

Kruskal Wallis p<0.001
Figure 16  Group analysis of highest hippocampal T2 (HT2) in patients with chronic active epilepsy versus control subjects
Figure 17 Group analysis of mean HT2 in patients with newly diagnosed partial seizures versus chronic active partial epilepsy.
Figure 18 Group analysis of mean HT2 in patients with newly diagnosed versus chronic active generalised (non-idiopathic) seizures
GTC, or non-GTC), seizure frequency (total, GTC, or non-GTC), gender, or a history of febrile seizures, significantly predicted HV loss. This was irrespective of whether all patients, or just those with partial onset seizures, were analysed.

HT2
None of the clinical variables, including age of onset, number of lifetime seizures (total, GTC, or non-GTC) seizure frequency (total, GTC, or non-GTC), gender, or a history of febrile seizures, significantly predicted HT2 elevation. This was irrespective of whether the analysis included all patients, or just those with partial onset seizures.

7.5 Discussion
7.5.1 Summary of major findings
Hippocampal damage, as determined by the group comparisons of mean and smallest HV, and mean and highest HT2 with control values, was present in the patients with newly diagnosed and chronic active non-idiopathic generalised seizures, but was statistically significant only in those with newly diagnosed and chronic active partial onset seizures. Patients with idiopathic seizures did not have evidence of hippocampal damage, irrespective of whether they were newly diagnosed or chronic.

The “head-to-head” comparisons revealed that the chronic active partial seizure patients had significantly higher mean HT2 than their newly diagnosed counterparts, but the differences in mean HV were, surprisingly, not statistically significant. No differences in either mean HV or HT2 were found between the two groups with non-idiopathic generalised seizures.

The logistic regression analyses failed to reveal any significant correlations between the extent of hippocampal damage and a variety of clinical variables pertaining to the severity of the epilepsy.

7.5.2 Methodological considerations
It has been well established (see section 1.5.4) that measurements of both HV, especially when corrected for ICV, and HT2, are reliable markers of HS, so long as the correct imaging techniques are used (Duncan, 1997). Furthermore, the quantitative methods used
in this study have been shown to be both accurate and reproducible, within and between individual raters (see section 5.4.4).

A small number of "highly abnormal" individuals were excluded from the newly diagnosed and chronic active epilepsy subgroups in order to eliminate the possibility of finding falsely significant correlations. Overall, this adds to the robustness of the study, and is unlikely to have masked important findings.

The study was restricted to adults (≥15 years of age) which may have partly influenced the findings, as discussed in section 6.5.3. HS associated with TLE most often has its onset in childhood. This is especially true of those with a history of childhood febrile seizures, who typically have a latent period before the emergence of habitual afebrile seizures. Consequently, the newly diagnosed cohort may have been biased towards having relatively normal hippocampi, whereas the chronic active cohort would have included a number of individuals whose epilepsy (including TLE) commenced in childhood. However, there was no evidence of a significant correlation between the age of onset of epilepsy and the amount of hippocampal damage, suggesting that the absence of children from the cohort probably made little difference.

Another important issue is the quality of clinical data concerning the severity of epilepsy. Although this was a prospective study with prospective collection of well-defined clinical variables, the fact is that certain continuous data were only obtainable by retrospective estimation including, sometimes, extrapolation based upon contemporary values. This was most notable for the estimations of seizure frequency and the lifetime number of seizures (GTC and non-GTC). The determination of the age of onset and duration of epilepsy was relatively immune to such approximation. It must be recognised, however, that these clinical data may have been sufficiently inaccurate to have obscured significant correlations between the severity of HS and the severity of the epilepsy.

Additionally, it has already been acknowledged that the seizure classification employed was a utilitarian scheme recommended by the ILAE Commission on Epidemiology and Prognosis in epidemiological studies (ILAE, 1993). This comprised a purely clinical classification, with no input from EEG, and, as such, some of the subjects with
"generalised" seizures (GTC without associated minor seizure types) may well have had secondarily generalised seizures. The majority of patients with idiopathic generalised seizures were, however, dissected out of the generalised group and analysed separately.

7.5.3 Biological implications

In the group comparisons, mean and smallest $HV_c$ was significantly smaller in patients with either chronic active or newly diagnosed partial onset seizures compared to healthy control subjects, with the volume loss being greater (but not statistically significant) in the chronic cohort. There was also a statistically significant degree of hippocampal volume loss in the newly diagnosed "generalised" group (after exclusion of the idiopathic subgroup), suggesting that this sample may have been contaminated by some patients with GTC which were secondarily generalised. In contrast, the chronic generalised idiopathic and non-idiopathic cohorts (who were more likely to have been assigned a correct seizure type, given that they had been followed up for a longer period) had a mean or smallest $HV_c$ which did not differ significantly from controls. Mean and highest $HT_2$ was not significantly different in any of the newly diagnosed subgroups compared to controls, suggesting that it is probably less sensitive than hippocampal volumetric analysis in detecting subtle damage, whereas mean or highest $HT_2$ was significantly higher in the chronic partial onset cohort, and showed a trend towards being higher in the chronic generalised group. Overall, these findings reiterate that hippocampal damage is a phenomenon relatively specific to partial onset epilepsy, and one which tends to be more apparent with epilepsy of longer duration. Hippocampal damage does not occur in idiopathic epilepsy, even when longstanding. As discussed in section 6.5.3, there are 3 viable explanations for these findings: (1) intractable epilepsy leads to progressive HS (2) HS is associated with a worse prognosis than other aetiologies of epilepsy, thus predisposing HS patients to developing chronic epilepsy (3) the restriction of MRI to adults in this study resulted in the relative exclusion of newly diagnosed children with TLE, who may have been more likely to have had HS as a consequence of early febrile seizures.

The first hypothesis is not supported by the absence of significant correlations between either $HV_c$ or $HT_2$ and the clinical variables pertaining to severity, although reservations have been expressed concerning the accuracy of estimations of the frequency and lifetime number of seizures. The hypothesis could, however, be explained by a sub-clinical
epileptogenic process causing slow progression of HS unrelated to overt epileptic activity. Alternatively, the patients with chronic partial onset epilepsy may have had more severe HS from the outset and were destined to develop chronic active seizures.

In contrast to the commonly-held theory that febrile seizures cause a significant proportion of HS (Cendes et al., 1993c; Kuks et al., 1993; Holthausen, 1994; Barr et al., 1997; Lewis, 1999), a number of investigators have proposed that HS or HA is effectively a pre-existing abnormality, most likely a developmental malformation (Kuks et al., 1993; Sloviter and Pedley, 1998; Fernandez et al., 1998; Roulet et al. 2000), which in turn predisposes to subsequent febrile seizures. This hypothesis was supported by a recent study by Bower et al. (2000) who found that, in patients with pathologically proven HS, the degree of HA was not influenced by whether or not there was a previous history of febrile seizures. In study 3 (chapter 6), quantitative hippocampal abnormalities were associated with a history of febrile seizures in 1/22 (4.5%) with newly diagnosed unprovoked seizures, and in 10/55 (18.2%) with chronic partial onset or “mixed” seizures (see end of section 6.5.2), and in this chapter the logistic regression analyses showed that a positive history of febrile seizures did not predict more severe hippocampal damage.

The data presented, whichever way they are interpreted, confirm that hippocampal damage is common and severe in patients with chronic partial epilepsy, although it was not possible to specifically demonstrate a correlation with epilepsy severity. The annual volume of epilepsy surgery for HS indicates that a potentially curative technique is currently being vastly under-used (Engel Jr, 1999).
CHAPTER 8

Study 5:
A quantitative MRI study of severe intractable epilepsy
in an adult residential epilepsy centre

8.1 Introduction
Despite advances in the management of epilepsy (Engel Jr, 1993; Walker and Sander, 1996; Blume, 1997; Duncan, 1997), approximately 1-2% of the estimated 300,000 people in the UK with epilepsy (Duncan et al., 1995b) require residential care. This is the consequence of severe, poorly controlled epilepsy, with or without concomitant learning disability or physical handicap. Although these residential epilepsy centres do not exist globally, there are similarly severely affected groups of patients attending epilepsy tertiary referral centres worldwide.

To date, few studies have investigated the causes of intractable epilepsies in such patients (Forsgren et al., 1990; Steffenburg et al., 1998) and none have employed magnetic resonance imaging (MRI). High resolution brain MRI has revolutionised the investigation of hospital based patients with intractable epilepsy, facilitating the identification of subtle abnormalities including HS and MCD (Kuzniecky et al., 1987; Jackson et al., 1990; Li et al., 1995; Raymond et al., 1995; Duncan, 1997; Kuzniecky, 1998).

8.2 Aims and hypotheses

Aims
1. To perform a descriptive analysis of the range and frequency of qualitative and quantitative MRI abnormalities (including HS and HA) amongst inhabitants of a large residential epilepsy centre with severe, intractable epilepsy.

2. To determine the effect of MRI upon epilepsy syndromic classification, by determining the proportion in whom MRI led to the discovery of a new aetiology.

3. To see whether there is a correlation between the severity of epilepsy and the extent of hippocampal damage.
Hypothesis

1. Epilepsy centre residents are likely to have a much higher prevalence of identifiable cerebral structural abnormalities on MRI than amongst the community based epilepsy population because the average severity of epilepsy will be greater, and the frequency of brain injury resulting from seizure-related cerebral hypoxia and head trauma will be higher.

2. MRI data will permit the identification of the cause of epilepsy in a significant number of subjects in whom aetiology was not previously known.

8.3 Methods

8.3.1 Subjects

EPILEPSY CENTRE RESIDENTS

The NSE provides inpatient and outpatient care for epilepsy patients from throughout the UK, and long-term residential care at any one time for 275 people with severe epilepsy. The 306 adults (median age 47 years, range 17-103 years) who were resident at the NSE between 1.7.95 and 30.06.98 were included in this study (Table 25).

CONTROL SUBJECTS

The 170 neurologically and intellectually normal volunteers (median age 37.5 years, range 14-85 years), who were identified by methods described in section 3.2.11 and subsequently used to form the control group in studies 2, 3 and 4, underwent brain MRI using a protocol identical to that performed in the residential population. These MRI data were used to define normative ranges for HV, HVR and HT2, as described in section 5.4.3.

8.3.2 Clinical data collection

Classification of epileptic seizures and epilepsy syndromes according to the standard ILAE classifications (ILAE, 1981 and 1989) was possible because of the availability of detailed clinical and EEG data.

The following data were collected: age at onset of habitual seizures; duration of epilepsy at midpoint of study (1.1.97); epilepsy syndromic classification (ILAE, 1989); seizure types (ILAE, 1981); annual seizure frequency of (a) primary or secondarily generalised tonic-clonic seizures and (b) seizure types other than generalised tonic-clonic seizures; presence
Table 25 Demographic and clinical features of the 306 residents

<table>
<thead>
<tr>
<th>Demographic or clinical variable</th>
<th>Size of variable /percentage of residents affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of residents</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>306 (100%)</td>
</tr>
<tr>
<td>male</td>
<td>214 (70%)</td>
</tr>
<tr>
<td>female</td>
<td>92 (30%)</td>
</tr>
<tr>
<td>Median age</td>
<td>47 years (range 17-103 years)</td>
</tr>
<tr>
<td>Median age at onset of epilepsy</td>
<td>5 years (range 0-44 years)</td>
</tr>
<tr>
<td>Median duration of epilepsy</td>
<td>39 years (range 5-86 years)</td>
</tr>
<tr>
<td>Median number of different seizure types</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Median number of generalised tonic-clonic seizures per year</td>
<td>5 (0-281)</td>
</tr>
<tr>
<td>Median number of non-generalised tonic-clonic seizures per year</td>
<td>11 (0-2455)</td>
</tr>
<tr>
<td>Median number of prescribed antiepileptic drugs</td>
<td>2 (0-5)</td>
</tr>
<tr>
<td>Number of residents with each seizure type</td>
<td></td>
</tr>
<tr>
<td>simple partial</td>
<td>60 (20%)</td>
</tr>
<tr>
<td>complex partial</td>
<td>203 (66%)</td>
</tr>
<tr>
<td>secondary generalised tonic-clonic</td>
<td>209 (68%)</td>
</tr>
<tr>
<td>absence</td>
<td>31 (10%)</td>
</tr>
<tr>
<td>myoclonic</td>
<td>54 (18%)</td>
</tr>
<tr>
<td>tonic/clonic/tonic</td>
<td>35 (11%)</td>
</tr>
<tr>
<td>other generalised tonic-clonic</td>
<td>71 (23%)</td>
</tr>
<tr>
<td>unclassified</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Remission of seizures at midpoint of study</td>
<td></td>
</tr>
<tr>
<td>seizures during preceding year</td>
<td>264 (86%)</td>
</tr>
<tr>
<td>remission of 1-2 years</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>remission of 2-5 years</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>remission of 5-10 years</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>remission of &gt; 10 years</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>Early history of febrile convulsion(s)</td>
<td></td>
</tr>
<tr>
<td>definite</td>
<td>30 (10%)</td>
</tr>
<tr>
<td>suggestive</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>uncertain</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>none</td>
<td>255 (83%)</td>
</tr>
<tr>
<td>Learning disability (DSM IV criteria)</td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>19%</td>
</tr>
<tr>
<td>borderline</td>
<td>22%</td>
</tr>
<tr>
<td>mild</td>
<td>34%</td>
</tr>
<tr>
<td>moderate</td>
<td>9%</td>
</tr>
<tr>
<td>severe</td>
<td>4%</td>
</tr>
<tr>
<td>decline to learning disability level</td>
<td>12%</td>
</tr>
</tbody>
</table>

212
and duration of seizure remission on 1.1.97; history of birth injury, febrile convulsion, meningo-encephalitis, head injury; previous electroencephalogram (EEG) and neuroimaging results; presumed aetiology and pathogenetic period (pre-natal, peri-natal, post-natal, mixed or unknown) as determined from all available electro-clinical and previous neuroimaging data; number of prescribed anti-epileptic drugs on 1.1.97; presence and severity of learning disability (American Psychiatric Association, 1987). The presumed aetiology and pathogenetic period were determined again, incorporating high resolution MRI data.

8.3.3 Extent of previous investigation
EEG data were available in 295/306 (96%) residents. 203 (66%) had had CT and/or standard MRI. The latter included coronal T1- and T2-weighted images (with non-contiguous 5mm slices), and no subsequent quantitative hippocampal analysis. CT (n=188) revealed focal cerebral abnormalities in 32% (of whom 7% had MCD), diffuse brain atrophy in 36% and no abnormality in 32%. Standard MRI (n=67) demonstrated relevant focal abnormalities in 45% (of whom 27% had HS and 10% had suspected dysembryoplastic neuroepithelial tumours, DNETs), diffuse atrophy in 21%, and no structural abnormality in 34%.

8.3.4 High resolution MRI scanning
After informed consent was obtained from either subject or carer, as appropriate, all epilepsy patients and control subjects underwent MRI scanning (GE Signa, 1.5 T) using a standardised high resolution “epilepsy” protocol (Wieshmann et al., 1996), including coronal T2-weighted, proton density, fast FLAIR sequences and thin coronal T1-weighted images, permitting subsequent HV, ICV, HVR and HT2 measurements, as described in section 3.3.3. HV was subsequently corrected for ICV and expressed as HVc. In a minority of subjects, the entire MRI protocol could not be performed because of movement in the scanner. Each MRI study was reported by two neuroradiologists (Drs John Stevens and Dr Brian Kendall).

The HVc and HT2 data from the epilepsy centre residents were then compared with normal values derived from the 170 control subjects. HA was defined by an HVc greater than 2 standard deviations (SDs) below the control mean HVc, and/or an HVR two or more SD
below the control mean (ie. less than 0.89). HS was defined as HA coupled with a significantly elevated ipsilateral mean HT2 (two or more SD above the control mean HT2). For simplicity, this spectrum of quantitative hippocampal abnormalities is hereafter collectively termed HS/HA. Significantly elevated HT2 without ipsilateral HA was not considered as part of this spectrum.

8.3.5 Statistical analysis

All statistical analysis was carried out using SPSS for Windows, version 8.0 (SPSS Inc., Chicago, IL, USA).

Ethical approval for this study was provided by the Joint Ethical Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

8.4 Results

8.4.1 Seizure classification and epilepsy syndromic classification

Overall, partial onset seizures were present in 68%, generalised onset seizures in 21%, mixed partial and generalised onset seizures in 11% and unclassified seizures in less than 1% (Table 25). The distribution of epilepsy syndromes, based on clinical and EEG characteristics, is shown in Table 26. The clinical features of the residents who had high resolution MRI did not differ significantly from those outlined in Tables 1 and 2.

8.4.2 High resolution MRI findings

High resolution MRI was performed in 263 (86%) residents (Table 27), of whom 53 completed most, but not all, of the sequences. MRI was not carried out in 43: refused or not tolerated, 17; death, 14; frailty, 7; contraindications to MRI, 5.

QUALITATIVE ANALYSIS (Figure 19)

MRI demonstrated qualitative (visible) structural cerebral abnormalities in 219/263 (83%). Visible diffuse cerebral atrophy was present in 103 (39%), cerebellar atrophy in 105 (40%), and generalised (cerebral and cerebellar) atrophy in 60 (23%). In 70 (27%), diffuse atrophy was the only visible MRI abnormality. Visible focal cerebral abnormalities (excluding small white matter lesions) were observed in 136 (52%), the most frequent being focal neocortical brain damage (focal atrophy, infarcts, scars or cysts), seen in 81 (31%).
### Table 26  Simplified epilepsy syndromic classification (based on clinical and EEG findings)

<table>
<thead>
<tr>
<th>Epilepsy syndrome</th>
<th>Category</th>
<th>Localisation</th>
<th>Percentage of 306 residents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localisation related</td>
<td>symptomatic</td>
<td>temporal</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>frontal</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>occipito-parietal</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>unlocalisable</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>cryptogenic</td>
<td>temporal</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>frontal</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>occipito-parietal</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>unlocalisable</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>subtotal</td>
<td></td>
<td>72%</td>
</tr>
<tr>
<td>Generalised</td>
<td>idiopathic</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>cryptogenic</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>symptomatic</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>subtotal</td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>Undetermined</td>
<td>both partial and generalised features</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>neither partial nor generalised features</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>subtotal</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

215
### Table 27 Combined qualitative and quantitative MRI findings in 263 residents

<table>
<thead>
<tr>
<th>Principal MRI finding</th>
<th>Number of residents</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated HS/HA with or without generalised brain atrophy</td>
<td>80</td>
<td>30.4</td>
</tr>
<tr>
<td>Focal neocortical brain damage* with HS/HA (dual pathology)</td>
<td>46</td>
<td>17.4</td>
</tr>
<tr>
<td>Focal neocortical brain damage (scar, atrophy, cyst or infarct) without HS/HA</td>
<td>35</td>
<td>13.3</td>
</tr>
<tr>
<td>MCD\†</td>
<td>18</td>
<td>6.8</td>
</tr>
<tr>
<td>Vascular anomaly (cavernoma, Sturge Weber syndrome)*</td>
<td>5</td>
<td>1.9</td>
</tr>
<tr>
<td>Brain tumours\†</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Cortical and/or cerebellar atrophy without other lesions*</td>
<td>46</td>
<td>17.5</td>
</tr>
<tr>
<td>No structural abnormality \▲</td>
<td>31</td>
<td>11.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>263</strong></td>
<td>100%</td>
</tr>
</tbody>
</table>

HS/HA  hippocampal sclerosis or hippocampal atrophy
MCD  malformation of cortical development

\* Focal neocortical brain damage includes focal atrophy, infarcts, cysts or post-traumatic scars
\† HS/HA also seen in 11 with MCD, 4 with vascular anomalies and 1 with a brain tumour
\* 15 had concomitant small ischaemic white matter lesions
\▲ 7 had concomitant small ischaemic white matter lesions

Hippocampal abnormalities were detected by visual inspection in 31 with isolated HS/HA and 23 with dual pathology
**Figure 19** Examples of MRI findings in residential population with epilepsy

A. Right fronto-parietal cortical brain damage and contralateral hippocampal sclerosis
B. Severe cerebellar atrophy
C. Right focal cortical dysgenesis, subependymal heterotopia and absent corpus callosum
D. Diffuse pachygria and cortical atrophy
E. Large right fronto-temporal dysplasia neurephthelial tumor (histologically proven)
F. Right occipito-parietal Sturge-Weber angiodysplasia
G. Left temporal cavernous haemangioma
H. Bilateral (left more than right) hippocampal sclerosis and diffuse cortical atrophy

Subjects C, D, E, and F had coexistent hippocampal sclerosis (not shown)
MCD were observed in 18 residents (Table 28). A further 2 residents had undergone temporal lobe resection for DNET prior to admission. MRI showed no residual tumour in either.

Other lesions were seen in 7 (3%): cavernous haemangiomas, 3; Sturge Weber syndrome, 2 (1 with visible HS); meningioma, 1; glioma, 1. An additional 2 residents (excluding the 2 with DNET) had surgery for brain tumours prior to admission.

QUANTITATIVE HIPPOCAMPAL ANALYSIS

MRI data acquisition permitted hippocampal volumetry in 210 (80%) and T2 relaxometry in 205 (78%), confirming all visually detected cases of HS (n=54), and detecting a further 71 with HS/HA. Unilateral HT2 abnormalities without ipsilateral HA were present in 17 residents. A further 6 with unilateral HS/HA had contralateral HT2 abnormalities without HA, and were not considered having as bilateral HS/HA. In total, HS/HA was detected in 125/263 (47.5%; unilateral 76, bilateral 49). Of these, 57 (46%) had coexistent (dual) pathology: focal neocortical brain damage, 43; MCD, 10; vascular anomalies, 3; brain tumours, 1.

8.4.3 Clinical-MRI correlations

HIPPOCAMPAL SCLEROSIS/ATROPHY

Of 125 with HS/HA (Table 29), 96 (77%; 58 unilateral, 38 bilateral) had electro-clinical evidence of localisation related epilepsies (temporal, 52; extratemporal, 25; unlocalisable, 19). Classical HS was present in 39/96 (41%; 30 unilateral, 9 bilateral), of whom 7 had HA contralateral to unilateral HS. Of these 39, 27 (69%) had electro-clinically temporal, 10 (26%) had extratemporal and 2 (5%) had unlocalisable epilepsies. The remaining 57 (59%; 35 unilateral, 22 bilateral) had HA without elevation of HT2 (temporal, 25; extratemporal, 15; unlocalisable, 17). Thus, in the 263 with high resolution MRI, HS/HA was present in 63% with temporal lobe epilepsy (TLE) and 41% with extratemporal epilepsies.

21 (17%; cryptogenic, 12; symptomatic, 6; idiopathic, 3) of the 125 had electro-clinically generalised epilepsies: one had unilateral HS, and the remaining 20 had HA (unilateral 14, bilateral 6). Seven (cryptogenic 3; idiopathic 3; symptomatic 1) of these 20 had visible diffuse cerebral atrophy, including 5 with bilateral HA.

218
### Table 28 Malformations of cortical development in 18 patients

<table>
<thead>
<tr>
<th>Malformation</th>
<th>n</th>
<th>Hippocampal analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymicrogyria</td>
<td>4</td>
<td>2 normal; 2 HA (1 bilateral)</td>
<td>Microcephaly, 1; GSW, 1</td>
</tr>
<tr>
<td>Cortical and/or subependymal tubers</td>
<td>3</td>
<td>3 normal</td>
<td>GSW, 1</td>
</tr>
<tr>
<td>Widespread gyral abnormalities with thickened cortex</td>
<td>2</td>
<td>2 normal</td>
<td>Childhood cerebral malaria, 1</td>
</tr>
<tr>
<td>Widespread pachygyria</td>
<td>1</td>
<td>1 HA</td>
<td></td>
</tr>
<tr>
<td>Partial agenesis of corpus callosum</td>
<td>1</td>
<td>1 normal</td>
<td></td>
</tr>
<tr>
<td>Agenesis of corpus callosum with subependymal heterotopia and focal cortical dysgenesis</td>
<td>1</td>
<td>1 HS with contralateral HA</td>
<td></td>
</tr>
<tr>
<td>Focal cortical dysgenesis</td>
<td>1</td>
<td>1 HS</td>
<td></td>
</tr>
<tr>
<td>Subependymal heterotopia and focal cortical dysgenesis</td>
<td>1</td>
<td>1 HS with contralateral HA</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>Subependymal and band heterotopia</td>
<td>1</td>
<td>1 HS (bilateral)</td>
<td>Hypomelanosis of Ito</td>
</tr>
<tr>
<td>Thick band heterotopia</td>
<td>1</td>
<td>1 HA</td>
<td></td>
</tr>
<tr>
<td>Diffuse heterotopia</td>
<td>1</td>
<td>1 HA (bilateral)</td>
<td></td>
</tr>
<tr>
<td>Dysembryoplastic neuroepithelial tumour</td>
<td>1</td>
<td>1 HA</td>
<td>Childhood cerebral malaria. GSW &lt;2.5 Hz</td>
</tr>
</tbody>
</table>

| Total | 18 | 8 normal; 6 HA; 4 HS ± HA | |

n = number of patients  
HA = hippocampal atrophy  
HS = hippocampal sclerosis  
GSW = generalised spike wave activity on electroencephalography  
All HS or HA unilateral, unless otherwise specified
Table 29 MRI evidence of HS/HA (isolated or dual pathology) in 263 residents and 170 normal control subjects

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Number and percentage with HS/HA per epilepsy syndrome</th>
<th>Quantitative hippocampal findings (available in 206/263)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total with MRI</td>
<td>unilateral</td>
</tr>
<tr>
<td>Subject category</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Control subjects</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td>Generalised epilepsy</td>
<td>55</td>
<td>46</td>
</tr>
<tr>
<td>Undetermined epilepsy</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>LR temporal</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>extra-temporal</td>
<td>70</td>
<td>61</td>
</tr>
<tr>
<td>unlocalisable</td>
<td>59</td>
<td>50</td>
</tr>
<tr>
<td>all</td>
<td>220</td>
<td>194</td>
</tr>
</tbody>
</table>

**Legend:**
- **HS/HA:** hippocampal sclerosis/atrophy [defined by one or more of the following: HCV < (mean HCV - 2SD); HCT2 > (mean HCT2 + 2SD); HC ratio < 0.87]
- HV<sub>C</sub>: hippocampal volume, corrected for intracranial volume
- HT2: hippocampal T2 relaxation time
- LR: localisation related epilepsy
- SD: standard deviation
Eight residents with HS/HA (6%; HS 1, HA 7; bilateral 5, unilateral 3) had epilepsies which were previously undetermined as to whether generalised or localisation related.

Amongst the 125 with HS/HA, there was a history of: febrile convulsion without other aetiological factors in 12 (10%); meningo-encephalitis in 11 (9%; 5 with bilateral HS/HA); birth injury in 15 (12%; 11 with concomitant neocortical brain damage); severe head injury in 11 (9%; 10 of whom had additional neocortical brain damage); post-vaccine encephalopathy in 4 (3%); cerebral malaria in 2 (2%; 1 of whom had a large DNET on MRI); other MRI abnormalities/brain insults in 31 (25%). In the remaining 39 (31%) with HS/HA, there was no additional MRI abnormality or history of brain insult.

At the time of MRI, 14 (11%) with HS/HA were in seizure remission: 2-5 years, n=4 (3%); 5-10 years, n=5 (4%); over 10 years, n=5 (4%). All others had active epilepsy, including 6 out of 7 residents with HS/HA contralateral to a previous temporal lobe resection.

There were no correlations between HV, HV_q, or HT2, and the age at onset of epilepsy, the duration of epilepsy, or the number of generalised tonic-clonic seizures per year.

MALFORMATIONS OF CORTICAL DEVELOPMENT
15 of the 18 with MCD on MRI had localisation related epilepsies electro-clinically. 3 had generalised spike wave activity on EEG. None was in seizure remission. 13/18 had learning disability: mild (8), moderate (3) and severe (2). Three had borderline learning disability and 2 (focal polimicrogyria, 1; multiple cortical and subependymal tubers, 1) had low normal intelligence. Ten (55.5%; 4 HS ± contralateral HA; 6 HA) had HS/HA (5 bilateral, 5 unilateral) which was only detected quantitatively (Table 28).

LEARNING DISABILITY
At the time of MRI, the proportion of residents in seizure remission was identical in those with and without learning disability (13% and 12%, respectively). In those with learning disability, the proportion with abnormal MRI was not significantly different in those with active epilepsy (86%) compared to those in seizure remission (94%). HS/HA was equally frequent in residents with and without learning disability (44% and 49%, respectively).
8.4.4 Impact of high resolution MRI upon aetiology

Overall, high resolution MRI revealed previously undetected, aetiologically relevant abnormalities (ie. excluding generalised atrophy) in 95 (47%) of the 203 who had undergone CT and/or standard MRI. Overall, high resolution MRI increased the proportion of residents with a definable aetiology from 50% to 68% (Table 30).

Occasionally, high resolution MRI revealed unexpected findings in residents in whom the pre-MRI aetiological diagnosis was considered as unequivocal. In 2 patients with a history of childhood cerebral malaria, MRI demonstrated a large DNET and widespread MCD, respectively. In a third who had surgery in childhood for a brain abscess, MRI revealed multiple cavernous haemangiomas.

8.5 Discussion

Although not all countries will have residential epilepsy centres such as the one described in this study, the patients included are representative of the most severely affected patients attending any epilepsy tertiary referral centre. The overall severity of the epilepsy (in terms of lifetime seizure activity) in these subjects is what makes the MRI findings of such interest.

8.5.1 Summary of major findings

High resolution MRI with quantitative hippocampal analysis revealed cerebral structural abnormalities in 86% of residents. Diffuse cortical and/or cerebellar atrophy was observed in approximately 40% and was the sole MRI abnormality in 19%. Aetiologically relevant cerebral lesions were apparent in 66%, the commonest abnormalities being focal neocortical brain damage, and hippocampal sclerosis/atrophy (HS/HA). In total, 47.5% had HS/HA, of whom almost half had dual pathology. HS/HA was not confined to subjects with TLE, but also observed in residents with electro-clinically classified extratemporal, generalised, and undetermined epilepsies. MCDs, tumours and vascular malformations were relatively infrequent. High resolution MRI revealed previously undetected, aetiologically relevant lesions in 47% of the 203 residents who had undergone previous CT and/or standard MRI and, overall, MRI increased the proportion of residents with a definable aetiology from 50% to 68%.
Table 30  Impact of MRI upon presumed aetiology of epilepsy

<table>
<thead>
<tr>
<th>Pathogenetic period and aetiology</th>
<th>Pre- MRI</th>
<th>Post-MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of residents</td>
<td>% of residents</td>
</tr>
<tr>
<td>PRE-NATAL:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCD (on MRI or histopathology)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other hereditary neurological conditions *</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Vascular anomaly</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>CNS infection</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Other</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>PERI-NATAL:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth injury</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>POST-NATAL:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS/HA</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>CNS infection</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Head injury</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Post-vaccine</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Current/previous brain tumour</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other static encephalopathy</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Subtotal</td>
<td>31%</td>
<td>48%</td>
</tr>
<tr>
<td>MIXED:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic (phenylketonuria)</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>MCD + childhood cerebral malaria</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vascular anomaly + brain abscess</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>UNKNOWN:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>48%</td>
<td>27%</td>
</tr>
<tr>
<td>Total</td>
<td>100% (306)</td>
<td>100% (306)</td>
</tr>
</tbody>
</table>

* includes residents with neurofibromatosis, tuberous sclerosis and dentato-rubro-pallido-Luysian atrophy
MRI=magnetic resonance imaging    HS/HA=hippocampal sclerosis/atrophy
MCD=malformations of cortical development CNS=central nervous system
In cases of dual pathology (focal MRI abnormality associated with HS/HA), aetiology was classified according to the primary neurological insult/focal MRI abnormality, and not as HS/HA.
8.5.2 Methodological and biological considerations

There was a gender bias with more than twice as many males as females, reflecting referral patterns, and a higher prevalence of concomitant learning disability than the 10-20% of patients affected at the population level (Duncan et al., 1995b). There was also an excess of localisation related epilepsies compared with recent population based studies (Hauser and Kurland, 1975; Goodridge and Shorvon, 1983; Keranen et al., 1988; Sander et al., 1990; Loiseau et al., 1991; Oka et al., 1995), and studies of epilepsy associated with learning disability (Forsgren et al., 1990; Steffenburg et al., 1996; Branford et al., 1998), reflecting the poorer prognosis of localisation related epilepsies (Sander, 1993).

Nearly one fifth of residents had generalised epilepsies on clinical and EEG grounds and one tenth of these had IGE. The proportion in this study with aetiologically relevant lesions was high. In contrast, previous MRI studies have generally been confined to patients with medically intractable localisation related epilepsies, particularly TLE (Li et al., 1995; Lehericy et al., 1997). In such studies, up to 70-80% of patients had a definable aetiology, most commonly HS (or HA), affecting approximately 30% with localisation related epilepsies (Li et al., 1995), and 55% with TLE (Lehericy et al., 1997). There are several possible contributory explanations for the high prevalence (47.5%) of HS/HA in the current study: (1) Selection bias: a high proportion of residents had localisation related epilepsies, although the effect of this may have been offset by the high prevalence of HS/HA in other epilepsy syndromes. (2) High sensitivity of quantitative MRI: only 43% of quantitatively proven HS/HA (predominantly HA) was noted at visual assessment by two experienced neuroradiologists, emphasising the high sensitivity of hippocampal quantitative MRI (Jackson et al., 1993a; Reutens et al., 1996). (3) Severity and duration of epilepsy: there has been longstanding debate as to whether HS is a cause or consequence of chronic localisation related epilepsies, especially TLE (Falconer et al., 1964; Mouritzen Dam, 1980; Meencke and Veith, 1991; Cendes et al., 1993d; Mathern et al., 1995b; Mathern et al., 1997). The extreme severity of epilepsy in our population, as compared to outpatients included in previous MRI studies (Li et al., 1995), might be a cause or effect of the high prevalence of HS/HA. No significant correlations between either HVc or HT2 and clinico-demographic characteristics were found, possibly because the vast majority had both a childhood onset and long median duration of epilepsy In the only study of a comparable population, HS (44% unilateral; 56% bilateral) was found at 30.5% of 650 autopsies at a
residential epilepsy centre (Meencke and Veith, 1991). (4) High frequency of HS/HA in syndromes other than TLE: epilepsy syndromic classification was based upon EEG, CT and clinical findings alone, so it is unsurprising that focal MRI abnormalities were discordant with syndromic classification in a proportion of residents. The majority of previous MRI studies have concluded that extratemporal epilepsies are not associated with HS/HA (Cook et al., 1992; Cascino et al., 1993; Luef et al., 1994), with some exceptions (Adam et al., 1994; Lawson et al., 1997). In the current study, subjects with extratemporal or unlocalisable localisation related epilepsies had a high prevalence of HS/HA and a significantly lower mean HVc than in control subjects. Few studies have investigated the prevalence of HS/HA in patients with symptomatic generalised epilepsies. Meencke and Veith (1991) found bilateral HS in up to half of patients with cryptogenic or symptomatic generalised epilepsies, though patient numbers were small. A recent quantitative MRI study revealed hippocampal asymmetry in approximately half of children with symptomatic generalised epilepsies (Lawson et al., 1997). In contrast, Watson et al. (1996b) found that symptomatic generalised epilepsies were not associated with HS/HA. In our study, HS/HA was present in 46% of those with electro-clinically classified generalised epilepsies (most of whom had cryptogenic/symptomatic epilepsies), though it was more often unilateral than bilateral. The mean HVc in subjects with generalised epilepsies was also significantly lower than in control subjects. The majority of these cases had HA without elevation of HT2. In a third of residents with generalised epilepsies and HA, the HA was bilateral and associated with diffuse cerebral atrophy. It seems unlikely that the HS/HA observed in these residents represented the primary aetiological abnormality, given the lack of partial seizures and localising EEG features in many. It is conceivable that HS/HA in such cases has resulted from seizure-related damage, though this does not account for its common unilaterality and the lack of correlation between HV, HVc or HT2 and either age of onset or duration of epilepsy, or frequency of generalised tonic-clonic seizures.

These MRI findings stimulate debate as to how MRI should influence epilepsy syndromic classification. At present, a fundamental classificatory division into generalised or localisation related epilepsies endures, but the relative importance of MRI compared to electro-clinical findings is unclear (ILAE, 1989; Lawson et al., 1997). It is likely, however, that a continuum exists encompassing epilepsies with and without localising features.
(Berkovic et al., 1994a), a concept which should be addressed with specific reference to MRI in future classifications (Everitt and Sander, 1999).

A high prevalence of focal neocortical brain damage was also observed, mostly relating to serious head injuries, meningo-encephalitis or cerebrovascular accidents pre-dating the onset of seizures and thus of aetiological relevance. In a small proportion, however, the damage may have been the consequence of seizure-related head trauma or hypoxia.

In previous MRI studies of localisation related epilepsies, MCD, tumours and vascular malformations have been demonstrated in more than 25% of patients (Li et al., 1995; Lehericy et al., 1997), but in the current study were observed in 9.5%. The low frequency of MCD (7%), despite the high overall prevalence (~50%) of learning disability, suggests that MCD are a relatively infrequent cause of epilepsy and learning disability. Alternatively, patients with very severe epilepsy, learning disability and MCD could have died in childhood or adolescence, leading to under-representation in the NSE population. Three quarters of residents with MCD had learning disability; this may have been an effect of selection bias and the severity of MCD, since a recent study found learning disability in just 9% of 100 outpatients with epilepsy and MCD (Raymond et al., 1995). HS/HA was present in just over half of the current study’s subjects with developmental lesions (MCD and vascular anomalies). Such dual pathology is well recognised (Cascino et al., 1993; Raymond et al., 1994; Cendes et al., 1995b) and most likely relates to either (1) seizure-induced (bystander) hippocampal damage in patients with MCD and previously normal hippocampi or (2) a shared pathogenetic mechanism (Raymond et al., 1994) with HS occurring in a developmentally abnormal (dysgenetic) hippocampus (Baulac et al., 1998). The similarly high prevalence of HS/HA in residents with post-natally acquired focal brain damage favours the former explanation.

The frequency of visible diffuse cerebral atrophy and/or cerebellar atrophy was higher than in previous studies (Ballenger et al., 1982; Ney et al., 1994; Bekkelund et al., 1996). One recent MRI study reported diffuse cortical atrophy in 2% of patients with chronic localisation related epilepsies (Li et al., 1995). The pathogeneses of cerebellar and cerebral atrophy in epilepsy is unclear (Ney et al., 1994). Peri-ictal brain hypoxia (Dam, 1970), chronic and/or toxic exposure to anti-epileptic drugs (especially phenytoin) (McLain et al.,
1980; Masur et al., 1989; Ney et al., 1994), and neuroexcitotoxic damage (Dam et al., 1984; Duncan R et al., 1990b; Ney et al., 1994; Savic and Thorell, 1996) are probably the most important factors, whilst normal ageing (Sostman et al., 1984; Raz et al., 1998), repetitive head trauma, and congenital cerebral structural abnormalities (Ney et al., 1994) may also contribute. Determination of the relative importance of these factors was not possible in this cross-sectional study since the majority of residents had been exposed to some or all of these factors.

Despite finding aetiologically relevant abnormalities in a high proportion of residents, referral for consideration of epilepsy surgery was inappropriate in the majority because of the coexistence of severe learning disability, psychological disability or psychiatric morbidity and/or MRI evidence of widespread brain damage or diffuse atrophy. The aetiology of epilepsy and learning disability remained cryptogenic in 32%. One possibility is that some patients may have harboured cerebral abnormalities too subtle to be resolved by current structural MRI (Meencke, 1994). Additional MRI post-processing techniques (Sisodiya et al., 1995 and 1996) might have further increased the yield, but it is likely that a small proportion of patients with localisation related epilepsies will remain “MRI-negative”, since the relevant pathogenetic mechanisms exist at molecular level. Future advances in functional neuroimaging may help to further reduce the proportion with cryptogenic epilepsies.
CHAPTER 9
Summary of results, conclusions and future directions

9.1 Summary of results

9.1.1 Study 1:
A prospective population based incidence and prevalence study of epilepsy in Buckinghamshire, UK

The incidence study population comprised 207,553 persons in Buckinghamshire, England. The age-corrected annual incidence of all afebrile seizures was 52.8 per 100,000 persons (95% confidence intervals 42.9-62.6). The age-specific incidence was highest in the 0-4 years (90.2/100,000) and over 75 years (93.6/100,000) age bands. The annual incidence of febrile seizures was 402/100,000 0-4 year olds (95% CI 289-514). Of the 165 newly diagnosed adults (15 years), 126 (76%) had unprovoked and 39 (24%) had provoked seizures, giving crude annual incidence rates of 36.9/100,000 and 11.4/100,000, respectively. The cumulative incidence of afebrile seizures was 5.7% by 75+ years.

In a sub-population of 159,388 adults, 279 had chronic active epilepsy (epilepsy of at least 4 years duration, with at least 1 seizure during the year preceding prevalence day), yielding a prevalence of 1.8 per 1000 adults (95% CI 1.55-1.96). In a smaller population of 12,178 adults and children, the point prevalence of active and inactive epilepsy (ILAE, 1993) was 5.6/1000 (95% CI 4.3-6.9) and 7.6/1000 (95% CI 6.1-9.2), respectively.

In the adult incident group, seizures were of partial onset in 58.8%, generalised in 39.4%, of mixed seizure type in 0.6% and unclassifiable in 1.2%. The median age at ascertainment (diagnosis) was 48 years (range 17-91 years) for patients with provoked seizures, and 50.5 years (15-90 years) for those with unprovoked seizures. 33.3% presented with a history of two or more seizures, and 37.3% of the remaining subjects with an initially isolated seizure experienced at least one further seizure by the time of case classification 14 months (median time, range 0-27 months) later. The median duration of seizures at MRI was 0.2 years (range 0-18 years).
Amongst the adult prevalent chronic active cases, seizures were of partial onset in 63.1%,
generalised in 23.3%, mixed in 2.9% and unclassifiable in 10.8%. The median age at
ascertainment was 38 years (range 15-93 years), the median age at onset of epilepsy was
15.5 years (range 0-84 years), and the median duration of epilepsy was 19.5 years (range
4-73 years).

In the 175 patients who had MRI, the median lifetime numbers of generalised tonic-clonic
seizures and other non-tonic-clonic (partial, absence or myoclonic) seizures were estimated
at 12 (range 0-1500), and 100 (range 0-160,000), respectively. The estimated frequencies
of generalised tonic-clonic seizures over the preceding 2 years were: >1/week (0%),
1/week-1/month (10.9%), 1/month-1/year (39.4%), <1/year (40.6%) and none (9.1%), and
the estimated frequencies all other seizure types (combined) were: >1/week (22.3%),
1/week-1/month (22.3%), 1/month-1/year (29.1%), < 1/year (8.0%) and none (18.3%).

9.1.2 Study 2:
Qualitative and quantitative high resolution cranial MRI in 170 community based,
neurologically normal volunteers
Three quarters of 170 neurologically normal volunteers (86 males, median age 37.5 years,
range 14-78 years) had qualitatively and quantitatively normal MRI. Small white matter
lesions (WML) were the most frequent visible abnormality (18.8%), and were seen
predominantly in older subjects. None had HS, MCD, or focal cortical brain damage,
lesions commonly observed in hospital based patients with localisation related epilepsy.
One subject had a probable temporal lobe cavernoma.

Quantitative hippocampal analysis revealed that 4.7% had hippocampal values outside 2
SD of the mean. In 7 of 8 such cases, this only involved 1 hippocampal parameter. Mean
uncorrected right HV was slightly, though significantly, larger than left HV in both young
(45 mm³ or 1.5%; p=0.003) and elderly (57 mm³ or 2.0%; p<0.01) subjects. Mean HV_c was
reduced in subjects aged 50 years and over. There was no significant gender difference in
mean HV_c or HT2, and no consistent correlation between HT2 and age.
9.1.3 Study 3:
The aetiology of epilepsy in adults: a prospective, population based MRI study

High resolution MRI was performed in 110/165 (66.7%) adults identified as having newly diagnosed seizures, 174/279 (62.3%) with chronic active epilepsy, and in 175 neurologically normal control subjects. Patients with newly diagnosed partial onset seizures (37.9%) were significantly more likely to harbour focal brain lesions (focal scars, HS, MCD, cavernomas and neoplastic lesions) detectable by MRI than those with generalised seizures (7.0%) (p=0.0003). Focal brain abnormalities were also found more frequently in those with chronic active partial onset seizures (54.4%) than in those with generalised seizures (4.5%) (p<0.0001) The most frequent abnormalities overall were multiple small WML and focal neocortical damage (from CNS trauma, infection, inflammation or stroke). HS was an infrequent finding in patients with newly diagnosed partial seizures (2.7%) , but considerably more common in patients with chronic active partial onset seizures (13.6%). However, quantitative hippocampal abnormalities were more frequent and were found in approximately one quarter of patients with newly diagnosed seizures (and in one fifth of those without large mesial temporal tumours), in one third with chronic active epilepsy, but in only 4.7% of control subjects. HA was more likely to be associated with a second (dual) MRI pathology in the chronic active epilepsy patients. In contrast to hospital-based studies, MCD, vascular malformations and CNS tumours were uncommon causes of chronic active epilepsy (6/174, 3.4%), although CNS tumours were the underlying cause in approximately 6% with newly diagnosed seizures. There was also a suggestion that cerebellar and/or cerebral atrophy were more common in the chronic active patients than amongst those with newly diagnosed seizures.

The approximate incidence rates of HS and of other quantitative hippocampal abnormalities were 1.3/100,000/year and 9.8/100,000/year, respectively. The approximate point prevalence rates of HS and of other quantitative hippocampal abnormalities was 0.2/1000 and 0.4/1000, respectively.

It was possible to assign a precise aetiology (including the idiopathic category) in more than three quarters of patients with newly diagnosed seizures, and in nearly two thirds with chronic active epilepsy, considerably more than in previous population based studies of epilepsy. The frequency of the most important aetiological categories varied according to
age, with epilepsy due to HS, pre-/peri-natal injury and head trauma being more common in young adults. Epilepsies due to CNS tumours, cerebrovascular disease and alcoholism were most evident in middle life whilst, in late life, cerebrovascular disease caused the majority of epilepsy, with dementias being implicated as a cause in a smaller number of patients.

9.1.4 Study 4:
The severity of hippocampal sclerosis in adults with newly diagnosed and chronic active epilepsy: a prospective, cross-sectional, population based quantitative MRI study
After the exclusion of a small number of patients with grossly abnormal mesial temporal lobe anatomy (newly diagnosed, 4, chronic active epilepsy, 4), group comparisons of the various quantitative hippocampal parameters revealed the following results:

Corrected hippocampal volumes
Compared to controls, mean HVc was 4.9% smaller (p=0.001) in those with newly diagnosed partial onset seizures, 4.8% smaller (p=0.005) in those with newly diagnosed generalised (non-idiopathic) seizures, and 1% larger (p=0.81) in those with newly diagnosed idiopathic seizures (Kruskal Wallis p=0.001). Comparisons of smallest HVc also showed a highly significant reduction in HVc amongst those with newly diagnosed non-idiopathic generalised seizures (5.5% smaller than controls; p=0.002) and partial onset seizures (6.1% smaller; p<0.001) compared to control subjects. Patients with newly diagnosed idiopathic seizures had HVc which were not significantly smaller (0.36%; p=0.8) than in controls (overall Kruskal Wallis p<0.001).

Compared to control subjects, mean HVc was 10.3% smaller (p<0.001) in patients with chronic partial onset seizures, slightly smaller (3.2%; p=0.47) in those with non-idiopathic generalised seizures, but was not significantly different (1.1%; p=0.35) in those with chronic idiopathic seizures (Kruskal Wallis p<0.001). Compared to control subjects, smallest HVc was 13.4% smaller (p<0.001) in patients with chronic partial onset seizures, 5.8% smaller (p=0.22) in those with non-idiopathic generalised seizures, and only 1.4% smaller (p=0.28) in the idiopathic group (Kruskal Wallis p<0.001).
Mean HVc was not statistically significantly smaller in the chronic partial or non-idiopathic generalised subgroups, compared to their newly diagnosed counterparts.

**Hippocampal T2**

Compared to control subjects, mean or highest HT2 were not significantly elevated in any of the newly diagnosed subgroups (Kruskal Wallis p=0.16 and 0.17, respectively), although there was a trend towards higher mean and highest HT2 in the newly diagnosed partial onset patients.

Compared to control subjects, mean HT2 was significantly higher in the chronic active epilepsy patients classified as having partial onset seizures (2.2%; p<0.001), slightly higher in the non-idiopathic generalised subgroup (1.6%; p=0.04), but not in the idiopathic group (0.4%; p=0.26) (Kruskal Wallis p<0.001). The pattern was similar when comparing highest HT2, in that values were significantly higher compared to controls in the chronic partial subgroup (3.4%; p<0.001), but not in the chronic non-idiopathic (1.8%; p=0.12), or in the idiopathic (0.3%; p=0.53) generalised subgroups (Kruskal Wallis p<0.001).

Mean HT2 was significantly greater in the chronic partial subgroup compared to their newly diagnosed counterparts (p=0.048), but was not different between the patients with newly diagnosed and chronic non-idiopathic generalised seizures.

To summarise, hippocampal damage, as determined by the group comparisons of mean and smallest HVc, and mean and highest HT2, with control values, was present in the patients with newly diagnosed and chronic active non-idiopathic generalised seizures, but was statistically significant only in those with newly diagnosed partial onset seizures and chronic active partial epilepsy (in whom the damage was greatest). Patients with idiopathic seizures did not have evidence of hippocampal damage, irrespective of whether they were newly diagnosed or chronic.

Logistic regression analyses failed to reveal any significant correlations between the extent of hippocampal damage and a variety of clinical variables pertaining to the severity of the epilepsy, including age of onset, number of lifetime seizures (total, GTC, or non-GTC), seizure frequency (total, GTC, or non-GTC), gender, or a history of febrile seizures. This
was irrespective of whether all patients, or just those with partial onset seizures, were analysed.

9.1.5 Study 5:
A quantitative MRI study of severe intractable epilepsy in an adult residential epilepsy centre

Of 306 inhabitants (214 male, 92 female; median age 47 years; range 17-103 years; learning disability 47%) of a residential epilepsy centre, 263 underwent high resolution MRI. Abnormalities of probable aetiological relevance were identified in 66%: hippocampal sclerosis/atrophy (HS/HA) without other focal pathology, 26%; focal neocortical brain damage and HS/HA, 16%; isolated focal neocortical brain damage, 14%; malformations of cortical development, 7% (of whom 55% had HS/HA); other, 3% (of whom 57% had HS/HA). Cerebellar, cerebral and generalised brain atrophy were observed in 40%, 39% and 23%, respectively. Quantitative hippocampal abnormalities were present in 47.5%, of whom 46% had dual pathology. HS/HA was not just present in patients with localisation related epilepsies, but also in those with epilepsies classified electro-clinically as generalised or undetermined. High resolution MRI revealed previously undetected, aetiologically relevant lesions in 47% of the 203 residents who had undergone previous CT and/or standard MRI and, overall, MRI increased the proportion of residents with a definable aetiology from 50% to 68%, and reduced the proportion with cryptogenic epilepsies from 50% to 32%.

9.2 Conclusions
Study 1 employed robust epidemiological methods in order to generate highly complete case ascertainment of subjects with newly diagnosed seizures and chronic active epilepsy. In addition to permitting the calculation of incidence and prevalence data from the study population, this allowed the identification of cohorts of epilepsy patients and control subjects who could be considered representative of the general population, for subsequent MRI investigation in studies 2, 3 and 4. As hypothesised, study 1 confirmed that the incidence of epilepsy is now greatest amongst the elderly, closely followed by infants and young children, and that the prevalence of chronic active epilepsy (approximately 1.8/1000) is considerably lower than prevalence rates reported for all epilepsy (including epilepsy in remission), confirming the generally favourable prognosis of epilepsy.
The importance of study 2 is that it demonstrated that lesions reported to be common in hospital based epilepsy patients (HS, MCD, and focal brain damage) did not occur in neurologically normal control subjects, thus confirming that these lesions can usually be considered as having aetiological relevance when discovered in patients with epilepsy. Small WML (presumed to be ischaemic in origin) were the only relatively common finding in control subjects, although these were generally few in number. Furthermore, it was shown that HV_c decreases in patients over the age of 50 years, emphasising that it is crucial to define a normative range for absolute HV_c with respect to age, something that has been largely ignored in previously hospital based quantitative hippocampal MRI studies. In contrast, HT2 was distributed over a much narrower range than HV_c and remained relatively constant across a wide spectrum of ages.

In the introductory chapter, the aetiology and importance of HS in epilepsy was discussed in detail, and it was emphasised that previously published studies of the frequency of HS have been heavily biased towards hospital based populations, such that its relevance to epilepsy sufferers in the community at large was simply unknown. Furthermore, a number of animal and human studies have suggested that HS may sometimes be the consequence of a hippocampal developmental abnormality, which possibly progresses as a result of intractable seizures, yet both these hypotheses remain a matter of fierce debate. In an attempt to resolve some of these issues, studies 3, 4 and 5 were consequently dominated by the investigation of the frequency and severity of HS in newly diagnosed and chronic epilepsy at the population level (studies 3 and 4) and, by way of comparison, in a residential population from an epilepsy centre (study 5). A number of key findings emerged. As hypothesised, in the community based study, HS was generally present only in those with partial seizures, and its frequency was significantly lower in patients with newly diagnosed seizures than in those with chronic active epilepsy. HS was not found in those with idiopathic epilepsy, even when of long duration, suggesting that GTC seizures per se do not cause hippocampal damage. In contrast, the frequency of HS and HA was much greater in the residential epilepsy population who had epilepsy which was generally much more severe than in the community based chronic active cohort. The possibility that this was also due, in part, to the high prevalence of learning disability cannot be completely discounted, although there are no reports of HS or HA associated with isolated learning disability. Furthermore, in this residential population, there was a much higher frequency
of "dual pathology" ie. HA associated with other focal cerebral lesions (most often neocortical brain damage), raising the possibility that the hippocampal damage may have occurred as a secondary phenomenon in these cases. Neither study 4 nor study 5 found a significant correlation between the severity of HS and the severity of epilepsy, as judged by a number of clinical variables including the age at onset, the duration of epilepsy, seizure frequency, and the estimated lifetime number of GTC and non-GTC seizures. In the case of study 4, this may have been due in part to relatively inaccurate seizure frequency and number data, but in study 5 this was certainly not the case since all seizures were accurately recorded by trained members of staff. Thus, the results presented cast some doubt on the idea that HS is a lesion which becomes progressively more severe as a consequence of uncontrolled seizures.

What new information do these studies provide concerning HS in epilepsy? Firstly, HS is substantially less frequent at the population level than it is in tertiary epilepsy centres. This statement does not undermine the fact that, overall, given the estimated 350,000 epilepsy sufferers in the UK, the frequency of HS indicates that it represents a very important cause of chronic epilepsy in the general population. Additionally, major head injury appears to be a significant risk factor in the development of HS in some adults, whereas a history of febrile seizures is comparatively uncommon, even in chronic active cases, suggesting that this factor has probably been over-estimated in past hospital based studies. Finally, evidence of hippocampal damage was demonstrated in a significant proportion of patients with newly diagnosed seizures, although typical HS was relatively rare. It is therefore postulated that HS of variable severity is already present at the time of first presentation in the majority of cases. When the HS is severe from the outset, it is most likely that the patient is pre-destined to have a poor prognosis and develop chronic intractable epilepsy. Although the possibility of progression of HS can neither be confirmed nor refuted by these cross-sectional studies, it is suggested that such progression, if it occurs, is likely to be very slow and may be unrelated to the overt severity of the epilepsy, with more subtle sub-clinical epileptogenic activity possibly having more significance.

The possibility that HS, and neocortical damage, are progressive, however, is currently being investigated by means of an ongoing longitudinal MRI study of the patient and control subject cohorts described in this thesis. Liu et al. (2002) have already reported that
neocortical volume loss occurs with surprising rapidity from a relatively early stage, but hippocampal volume changes have not been striking. This important study should also help to determine whether HS and brain atrophy are caused by intractable seizures, or some other factor(s), and will help confirm whether long-term prognosis is largely dictated by the presence of particular structural brain abnormalities. Although Fuerst et al. (2003) in a small longitudinal MRI study of severe intractable TLE reported significant reductions in HV ipsilateral to the seizure focus over a mean of 3.4 years, the duration of follow up required to demonstrate progressive hippocampal changes in a community based cohort with less severe epilepsy is not known. Co-registration of MRI scans should facilitate detection of minor changes more readily (Lemieux et al., 2000). A number of longitudinal MRI studies of children with epilepsy are also underway. There is a compelling need to identify patients with an increased vulnerability to progressive epilepsy syndromes, and the development of hippocampal, neocortical and cerebellar atrophy, so that a decision can be made as to how aggressive early treatment should be (Theodore, 2003), and the outcome of these studies is awaited with great interest.

In studies 3 and 5, MRI also demonstrated that lesions other than HS or HA are frequently significant in the aetiology of epilepsy, both in the community and in facilities for those with severe epilepsy. In the case of newly diagnosed patients, small critically-placed vascular lesions which would have been undetected by CT scanning appear to be the commonest cause of seizures in middle or late life. The secular trend of increasing longevity, coupled with the increased survival after large vessel stroke, indicates that we are likely to see a continued rise in the frequency of late onset epilepsy due to cerebrovascular disease, which will inevitably place a heavy burden on epilepsy services in the UK. One further challenge is to understand the pathogenesis of epilepsy secondary to small ischaemic lesions. A detailed statistical analysis of the total lesion volume and the precise spatial distribution of lesions (to see whether they are predominantly sub-cortical) in such patients, compared to healthy control subjects, might shed further light on their epileptogenic potential. Other focal lesions, including MCD, vascular malformations and low grade tumours, which are all recognised important causes of intractable epilepsy in the tertiary epilepsy centre clinics (Li et al., 1995; Duncan, 1997) were surprisingly infrequent in the community based population, thus emphasising the value of performing epidemiologically-valid high resolution neuroimaging studies in the assessment of the
“true” causes of epilepsy.

Despite the undoubted usefulness of MRI, a significant proportion of patients, even those with severe and unequivocally localisation related epilepsy, failed to have an aetiology demonstrated by high resolution imaging. It is highly likely that this proportion could have reduced slightly by the additional application of hippocampal morphometry (which may uncover highly focal HS), 3-D cortical surface renderings, diffusion tensor imaging, magnetic transfer imaging, and MR spectroscopy, but to even consider such an ambitious MRI protocol and post-processing analysis was far beyond the scope of this thesis.

One final focus of interest throughout this thesis has been the role of MRI in the classification of epilepsy. Study 5 showed that MRI increases the accuracy and usefulness of the ICEES syndromic classification, whilst study 3 confirmed that high resolution MRI significantly increases the likelihood of detecting aetiologically relevant structural brain lesions in patients with epilepsy, particularly those with partial onset seizures. As a result, the proportion of community based patients with cryptogenic epilepsy was reduced to less than one third, compared to two thirds in previous epidemiological studies of epilepsy, and the proportion of residents with cryptogenic epilepsy was reduced from 50% down to 32%. In the future, it seems likely that the current epilepsy syndromic classification will be replaced by an MRI based aetiological classification which is of more practical utility (Engel Jr, 2001). There is also increasing evidence that the prognosis of patients with epilepsy is largely dependent upon the underlying aetiology, especially if HS or dual pathology are present (van Paesschen et al., 1997a; Semah et al., 1998). For these reasons it is essential to classify aetiology as accurately and as early as possible, since this will dictate management, including consideration of early epilepsy surgery (which is currently under-used), and may influence outcome. Early, high resolution MRI should therefore be the neuroimaging investigation of choice in all patients with epilepsy.

9.3 Future directions

Two immediate conclusions can be drawn from the studies reported in this thesis:

1. There is probably no need for further incidence or prevalence studies of epilepsy in this country, at least in the foreseeable future.
2. Information from brain MRI should be incorporated into future epilepsy classifications, with precise instructions as to how to weight such data, especially when they are discordant with other investigations such as EEG or clinical manifestations.

In addition, a number of important possible future MRI studies stem directly from this work:

1. Longitudinal MRI studies of patients with newly diagnosed seizures with prolonged follow up are required in order to determine beyond doubt whether hippocampal, neocortical and cerebellar damage is progressive. Such studies should include collection of detailed, prospectively acquired data concerning seizure type, frequency and number, in order to see whether overt seizure activity is directly correlated with neuronal loss. Co-registration of MRI datasets in such studies will be essential to facilitate detection of small changes.

2. Further MRI studies (especially longitudinal) in children with seizures will help confirm when HS first becomes evident and also resolve the issue of whether pre-existing hippocampal damage causes complicated febrile seizures, or whether prolonged febrile seizures per se can cause damage to the hippocampus.

3. Further detailed MRI analysis of MRI negative epilepsy patients using some of the new scanning and post-processing techniques already described will determine the proportion with very subtle structural lesions.

4. Case-controlled MRI studies of late onset epilepsy due to cerebrovascular disease, in order to see whether the the distribution and volume of sub-cortical white matter, or grey matter, lesions influences the capacity to cause seizures.

5. Prospective, longitudinal studies of prognosis in patients with newly diagnosed seizures, in order to further assess the usefulness of MRI (including hippocampal quantitative analysis) in determining long-term prognosis, and to see whether this will aid decisions regarding the timing of institution of AED treatment, and at what stage to consider epilepsy surgery in lesional cases.
REFERENCES


Neuroradiol, 11, 93-99.


CAVAZZUTI GB (1980) Epidemiology of different types of epilepsy in school age children of Modena, Italy. Epilepsia, 21, 57-62.


COCKERELL OC, ECKLE I, GOODRIDGE DM, SANDER JW, SHORVON SD (1995b)


FOX NC, WARRINGTON EK, FREEBOROUGH PA, HARTIKAINEN P, KENNEDY


GOWERS WR (1881) *Epilepsy and other chronic convulsive disorders: their causes, symptoms and treatment.* London: Churchill, J & A.


HAGEMANN G, LEMIEUX L, FREE SL, KRAKOW K, EVERITT AD, KENDALL BE,


ILAE Commission on Epidemiology and Prognosis (1993) Guidelines for epidemiologic studies on epilepsy. Epilepsia, 34, 592-596.


JOSHI V, KATIYAR BC, MOHAN PK, MISRA S, SHUKLA GD (1977) Profile of epilepsy in a developing country: a study of 1,000 patients based on the international classification. *Epilepsia*, 18, 549-554.


epilepsy: a study of patients in long term residential care. *J Neurol Neurosurg Psychiatry*, 56, 149-152.


KUZNIECKY R, DE LA SAYETTE V, ETHIER R, MELANSON D, ANDERMANN F,


OLNEY JW, RHEE V, HO OL (1974) Kainic acid: a powerful neurotoxic analogue of


REYNOLDS EH (1994) Mechanisms of intractability. In: Epileptic seizures and


Livingstone. 63-92.


SISODIYA SM, STEVENS JM, FISH DR, FREE SL, SHORVON SD (1996) The demonstration of gyral abnormalities in patients with cryptogenic partial epilepsy using
three-dimensional MRI. *Arch Neurol*, **53**, 28-34.


STEINLEIN OK, MULLEY JC, PROPPING P, WALLACE RH, PHILLIPS HA, SUTHERLAND GR, et al. (1995) A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal
frontal lobe epilepsy. Nat Genet, 11, 201-203.


VAN PAESSCHEN W, DUNCAN JS, STEVENS JM, CONNELLY A (1998) Longitudinal
quantitative hippocampal magnetic resonance imaging study of adults with newly

VAN PAESSCHEN W, REVESZ T, DUNCAN JS, KING MD, CONNELLY A (1997c)
Quantitative neuropathology and quantitative magnetic resonance imaging of the

VAN PAESSCHEN W, SISODIYA S, CONNELLY A, DUNCAN JS, FREE SL,
RAYMOND AA, et al. (1995) Quantitative hippocampal MRI and intractable temporal
lobe epilepsy. Neurology, 45, 2233-2240.

resonance imaging evidence of hippocampal injury after prolonged febrile convulsions.
Ann Neurol, 43, 413-426.

VERITY CM, BUTLER NR, GOLDING J (1985) Febrile convulsions in a national cohort
followed up from birth. I—Prevalence and recurrence in the first five years of life. Br Med
J, 290, 1307-1310.

syndromes: advantages and limitations for evaluation of childhood epileptic syndromes in

VICTOR M, BRAUSCH V (1967) The role of abstinence in the genesis of alcoholic
epilepsy. Epilepsia, 6, 1-20.

WALKER MC, SANDER JW (1996) The impact of new antiepileptic drugs on the
prognosis of epilepsy: seizure freedom should be the ultimate goal. Neurology, 46,
912-914.

WALLACE HK, SHORVON SD, TALLIS R (1998) Age-specific incidence and prevalence
rates of treated epilepsy in an unselected population of 2 052 922 and age-specific fertility


WOERMANN FG, SISODIYA SM, FREE SL, DUNCAN JS (1998) Quantitative MRI in


ZIELINSKI JJ (1974) Epidemiology and medico-social problems of epilepsy in Warsaw (Poland). Final report on research program No 19-P-58325-F-01. (Abstract)