David W. McCandless

Epilepsy

Animal and Human Correlations

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David W. McCandless
The Chicago Medical School
Department of Cell Biology and Anatomy
Rosalind Franklin University
Chicago, IL, USA

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This volume is dedicated to
Jason David McCandless.

Foreword

In April 2011, just a few weeks after our dad submitted the manuscript for this book, he unexpectedly passed away. Dad devoted his career to science and teaching. Over the final few years of his life, he became especially focused on writing medical books. His strong commitment and devotion to sharing his knowledge and contributing to scientific discourse were evident to everyone around him. These books are Dad's legacy and symbolize his dedication to education and the advancement of science. This book on epilepsy was especially meaningful to him. We are particularly grateful to Dr. Richard Wiggins for editing the final proofs of the manuscript. Not only was Dr. Wiggins a colleague and collaborator with our dad, he was also a close friend.

We feel honored that Dad was such an integral part of our lives. He was an outstanding role model and a strong influence on our own educations. We will miss him dearly.

Jeffrey and Steven McCandless

Preface

This volume is intended to be a synopsis of seizure disorders with a goal of describing key studies in animals and humans. The translation of pertinent findings from animal to human studies, and to potential human studies, is emphasized where possible. Specific cogent animal studies/results that deserve exploration in human seizure disorders are identified. The current rate of translation is estimated to be from 7 to 9 years, and the success rate of translation was very recently listed as less than one half. The success rate is defined as results in human studies which were predicted in advance by animal studies. Both the time between animal and human attempts plus the success rate clearly need improvement. A clear cause of delay is a lack of controlled randomized placebo studies in humans once suggestive data are identified in animals.

This epilepsy volume is not intended to be a 3-volume, 3,000-page encyclopedic description of epilepsy. It does not cover every published study relating to epilepsy in animals and humans. Several excellent recent publications filling the need for inclusiveness have been published, and the reader is referred to them.

This volume is designed to facilitate translation and be synoptic in nature. The arrangement of epilepsy chapters is in two parts whenever possible: animal studies, and related human studies. Each chapter has a similar organizational format. The chapters have a brief introductory section, followed by clinical descriptions. Animal studies with a bearing on human clinical issues are presented. The rationale for future human clinical investigations based on animal results is clearly presented when available. Translation is an important consideration in such a complicated field as epilepsy, and its facilitation is critical.

The complicated nature of the study of epilepsy is obvious even at the start by the confusion and controversy regarding even the classification of seizures. Several systems are in use, ranging from those based on genetics, age, metabolism, etc. In this volume, the 1981 classification is used, supplemented by some expansion supported by an updated version from 2006. Classification of seizures is certainly subject to change based on new knowledge gleaned from new technological advances in imaging, diagnostics, new drug development, and new molecular biology concepts.

This volume examines features of animal and human studies related to both simple and complex partial seizures. Partial (focal) seizures that spread and evolve into

secondary generalized seizures are described. Attention is paid to those seizure types which produce the most numbers of human epilepsies. Generalized onset seizures will be examined, including absence seizures, as well as clonic, tonic, tonic clonic, etc. Typical as well as atypical seizures are discussed. Some seizure disorders that do not clearly fit into a classification are described, as well as nocturnal epilepsy. Whenever possible, studies in primates receive careful attention. These descriptions are always mindful of translation.

Other areas such as pediatric considerations, status epilepticus, and surgical approaches are included. As stated above, the focus is on the presentation of data from animal studies, which is timely and appropriate for translation to human disorders. The issue of world health concerns is neglected. Epilepsy in third world countries is largely untreated, and so studies applicable to patients in these settings are described. Possible treatments that might be applied or investigated with this in mind receive special attention in this volume.

Therefore, this volume is not intended to be all inclusive, but rather a synopsis of sorts, with a clear focus. If certain studies have been replicated 25 times over the last 10 years, not all will be cited. Studies with no bearing on the stated purpose of this volume are likely omitted. There are other very good sources of this material.

An important feature of this synoptic epilepsy book is to try to provide credence for each quoted study by including salient characteristics of each study. One often sees quotes such as "epilepsy was associated with dementia (followed by references) 32, 34, 36–40, 42, 43, and 48–51". The reader cannot tell if these references are significant or not. In this volume, we have tried to include enough actual information (ages, numbers of patients, epilepsy features, materials and methods, statistics used, etc.) in order for the reader to at least partially evaluate the validity/reliability of the results. We even occasionally state "this is an outstanding study".

In the preparation of this synopsis, we felt it was better to present less papers, but in a way for the reader to judge their significance, than to present 5,000 references which cannot be evaluated. As an aside, many journals now have the Materials and Methods sections at the end of a manuscript, when actually they should be first!

This synopsis of epilepsy – both experimental and clinical – will have appeal to physician assistants, primary care physicians, nurse anesthetists, osteopathic physicians, psychologists, radiologists, psychiatrists, dieticians, neurosurgeons, as well as neurologists will all find value in this book. More and more a team approach is most effective in epilepsy study and treatment. Increasing numbers of patients in the US accessing health care will place additional burdens on already overworked health care providers.

This book is as timely as is possible. As stated above, new technology and drug development are progressing. Thousands of epilepsy-related papers are published annually. It is important to try to identify those results which are of significance. Sources known for publishing high-quality investigations are identified in order to select the best papers.

It is our goal to produce a volume on epilepsy which will provide results of excellent critical investigations which will stimulate further thinking about aspects of this highly interesting, yet complicated subject area. It is our hope that this information, concisely presented, will motivate others to attempt to translate animal results into productive human studies. In this way, it is expected that human epilepsy will be modulated in ways which will reduce the severity and frequency of seizures.

Acknowledgments

The author wishes to thank Jeremy Carter, Candace Larson, and Laura Muncie for important and significant chapter contributions. Jeremy S. Carter and Candace L. Larson contributed a chapter on anesthesia in epilepsy, detailing procedures and methodology surrounding anesthetizing patients undergoing surgery for intractable seizures. Laura Muncie contributed an excellent chapter on diagnostic methodology currently used in evaluating patients prior to surgery to correct epileptic seizures. Jeffrey McCandless provided much valuable input into the Gene Therapy chapter, both in terms of content and organization.

Mrs Cristina Gonzalez spent many hours seeking both references and permissions to use various figures and tables in our book. Mrs Vilmary Friederichs aided in facilitating the completion of this volume and providing encouragement and support. My son, Jeffrey McCandless, NASA Ames Research Center, provided valuable input into the preparation and production of over 30 figures and tables. This consumed many hours.

Ms. Ann Avouris, Senior Editor at Springer Science and Business Media, helped us in many details of producing this book. As I have stated before, she is the most outstanding editor I have ever known. She is always responsive and ready to solve problems. She told me once, that she "loves solving problems", and she is outstanding in that regard.

My wife Sue has spent many years in support of these endeavors, and without her support and patience, this volume, and others, would not have been possible. I owe her a huge debt for her encouragement.

Contents

Part I
Introduction

Chapter 1
World Health Concerns

The World Health Organization (WHO) estimates that there are 50 million people suffering from epilepsy worldwide. In addition, about 75% or more are living in developing countries, sometimes with suboptimal medical care. It is estimated that 2.4 million new cases occur globally each year, and over half have their first seizure in childhood. Probably 70% of epilepsy patients have a measure of treatment success, allowing many to have essentially normal lives. In third world countries, most epileptics receive no treatment for various reasons, including lack of health care, lack of money, and/or lack of knowledge.

Epilepsy has a profound impact on childhood education. Many times, children do not attend school due to parental fears and teacher disdain. They may view epileptic children as disruptive, etc. In schools, there is usually no provision for first aid for a seizure patient. Side effects of anticonvulsant drugs (AEDs) and social stigma frequently lead to school dropouts. This all serves to create an inferiority complex for the epileptic child which lasts forever.

These effects in early schooling carry over into adulthood, where poor schooling may lead to an inability to gain employment. This may lead to a feeling of hopelessness, and worthlessness, leading to a suicide rate many times that of the general population.

In many cases in developing countries, the causes of epilepsy could be prevented. For example, in Ecuador, over 50% of epilepsy cases are caused by neurocysticercosis, which is an infection of the CNS caused by cysticerci of the pork tapeworm. Preventative treatment for those infected with tapeworm is about $0.10 per day. Conversely, the costs of first-line AEDs in some countries can exceed the total wages earned by a family annually. There are variations in costs of AEDs in different countries, and the reasons are not clear. It is obvious that there is a large gap in epilepsy treatment across the globe. A prime example is Zimbabwe where until a few years ago, there was only one fully trained neurologist in the country. He has since moved to the USA. Phenobarbital is often used in developing countries as an AED due to its low cost, whereas it is not frequently used in the USA because of adverse side effects.

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The International League Against Epilepsy (ILAE). The International Bureau for Epilepsy (IBE) and the WHO joined together to form a global campaign against epilepsy. This effort is based in part on the startling statistics concerning epilepsy, suggesting it is most likely one of the most universal of all medical/neurological disorders. There is no age, race, social classes, or geographical borders to becoming an epileptic. The estimate of 50 million epileptics is surely an underestimate due to limited diagnostic capabilities in developing countries. In addition, political considerations limit incidence reporting in some countries.

The goal of the combined campaigns is to "bring epilepsy out of the shadows." This would be achieved by increasing awareness that epilepsy is a treatable brain disorder. The effort should improve education about epilepsy and elevate acceptability of epileptics. The needs of patients with epilepsy should be identified and met, and governments should address needs of epileptic patients. A phase 3 objective for IBE and ILAE is to develop greater regional involvement in the campaign.

In terms of underdeveloped countries, the estimate is of the worldwide population of epileptics, about 40 million live in developing countries. The incidence of epilepsy in low income countries may be 190/100,000 people (Placencia et al. 1994). The high incidence rates are likely due to parasitic and infectious diseases not present in developed countries. As many as half of epilepsy cases are untreated worldwide.

Psychosocial issues are also significant. One study shows that those with epilepsy had a lower income, more sick days, and a lower life quality than those without epilepsy (Wiebe et al. 1999). Children with epilepsy performed lower than nonaffected children and even lower than other chronically ill children.

Various factors place restrictions on epilepsy treatment, including economic, political, as well as culture of third world societies. Lack of knowledge is a key element in problems of obtaining treatment, and in compliance. As described earlier, treatment costs may exceed a family's annual income. And there may be a problem with drug supply. Phenobarbital is the favorite first-line AED proposed by WHO. This decision is no doubt based on cost.

Successful approaches in Africa involve a combination of availability of health care workers, availability of free AEDs, and availability of education for the local population regarding epilepsy and its treatment. Follow-ups were initiated, and mobile clinics were instituted in order to make medical help more accessible. The success was measured by the fact that after six months, 56% of patients were seizure free (Watts 1989).

As a part of the global campaign against epilepsy, surveys of epilepsy prevention were conducted regionally, including the Western Pacific region (Li et al. 2005). This region has 37 countries, and about 10 million epileptics reside there, although more than 60% do not have any epileptic care. Even in this area, developed countries have problems of stigma and lack of access to good treatment. The questionnaire sent to governments regarding epilepsy care was only returned from 20 of the 37 countries in the Western Pacific region.

There was a great degree of diversity in the results gained from the Western Pacific region survey. In some ways, for example, prevalence rates (3.8–4.6 per 1,000)

were similar to others, but there was a large range in the results. There is a clear need for improvement in delivery of health care to those with none. Large gains can be achieved with just a modest investment.

The importance and need for employment in epileptic patients has been examined (de Boer 2005). People whose epilepsy starts during employment years, especially early, are at a disadvantage as regards employment. The onset of seizures may lead to short term, and perhaps permanent unemployment. The medical opinion is that most epileptic patients should be able to compete with anyone as regards the work place, but epileptics do not perform as well as others.

A project in the Netherlands was undertaken to determine characteristics of education and employment in a group of 1,000 epilepsy patients. Results showed a mean age of 38 years, and an equal distribution of men and women. Complex partial seizures were the most frequent type of seizure, followed by tonic-clonic seizures. Ninety-six percent were on AED treatment, with 32% taking one drug, and 34% taking two different AEDs. Twenty percent were seizure free. Compared to the general Dutch population, the epileptic group had a lower level of education. Forty-four percent were employed, 49% were unemployed or disabled. There was a correlation between the number of AEDs taken and employment: the lower the number of drugs, the higher the number of employed people. There was also an inverse correlation between the seizure severity and the employment rate.

The author notes that two areas need attention. The first is education of the public, especially employers, and second, employment training programs for people with epilepsy. To that end, a work integration program was developed (de Boer 1997) with an objective to facilitate the introduction into the workplace of epileptic patients. This was achieved by bringing together those in government, etc., and sharing each others knowledge. Job placement aims to place the epileptic patient to the proper job.

A brief report from India (Ramaratnam and Narasimha 2005) examined both prevalence and patterns of epilepsy in India. The authors reviewed 21 previous studies which covered 837,000 people, 4,220 of whom were epileptic. This gave a crude prevalence rate of 5.04/1,000. Age standardization revealed a prevalence rate of 5.39/1,000. Onset of seizures was in the first 30 years of life in all cases.

There were significant heterogeneities in results due to criteria such as malaria incidence, denial of epilepsy, prevalence of cysticercosis, etc. The overall number of epileptics in India is about 5.5 million and three-fourths are estimated to live in rural areas. Of these, 75% will probably not receive any treatment. This presents a significant potential burden on the economy and medical resources of the country.

Epilepsy results in a significant burden worldwide. Estimates are based on calculating disability adjusted life years (DALY). One DALY is one lost year of healthy life, and epilepsy contributes about 7 million DALYs (Chisholm 2005). The burden is magnified in places where there is a treatment gap, or lower treatment rate, than seen in developed countries (see Table 1.1).

One concern of WHO is in choosing interventions in treatment which are cost effective. A standardized approach has been developed comparing costs and effects of both current and proposed plans. Diseases are “modeled,” and epilepsy was modeled as a disabling chronic condition with an increased risk of premature death.

Table 1.1 Percentage of DALYS lost worldwide

Disorder	Percentage of total DALYs lost worldwide in 1 year
Infectious	23.4
Neuropsychiatric (including epilepsy)	11.5
Trauma	11.3
Cardiovascular	10.3
Respiratory problems	6.2

Adapted from Scott et al. Bull. W. H. O. 79: p. 346, 2001

The classification of epilepsy was based on idiopathic epilepsy, not symptomatic epilepsy, and also based on two or more seizures in the past 5 years. Seventy percent of epilepsy cases are unprovoked, while 30% have a clear cause.

In developing countries, emphasis is on available low cost AEDs for first-line intervention. Four AEDs were compared: phenobarbital, phenytoin, carbamazepine, and valproate. In addition, analysis of costs and efficacy of treatments were performed at a primary health center.

Results showed that there were no measurable differences between the AEDs tested as regards efficacy or effectiveness. DALYs averted per million population ranged from 90 to 350 depending on geographic region. Treatment costs were as little as 70 international dollars (one international dollar equals one US dollar in purchasing power) per year up to 210 I.D. per year for valproate. The most efficient choice was using phenytoin or phenobarbital.

The author comments that there is a low priority and high treatment gap in some world geographic areas regarding epilepsy treatment. This could be averted in some measure by increasing the availability of affordable AEDs. Defects in this overall analysis include not always using the drug of choice for the seizure type. Comorbidity is an unmeasured variable which can increase costs appreciably. Disability weights may have been too low in the estimations of health benefits and averted burdens. The author also states that cost-effectiveness analysis is only one factor in the allocation and priority of health resources for epilepsy. There also needs to be attention paid to psychosocial issues.

The stigma mentioned earlier towards epileptics is a pervasive influence on responses of others at all levels from friends and neighbors to governments. The cost of stigma in terms of reluctance to work, or seek medical/psychological help, is not well studied. There is a growing awareness of this problem (which dates to antiquity), and a recent brief paper addresses some of the problems (Keusch et al. 2006).

There is a strong stigmatization of people with certain disorders. This could be a fear of physical contact, strong feelings about the manner in which some diseases are transmitted, etc. These feelings against certain groups with certain diseases (leprosy) go back thousands of years. The stigma of epilepsy similarly occurred in ancient times.

The recognition of the need to try to deal with, and educate against stigma, motivates health care workers to try to define the cultural disease of stigma. In 2001,

an NIH sponsored international conference to examine aspects of stigma. Diseases covered were AIDS, epilepsy, mental illness, addiction, and physical deformities. The major goal was to examine ways stigma could be reduced given its almost endless history.

The view emerged that stigma reduction will occur through action taken according to the condition, country, and culture. A start should be made to define circumstances that amplify fear and discrimination. Various people such as psychologists, behavioral scientists, physicians, health care workers, etc. should work together to implement educational directional concepts in order to develop a better understanding of these afflictions by the general public.

Malaria is a disease in which hundreds of millions of people worldwide suffer. Cerebral malaria is the most severe expression of malaria and carries a morality rate of 10–40% (Molneux 2000). Cerebral malaria results from *Plasmodium falciparum*. The country Mali is endemic for malaria and has a 1.3% prevalence for epilepsy. The present study was undertaken in order to evaluate the role of cerebral malaria in epilepsy in Mali children.

This study is a result of a several year-long examination of risk factors for complicated and severe malaria in children 6 months to 15 years of age. Patients with severe malaria were diagnosed using WHO clinical criteria (Warrell et al. 1990). Malaria was carefully diagnosed, including *P. falciparum* in blood, fever, and coma. Patients were considered as epileptic when they had at least two unprovoked seizures within a time frame greater than 24 h.

Overall results showed 101 children in the cerebral malaria group and 222 patients in the noncerebral malaria group. In the cerebral malaria group, 77% had exhibited convulsions before the onset of coma, and 15% developed status epilepticus. Fifteen percent of the noncerebral malaria patients also developed seizures. Other sequelae included mental retardation, speech delay, oral dyspraxia, and behavior problems.

EEGs were recorded in only two patients who were subsequently confirmed as epileptic. These two patients from the cerebral malaria group showed bilateral centro occipital spikes and age-dependent occipital spikes. CT scans were performed in eight patients, four with epilepsy, and four with other neurological sequelae. Five of the eight showed abnormalities, including atrophy of the affected hemisphere, and diffuse atrophy. In the other neurologic sequelae group, CT results showed one case with dilated ventricles, and two had necrosis of both pallidi and bilateral peri sylvian atrophy in one patient, and another case of a cortico subcortical large zone of atrophy.

The authors note that epilepsy was significantly more frequent in children with cerebral malaria than in noncerebral malaria patients. A nonmalarial group was not a part of the protocol. In a rural tropical context, it is difficult to determine the date of onset of seizures or much else regarding initial seizures such as body temperature. The finding that cerebral malaria is a risk factor for epilepsy has been previously noted (Schmutzhard and Gerstenbrand 1984). Another study (Carter et al. 2004) showed a higher prevalence of epilepsy after the cerebral malaria.

In acute malaria, seizures occur in over half of patients before encephalopathy. Status epilepticus may occur, worsening the prognosis. The authors conclude saying

that cerebral malaria dramatically damages the brain, and produces severe cognitive and motor sequelae. Phenobarbital, however, served to exert an easy control on seizures. Phenobarbital is relatively inexpensive, therefore representing an excellent choice in an AED.

Results of the ILAE, IBE, and WHO global campaign against epilepsy survey were published (Dua et al. 2006). Epilepsy care worldwide was evaluated from questionnaires asking for information for a multitude of questions. Data was collected from 160 countries. The questionnaire was translated into multiple languages before distribution. An atlas of epilepsy care in the world was developed in order to present all data in an easy to read form.

Results showed that professional organizations for epilepsy specialists exist in 61% of responding countries; 66% of low income countries have no such organizations. First-line AEDs were listed as phenobarbital (95% of responders), carbamazepine (93%), phenytoin (86%), and valproate (87%). The least expensive by far is phenobarbital. Epilepsy specialists were available in 70% of responding countries. By contrast, 30% did not have an epilepsy specialist for their country. Disability benefits were available in 47% of countries. The high was in high income countries (86%), and only 15% received benefits in low income countries.

Major problems in health care for epileptics included lack of drug supply, low level of community knowledge/awareness of epilepsy, stigma, lack of governmental concern, lack of infrastructure, etc. Social concerns that included help on employment, driving, education opportunities, etc., were identified as problems.

The authors comment that the atlas is a key activity coming from the campaign. It provides a visual way to assess the data. The only possible drawback to the atlas is that only one person in each country provided all the data for that particular country. Responses were mostly "yes" or "no," with limited information which was variable.

The treatment gap should be viewed, state the authors, in the context in which it comes. Areas such as economics, social, political, and cultural all need to be considered. This consideration modifies one's view of limitations. For example, the authors note that epilepsy surgery might be very desirable, but in some countries it is not obtainable at this time. There is also a difference in availability and how is a certain service actually used. In conclusion, these data and resultant atlas are very important, but must be considered carefully and in light of additional factors.

An ILAE report on epilepsy in North America which resulted from the campaign against epilepsy was published (Theodore et al. 2006). In this report, the estimate was that there were over 3 million people in North America with epilepsy. The comment is made that while epilepsy is more common than multiple sclerosis, Parkinson's disease, or autism, research funding is higher in the latter three, and epilepsy stigma extends to epilepsy patients and their family members.

The incidence of epilepsy in the USA, based on the Rochester study (op cit), is 44 per 100,000 people per year (1935–1984) and was 48 per 100,000 in 1975–1984. The age results showed an incidence of 60–70/100,000 under 5 years of age to less than 30/100,000 in older patients (65–74 years old). Since prevalence data include both existing cases plus new cases, the numbers tend to rise. In the Rochester study, prevalence rose from 2.73/1,000 to 6.79/1,000 people 40 years later.

In Canada, the incidence of epilepsy is estimated to be from 40 to 70 per 100,000 people, which would represent about 15,000 new cases per year (Kotsopoulos et al. 2002). In English-speaking Caribbean countries, Jamaica had over 8,000 hospital admissions for epilepsy over a 7-year period (population over 2.6 million).

In terms of etiology and classification in the U.S. Rochester study, about two-thirds of cases were cryptogenic or idiopathic. The remainder had insults such as trauma, stroke, cerebral infections, etc. Similar results were seen in the Texas study (Annegers et al. 1999). Tonic-clonic and complex partial seizures were most common. Mortality rate of epileptics in the USA was 2.3 times that of the general population.

Quality of life was assessed, and showed that there was a significant increase in the perception by the patient, that they were disabled as compared to the general population. Employment and financial differences were significantly different, with epilepsy patients having a mean annual income of $19,000 vs. $32,000 for the general population. In one survey, epileptics reported the fear of having a seizure was the worst aspect of epilepsy. Data in this study put the risk for suicide at about ten times that of nonepilepsy patients.

US public policies have not been successful in dispelling the perception that epilepsy is a stigmatizing condition, and so this attitude prevails in epilepsy patients as well. Epilepsy is a social label as well as a clinical disorder. The US public tends to overestimate the severity of the disorder in terms of both medical problems and social interactions.

In terms of care for epileptics, 41% of members of the American Academy of Neurology state that epilepsy is a focus of their practice. This translates to about 4,000 neurologists for 3 million epileptic patients. Resources reveal about 100 epilepsy centers have procedures such as video EEG, CT, MRI, SPECT, etc. In Canada, there were 45 video EEG beds in 2002.

Health care for epilepsy is generally and widely available in the USA. In one survey, 90% of epilepsy patients were taking AEDs, 56% were receiving monotherapy, 26% were taking two AEDs, 6% were taking three, and 2% were taking four AEDs. About 70% were very satisfied with their medications. The increased use of generic drugs can affect epilepsy care in a significant negative way including increased hospital admissions, and a negative impact on quality of care (Christian-Herman et al. 2004).

The annual cost of epilepsy in the USA is about 12.5 billion dollars. In terms of NIH dollars for research, epilepsy seems to be underfunded as compared to other chronic neurological disorders such as multiple sclerosis and Parkinson's disease. The USA is behind other countries in terms of life expectancy and infant mortality.

The report states that advances in neuroscience research show great promise, but weak links (translation) between advances (genetics and gene therapy) must be strengthened. Results of animal studies of new AEDs should be tried in patients at an accelerated pace whenever possible. Improved access to care and new advances should reduce morbidity and mortality. Translation of clinical trial evidence to community settings is needed.

Finally, there should be cooperation with the psychiatric community since many epilepsy patients have special needs, which psychiatrists can help. In many developing countries, it is psychiatrists who first diagnosis epilepsy due to behavioral problems. There should be interaction between developing countries and developed countries as regards epilepsy. Improved seizure control should be the first goal of all efforts. Secondary goals include mental health and education.

The health care and outcomes to assess epilepsy burden in China has been studied (Ding et al. 2006). In this study, prevalence/incidence have been used in order to assess disease burden in China. The DALY (see Chap. 3) was utilized. Characteristics such as age groups, prevalence, mortality rates, disability, and DALYs were all estimated.

Results showed that epilepsy caused 1.31–1.52 years of life lost per 1,000 general population. Years lived with disability due to epilepsy were 0.46–1.01 per 1,000 population. The greatest number of years of life lost was in the 15- to 29-year-old age group. Over 3.2 DALYs were lost per 1,000 in the 15 to 44-year-old age group. The highest prevalence rate was 12.55 in males in the 60–69 age group. Epilepsy mortality rates in China were between 3 and 7.9 per 100,000 people.

The authors note the overall DALY lost rate was 2.08 per 100,000 population. The authors state that for a complete assessment of the epilepsy disease burden, all DALYs for all diseases should be acquired, and this has not been done. The rate for cerebrovascular disease is 9.86 per 1,000 population, so the epilepsy rate seems reasonable. The DALY rate can be significantly reduced by a cost-effective treatment such as phenobarbital.

Another paper was published using a matched population-based cross-sectional case-controlled survey to examine the relationship between epilepsy and malnutrition in Benin. In sub-Saharan Africa, both epilepsy and malnutrition are health problems which have significant impact on medical and economic problems in Benin.

The prevalence of epilepsy in sub-Saharan Africa is from 10 to 55 per 1,000, whereas it is much lower in industrialized countries. Estimates on malnutrition are that at least one-thirds of the African population is undernourished (Food and Agriculture Organization 2006). A relation between epilepsy and malnutrition was suspected for many years (Hackett et al. 1997).

In this study, patients with epilepsy were matched with control subjects (1–2 ratio) based on age and area of residence. Anthropometric measurements were taken, and clinical examinations were done. Questionnaires were administered.

Results showed the prevalence for epilepsy in the studied region of Benin was 12.7%; 95% CI: 10.8–14.8. The study utilized 131 epileptic patients and 262 controls. The mean age was 25.4. The ages of epileptic cases were 17% children, 18% adolescents, and 65% were adults. Controls were almost identical. Epileptics and controls took a questionnaire asking about occupations, etc., plus questions regarding food. Twenty-two percent of the cases were malnourished versus 9.2% for controls ($p=0.0006$). Height and weight for height were not significantly different. Four clinical signs of malnutrition (hair depigmentation, curly hair, dry skin, and tooth decay) were all highly significantly evident in epileptic patients as compared to controls.

The authors comment that both epilepsy and malnutrition are major health problems in Benin. Malnutrition was found to be more frequently associated with epileptic patients than with controls. Since epilepsy is stigmatized, often actual

patients were reluctant to answer questions and a surrogate respondent was used. There was an association between epilepsy and nutritional status, but no inference about the direction can be made.

If epilepsy begets malnutrition, it could be because of the stigma in which epileptic patients (children) might not be fed as well or as often (benign neglect). Food taboos could also have contributed to malnutrition in Benin. If malnutrition contributed to epilepsy, several mechanisms might be active, such as a reduction in seizure threshold. Biochemical variations such as electrolyte abnormalities, hypoglycemia (and altered energy metabolism), or a decrease in inhibitory amino acid neurotransmitters might contribute. Hippocampal damage from a low protein diet (high frequency in Africa) might play a role in increasing susceptibility to epilepsy.

The authors conclude saying it is difficult to study these phenomena due to the almost complete lack of record keeping. Differently designed studies such as a cohort study are essential to clarify the direction of the association between epilepsy and malnutrition. Animal studies of the neurochemical results associated with malnutrition (hypoglycemia, neurotransmitters) certainly support via potential translation this explanation for the results. Future studies should resolve this issue.

A study of epilepsy, its stigma, and treatment in the African country of Togo have been performed (Balogou et al. 2007). The background is that in sub-Saharan Africa, 80% of epilepsy patients receive no treatment – the treatment gap is 60–98%, and about 70% of epilepsy cases could be controlled. An interesting statistic was that in a northern district of Togo (Kara district) where cysticercosis prevalence was 23%, the epilepsy rate was 16%. In southern Togo (Kloto), cysticercosis is rare, and the epilepsy rate was 12.3%.

The stated purpose of this study was to describe methods aimed at managing epilepsy in an underdeveloped country. The study implemented members of an indigenous tribe called the Batamariba tribe, with a population of 9,750 members. The tribe was primitive in that they relied on traditional healers. Attendance at a health clinic was 1.1% vs. 23% for the rest of Togo.

In the study, questionnaires were completed by over 600 residents to evaluate attitudes, etc. as regards epilepsy. A national campaign was conducted, followed by a detection phase. This consisted of a door-to-door survey looking for epileptic patients. This effort involved multiple neurology interns, neurologists, and a pediatrician, among others. Home follow-up and free drugs were distributed by a health care worker. Phenobarbital was the basic AED.

Results showed that the management of epilepsy was integrated into the daily routine of the identified epileptics. Of the initial 6,250 people participating in the study, 98 were considered to have epilepsy. The prevalence of epilepsy was determined to be 15.7% (95% confidence interval, CI 12.7–19.2). The seizure types were tonic-clonic – 36% and complex partial seizures equaled 33%. Suspected or confirmed causes were found in 76 patients, including 10 with head trauma. In follow-up, 93% of patients treated with phenobarbital had no more seizures, and most of the rest had a reduction of seizures.

The authors comment that their study conclusively shows that epilepsy can effectively be managed in a rural setting in a developing country. The success was based on determining beliefs which originally prevented epileptic residents from seeking

help, and a sensitization program resulted in their treatment. The compliance rate was 98% compared to a compliance rate in a study in Tanzania of 90% (Jilek and Jilek-Aall 1970). The study was reproducible since the team of specialists used the same diagnostic criteria throughout the studies.

The present study used EEG methods to better clarify seizures and to minimize false positives. The authors conclude saying the use of the cheapest AED, phenobarbital, was highly successful. The treatment gap decreased from 100% before the study to only 4.1% after 2 years, and to 0% 4 years after program onset.

Another study has examined the prevalence and patterns of epilepsy in Brazil (Noronha et al. 2007). Previous studies in Brazil have shown a prevalence range of from 11.9/1,000 to 21/1,000 people. Similar results are derived from other South American countries. The treatment gap is high in low income countries. The objective of the present study was to assess prevalence and treatment gap in epileptic patients in Brazil, and determine if socioeconomic class played a significant role in these data.

Door-to-door surveys were conducted in three separate Brazilian areas representing three different socioeconomic geographic areas. Clinical epilepsy classification included active epilepsy, adequate AED treatment epilepsy, treatment with monotherapy, treatment with polytherapy, and nontreated epileptic patients. Socioeconomic class was also determined, ranging from 1 to 7, then combined into four classes – A, B, C, and D in decreasing order.

Results showed that of 54,000 people surveyed, 496 were positive for epilepsy. This represented 0.9% of the people surveyed. The minimum lifetime prevalence was 9.2/1,000 people. No differences were found between the social classes in terms of prevalence. Thirty-eight percent of those with active epilepsy had inadequate treatment. Of these, 12% were taking inappropriate medications, 19% were taking no drugs, and in 7%, the treatment was unknown.

The authors note that their study is the first door-to-door epidemiological survey in Brazil. The prevalence of epilepsy in Brazil is similar to other poor countries (Nicoletti et al. 2005). The patient lack of appropriate treatment even extended to more well-to-do patients. The treatment gap was rather equal across socioeconomic groups. The authors further note and conclude that these results indicate a commitment from the government may be inadequate. There should be overall health care management and a decent availability of AEDs. There should also be a campaign to educate the population regarding epilepsy and its treatment.

A recent paper (Co et al. 2007) has examined diagnosis and treatment of neonatal seizures in developing countries. Neonatal seizures can be relatively benign or can be life threatening. One goal of the ILAE/WHO campaign against epilepsy is to investigate the possibility of clinical guidelines and diagnostic/treatment algorithms for seizure patients that could be widely applied. This process has been done, and the present paper examines results. The authors state the guidelines are not a sole source of information for the evaluation of neonatal seizures. They are rather a framework for clinical workup.

The paper suggests several important features necessary for the proposal. First is a complete history. Family history of seizures is important, as are details of pregnancy

and delivery. Head trauma, hypoxia, etc., all may be critical. The physical exam of the patient, with emphasis on evidence of trauma, level of consciousness, muscle tone and movement, tendon reflexes, etc. Attention should be paid to possible causes of seizures such as metabolic abnormalities (inborn errors, stroke, etc.), infections, intracranial hemorrhage, etc.

Neonatal infants with continuing seizures require immediate treatment and attention to breathing, and circulation. Abnormal movements have a correlation with electrographic seizures as shown on EEG. AED treatment should begin with a first-line drug such as phenobarbital, phenytoin, diazepam, or lorazepam.

Prognosis is generally tied to the underlying etiology of the seizures. Diffuse brain injury is associated with a poor prognosis. Diffuse brain damage is a feature of generalized myoclonic seizures, tonic seizures, and motor automatisms. Early onset of seizures (under 48 h), status epilepticus, comorbidities, etc., are also predictors of poor prognoses.

The overall view of this report is that there should be consistencies in all phases of epilepsy examination, diagnosis, and treatment. This is essential for consistency in comparing results from different geographic regional studies.

A brief paper (Tran et al. 2008) examines epilepsy in Laos, and represents one of the worst examples of lack of epilepsy care, emphasizing the difficult task of improving diagnosis and treatment. The WHO indicates that at least 80% of epilepsy patients live in areas with poor resources, and never receive treatment. Laos is a small country with a population of about 5.6 million people, mostly living in rural areas. Laos ranks 133rd in the Human Development Index, and has an annual per capita income of US $491. The epilepsy prevalence is 7.7% (Tran et al. 2006). In Laos, there are no guidelines, and many misconceptions and stigma towards epilepsy. Only one half of pharmacies can supply phenobarbital.

A group of medical health workers developed an epilepsy program to provide phenobarbital to epileptic patients. In this program, information was provided to epilepsy patients who were diagnosed on clinical criteria. Ultimately, 46 active cases were identified. Of these, only four had ever received AEDs previously. The daily income of the group was less than US $1.00. Twenty percent were mentally retarded. Seizure frequency ranged from 2 per year to three per week.

Eleven patients did not attend the program, and 16 dropped out. Only ten showed full compliance. Premature death occurred in 11%, from drowning, falls, burns, and sudden deaths. In the group who completed the program, seizure frequency dropped from 3.5 to 0.3 per month, and 70% were seizure free. The major problem was the distance needed to travel for medical accessibility. Phenobarbital was efficient, economical, and well tolerated at the community level.

Low education, low income, and lack of access all may have influenced poor compliance. The mortality rate was strikingly high. Stigma and mental retardation also no doubt contribute to the low success. This study illustrates the highly complicated and difficult problems which can be encountered in trying to provide epilepsy care to developing areas. Nevertheless, there were positive achievements, and not trying is no option.

Chapter 2
Metabolism and Epilepsy

This chapter will examine some aspects of the metabolic (especially energy metabolism) and pharmacologic responses to epileptic seizures. This involves animal models as well as imaging studies in patients. Some results are in conflict, and this is probably linked to the usual differences in methodology, and in definitions and data interpretation.

What's certain is that in seizure activity, there is significant electrical discharge of groups of neurons sufficient to usually result in an uncontrolled motor response. This in turn is associated with a change in cerebral energy metabolism and changes in synaptic function.

Methodological techniques include two basic mechanisms. The first includes directly measuring metabolites and neurotransmitters, mostly in experimental animals. The second method is to estimate energy metabolism using 2-deoxy-glucose PET, and magnetic resonance spectroscopy, both suitable for measuring glutamate turnover. Imaging methods have the advantage of being able to evaluate many cerebral areas simultaneously.

Dozens of studies have been performed looking at the direct measurement of energy metabolites in brains of seizing laboratory animals. There have been studies showing little change in adenosine triphosphate (ATP) or phosphocreatine (PCr), however many studies have shown dramatic alteration in energy metabolites.

One key is to be mindful of the concept that many metabolic encephalopathies have highly regional cerebral effects, and that includes seizures. Studies in which effects on energy metabolism of seizures gained by analyzing whole brain are much less meaningful when compared to regional studies.

Glutamate, the most prominent excitatory neurotransmitter in brain, has turnover which is tightly coupled to glucose metabolism (Magistretti and Pellerin 1996).

The rapid removal of both glutamate and GABA from the synapse is an energy (ATP) requiring process, explaining the coupling between neurotransmitter and glucose metabolism. Compensatory mechanisms such as increased cerebral blood flow during seizures provide increased oxygen and glucose to the stressed brain.

Transporters which serve to remove glutamate and GABA from the synapse are an astrocyte product, and the astrocytes are in close proximity to the synapse. In the

D.W. McCandless, *Epilepsy: Animal and Human Correlations*,
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