neurology

A QUEEN SQUARE TEXTBOOK

second edition

edited by

CHARLES CLARKE | ROBIN HOWARD | MARTIN ROSSOR | SIMON SHORVON

WILEY Blackwell

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Beginnings

A conversation with Professor Ian McDonald

Ian McDonald[1] kindly agreed to write the foreword for the first edition of this book. Sadly, he died shortly before it was completed. We met one sunny morning in 2004 and talked, sitting together on a bench in Queen Square.

I explained what I had in mind: an integrated, practical textbook from the National Hospital and the Institute of Neurology. 'That is quite splendid', Ian responded, in his inimitable way. 'Of course', he continued: 'a book like this has never been produced and I think no one has been able to draw together the different personalities here – and that will not be at all easy …'. Ian went on: 'Charlie Symonds[2] once told me that he had suggested a similar project to the National Hospital Medical Committee in the 1930s'. Dr Charles Symonds, who had been recently appointed to the staff had received an immediate veto from his senior colleague Dr Samuel Kinnier Wilson.[3] 'Symonds, there is no place for *that*. I have already written the definitive book, and there is no need for another,' Kinnier Wilson is said to have responded, acidly.

During the last five decades, neurology has progressed immeasurably. Queen Square has become a truly international centre. The editors integrated this international dimension, drawing on clinical experience and perspectives for the first edition from Australia, Canada, China, Europe, India and the United States. We thank our international editors for their comments and guidance.

This book came to fruition slowly and was quite a challenge. The authors are busy, distinguished in specialist fields, but they came together to produce the first edition, and now the second. The editors are most grateful to them all.

We hope *Neurology: A Queen Square Textbook* in this second edition continues to achieve its object – to reflect the clinical practice of neurology as we know it and to illustrate the approach we teach and follow at the National Hospital for Neurology & Neurosurgery and the Institute of Neurology, Queen Square.

We all valued Ian McDonald's encouragement and hope that if he were still with us, he would feel the finished product was worthy of the institutions and teachers that have guided our thoughts and practice over the years.

Charles Clarke
Queen Square
London WC1

1. Ian McDonald (1933–2006) was Professor of Neurology at Queen Square from 1978 to 1998, and was well known for his work on multiple sclerosis.
2. Sir Charles Symonds, KBE, CB (1890–1978) was appointed physician to The National in 1926. A selection of his many papers entitled *Studies in Neurology* was published in 1970.
3. Dr Samuel Kinnier Wilson (1878–1937) was appointed physician to The National in 1912. He had written the seminal paper on progressive hepatolenticular degeneration shortly before this. *Neurology*, his well-known textbook, was published posthumously in 1940.

Foreword to the First Edition

Queen Square in Bloomsbury, London, is known the world over as a centre for neurology and clinical neuroscience. Like many institutions, The National, initially The National Hospital for the Relief and Cure of the Paralysed and Epileptic, was founded through the hard work and generosity of people with a broad sense of charitable intent, especially the Chandler family – Johanna Chandler, her sister Louisa and their brother Edward. The doors of the original building opened in Queen Square in 1860. Dr Jabez Spence Ramskill was the first physician appointed, followed shortly by Dr Charles Brown-Séquard. Since 1860 there has been an unbroken record of progress across the clinical neurosciences. The names of all those who contributed in those early years are too numerous to mention, but amongst those who stand out today in an historical perspective are Dr Charles Brown-Séquard, Dr John Hughlings Jackson, Sir William Gowers, Sir David Ferrier, Sir Victor Horsley, Sir Gordon Holmes, Dr Samuel Kinnier Wilson, Sir Francis Walshe, Sir Charles Symonds and Dr Macdonald Critchley.

The National Hospital has undergone many changes and revolutionised its approach, for example towards neurological rehabilitation and brain injury, and has developed close and inseparable links with the UCL Institute of Neurology, which has helped to promote research at Queen Square in both basic and clinical sciences. Both Hospital and Institute are now involved in advancing an extensive range of developments in translational medicine that are transforming the treatment of neurological diseases. These developments are reflected in this book.

The UCL Institute of Neurology

The UCL Institute of Neurology was established in 1950 and has been part of University College London since 1997. The Institute provides research and teaching of the highest quality in neurosciences, and professional training for clinical careers in neurology, neurosurgery, neuropsychiatry, neuroradiology, neuropathology and clinical neurophysiology. With its concentration of clinical and applied scientific activity, the Institute provides a unique national resource for both postgraduate training and research in the basic neurosciences and its associated clinical disciplines. The Institute currently holds active grants for research into the causes and treatment of a wide range of neurological diseases, including movement disorders, multiple sclerosis, epilepsy, brain cancer, stroke and brain injury, muscle and nerve disorders, cognitive dysfunction and dementia; the work of the Institute's clinical academic staff remains closely integrated with The National Hospital.

The National Hospital for Neurology & Neurosurgery today

The National, now part of University College London Hospitals NHS Foundation Trust, is a thriving hospital, largely refurbished behind the 1890 façade. The hospital receives over 1000 new outpatient referrals each month and has over 200 beds, a dedicated ITU, extensive rehabilitation services and all ancillary departments in the most substantial specialist neurological hospital within the UK. The hospital provides the surrounding district general hospitals with specialist services. Many of the consultant staff continue to hold appointments that are linked to both general hospitals, the UCL Institute of Neurology and The National itself. This maintains unique contact between the disciplines of research and clinical practice.

Neurology: A Queen Square Textbook

This book, the first of its kind to come from these two institutions, has a distinctly clinical flavour. It has been written very largely by clinicians, each in the forefront of their field, and focuses on the practical aspects of diagnosis, treatment and patient care. The book also provides an introduction to the basic sciences of neurology, of increasing importance in medical practice. It has been a pleasure to be one of the contributing authors.

Professor Roger Lemon PhD FMedSci
Sobell Chair of Neurophysiology & Director, UCL Institute of Neurology (2002–2008)

Foreword to the Second Edition

I am delighted to be asked to celebrate the publication of this second edition of *Neurology: A Queen Square Textbook*. When I first learnt about this project some 10 years ago I had some misgivings – it seemed to me that neurology had become so specialised that it would be difficult to assemble a coherent book that spanned the whole of the field. I am glad to have been proved wrong, for this work really does encompass the scope of neurology in the twenty-first century.

In the past, neurologists by and large dealt with *all* neurological conditions; today specialisation has taken over and to be a neurologist without a special interest is a rarity. It is thus fitting that the four editors combine vast and broad clinical experience with specialist academic expertise. From the National Hospital for Neurology & Neurosurgery, Charles Clarke, who was the driving force behind the initiation of the project over 10 years ago, is a general neurologist, much of whose work has been in UK district general hospitals. He prides himself on being a 'general practitioner of practical neurology'. His colleague Robin Howard, who works jointly at St Thomas' Hospital in London and the National, is also a highly experienced general neurologist; his specialist interests are intensive care neurology and neuromuscular disease.

From the UCL Institute of Neurology, Martin Rossor has developed his interests in cognitive impairment to establish a unit in Queen Square specialising in dementia, a subject of major importance, long neglected. Simon Shorvon has been consultant neurologist at the hospital since 1983; his specialist expertise is in epilepsy, a field in which he has an international reputation.

This book epitomises this combination of practical experience and academic specialisation, and collaboration between institute and hospital, where as part of our daily workload we continue the tradition of teaching, both as a national centre and internationally to Queen Square postgraduate students from all over the world.

The editors and the authors are experienced and distinguished writers who have devoted time to draw together their practical experience. Each chapter has been carefully edited, so essential for a good finished product. I know that this book has been produced within an atmosphere of cordiality and friendship. The text reflects this.

Here, even at a glance, the reader can understand how large a subject neurology has become and how scientific advances, many pioneered within the UCL Institute of Neurology, have become translated into clinical practice. One can find here well-illustrated neuroanatomy, detailed assessments of common conditions such as stroke and dementia, up-to-date aspects of neurogenetics and ion channels, the philosophy and practicalities of rehabilitation, and rarities such as metabolic disorders of copper, unusual muscle diseases or little-known varieties of headache.

As a measure of its authority, *Neurology: A Queen Square Textbook* has become a standard text for the UK neurologists-in-training exit examination. It is already over 5 years since the first edition was published and while neurology and neuroscience continue to advance, I fully endorse the move to complete this new edition without delay.

> A man would do nothing if he waited until he could do it so well that no one could find fault in what he had done.[1]

This book to my mind really does achieve its purpose and, like my predecessor Roger Lemon, I am delighted to be a contributing author.

Professor Michael Hanna MD FRCP
Professor of Clinical Neurology
Director, UCL Institute of Neurology

1. John Henry Newman, a nineteenth-century English clergyman.

Preface

All Editors, Authors and Specialist Advisory Editors of *Neurology: A Queen Square Textbook* hold or recently held consultant or equivalent posts at the National Hospital for Neurology & Neurosurgery and/or the UCL Institute of Neurology, Queen Square.

The National Hospital is part of University College London Hospitals NHS Foundation Trust, and the Institute of Neurology part of University College London.

Twenty-three Co-ordinating Authors organised individual chapters, encouraged and liaised with over 70 contributors and with them wrote this book.

The Specialist Advisory Editors gave invaluable advice and guidance in their respective fields. To ensure a worldwide perspective, for the first edition our International Regional Editors, all of whom had close connections with Queen Square, provided guidance and comment.

This book is an attempt to provide a fresh and up-to-date approach to the fascinating subject of neurology. We encouraged each author to relate their own clinical experience but, in order to achieve a degree of consistency, we took a robust overview of the important specialities within neurology and their relevance. Each chapter has been coordinated by an expert in the field, to give the reader an overall grasp of each major subject, indicating where developments within neurosciences fit into a broader picture.

On spelling and use of the English language, whilst appreciating that as a living, multicultural tongue there are wide varieties, we have opted for British English – the sort of way we write our letters, and continue to spell 'neurone' with its terminal -e. On medical conditions named after famous figures, we appreciate that many publishers no longer use the apostrophe to describe the disease named after Alzheimer, Wilson, Parkinson and so on. Our authors by and large did not follow this; thus we have left matters much as they signed off their chapters.

The limited size of this book means that it has not been possible to provide references for all material. With the growth of information technology, a wealth of detailed sources is readily available.

We are most grateful to all those who have helped in this joint venture.

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Acknowledgements

We know that the skills of clinical practice are handed down, both by teachers and role models. The editors wish to thank all those who have taught, advised and inspired them in many aspects of neurology and its related disciplines, in neuroscience and in research. When we came to list these many individuals, we soon realised we would be unable to mention each by name. Instead, we trust that all who read this book will understand how much the editors and authors owe to others. We hope we can pass on that knowledge and experience.

We thank those who contributed to the first edition and have moved on, reflecting for most retirement, promotion or in the case of Philip Lee, his death at an early age. Those contributing to the first edition were Peter Brown, Adrian Casey, Sohier Elneil, Clare Fowler, Richard Frackowiak, Peter Goadsby, Andrew Lees, Giovanna Mallucci, Jon Marsden, Geoffrey Raisman, Mary Robertson, Geoffrey Schott, Anette Schrag, Susan Short, Shelagh Smith, David Thomas, Emma Townsley, Michael Trimble and Gelareh Zadeh. Each made a valued contribution.

We thank our publishers, Wiley Blackwell, and especially Rob Blundell, Claire Bonnett and Nick Morgan, as well as Kathy Syplywczak and Jan East for their unstinting patience.

The authors have worked hard and provided the substance of the book, for no personal reward and, despite numerous requests for text, diagrams and amendments, have remained firmly behind this project. We are most grateful to all who have contributed.

Secretarial help has been invaluable, and amongst those who have contributed over and above their normal duties, we thank especially Claire Bloomfield and Wyn Jagger.

The Rockefeller Library provided its valuable resources, both historical and current. The Audio Visual Services Unit was most helpful with the sourcing of some figures and photographs.

Royalties from *Neurology: A Queen Square Textbook* pass directly to The National Brain Appeal (National Hospital Development Foundation), the registered UK charity (No. 290173) that supports projects at Queen Square.

Charles Clarke
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June 2016

CHAPTER 1

Neurology Worldwide: The Epidemiology and Burden of Neurological Disease

Simon Shorvon
UCL Institute of Neurology

Neurological disease casts a heavy shadow over the lives of the patient, their family and friends and over society. In a recent survey, in Europe about one-third of all burden of disease was caused by brain disease – 23% of the years of healthy life is lost (YLL), 50% of years lived with disability (YLD) and 35% of disability-adjusted life years (DALYs). The aim of all neurological services must be to alleviate the suffering associated with the disease, and to realise this aim the rational planning of such health services requires epidemiological knowledge in five broad areas:

1. Epidemiology of the condition – its frequency and distribution within a population, its causation, mortality and co-morbidity.
2. Broad impact of the disease (the 'burden of illness') on individuals, families, health services and societies and also its financial cost.
3. Effectiveness and cost-effectiveness of diagnosis, investigation and treatment.
4. Existing health care resources – their distribution and priorities, and the potential for prevention.
5. Prognosis and outcome, via cohort studies and case–control studies.

The last three areas are outside the scope of this chapter; here an overview of selected issues related to the epidemiology and burden of neurological illness is given and, as this book is based on practice at Queen Square, here too I emphasise studies from the National Hospital for Neurology and Neurosurgery and the UCL Institute of Neurology. These set the scene for the more detailed consideration of neurological disease contained in the rest of the volume.

Epidemiology of neurological disease

It is self-evident that knowledge of epidemiology is important to underpin any decision about the provision of health care resources. It is also clear that epidemiological data (on frequency, distribution, mortality, etc.) are of little practical value unless related to an intervention or therapeutic advance. Sadly, however, in practice, even where reliable data exist, these are used only inconsistently in planning health care. Neurological disease is one example of this depressing fact, for the amount of education and expenditure is far below its estimated impact. In many, indeed perhaps most, health care settings, the provision of facilities for neurological care is often surprisingly fragmented and inappropriately targeted, even where, as in the United Kingdom, there is a nationwide health service.

Frequency and distribution of neurological disease

Incidence and prevalence rates are the most common measures of frequency used in medicine.

Incidence is a measure of the rate at which new cases occur in a specified population during a specified period. The incidence rate is usually calculated as the number of new cases occurring per 100 000 of the general population per year.

Prevalence is defined as proportion of a population that are cases at a point in time. The prevalence rate is usually calculated as the number of existing cases per 1000 of the general population. Point prevalence is calculated as the number on a particular day (prevalence day) and period prevalence is calculated as the number in a population over a specified period of time. Lifetime prevalence is defined as the risk of acquiring the condition at any time during life and is another important figure.

For many neurological diseases, information on even these basic measures is incomplete. Furthermore, the frequency of many neurological disorders varies markedly in different geographical regions, differs in urban when compared with rural settings, may differ with ethnicity, and is often linked to lifestyle and socioeconomic factors.

In most neurological illnesses there are also striking differences in frequency at different ages, and so the age distribution of the population will affect the frequency, and some diseases have marked gender differences. For these reasons, age-specific or sex-specific rates, or frequency estimates in restricted age ranges, are generally more informative than crude rates. For instance, the annual incidence of stroke in a general population is about 190/100 000/year, but in the population over 65 years the rate is 1100/100 000/year. Similarly, the incidence and prevalence of Parkinson's disease in the general population are 20/100 000/year and 2/1000, and in those over 65 years are 160/100 000/year and 10/1000.

Changes in age structure in populations will impact on the number of patients with neurological diseases that have age-specificity. In most developing countries, the population has a far greater proportion of children and young adults than in developed countries. Figure 1.1 shows age structures in a typical developed (Sweden) and

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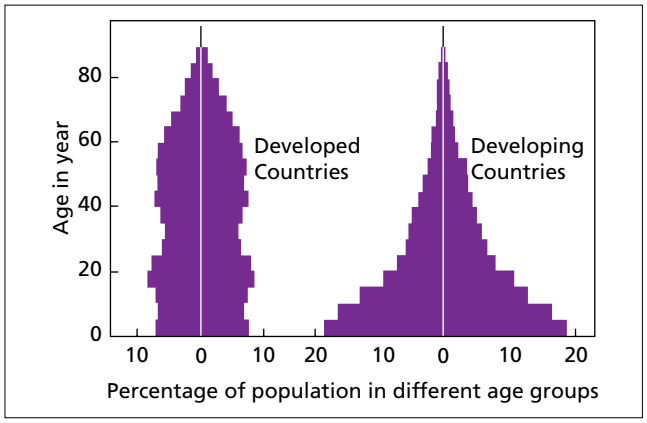

Figure 1.1 Age structure in developed and developing countries.

developing country (Costa Rica). However, globally, the number of people over the age of 65 years is estimated to double by 2030 and so the number of people with degenerative neurological disease is rapidly increasing. It is also important to recognise that although worldwide human populations are growing in an exponential fashion, growth rates vary widely among different countries and regions and the concept of 'doubling time' is a useful way of quantifying this. Doubling time – the time it is predicted to take for a population to double in size – depends not only on population size and mortality rates, but also on the number of children per woman (Table 1.1) and other social and health care parameters.

The approximate non-standardised figures for the prevalence and incidence of neurological disorders in a developed country are shown in Table 1.2. This table illustrates another important point – that for chronic diseases, as are many neurological diseases, the incidence rates may be low but the prevalence rates are high. This is important for health service planning, as the facilities required for incident cases are very different from prevalent cases. The former require provision for investigation and acute therapy and the latter largely for follow-up, social care, long-term therapy and rehabilitation.

The results of age-adjusted incidence and prevalence figures in a population of 100 230 persons in a selection of general practices served by the National Hospital for Neurology and Neurosurgery, London, from a research project published by the author in 2000 are shown in Tables 1.3 and 1.4. The incidence rates of 625 neurological disorders during a single year of observation were reported. Six per cent of the population in whom lifetime prevalence was surveyed had had a neurological disorder. In the United Kingdom, diseases of the nervous system accounted for 7.6% of all GP consultations between 1981 and 1982. The frequency of disability in private households amongst those over 16 years of age in the United Kingdom in 1971 was comprehensively delineated in the Harris Report in 1971. Disabilities relevant to neurology – CNS disorders, muscular dystrophies, congenital malformations of the spine and hydrocephalus, cerebral birth injury, senility as a cause of cognitive disability – occurred with a prevalence of 78/1000. The UK Office for Population Censuses and Surveys (OPCS) survey of disability 16 years later graded disability according to severity as well as overall frequency. The prevalence of complaints relevant to neurology was 13% for 'CNS disorders', 2% each for dementia and mental retardation, and 6% for back complaints. In a later study, 'CNS complaints' accounted for 7% of disability overall but for 16% of conditions with a high severity score. Roughly similar figures are found elsewhere. Population-based estimates from the United States, for instance, report point prevalence rates of neurological conditions (excluding headache, back pain and discs, mental retardation, psychosis, non-neurological visual and hearing loss and nervous system trauma) of 36/1000.

Ethnic differences in disease were shown by Stewart *et al.* in 1999 who studied stroke in a multi-ethnic region of London. A stroke register was used with 12 sources of case ascertainment. The population size was 234 533 with 72% Caucasian, 21% black (11% Afro-Caribbean, 7.5% West African and 2.5% mixed) and 3% South Asian. Incidence rates were standardised for age and sex. The crude annual

Table 1.1 Population size in selected developing and developed countries – doubling time.

Country	Approximate population size (millions)	Fertility (mean number of children per woman)	Doubling time* (years)
Yemen	15	7.2	20
Nigeria	107	6.2	23
Pakistan	138	5.6	25
Iran	68	4.7	26
Philippines	73	4.1	30
Mexico	95	3.1	32
Bangladesh	122	3.6	35
India	970	3.5	36
Brazil	160	2.5	48
China	1236	1.8	67
USA	268	2.0	116
France	59	1.7	204
Japan	126	1.5	289
UK	60	1.7	433
Italy	57	1.2	NPG
Germany	82	1.3	NPG
Russia	147	1.3	NPG

NPG, no population growth.
*Doubling time is the predicted time it will take for the population to double in size. The doubling time depends on population size, age structure, number of children per women and mortality rates. These figures were taken from the Population Reference Bureau, and predate improvements in child health, reductions in mortality rates amongst children and young adults and the HIV epidemic.

Table 1.2 Annual incidence and point prevalence figures of common neurological disorders. The table includes only those conditions with an incidence above 1/100 000/year; whole populations considered, without age standardisation, and excludes shingles.

Disorder	Incidence (per 100 000 persons/year)	Point prevalence (per 100 000 persons)
Migraine	370	12 100
Acute stroke	190	900
Epilepsy	50	710
Febrile convulsions	50	
Dementia	50	250
Chronic polyneuropathy (all types)	40	24
Transient ischaemic attacks	30	
Bell's palsy	25	
Parkinson's disease	20	200
Meningitis	15	
Subarachnoid haemorrhage	15	
Metastatic brain tumour	15	
Primary brain tumour	5	6
Trigeminal neuralgia	4	1
Multiple sclerosis	4	90
Motor neurone disease	2	4
Acute post-infectious polyneuropathy	2	1
All muscular dystrophies	1	6

Source: data derived from Kurtzke 1982; Hopkins 1993; Zakrzewska and Hamlyn 1999; Hughes 2002; Hirtz *et al*. 2007.

incidence rate of stroke was 130 (120–141)/100 000/year and the age-adjusted rate (to a standard European population) was 125 (115–135)/100 000/year. The rate in the black population was significantly higher with an incidence rate of 221 (177–276)/100 000/year. The rate, not surprisingly, increased with age. The study also looked at social class and found higher rates in those less than 64 years in lower social classes. This sort of study generates hypotheses about causation (as yet not explained) and provides data for rational health care planning (partially implemented).

Table 1.3 The National Hospital for Neurology and Neurosurgery (NHNN) record linkage study: age- and sex-adjusted incidence rates for neurological conditions (MacDonald et al. 2000) compared with previously reported rates.

Conditions	NHNN linkage study: age- and sex-adjusted rate (95% CI)/100 000/year	Previously reported incidence rates/100 000/year
Stroke		
First cerebrovascular episode	205 (183–230)	200
Second cerebrovascular episode	42 (33–55)	28–35
Intracranial haemorrhage	10 (5–17)	5% of stroke, i.e. 10
Seizure disorders		
Epilepsy	46 (36–60)	24–53
Single seizures	11 (7–18)	20
Tumours		
Primary CNS tumours (benign and malignant)	10 (5–18)	7; 15
Parkinson's disease	19 (12–27)	12–20
Compressive mononeuropathies – all except carpal tunnel syndrome (CTS)	49 (39–61)	40
Arm – all excluding CTS	24 (17–33)	
Leg – all	20 (14–29)	
Polyneuropathies		
Diabetic polyneuropathy	54 (33–83)	40
All excluding diabetic and alcoholic	15 (9–23)	11
Shingles	140 (104–184)	71; 131; 400; 480
Other conditions		
Post-herpetic neuralgia	11 (6, 17)	13; 34; 9% of shingles
Bacterial CNS infection (overall)	7 (4–13)	10; 11
Essential tremor	8 (4–14)	24
Trigeminal neuralgia	8 (4–13)	2; 4

(continued)

Table 1.3 (continued)

Conditions	NHNN linkage study: age- and sex-adjusted rate (95% CI)/100 000/ year	Previously reported incidence rates/100 000/ year
Benign CNS tumour	7 (3–13)	10
Multiple sclerosis	7 (4–11)	2–8
Traumatic brain injury	7 (3–12)	4–6
Subarachnoid haemorrhage	7 (3–12)	10–15
Subdural haematoma	6 (3–12)	
Cluster headache	6 (3–10)	6–14
Cranial nerve disorder (excluding II, III, IV, VI, Bell's palsy or trigeminal neuralgia)	6 (2–10)	

Note: Other conditions that were encountered in the study, but which occurred with an incidence of 1–5/100 000: aseptic meningitis, metastatic CNS tumour, presenile dementia, neonatal encephalopathy, other congenital CNS abnormalities, brachial neuritis, Guillain–Barré syndrome, myasthenia gravis, primary malignant CNS tumour, transient global amnesia, spinal cord injury, acute cervical myelopathy, cranial nerve injury, demyelinating conditions (excluding MS), HIV encephalopathy, idiopathic myelopathy, motor neurone disease, spondylitic myelopathy, truncal mononeuropathy, diabetic amyotrophy, focal dystonia, non-cervical disc or cada equina damage, optic neuritis, spinal malformation.
In addition, a small number of cases of the following diseases were also found in this study: cerebellar degeneration, dementia of uncertain cause, frontal dementia with anterior horn cell disease, neurosarcoid with cord involvement, neurofibromatosis, tuberous sclerosis, communicating hydrocephalus, aqueduct stenosis, cerebral cyst, tonsillar herniation with Chiari malformation, syringomyelia, myotonic dystrophy, myositis, idiopathic neurogenic bladder, tubercular meningitis, meningococcal meningitis, syphilis, streptococcal meningitis, *Streptococcus pneumoniae* brain abscess, *Listeria* meningitis, cryptococcal meningitis, and an unidentified ventriculitis.

The collection of epidemiological statistics relating to neurological disorders is difficult; existing figures are probably underestimates and most biases lead to under-ascertainment. Such issues apply to epidemiological studies in all areas, but in addition to the varied general issues there is a particular problem for neurology that requires mention. This is the difficulty of 'case definition' (and thus case ascertainment). Many neurological disorders are defined on clinical criteria, with the inevitable subjectivity this entails. Thus, boundaries exist in which symptoms are occurring without formal diagnosis – for instance, the boundaries between ageing and Alzheimer's disease and between chronic headache and migraine. Similarly, in epilepsy, the inclusion of febrile seizures, single seizures and acute symptomatic seizures within a definition of epilepsy will more than double the apparent incidence rates. In neurological disorders that are only mildly symptomatic in their early stages, such as migraine, some neuropathies, some dementing illnesses and Parkinson's disease, only 'the tip of the iceberg' cases are known to health care professionals. Severity also varies markedly in many neurological conditions, and the inclusion of mild cases will lead to high prevalence rates with relative little impact on burden of illness. Studies of epilepsy from the National Hospital provide examples of this – with over 60% of patients with epilepsy entering long-term remission and thus having only a minor impact on health services. However, any method using hospital statistics will greatly underestimate the true number of cases as many minor or static neurological conditions are cared for outside the hospital setting. Case finding methods also need to be tailored to the disease's spectrum of severity and frequency.

Similar considerations apply when considering rarer conditions, especially those requiring complex medical care where a sound estimate of frequency is important. A study of the prevalence and causation of dementia in those under 65 years, carried out by Harvey *et al*. in 2003 in West London, is one example. In this population of 567 500 people, the prevalence of dementia in those aged 30–64 years was 0.54/1000 (0.45–0.64). For those aged 45–64 years, the prevalence was 0.98/1000 (0.81–1.18). From the age of 35 onwards, the prevalence of dementia was found to approximately double with each 5-year increase in age. On the basis of these figures, it was estimated that in 2003, there were 18 319 (15 296–21 758) people with dementia under the age of 65 in the United Kingdom. Using diagnostic algorithms, 34% had Alzheimer's disease, 18% vascular dementia, 12% frontotemporal dementia, 7% dementia with Lewy bodies and 19% had other causes which included Huntington's disease, multiple sclerosis, corticobasal dementia, prion disease, Down's syndrome (probably underestimated), Parkinson's disease and others.

Neurology is also distinguished from other areas of medicine by the large number of uncommon conditions within its purview (neurology has the highest number of conditions listed in the International Classification of Diseases), and therefore large populations must be studied to obtain accurate population-based data with appropriate statistical reliability. Sampling error increases with rarer events and for many of the uncommon neurological diseases there are few reliable data.

From the perspective of health services, figures of prevalence and incidence of the cases receiving treatment are important, as it is these cases that consume resources, not untreated (usually mild) or cases before diagnosis. In 1998, a large study of epilepsy was published by Wallace *et al*. amongst a population of 2 052 922 persons in England and Wales of the numbers with epilepsy receiving antiepileptic drugs. This provided accurate age-specific rates shown in Figure 1.2.

Causation

Epidemiological studies are also vital for studying the causes of disease. The attribution of causation to neurological disease is rarely a simple matter. Most neurological diseases are multifactorial in nature, being the result of complex interactions between genetic and environmental influences. The balance between the two varies. The genetic influences can be very strong – for instance, in single gene disorders with high penetrance (e.g. Huntington's disease). In others the genetic influence is the result of more complex epigenetic and epistatic interactions (e.g. epilepsy), and in other diseases identifiable Mendelian genetic influences do exist but are seen in some families cases only (Alzheimer's disease for instance is familial in about 10% of cases). The environmental influences are predominant in many diseases, for instance head injury or cerebrovascular disease. An interaction between genetic and environmental factors occurs in other diseases, for instance

Table 1.4 The National Hospital for Neurology and Neurosurgery record linkage study: 'lifetime prevalence' of neurological conditions (MacDonald et al. 2000) compared with previously reported rates.

Conditions	'Lifetime prevalence'/1000 population (95% CI)	Previously reported point prevalence (PP) rates/1000
Stroke	9 (8–11)	5
Transient ischaemia	5 (4–6)	2; 6
Epilepsy	4 (4–5)	5
Congenital neurological deficit	3 (3–4)	3, 2/1000 between 7 and 10 years; CNS malformation 0.7, Down's syndrome 0.5
Parkinson's disease	2 (1–3)	1; 2 (1); 2
Multiple sclerosis	2 (2–3)	1; 2
Diabetic polyneuropathy	2 (1–3)	3
Compressive mononeuropathies (except CTS)	2 (2–3)	0.4
Subarachnoid haemorrhage	1 (0.8–2)	0.5
Polyneuropathy (excluding diabetic and alcoholic)	1 (0.8–2)	0.4
Single seizures	1 (0.9–2)	
Bacterial meningitis	1 (0.8–2)	Abscess 0.02, meningitis 0.05
Other meningitis or encephalitis	1 (1–1)	
Aseptic meningitis	0.9 (0.6–1)	
Essential tremor	0.8 (0.5–1)	3 (1)
Polio	0.7 (0.4–1)	
Severe head injury	0.6 (0.4–1)	1
Optic neuritis	0.6 (0.3–1)	0.1
Benign CNS tumours	0.5 (0.3–1)	0.6 in brain, 0.1 in cord
Intracranial haemorrhage	0.5 (0.2–0.8)	

CTS, carpal tunnel syndrome; HTLV 1, human T-lymphotrophic virus type 1; MS, multiple sclerosis; PN, peripheral nerve.
'Lifetime prevalence' was here defined as a history of the condition at any point up until the survey in this population.
Note: Other prevalent conditions encountered in the study, which occurred with a prevalence of less than 0.5/1000 were: other movement disorders, viral encephalitis, spondylitic and compressive myelopathy, cluster headache, subdural haemorrhage, malignant CNS tumours, peripheral nerve or plexus injury, demyelinating condtions other than MS, cauda equaina lesions, dystonia, benign intracranial hypertension, myelopathy, spinal cord injury, narcolepsy, motor neurone disease, aqueduct stenosis and hydrocephalus in adults, HTLV myelopathy , transient global amnesia, mononeuropathy (excluding carpal tunnel syndrome), trigeminal neuralgia, post-herpetic neuralgia, muscular dystrophies, myasthenia gravis, eye-movement disorders, brachial neuritis, Guillain–Barré syndrome, Horner's syndrome, pupillary abnormalities, sacral plexitis/plexopathy.

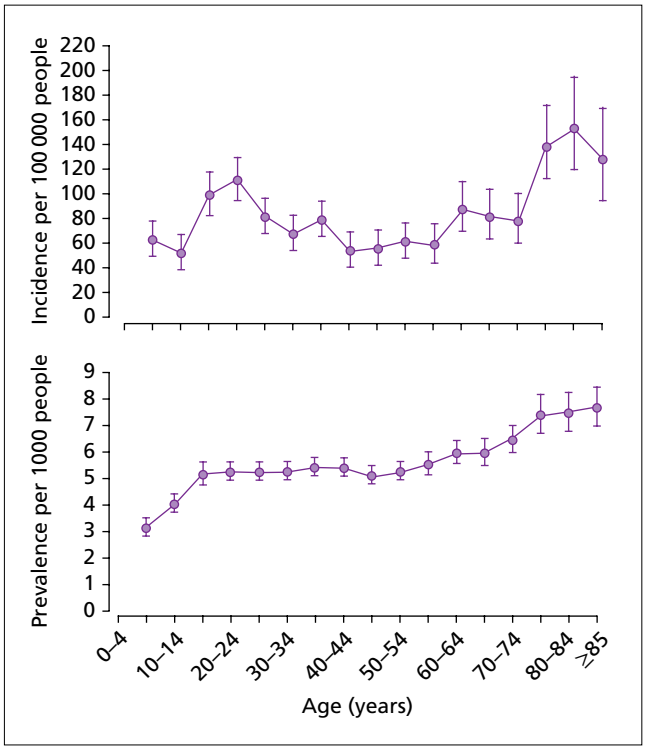

Figure 1.2 Standardised prevalence and incidence rates of treated epilepsy in a population of 2 052 922 persons in England and Wales in 1995. (Bars indicate 95% CI.) Prevalence of treated epilepsy: overall 5.15/1000 people (95% confidence interval [CI] 5.05–5.25) Source: Wallace *et al*. 1998. Reproduced with permission of Elsevier.

the interaction of smoking and genetic susceptibility in Parkinson's disease, or geographic location and genetic susceptibility in multiple sclerosis. The latter is an interesting example as there are often unexplained geographical variations which may reflect either environmental or genetic influences or both. In most neurological diseases, even the common diseases, the primary causes are not clearly understood. Factors which play a part in causation can be divided into the following:

- Predisposing factors (e.g. age, sex, genetic susceptibility);
- Enabling factors (e.g. poor nutrition, housing, inadequate medical care);
- Precipitating factors (e.g. exposure to infectious or noxious agent);
- Reinforcing factors (e.g. repeated or prolonged exposure).

It should be noted that the epidemiological approach to causation is very different from the laboratory approach which studies mechanisms. Cause and mechanism of disease are not necessarily the same (this was a distinction which Hughlings Jackson recognised in relation to epilepsy).

Most neurological diseases are the result of multifactorial causal influences, each of which on their own would not result in the disease, but together have resulted in the disease. In such multifactorial disease, it is often helpful to define 'risk factors' which can be defined as factors that are positively associated with the development of a disease but which on their own are not sufficient to cause the disease. Risk factor studies rely in particular on case–control methodologies, and these can give important clues as to relative importance of different risk factors. The use of hazard ratio (HR) and odds ratio (OR) calculations allow meaningful comparative statistics to be drawn up.

The value of risk factor analysis can be demonstrated by the example of epilepsy resulting from cerebrovascular disease. In one study, a history of stroke has been found to be associated with an increased lifetime occurrence of epilepsy (OR 3.3; 95% confidence interval (CI) 1.3–8.5). Among the other vascular determinants, only a history of hypertension was associated with the occurrence of unprovoked seizures (OR 1.6; 95% CI 1.0–2.4). The risk of unprovoked seizures rises to 4.1 (95% CI 1.5–11.0) in subjects having a history of both stroke and hypertension. Haemorrhagic stroke (subarachnoid haemorrhage and, to a lesser extent, primary intracerebral haemorrhage) are followed by a higher risk of seizures. The cumulative probability of developing seizures after a first stroke is about 6% after 1 year and rises to 11% at 5 years, with significant differences across stroke subtypes. A study by Cleary *et al*. in 2004 compared the frequency of stroke after the development of late-onset seizures, and found late-onset seizures to be a risk factor for stroke as important as high cholesterol or blood pressure. A total of 4709 individuals who had seizures beginning at or after the age of 60 years were compared with 4709 randomly selected matched controls with no history of seizures. Log-rank testing, adjusted for matching, showed a highly significant difference in stroke-free survival between the two groups (P <0.0001) and the relative hazard of stroke at any point for people with seizures compared with the control group was 2.89 (95% CI 2.45–3.41).

The Human Genome project also has added a new dimension to the study of causation of neurological illness, and will in the future also influence studies of the burden of disease. Over 200 Mendelian neurological conditions have been identified and here genomics has had a major impact in understanding the epidemiology and causal mechanisms of disease. Most such diseases are rare and it is clear that the genetic influence on the common neurological diseases is complex and may vary from population to population. To date, around 100 genome-wide association studies of common neurological diseases have been initiated. Eventually, it is to be hoped that such studies will provides estimates of disease heritability, provide unbiased populations for conventional disease-burden studies, and help define the clinical and therapeutic relevance of genetic variants.

The co-morbidities of neurological disease are another area in which risk factor analysis is revealing, but the nature of the association can be complex and not necessarily causal. Some of the causal influences on a disease may also be causal influences on co-morbidity – for instance, smoking resulting in vascular disease causing stroke also increases the risk of renal disease, and thus results in a non-causal association between renal disease and stroke. The treatments of some diseases also result in co-morbidities (e.g. behavioural effects caused by antiepileptic drugs) as does the social handicap of some neurological disorders. The psychiatric co-morbidity of cerebral neurological disorders is particularly complex with genetic, environmental, shared underlying causes and also treatment and direct cerebral damage all potentially contributing. Psychosis, depression and anxiety for instance occur much more frequently in patients with epilepsy than in matched non-epileptic persons, and the relationship of psychiatric disease and epilepsy has been shown to be 'bidirectional'. One explanation of such a bidirectional relationship is that both conditions share risk factors, and particularly genetic risk factors, and several recent studies have found the same copy number variations (CNVs) in epilepsy, autism, schizophrenia, mental retardation and attention deficit hyperactivity disorder.

Mortality

The mortality rate of any condition is defined as the number of persons with that condition dying during a specified period divided by the number of persons in the same population. This information is of limited value, particularly in chronic neurological disease, without a knowledge of the underlying rate of death in patients without the condition or of age distribution. Therefore, mortality is often expressed as the ratio between the observed and expected numbers of death – this measure is known as the standardised mortality ratio (SMR). Expected deaths are calculated by measuring the death rates of a reference population with an age distribution that is similar to the study population. When there is no difference in mortality between the study and reference population the SMR is 1. The 95% CI provides an estimate of the significance of the calculated SMR. Another useful measure is the proportional mortality ratio, which is the percentage of deaths that are due to any one cause. Life expectancy, defined as the median survival, is linked to age and is often lowered in neurological disease when compared with a healthy population, but statistics are complex to derive and there are few studies of this in neurological disease.

Taking epilepsy as an example, in a UK cohort study, reported by Gaitatzis *et al.* in 2006, we followed a cohort of 564 newly diagnosed cases of epilepsy for 11–14 years and found an overall SMR of 2.1 (95% CI 1.8–2.4). The study also calculated the hazard ratio (HR), or risk of mortality in a particular group with a particular risk factor compared with another group without that particular risk factor. For epilepsy overall, it was 6.2 (95% CI 1.4–27.7; $P = 0.049$). Rates varied with the cause of epilepsy: cerebrovascular disease (HR 2.4; 95% CI 1.7–3.4; $P < 0.0001$), CNS tumour (HR 12.0; 95% CI 7.9–18.2; $P < 0.0001$), alcohol (HR 2.9; 95% CI 1.5–5.7; $P = 0.004$) and congenital neurological deficits (HR 10.9; 95% CI 3.2–36.1; $P = 0.003$). An older age at the time of diagnosis was also associated with significantly increased mortality rates (HR 1.9; 95% CI 1.7–2.0; $P < 0.0001$). Life expectancy has also been calculated in the same population based on the Weibull distribution. This depends on age at time of diagnosis and aetiological group, and of course reductions in life expectancy diminish over time. In our study of epilepsy, overall reduction in life expectancy, at the time of diagnosis, was found to be up to 2 years for people with a diagnosis of idiopathic or cryptogenic epilepsy, and up to 10 years in people with symptomatic epilepsy.

Mortality rates can be a useful way of quantifying treatment, but it is equally important in some neurological conditions to consider quality of life. This was well shown in a study of survival after radiotherapy in patients with glioma by Davies *et al.* in 1996. Radiotherapy is known to prolong life if only to a modest extent (in one trial to 38 weeks with radiotherapy compared to 14 weeks with steroids alone). However, the side effects of radiotherapy can be severe, and the trade off between survival and quality of life is important to consider. It was found that the clinical status before radiotherapy was a good indicator of the duration of disability-free life after radiotherapy. The authors showed clearly that for those already disabled by the tumour, radiotherapy offered little physical gain and even if not severely disabled the treatment could cause severe adverse effects.

Other measures and rates

Other epidemiological measures and rates can be derived, for instance related to childbirth or co-morbidity, and are of importance in certain health care areas:

- *Birth rate* is usually defined as the number of live births per mid-year population;
- *Fertility rate* is usually defined as the number of live births per number of women aged 15–44 years;
- *Infant mortality rate* is defined as the number of infant (<1 year) deaths per number of live births;
- *Stillbirth rate* is defined as the number of intrauterine deaths after 28 weeks per total births;
- *Perinatal mortality rate* is the number of stillbirths + deaths in first week of life per total number of births.

Such epidemiological data can be used to investigate causation and assist prevention, but the issues are often complex.

This is well illustrated in a study of fertility in epilepsy amongst a general population of 2 052 922 persons in England and Wales, carried out from Queen Square and reported by Wallace *et al.* in 1998. Age-specific fertility rates were defined as the number of live births per 1000 women-years at risk, in each age category. Fertility was about 30% lower among women with treated epilepsy, with an overall rate of 47.1 live births per 1000 women aged 15–44 per year (42.3–52.2), compared with a national rate of 62.6 in the same age group. The standardised fertility ratios were significantly lower between the ages of 25 and 39 years in women with epilepsy ($P < 0.001$; Figure 1.3). The reasons for these lower rates are complicated. There are undoubtedly social effects: women with epilepsy have low rates of marriage, marry later, experience social isolation and stigmatisation. Some avoid having children because of the risk of epilepsy in the offspring, and some because of the teratogenic potential of antiepileptic drugs. Other patients have impaired personality or cognitive development. However, there are other biological factors that could lead to reduced fecundity. These include genetic factors and adverse antiepileptic drug effects. The lowering of fertility is a worrying finding which is another and important source of disadvantage for women with epilepsy. If there are potentially preventable causes, these should be sought.

Many neurological conditions take a chronic course, so long-term follow-up is important to our understanding of their prognosis and resource implications. Epidemiologically based prospective cohort studies are the optimal method of study to assess the full impact of the disease.

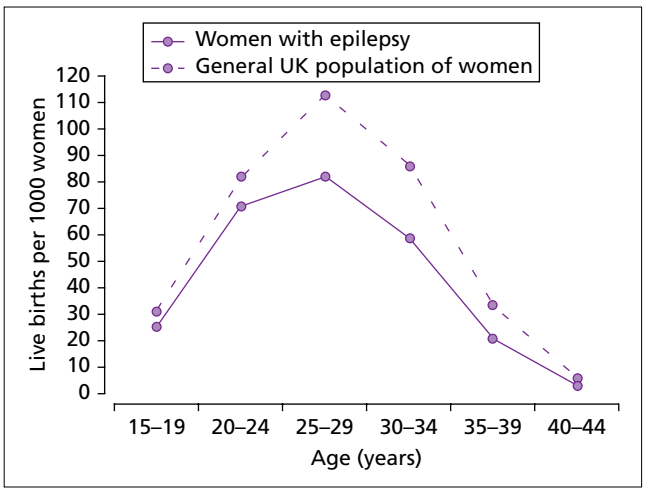

Figure 1.3 Comparison of age-specific fertility rates in women with treated epilepsy and general UK population of women in 1993 (study of a population of 2 052 922 persons). Source: Wallace *et al.* 1998. Reproduced with permission of Elsevier.

Burden of illness

Although the study of the epidemiology of disease provides figures on incidence, prevalence, risk factors and distribution within a population, such information is of limited practical value in terms of population health unless linked to a treatment (or prevention) programme and resource utilisation. A problem that lies at the heart of care provision is the need to focus interventions where needed.

Definitions

The words 'burden of illness' in their widest sense incorporate all negative impacts of illness, although they are often used to denote only the financial costs of illness where costs are understood to encompass the full social costs, both subjective hard to quantify elements as well as objective more easy to quantify measures. These cost of illness studies have the advantage of attempting to quantify a range of negative effects in monetary terms and thus allow comparisons to be drawn. Their disadvantages are obvious – notably the inherent inaccuracies and absurdities of trying to define quality of life issues in terms of monetary loss. Utility measures (e.g. quality-adjusted life years, QALYs, and disability-adjusted life years, DALYs) have also been derived to try to quantify burden more widely, and a particularly important project has been the Global Burden of Disease project sponsored by the World Health Organization (WHO) and World Bank. The burden of illness on individuals and on carers are not comprehensively accounted for in such studies which focus on broad categories biased towards societal and economic considerations.

Cost of illness studies

The principal concern of physicians is to provide individual care, but as health care costs are rising so fast, and even the richest economies are seeking to limit expenditure, clinicians are necessarily now involved in factoring in economic considerations when making therapeutic decisions. This has led to cost of illness studies, which although important are bedevilled with methodological problems that limit their usefulness and validity.

The perspective taken in the analysis is of primary importance in any study of cost of illness. The cost (and burden) for individuals has quite different parameters to the burden for families, for health services or for society in general. Most cost of illness studies are carried out from the point of view of society, with social costs estimated in terms of lost employment, lost productivity and premature death.

Costs are usually divided into two types: direct and indirect. In outline, the direct costs are defined as any resource utilisation required in the care of the illness. These include medical costs such as primary care, hospital outpatient, hospital inpatient, investigation, drugs and non-medical costs such as residential care, community care, training and rehabilitation. Indirect costs are defined as the costs resulting from lost economic production and include premature mortality, dependency, unemployment and underemployment. There are various categories of cost, and any comprehensive analysis should include opportunity costs and transfer payments. Estimation of indirect costs may use the 'human capital' approach which ascribes a monetary value to a person in terms of their potential productivity. In health economic analysis the willingness to pay approach has become popular, which defines costs in terms of how much a person would be willing to spend. This has the advantage of accounting for intangible as well as tangible effects. Both methods are difficult to carry out and both are open to a wide variety of biases and criticisms. With all neurological disorders, the indirect costs are greatly in excess of the direct costs. In one study of epilepsy in 1994, for instance, direct costs accounted for only 13% of all costs in spite of relatively narrow definition of cost.

There are four common methodologies for carrying out economic appraisal:

1. Cost minimisation analysis, which compares interventions where the outcomes are the same;
2. Cost-effectiveness analysis, where outcomes are compared using a single natural measure (e.g. in epilepsy, cost per 50% reduction in seizure frequency);
3. Cost–utility analysis, which is particularly useful for comparing costs between diseases, in which different outcomes can be accounted for and costs are compared in terms of their effects on a utility measure (e.g. the effect on QALYs);
4. Cost–benefit analysis, which measures outcome in terms of economic benefit – accounting for both direct and indirect costs. The latter analysis is the most comprehensive, but in neurology there have been few examples of robust cost–benefit studies. With the increasing availability of expensive therapies and investigations, however, there is a pressing need for good economic appraisal.

Ethical issues relate also to cost-effectiveness. The primary responsibility of a doctor is to the individual patient and not to society. Therapies which are not 'cost-effective' from the epidemiological or societal point of view, may be nevertheless beneficial in an individual – and here the societal and clinical perspectives may clash (indeed, many cultures that purport to put society before the individual usually apply hypocritically different standards to the rulers and the ruled). The impact of social policy, for instance in relation to financial benefits and social support, on the burden of illness is another area that can greatly influence the individual burden.

WHO burden of illness studies

In recent years, the WHO and World Bank have evolved a more comprehensive series of measures of the impact of disease. The best known are the QALY and DALY. The DALY uses a methodology that focuses on disability whereas the QALY focuses on quality of life. These were formidable efforts, involving the WHO in 40 person-years of effort and the collection of data on 483 separate sequelae in 107 diseases and 14 million death certificates. It has to be said, as will be quite obvious to all, that reducing the impact of illness into a one-dimensional measure presents as many methodological difficulties as do studies quantifying illness in monetary terms. The Global Burden of Disease study provides comparative statistics on the impact of disease from 107 countries. To what extent this effort is worthwhile, finally, in helping set priorities has been seriously questioned.

The DALY is an indicator that is most useful in making comparisons between diseases and between regions, and in Table 1.5 some comparative figures are shown for neurological and psychiatric disease. On the basis of this analysis, neuropsychiatric disease accounted for about 15% of the global burden of disease (and 34% of the global burden of disability). For instance, cerebrovascular disease accounts for about 10% of the global burden of neuropsychiatric disease, dementia 2% and epilepsy 1%.

A recent study of disease burden focusing on Europe showed that three of the five highest DALY scoring medical conditions were psychiatric or neurological (stroke, unipolar depression and dementias) and, furthermore, the greatest proportion of DALYs caused by neuropsychiatric diseases were in the highest income group of European countries.