

PREFACE

A Certain Kind of Wisdom

In Plato's *Apology*, the Greek philosopher Socrates is on trial to defend himself against the allegation of corrupting the youth of Athens. Socrates denies this charge and offers an alternate reason for why he is on trial. He explains, "[w]hat has caused my reputation is none other than a certain kind of wisdom. What kind of wisdom? Human wisdom, perhaps (*1*).” He proceeds to tell the story of his friend Chaerophon, who once asked the Oracle at Delphi whether there was anyone wiser than Socrates. The Oracle answered that there was not. Socrates did not agree and thought that he would try to prove the Oracle wrong. And so he set about seeking out Athenians with a reputation for wisdom in various regards in order to test their claims to knowledge through questioning. He discovered many with false claims to knowledge and none with genuine wisdom and ultimately concluded that he was the wisest. He reached this conclusion not because of any special knowledge he possessed that others did not, but rather because he recognized his own lack of knowledge and strived to learn more, while others thought that they were knowledgeable but were not.

Socrates' conclusion that there is wisdom in recognizing the limitations of accepted knowledge represents the motivation for this book. In the process of asking questions and delving into the neuromuscular literature in an effort to find answers, one is left with the impression that we know less about the diagnosis, treatment, and prognosis of a range of neuromuscular disorders than we perhaps realize. It is not expected that everyone will accept this premise, but *Neuromuscular Disease: Evidence and Analysis in Clinical Neurology* has been written as much for those who doubt this claim as for those who already accept it.

Although Socrates did not claim to be knowledgeable, he believed that knowledge could be acquired by engaging in a series of questions to test someone else's claim to knowledge. This method of enquiry, known as “Socratic dialogue,” entails a series of questions traded back and forth between the questioner and his interlocutor. Although this approach is not easily reproduced in written form, the present book employs a question–answer format in an effort to emulate the style (and, it is hoped, the effectiveness) of the Socratic dialogue.

Obstacles to Knowledge

If the first step to wisdom is the recognition that our knowledge is limited, then the second step requires discerning the reasons for this limitation. The answer seems to be that there are numerous obstacles to the acquisition of knowledge, including a relative paucity of high-quality evidence and difficulties that arise in the understanding and interpretation of the available evidence, as well as inadvertent misrepresentation of the published data.

Lack of High-Quality Evidence

In many instances, our collective lack of knowledge results from to a simple lack of good-quality data. For example, the lack of high-quality data is responsible for our uncertainty as to which patients, if any, will benefit from surgery for the management of cervical spondylotic myelopathy, whether steroids or other immunosuppressive therapy should be used to treat patients with ocular myasthenia gravis, what sort of immunosuppression is most appropriate for patients with vasculitic peripheral neuropathy, or what the indications are for surgical treatment of ulnar neuropathy at the elbow.

There are numerous reasons, many of them complex, for the paucity of high-quality evidence. In some instances, a particular treatment modality has become sufficiently well established that clinical equipoise no longer exists and so a randomized placebo-controlled trial cannot be justified. The use of steroids in the management of generalized myasthenia gravis is one such example. A second problem is that many individual neuromuscular disorders are quite rare, the consequence of which is that it is difficult for one (or even a selection) of neurologists to recruit sufficient number of patients with the disorder in question within a reasonable period of time to participate in a controlled trial. A third problem arises from the difficulty of marrying clinical practice and clinical research. The pressures of the daily practice of medicine frequently do not permit clinicians the luxury to gather the sort of detailed information in a scientifically rigorous fashion that will be required to reach unbiased conclusions.

Yet another reason relates to the limitations of clinical investigators' knowledge of study design. This is less of a problem for studies of therapeutic interventions because most investigators and clinicians are aware of the methodological advantages of the randomized controlled trial and recognize the limitations of other study designs such as case series, case-control, and cohort studies. But even within the realm of the randomized controlled trial, there are many aspects of study design, such as allocation concealment, patient and observer blinding, the proportion of patients who are lost to follow-up, and other sources of bias that often receive less attention. Limited knowledge of study design is an even greater problem for studies of diagnostic tests and prognosis. The STAndards for Reporting Diagnostic tests (STARD) initiative has recently drawn attention to the serious shortcomings in much of the literature on diagnostic studies, pointing out the importance of issues such as the use of a clearly identified and well established reference standard and the need for investigator blinding in the interpretation of the diagnostic test under investigation (2).

Inadequate Understanding and Interpretation of the Evidence

The basic tools of clinical research are founded on the principles of epidemiology and biostatistics and yet relatively few clinical researchers and even fewer clinicians have any formal training in the methodology of clinical research. This state of affairs has two unfortunate consequences. The first is that those who are engaged in clinical research often do not have the necessary skills to design and perform clinical studies that conform to the rigorous standards required in order to reduce random error and bias (systematic error). This issue is discussed in the previous section. The second consequence is that those who read the literature have limited ability to critically appraise publications and to discern the strengths and limitations of the studies being read.

Moreover, it is commonplace for people to skip over the methodology section of a paper (and perhaps even the results section as well) and to read only the introduction and

discussion. Frequently, the abstract of a paper is all that will be read. If the methods section of a paper is not read carefully, there is no chance that the reader will be able to discern the strengths and shortcomings of the study. The natural tendency to skip over the methodology section of a paper is fostered by the recent trend among journals (even prominent journals such as *Neurology*) to decrease the size of the font in which the methodology section is printed. These trends place a greater burden on journal editors and reviewers to carefully scrutinize manuscripts for methodological shortcomings and to insist that authors adequately address these issues. Unfortunately, this burden is not easily shouldered by reviewers because they too frequently lack any formal training in clinical research methodology. And there is covert pressure on authors to emphasize the strengths and to minimize the weaknesses of their studies in order to maximize the chances of publication in a reputable journal.

The result of all of this is that the published literature is often interpreted as providing evidence for some conclusion, when in fact this is not the case. Investigations of diagnostic studies are especially prone to this particular problem. Investigators frequently choose to study the utility of a diagnostic test in a population of subjects that is not representative of the patient population in which the test will be used. For example, many studies of the accuracy of single-fiber electromyography for the diagnosis of myasthenia gravis have examined patients who are already known to have myasthenia and have compared them with subjects who are known to be healthy or to have some other disease (3–6). Similarly, studies of the utility of nerve conduction studies for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have compared patients known to have CIDP with those known to have other diseases such as diabetic polyneuropathy or amyotrophic lateral sclerosis (7–10). Studies such as these provide estimates of the sensitivity and specificity of the test in question, but do not provide information about how useful the test will be in clinical practice because the positive and negative predictive values of the test will be determined by the pretest probability of disease, which is strongly influenced by the prevalence of the disease in the population in which the test is being used. A better approach is to evaluate the performance of a diagnostic test in the broader patient population in which the test will be used. Studies that only include subjects with already established disease as well as either healthy subjects or those with other diagnoses are susceptible to a form of selection bias known as “spectrum bias,” in which only a select component of the full spectrum of patients with the disease is studied. Such issues have historically been neglected and the result is that our knowledge of the accuracy of tests used in the diagnosis of neuromuscular disease is quite limited, even if not widely recognized.

Such problems are not restricted to studies of the accuracy of diagnostic tests. The literature is filled with case series (often mistakenly described as cohort studies) in which the clinical manifestations or clinical outcome of a group of patients with a particular disorder are described. These case series are most frequently based on patient populations seen in tertiary referral centers and so are less likely to be representative of the spectrum of manifestations of the disease that would be encountered in the general population. Very often, such case series do not include consecutive patients, further increasing the potential for selection bias. The result is that such studies do not provide meaningful information about the sensitivity of a particular clinical finding or the sensitivity of the results of a diagnostic study. Because these case series almost invariably include only patients who have the condition of interest (rather than all patients who were initially thought to possibly have the condition of interest), it is not possible to determine the

specificity of the clinical findings or results of diagnostic studies. The consequence of such methodological shortcomings is that much of the literature turns out to be not very informative and certainly not very scientific. To make matters worse, such studies are often mistakenly regarded as definitive.

Misrepresentation of the Evidence

There are a number of practices that have, albeit unintentionally, the consequence of providing misleading information about the available evidence. It is commonplace, for example, for authors to cite review articles rather than original data in referencing a particular claim. In researching the literature to write this book, I have frequently tried to track down the primary data that supports a particular claim, but have been frustrated to find that the reference cited to support the claim is a review article, which in turn references a review article or provides no reference at all. A related problem is that although an article with primary data is referenced, the primary data does not adequately support the claim that has been made.

The second practice, which is perhaps even more worrying than the first, is the publication of evidence-based guidelines that make statements or recommendations under the guise of being based on evidence but that, in reality, are based on very little (if any) real evidence. For example, the practice parameter published by the American Academy of Neurology recommends that percutaneous endoscopic gastrostomy (PEG) feeding tube placement should be performed before the forced vital capacity (FVC) falls to less than 50% of predicted (11). As discussed in much more detail in Chapter 5, the evidence does not really support this claim, and it is certainly the case that the quality of data cited by this practice parameter is sufficiently poor that some qualification of the recommendation to place a PEG before FVC falls to less than 50% would be in order. The evidence-based guidelines published by the American College of Cardiology regarding indications for pacemaker placement in patients with myotonic dystrophy are subject to the same criticism (12,13). These guidelines were revised and updated between 1998 and 2002, with the revised guidelines indicating that pacemaker placement should be considered in patients with myotonic dystrophy in the presence of even first or second degree heart block (13). Interestingly, the revised guidelines do not cite any new literature to support this new “evidence-based” recommendation.

The Goals and Scope of This Book

The goal of *Neuromuscular Disease: Evidence and Analysis in Clinical Neurology* is to review the literature with respect to the diagnosis, treatment, and prognosis of a range of neuromuscular disorders and to present a description, analysis, and discussion of the quality of this literature. The intention is not simply to provide the reader with an easy reference to the publications that are most clinically relevant to neurologists who evaluate and treat patients with neuromuscular disease. The intention is also to offer an analysis of the evidence in the form of a critique of study methodology such that the reader will be aware not just of the content of the literature but also of its quality. The hope is that the analyses presented will also help the reader to think more critically about the design of clinical research studies in general and to be more inquisitive about study methodology when reading and evaluating publications in the future.

The scope of *Neuromuscular Disease: Evidence and Analysis in Clinical Neurology* is fairly broad within the field of neuromuscular disease, but is by no means exhaustive.

It could not possibly be as extensive as many readers might like, given the space constraints of a book such as this. But an effort has been made to cover those neuromuscular disorders that the adult neurologist is likely to encounter in routine clinical practice. Almost without exception, individual chapters are devoted to particular disorders with relatively well defined etiologies whereas such syndromic diagnoses as brachial and lumbosacral plexopathy that are not unitary disorders have been excluded. Although it would be possible to review the literature pertinent to the diagnosis of these disorders, the specific treatment and prognosis will very much depend upon etiology. Similarly, disorders that manifest primarily in childhood, even if there is survival into adulthood (such as with the dystrophinopathies), have not been included.

Within each chapter, there are sections devoted to the diagnosis, treatment, and prognosis of the relevant neuromuscular disease. In order to mirror this individual chapter structure, introductory chapters describing the epidemiological and biostatistical principles relevant to diagnosis, treatment, and prognosis have been included.

There are several important differences between *Neuromuscular Disease: Evidence and Analysis in Clinical Neurology* and the systematic reviews published by the Cochrane Collaboration. First, although the chapters in this book are not as comprehensive as the Cochrane reviews, they do provide much broader coverage of individual diseases insofar as they focus not only on treatment, but also on issues related to diagnosis and prognosis. Second, because the methodology for meta-analysis of observational studies has not yet been adequately refined, the Cochrane reviews have focused almost exclusively on the content of randomized controlled trials (although data from observational studies are often included in the discussions that accompany the systematic reviews). This book considers evidence not only from randomized controlled trials, but also from observational studies. Some might be critical of the present work for this reason, but it is not possible to explore issues related to the diagnosis and prognosis of neurological disease without considering these other types of studies. *Neuromuscular Disease: Evidence and Analysis in Clinical Neurology*, therefore, should be seen as complementary to the systematic reviews that are published in the Cochrane Database of Systematic Reviews.

Conclusion

It is not only in the realm of neuromuscular disease that our knowledge is limited. The impediments to understanding that I have described are also relevant to a range of other disciplines within neurology. The hope is that this book will be the first in a series of books dedicated to an analysis of the evidence within a range of subspecialties within neurology. Already in preparation is a text devoted to the field of neuro-ophthalmology. The intention is that this book, and others that follow, will help to encourage the Socratic approach, and that this will lead to greater awareness of the limitations of our current knowledge. It is hoped that insight into the shortcomings of the available literature will provide a stimulus for further research to address the clinical questions that, until now, have remained unanswered.

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References

1. Plato. Apology, 360 BCE.
2. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Br Med J* 2003;326:41–4.

3. Kelly JJ, Daube JR, Lennon VA, Howard FM, Younge BR. The laboratory diagnosis of mild myasthenia gravis. *Ann Neurol* 1982;12:238–242.
4. Sanders DB, Howard JF. AAEE Minimonograph #25: Single fiber electromyography in myasthenia gravis. *Muscle & Nerve* 1986;9:809–819.
5. Oh SJ, Kim DE, Kuruoglu R, Bradley RJ, Dwyer D. Diagnostic sensitivity of the laboratory tests in myasthenia gravis. *Muscle & Nerve* 1992;15:720–724.
6. Milone M, Monaco M, Evoli A, Servidei S, Tonali P. Ocular myasthenia: diagnostic value of single fiber EMG in the orbicularis oculi muscle. *J Neurol Neurosurg Psychiatry* 1993;56:720–721.
7. van den Bergh PY, Pieret F. Electrodiagnostic criteria for acute and chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle & Nerve* 2004;29:565–574.
8. Nicolas G, Maissonobe T, Le Forestier N, Leger J-M, Bouche P. Proposed revised electrophysiological criteria for chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle & Nerve* 2002;25:26–30.
9. Haq RU, Fries TJ, Pendlebury WW, Kenny MJ, Badger GJ, Tandan R. Chronic inflammatory demyelinating polyradiculoneuropathy. A study of proposed electrodiagnostic and histologic criteria. *Arch Neurol* 2000;57:1745–1750.
10. Bromberg MB, Feldman EL, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy: comparison of patients with and without an associated monoclonal gammopathy. *Neurology* 1992;42:1157–1163.
11. Miller R, Rosenberg J, Gelinas D, et al. Practice parameters: the care of the patient with amyotrophic lateral sclerosis (an evidence-based review). *Neurology* 1999;52:1311–1323.
12. Gregoratos G, Cheitlin M, Conill A, et al. ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices: Executive Summary—a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). *Circulation* 1998;97:1325–1335.
13. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 Guidelines Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices—Summary Article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *J Am Coll Cardiol* 2002;40:1703–1719.

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