PART I

THE SEARCH FOR THE AETIOLOGY OF CHRONIC FATIGUE SYNDROME/ MYALGIC ENCEPHALOMYELITIS

One of the most striking contributions of Hippocrates is the recognition that diseases are only part of the processes of nature, that there is nothing divine or sacred about them. . . . [He] remarks that each disease has its own nature, and that no one arises without a natural cause.

— Sir William Osler (1849–1919)

Denn die einen sind im Dunkeln
Und die andern sind im Licht
Und man siehet die im Lichte
Die im Dunkeln sieht man nicht

There are some who are in darkness
And the others are in light
And you see the ones in brightness
Those in darkness drop from sight (1)

Bertholt Brect (1898–1956)

INTRODUCTION

When patients see their medical doctor, it is essentially a meeting between someone who is an expert on him- or herself and someone who is an expert on the management of current medical knowledge within the medical culture of a particular society. Patients have consciously studied themselves their entire lives. The medical doctor has studied medicine for six years and subsequently gained clinical experience. Usually the cooperative efforts between patient and doctor work out satisfactorily, especially when the patient's concerns are well understood by the doctor and the aetiology or effective treatment of the medical problem is well known.

Unfortunately, this is not always the case. When a patient feels ill to such an extent that her physical, social, and psychological functions are seriously impaired, seeing a doctor who understands nothing about the causes or treatment of the illness may be a rather nasty experience for both of them. (2–6) Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is an example of one such illness. (7,8)

---

1. Brecht B. Die Moritat von Mackie Messer, Die Dreigroschenoper. 1930 version [The Ballad of Mack the Knife, The Threepenny Opera]. Blitzstein translation 1954. In: Wikipedia, the free encyclopedia. December 1, 2013. http://en.wikipedia.org/wiki/Mack_the_Knife

2. Werner A, Malterud K. It is hard work behaving as a credible patient: encounters between women with chronic pain and their doctors. *Soc Sci Med* 2003;57:1409-19.

3. Deale A, Wessely S. Patient's perceptions of medical care in chronic fatigue syndrome. *Soc Sci Med* 2001;52:1859-64.

4. Åsbring P, Närvänen A. Ideal versus reality: physicians' perspectives on patients with CFS and fibromyalgia. *Soc Sci Med* 2000;57:711-20.

The legitimacy of CFS/ME has been questioned by many medical doctors and by the health care system. Three main reasons for this have emerged: lack of a consistent biological marker for CFS/ME, little or infinitesimal understanding about its aetiology and treatment, and the fact that those experiencing symptoms are more likely to be women. As a result, CFS/ME has been perceived as a somatization disorder. (9–12) It is unfair of the medical community, however, to disbelieve patients who are seriously debilitated, thereby belittling them, because of an insufficient understanding of the pathogenesis of their illness.

The insufficient understanding of the pathogenesis of CFS/ME has legitimized disbelief in the patients' descriptions of their disease and illnesses. Therefore, these patients much too often report being met with moralization and humiliation. Such attitudes are just as unhelpful to the patients as they are to the progress of medical science. The sole purpose of moralization has always been—and still is—to sustain the privileges of the ruling elite and to justify indifference to the problems of those who are disadvantaged.

The National Institute for Health and Clinical Evidence (NICE) published guidelines on the diagnosis and management of CFS/ME in 2007. (13) The Guideline Development Group (GDG) strove to reverse the condemnation of these patients and to promote a humanistic approach "with the patient's preferences and views firmly driving decision-making." Such an attitude should be a model for guidelines on the treatment of all patients with illnesses that are not understood by the medical community.

As stated by the GDG, "the aetiology of CFS/ME was outside the scope of this guideline," but it recognized—expressed with British understatement—"that research in this area would be very helpful" (p. 59). However, what patients with CFS/ME long

5. Schwenk TL, Marquez JT, Lefever RD, Cohen M. Physician and patient determinants of difficult physician-patient relationships. *J Fam Pract* 1989;28:59-63.

6. Nettleton S. "I just want permission to be ill": towards a sociology of medically unexplained symptoms. *Soc Sci Med* 2006;62:1167-78.

7. Söderlund A, Skoge AM, Malterud K. "I could not lift my arm holding the fork. . ." Living with chronic fatigue syndrome. *Scand J Prim Health Care* 2000;18:165-9.

8. Johnson H. Osler's web: inside the labyrinth of the chronic fatigue syndrome epidemic. iUniverse, 2006.

9. McWhinney IR, Epstein RM, Freeman TR. Lingua medica: rethinking somatization. *Ann Intern Med* 1997;126:747-50.

10. Thomas MA, Smith AP. Primary healthcare provision and chronic fatigue syndrome: a survey of patients' and general practitioners' beliefs. *BMC Fam Pract* 2005;6:49.

11. Undeland M, Malterud K. The fibromyalgia diagnosis—hardly helpful for the patients? *Scand J Prim Health Care* 2007;25:250-5.

12. Richman JA, Jason LA, Taylor RR, Jahn SC. Feminist perspectives on the social construction of the chronic fatigue syndrome. *Health Care Women Int* 2000;21:173-85.

13. National Institute for Health and Care Excellence (NICE). Clinical guideline CG53. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children. NICE, 2007. http://www.nice.org.uk/nicemedia/pdf/CG53FullGuidance.pdf

for more than anything else is knowledge about the aetiology and treatment of their disease. (14) Such research is lacking for a number of reasons:

1. CFS/ME is the least "prestigious" disease today (15) and hence of minor interest to the medical research community. The prestige of the medical researcher depends on the prestige of the fund-raisers and of the patients for whom the research is conducted.
2. CFS/ME mainly affects women. Their well-being is of less importance compared with that of men in nearly all cultures on earth. (16)
3. CFS/ME is not at all a spectacular disease because it does not take lives—it just takes the joy of life from people who are biologically alive. Patients with chronic non-malignant pain consider their health-related quality of life to be as poor as that of dying cancer patients (17), but the drama and attention of premature death are lacking.
4. CFS/ME is a costly disease, both for individual patients and for the nation (18,19), but such aspects are irrelevant when resources for medical research are distributed. Instead of asking which medical problems are causing the most disability and therefore need to be solved, the authorities ask who has demonstrated the type of excellence that shows they deserve to make a living in publicly funded medical research.
5. CFS/ME is neither a rare nor a genetic disease. If it were, this might compensate for the lack of spectacular attributes of the disease.
6. CFS/ME seldom affects affluent and powerful people, movie stars, or celebrities.

The aetiology of CFS/ME is unknown: whether it is physical, psychiatric, or—the hedging compromise—biopsychosocial (which is nothing more than an academic expression for lack of insight) remains controversial. When medical researchers resign from trying to unravel the biomedical aetiology of a disease, they concentrate on diagnostic criteria and illness management, an example of which is research in CFS/ME. Such approaches may be helpful, but are an unsatisfying substitute for genuine search into the aetiology of the disease.

Patients with CFS/ME, who are the real experts on themselves, consider the disease to be physical and not psychological. (20) They find it rather provoking

14. Söderlund A, Malterud K. Why did I get chronic fatigue syndrome? *Scand J Prim Health Care* 2005;23:242–7.

15. Album D, Westin S. Do diseases have a prestige hierarchy? *Soc Sci Med* 2008;66:182–8.

16. De Beauvoir S. Le deuxième sexe [The second sex]. Borde C, Malovany-Chevallier S, trans. Jonathan Cape, 2009 (original work published by Gallimard, 1949).

17. Fredheim OM, Kaasa S, Fayers P, Saltnes T, Jordhøy M, Borchgrevinck PC . Chronic non-malignant pain patients report as poor health-related quality of life as palliative cancer patients. *Acta Anaesthesiol Scand* 2008;52:143–8.

18. Reynolds KJ, Vernon SD, Bouchery E, Reeves WC. The economic impact of chronic fatigue syndrome. *Cost Eff Resour Alloc* 2004;2:4.

19. Jason LA, Benton MC, Valentine L, Johnson A, Torres-Harding S. The economic impact of ME/CFS: individual and societal costs. *Dyn Med* 2008;7:6.

20. Cornes O. Living with CFS/ME. *BMJ* 2011;342:d3836.

and insulting that the Medical Research Council in Great Britain has funded no biomedical research into CFS/ME for 30 years and that the rather limited resources spent on CFS/ME research have been used for a psychiatric approach. (21,22) The proposal of xenotropic murine leukaemia virus-related virus (XMRV) as a possible infectious cause of CFS/ME gave some patients hope for discovery of the biomedical aetiology of CFS/ME. (23) However, the finding was later disconfirmed, as it was probably due to contamination in the laboratory. (24–26) The fact that some patients with CFS/ME still cling to a dogmatic belief in XMRV probably reflects their wish for more research from a biomedical rather than a psychological approach. In their opinion, the aetiology of CFS/ME would have been known by now if serious efforts had been made. (21)

The enormous research endeavour to understand the aetiology of HIV/AIDS and to develop effective treatment for it in just two decades is impressive and demonstrates that fighting disease is possible if it is prestigious to do so and the research is properly funded. However, the endeavour to understand the aetiology of CFS/ME stands in glaring contrast to the efforts made to unravel the aetiology of HIV/AIDS.

The medical research community today seems to be characterized by defeatism regarding the idea of unravelling diseases whose aetiology is still unknown. A "baroque" style of research, which adds intricate detail to basic discoveries more often than it seeks new discoveries (27), has gained control of medical research. Among several reasons for this attitude, one of the most apparent is that most clinical medical researchers have gone into hiding from the everyday world of patients. (28) Ambition for increased professionalism and objectivity in modern medical research has displaced personal interaction with real patients. When researchers are protected from clinical encounters, it seems to be more important for research funding purposes to demonstrate certain types of personal excellence than it is to adhere to the genuine purpose and clinical relevance of medical research.

Another important reason for this defeatism in medical research may be that research funding is deadlocked in a model demanding "results," defined as "significant findings" and bibliometric parameters. When significant findings are requested, a hypothesis fishing industry is the result, which more or less consciously

21. Hawkes N. The dangers of research into CFS/ME. *BMJ* 2011;342:d3780.

22. Davis C. Let psychiatric and biomedical lobbies be heard equally. *BMJ* 2011;343:d4544.

23. Lombardi VC, Ruscetti FW, Gupta JD, Pfost MA, Hagen KS, Peterson DL, Ruscetti SK, Bagni RK, Petrow-Sadowski C, Gold B, Dean M, Silverman RH, Mikovits JA. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science* 2009;326:585-9.

24. Knox K, Carrigan D, Simmons G, Teque F, Zhou Y, Hackett J Jr, Qiu X, Luk KC, Schochetman G, Knox A, Kogelnik AM, Levy JA. No evidence of murine-like gammaretroviruses in CFS patients previously identified as XMRV-infected. *Science* 2011;333:94-7.

25. Paprotka T, Delviks-Frankenberry KA, Cingöz O, Martinez A, Kung H-J, Tepper CG, Hu WS, Fivash MJ Jr, Coffin JM, Pathak VK. Recombinant origin of the retrovirus XMRV. *Science* 2011;333:97-101.

26. Alberts B. Editorial expression of concern. *Science* 2011;333:35.

27. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's pharmacology. Churchill Livingston Elsevier, 2007.

28. Le Fanu J. The rise and fall of modern medicine. Carroll & Graf Publishers, 1999.

disregards its pitfalls. (29–32) And when bibliometrics are sought, defined as number of papers, citations, and impact factors, that is exactly what one gets. (33–36) When a high impact factor is the main goal of research, research becomes fragmented and short-lived. (37)

The correlations and "sterile observations" (38) produced by medical research fulfil the preferred requirement of our time to apply frequentist statistics and produce p-values, but such a focus is at least partly detrimental to substantial progress in medicine. The demand for significant results in medical research makes the risk of failure to answer a research question on the aetiology of a disease much too high to attract attention and funding. However, no matter how impressive the production of PhDs, medical papers, citations, and impact factors in thousands of medical journals may be (39,40), allowing it to displace the substance and clinical relevance of research efforts betrays clinicians' and patients' trust and expectations of medical research.

Furthermore, the academic system of reward and merit based on the number of papers and impact factors of the medical journals is, no matter how unintentional, a driving force for scientific misconduct, as clearly demonstrated by the disgraceful Sudbø case. (41) Rather than being simply a case of a "bad apple," this case probably unravelled a tiny tip of the iceberg of scientific misconduct. (42–44) Equally disgraceful is the Wakefield case (45,46), which probably led to a significant setback in the goal of eliminating measles from Europe by 2015. (47)

29. Dahl FA, Benth JS. Do split your epidemiological data. *Eur J Epidemiol* 2010;25:759-60.

30. Dahl FA, Grotle M, Benth JS, Natvig B. Data splitting as a countermeasure against hypothesis fishing: with a case study of predictors for low back pain. *Eur J Epidemiol* 2008;23:237-42.

31. Ioannidis JPA. Why most published research findings are false. *PLoS Med* 2005;2:696-701.

32. Ransohoff DF. Discovery-based research and fishing. *Gastroenterology* 2003;125:290.

33. Aksnes DW, Rip A. Researchers' perceptions of citations. *Res Policy* 2009;38:895-905.

34. Frey BS, Rost K. Do rankings reflect research quality? *J Appl Econ* 2010;13:1-38.

35. Sala SD, Brooks J. Multi-authors' self-citation: a further impact factor bias? *Cortex* 2008;44:1139-45.

36. Falagas ME, Kavvadia P. "Eigenlob": self-citation in biomedical journals. *FASEB J* 2006;20:1039-42.

37. Wang N-X. China's chemists should avoid the Vanity Fair. *Nature* 2011;476:253.

38. Bernard C. Introduction à l'etude de la médecine expérimentale, 1865 [An introduction to the study of experimental medicine]. Dover Publications, 1927.

39. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? *PLOS Med* 2010;7:e1000326.

40. Greenberg SA. How citation distortions create unfounded authority: analysis of a citation network. *BMJ* 2009;339:b2680.

41. Eaton L. Norwegian researcher admits that his data were faked. *BMJ* 2006;332:193.

42. Martinson BC, Anderson MS, de Vries R. Scientists behaving badly. *Nature* 2005;435:737-8.

43. Anderson MS, Ronning EA, de Vries R, Martinson BC. The perverse effects of competition on scientists' work and relationships. *Sci Eng Ethics* 2007;13:437-61.

44. Lock S, Wells F, Farthing M, eds. Fraud and misconduct in biomedical research. BMJ Books, 2001.

45. Deer B. How the case against the MMR vaccine was fixed. *BMJ* 2011;342:c5347.

46. Deer B. How the vaccine crisis was meant to make money. *BMJ* 2011;342:c5258.

47. EUVAC.NET. Measles surveillance annual report 2010. EUVAC.NET, 2011. www.euvac.net/graphics/euvac/pdf/annual_2010.pdf

Another motive for the lack of focus on research into the aetiology of chronic diseases is the enormously greater profits that are generated from treating biomarkers and surrogate end points compared with treating the fundamental causes of diseases. No matter how minimal or unproved the benefit of treating biomarkers might be, and regardless of the widening definitions of risk, the cost of drug prescriptions increases and so do the profits for drug companies. (48–50) The porous relationships between the drug industry, professional medical associations, the "indicator evaluation industry," and science promote the seductive assumption that improving a person's numbers will automatically improve their health. (51) No matter how much of a delusion the assumption proves to be, research in risk factors easily attracts funding compared with research into the aetiology of diseases.

Some years ago I had a consultation with a patient diagnosed with fibromyalgia who had severe pain. She was a widow with children under the age of 10 and had great problems coping with a strenuous life. She accused me, as a representative of the medical profession, of not finding out why she was ill. "Why don't you find out? There is something wrong and it is your job to find out." When I answered that it is the job of professional medical researchers, she asked: "Why don't they find out?" I remember that I felt somewhat uncomfortable because her accusation was not at all unreasonable. Even though most patients are characterized by resignation about their medically unexplained symptoms, the episode has been lurking in my mind for several years.

My subjective discomfort caused by the medical research community's lack of interest in diseases that are of vital importance to a vast number of debilitated patients, (52–55) the clinically purposeless search for correlations, (56) the fear of trying to unravel the aetiology of medically unexplained diseases, the disgraceful Sudbø case, (41) and the cover-up of the responsibilities of his co-authors (57) finally made me so indignant that during the summer of 2006, I decided to use my

48. Moynihan R. Surrogates under scrutiny. *BMJ* 2011;343:d5160.

49. Micheel CM, Ball JR, eds. Institute of Medicine. Evaluation of biomarkers and surrogate endpoints in chronic disease. National Academies Press, 2010.

50. Shaugnessy A, Slawson D, Lewis Barnett B. What happened to the valid POEMs? A survey of review articles on treatment of type 2 diabetes. *BMJ* 2003;327:266.

51. Greene J. Prescribing by numbers: drugs and the definition of disease. Johns Hopkins University Press, 2007.

52. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009;374:86-9.

53. Gross CP, Anderson GF, Powe NR. The relation between funding by the National Institutes of Health and the burden of disease. *N Engl J Med* 1999;340:1914-5.

54. Stuckler D, King L, Robinson H, McKee M. WHO's budgetary allocations and burden of disease: a comparative analysis. *Lancet* 2008;372:1563-9.

55. Perel P, Miranda JJ, Ortiz Z, Casas JP. Relation between the global burden of disease and randomized clinical trials conducted in Latin America published in the five leading medical journals. *PLoS ONE* 2008;3:e1696.

56. Getz L, Luise Kirkengen A, Hetlevik I. Too much doing and too little thinking in medical science! *Scand J Prim Health Care* 2008;26:65-6.

41. Eaton L. Norwegian researcher admits that his data were faked. *BMJ* 2006;332:193.

57. Report from the Investigation Commission appointed by Rikshospitalet-Radiumhospitalet MC and the University of Oslo January 18, 2006. June 30, 2006. http://www.rr-research.no/general/docs/ekbom/Report_Investigation_Commission.pdf

own intelligence (58) to try to understand the aetiology of CFS/ME. (59) More than 25 years of clinical experience in the same practice with patients who had CFS/ME had taught me that it definitely had to be some sort of physical disease and that the problem should be solvable.

METHODS

> In a classic paper on the natural history of disease, John Ryle (60) defined the cornerstones [of clinical research] as: observing, recording, classifying and analyzing. . . .
>
> Research based on these four cornerstones is within the reach of any family physician. The method is simple and straightforward. It can be done without big research grants, and it does not require knowledge of advanced statistics. (61)
>
> Ian R. McWhinney (1926–2012)

> General practice has four advantages as an environment for clinical research. First, for any disease, we see the whole range, from the mildest cases to the most severe, so we are in a position to give a fuller description than a referral clinic. Some diseases with low referral rates can be studied only in general practice. Second, because of our long-term relationships with patients, we can follow them for long periods and can obtain very complete follow up by using tracing strategies. Third, we are in position to add important contextual detail. Fourth, because we see the earliest stages of illness, we can describe its whole natural history, including all the circumstances surrounding its onset. (62)
>
> Ian R. McWhinney (1926–2012)

> At the early creative stage, our method does not have to fit into the pigeonholes developed for other disciplines. It does not have to be given a name. The main thing is that it should be true to the experience of family practice. If asked what your hypothesis is, we might say, "I don't know yet." If asked how we got our sample size, we might say, "I didn't. The sample is my patients with the condition I'm studying." Did I get ethical approval? "No, because I wasn't doing formal research. I was just trying to improve my usual care." (63)
>
> Ian R. McWhinney (1926–2012)

58. Heath I. Dare to use your own intelligence. *BMJ* 2008;337:a1319.

59. Spence D. We need ideas based medicine. *BMJ* 2009;339:b3432.

60. Ryle JA. The natural history of disease. Oxford University Press, 1936; pp. 1-23.

61. McWhinney IR. Why are we doing so little clinical research? Part 1: Clinical descriptive research. *Can Fam Physician* 2001;47:1713-5.

62. McWhinney IR. Why are we doing so little clinical research? Part 2: Why clinical research is neglected. *Can Fam Physician* 2001;47:1944-6.

63. McWhinney IR. Creativity in clinical research is alive and well in Canadian family practice. Do we know it when we see it? *Can Fam Physician* 2004;50:1194-6.

> An anticipative idea or an hypothesis is, then, the necessary starting point for all experimental reasoning. Without it, we could not make any investigations at all nor learn anything; we could only pile up sterile observations. (38)
>
> Claude Bernard 1813–1878

> If we wish to foresee the future of mathematics, our proper course is to study the history and present condition of the science. . . .
>
> In proportion as the science develops, it becomes more difficult to take it in its entirety. Then an attempt is made to cut it in pieces and to be satisfied with one of these pieces—in a word, to specialize. Too great a movement in this direction would constitute a serious obstacle to the progress of science. As I have said, it is by unexpected concurrences between its different parts that it can make progress. Too much specialising would prohibit these concurrences. (64)
>
> Henri Poincaré (1854–1912)

> As far as I can conjecture, the art [of discovering undiscovered things] consists in habitually searching for causes or meaning of everything which occurs. This implies sharp observation and requires as much knowledge as possible of the subject investigated.
>
> Louis Pasteur (1822–1895)

> Medicine is a science of uncertainty and an art of probability.
>
> William Osler (1849–1919)

> The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them.
>
> William Bragg (1890–1971)

The aim of this work was to unravel the aetiology of, or to diagnose, the disease that causes the symptoms that are nowadays labelled as CFS/ME. Frequentist statistical methods can only rule out correlations and are inappropriate to rule out the aetiology of a disease with an unknown cause. (65) This is in accordance with what Sir Austin Bradford Hill expressed in his famous lecture in 1964 (66) and in his landmark 1965 paper. (67,68) Unravelling the unknown deterministic causes of a disease is in essence similar to diagnosing a patient's disease in everyday clinical work. For

38. Bernard C. Introduction à l'etude de la médecine expérimentale, 1865 [An introduction to the study of experimental medicine]. Dover Publications, 1927; p. 32.

64. Poincaré H. Science et méthode [Science and method]. Forgotten Books (original work published by Thomas Nelson and Sons, 1908). Chapter II: The future of mathematics; pp. 25–45.

65. Penston J. Stats.con: How we've been fooled by statistics-based research in medicine. The London Press, 2010.

66. Martyn C. Fighting a lost cause? *BMJ* 2009;338:b1621.

67. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300.

68. Phillips CV, Goodman KJ. The missed lessons of Sir Austin Bradford Hill. *Epidemiol Perspect Innov* 2004;1:3.

this reason, I found the method that has proved to be the most useful tool for medical doctors for more than 2000 years—clinical reasoning—to be most appropriate.

The method I use in this work—variously named clinical reasoning, clinical Bayesian thinking, inferential reasoning, heuristic reasoning, or heuristic strategies—is basically what I have learned during 30 years of general practice in a rural community. The cognitive processes involved are a sort of tacit knowledge and difficult to express in detail. Hence, available literature on clinical reasoning is scarce and inversely related to its importance in clinical medicine. The best clinical textbook I have found on this matter is *Learning Clinical Reasoning*, written by J.P. Kassirer and R.I. Kopelman. (69) George Pólya has presented heuristic reasoning (to discover the solution of a problem) in an excellent way in his classic introduction to mathematical problem-solving. (70) He divides the process of problem-solving into four phases:

- Understand the problem.
- Consider related problems whose solutions are already known and use reason by analogy to devise a plan.
- Carry out the plan.
- Examine the solution obtained.

As clinical work deals with decision-making under uncertainty, an essential part of clinical reasoning is to overcome the fear of being wrong. In daily clinical work, medical doctors have to accept and live with this reality. Even more, during demanding work such as this, medical doctors must not only accept the possibility of being wrong during the process in order to reach the right diagnosis, but they must even dare to be regarded with obliquity and scepticism among colleagues because of seemingly strange ideas.

Basically the method that I applied in this work is the same as that which clinical medical doctors use every day: a detailed and ever-increasing patient story, clinical findings, laboratory results, and medical imaging, combined with basic medical knowledge, as the foundation of clinical Bayesian reasoning to find the most probable diagnosis. (71–73) The only difference in my method is the amount of effort and perseverance I have put into the diagnostic process to unravel the aetiology of CFS/ME.

The first element of the method was expressed by Sir William Osler: "Listen to the patient because he is trying to tell you the diagnosis." (74) The truth of this expression is known by any experienced general practitioner and clinician in general. The patients presented their story to me partly spontaneously and partly as answers to my ever-increasing number of questions. Patients are experts on their own symptoms and they alone are able to describe the subtlety, the variability, and the context of the symptoms. (75) The information from the patients was merely collected in the

69. Kassirer JP, Kopelman RI. Learning clinical reasoning. Williams & Wilkins, 1991.

70. Pólya G. How to solve it. Penguin Books, 1990 (original work published by Princeton University Press, 1945).

71. Gill CJ, Sabin L, Schmid CH. Why clinicians are natural bayesians. *BMJ* 2005;330:1080–3.

72. Rapezzi C, Ferrari R, Branzi A. White coats and fingerprints: diagnostic reasoning in medicine and investigative methods of fictional detectives. *BMJ* 2005;331:1491–4.

73. Dhaliwal G. The mechanics of reasoning. *JAMA* 2011;306:918–9.

74. Tate P. The doctor's communication handbook. 5th ed. Radcliffe Publishing, 2007; p. 54.

75. Audet N. The power of listening. *Can Fam Physician* 2011;57:e35–6.

form of descriptions. I did not use any questionnaires because such things would limit obtainable information. (76) My fear of missing possibly important information from the patients far exceeded my fear of bias, as I realized that the only remedy for bias whatsoever is genuine curiosity and the search for truth, honesty, and critical interpretation. (77)

Medical knowledge has increased considerably since I was studying medicine approximately 40 years ago, but not as much as we like to believe. The quality of medical textbooks and the access to medical papers have, however, increased immensely during these years. Basic medical knowledge outlined in medical textbooks has been essential for the fundamental part of the work outlined in this book, while PubMed and ISI Web of Science have been invaluable concerning the most specialized topics.

Initially I thoroughly studied the history and clinical findings of three female patients with symptoms of CFS/ME who were the most debilitated and disabled patients of my practice. Their principal symptom was severe fatigue and they were all rather young: 32, 36, and 43 years old at the beginning of this work. Selection was based on a fact that every clinician has experienced—that it is easier to diagnose a seriously ill patient than a less seriously affected patient from any given disease. This approach made the discussion about the different sets of diagnostic criteria for CFS/ME of little importance. (78,79) The principal difference between different sets of diagnostic criteria for CFS/ME is simply how broad or restricted the diagnostic criteria are and the degree of symptom severity that qualifies for diagnosis. In addition, I studied other patients in my practice with similar symptoms. What I tried to do was to proceed from the particular to the universal (64,80,81) and to establish increasing numbers of probable facts/assumptions about the disease. The method may seem to be rather unsophisticated, but according to Albert Einstein, the "whole of science is nothing more than a refinement of everyday thinking."

Five falsifiable microbiological working diagnoses were sequentially elaborated from basic medical knowledge and what I found to be probable facts/assumptions about the disease and the transmission of suspected microorganisms. The working diagnoses were falsified partly by a test of treatment as a diagnostic test (82), polymerase chain reaction (PCR) examination of cerebrospinal fluid (CSF), and theoretical considerations. As the aetiology of CFS/ME is unknown, the pretest probability

76. McWhinney IR. Assessing clinical discoveries. *Ann Family Med* 2008;6:3-5.

77. McCormack J, Greenhalgh T. Seeing what you want to see in randomised controlled trials: versions and perversions of UKPDS data. *BMJ* 2000;320:1720-3.

78. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994;121:953-9.

79. Reeves WC, Wagner D, Nisenbaum R, Jones JF, Gurbaxani B, Solomon L, Papanicolaou DA, Unger ER, Vernon SD, Heim C. Chronic fatigue syndrome—a clinically empirical approach to its definition and study. *BMC Med* 2005;3:19.

64. Poincaré H. Science et méthode [Science and method]. Forgotten Books (original work published by Thomas Nelson and Sons, 1908). General conclusions; pp. 284-8.

80. McWhinney IR. William Pickles Lecture 1996. The importance of being different. *Br J Gen Pract* 1996;46:433-6.

81. Whitehead AN. An introduction to mathematics, 1911. Rough Draft, 2007; p. 11.

82. Glasziou P, Rose P, Heneghan C, Balla J. Diagnosis using "test of treatment." *BMJ* 2009;338:b1312.

of a significant response by any medication is very low, nearly zero. However, there may be symptom fluctuations for unknown reasons. To avoid this disturbance, I accepted only an obvious and undoubted response to a test of treatment, according to the patient. The undoubted treatment response (according to the fifth working diagnosis) and basic medical and veterinary knowledge were the basis for the final theoretical refinement of the infectious diagnosis of CFS/ME.

Patients receiving the diagnostic test of treatment were thoroughly informed verbally and in writing about the theory behind targeting the microorganism and about the antibiotics in question. Several patients were informed in this way regarding the fifth working diagnosis. Some of them rejected the test of treatment for this working diagnosis because they found the theory too strange or exceptional. In addition to the author himself, 16 patients consented to and completed the test of treatment with the antibiotic in question for two weeks or more. Pharmacological treatment was discontinued when there was no treatment response, when the liver transaminases became elevated, or when the medicine was not available for various reasons. The author and six patients used the antibiotic for several months.

INDUCTION OF WORKING DIAGNOSIS 1.

> Because he is so complex, he is an excellent patient to study. After all, clinical medicine is primarily the study of the difficult aspects and complexities of disease. When a patient calls on you, he is under no obligation to have a simple disease just to please you.
>
> Jean-Marie Charcot (1825–1893)

> In the biological sciences as a whole experiment and laboratory observation have by no means abolished the necessity of fieldwork. Indeed the importance of fieldwork is being more than ever widely acclaimed. With medical science it should not be otherwise and, although the journals of today are so largely occupied with the results of biochemical, biophysical, and bacteriological research, there is still, I believe, ample scope and genuine need for plain clinical description and discussion. The physician is, in fact, and will remain, the field naturalist of those numerous branches of human biology which medicine comprises. (60)
>
> John A. Ryle (1889–1949) in 1936

> To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all.
>
> William Osler (1849–1919)

> The most interesting facts are those which can be used several times, those which have a chance of recurring. . . .
>
> It is with regular facts, therefore, that we ought to begin; . . . Then it is the exception which becomes important. We cease to look for resemblances,

60. Ryle JA. The natural history of disease. Oxford University Press, 1936.

> and apply ourselves before all else to differences, and of these differences we select first those that are most accentuated, not only because they are the most striking, but because they will be the most instructive. . . .
>
> But what we must aim at is not so much to ascertain resemblances and differences, as to discover similarities hidden under apparent discrepancies. . . .
>
> It is because simplicity and vastness are both beautiful that we seek by preference simple facts and vast facts; . . .
>
> Thus we see that care for the beautiful leads us to the same selection as care for the useful. Similarly economy of thought, that economy of effort which, according to Mach, is the constant tendency of science, is a source of beauty as well as practical advantage. (64a)
>
> Henri Poincaré (1854–1912)

> Discovery consists precisely in not constructing useless combinations, but in constructing those that are useful, which are an infinitely small minority. Discovery is discernment, selection . . .
>
> These sudden inspirations are never produced except after some days of voluntary efforts which appeared absolutely fruitless, in which one thought one had accomplished nothing, and seemed to be on a totally wrong track. These efforts, however, were not as barren as one thought; they set the unconscious machine in motion, and without them it would not have worked at all, and would not have produced anything. . . .
>
> The necessity of the second period of conscious work can be more readily understood. It is necessary to work out the results of the inspiration, to deduce the immediate consequences and put them in order and to set out the demonstrations; but, above all, it is necessary to verify them. (64b)
>
> Henri Poincaré (1854–1912)

According to clinical reasoning as the method in this work, my thought process is described by an increasing number of clinical, theoretical, and infectious transmission assumptions leading to five consecutive principal working diagnoses. My first assumption is about the probable infectious nature of CFS/ME.

Clinical assumption 1: CFS/ME is caused by some sort of infectious agent.

Postviral fatigue syndrome and epidemic neuromyasthenia, two of the many earlier terms used to describe CFS/ME, reflect the idea that it was initially thought

64a. Poincaré H. Science et méthode [Science and method]. Forgotten Books (original work published by Thomas Nelson and Sons, 1908). Chapter I: The selection of facts; pp. 15-24.

64b. Poincaré H. Science et méthode [Science and method]. Forgotten Books (original work published by Thomas Nelson and Sons, 1908). Chapter III: Mathematical discovery; pp. 46-63.

to be related to an infection of some sort. (83) Some patients claim that CFS/ME followed an infection with clinical symptoms resembling mononucleosis. During the chronic stage of the illness, many patients feel they "have an infection in the body," but no apparent clinical symptoms or results from serological or biochemical testing can confirm an infectious aetiology. It is possible, however, for an acute clinical infection to change to a low-virulent chronic infection. (84) Years of clinical experience have taught me to rely on patients' assessments more than surrogate markers in medicine when assessing somewhat conflicting facts.

Clinical assumption 2: CFS/ME involves pathological processes in the medulla oblongata and/or other central parts of the central nervous system (CNS).

Two of the three most affected patients in my practice experienced chronic pain and impaired and delayed skin sensation in the right part of their body, including their face. One of these patients experienced motor dysfunction of the entire right part of the body. The third patient experienced fine finger tremor, inconstant ptosis of the right eye, taste dysfunction/hallucination, motor dysfunction of the tongue, and swallowing dysfunction.

Clinical assumption 3: CFS/ME is caused by chronic focal subclinical infections in the CNS and may be localized in different parts and to a different extent in the CNS of different patients.

A central feature among patients with CFS/ME who have neurological findings or symptoms is the great variability in localization, extent, and degree of sensory and motor disturbances. The symptoms range from hypoaesthesia in a localized area of which the patient may be unaware, to anaesthesia that is well known by the patient. This great variability may seem a bit confusing at first sight.

Organs of the human body such as the liver and lungs have the same principal physiological functions in all parts of the organ. The brain, however, has highly specialized functions in different parts of the brain. Physiologically, the CNS may be characterized as a collection of "mini-brains" with different functions interacting with each other. The consequences of this highly specialized organization become apparent in vascular occlusions of different parts of the brain, which result in highly differing symptoms, in contrast to the consequences of an embolus of the lung, which results in the same symptoms no matter which part of the lung is affected, as long as the volume of lung tissue affected is the same.

Principally, the same applies to localized infections. Infection of one or another part of the lungs may cause symptoms of lung infection, depending on the *extent* of the infection. There is no consequential difference in physiological respiratory symptoms whether the infection is localized in one or the other lung lobe. A local infection of the brain, however, will cause highly different symptoms depending on the *localization* of the infection. If CFS/ME is hypothesized to be caused by localized infections affecting different parts of the CNS, it is possible to explain why patients present rather different neurological symptoms.

83. Parish JG. Early outbreaks of "epidemic neuromyasthenia." *Postgrad Med J* 1978;54:711–7.

84. Mims C, Nash A, Stephen J. Mims' pathogenesis of infectious disease. Elsevier Academic Press, 2002; pp. 339–60.

Clinical assumption 4: The infectious agent causing CFS/ME does not destroy brain cells to a notable extent: it primarily interferes with the normal function of brain cells.

Medical imaging reveals no specific pathological findings among patients with CFS/ME. (85) Apparently, the infectious agent either resides in the brain without destroying brain cells, or destroys too few brain cells to be apparent on medical imaging. However, the neurological findings can only be explained if the infectious agent is able to cause dysfunction of the brain cells affected.

Theoretical assumption 1: CFS/ME is caused by a known infectious agent.

The infectious agent responsible for CFS/ME may be known or unknown to the medical community of today. Relying on the impressive work done by researchers in microbiology during the last two centuries, I made a qualified assumption on this matter.

Working diagnosis 1: CFS/ME might be caused by Chlamydiaceae, *Rickettsia*, and *Coxiella* species.

The initial assumptions were the starting point in my elaboration of a first working diagnosis. I theorized that intracellular bacteria known to parasite the ATP production of human cells might explain the neurological dysfunction among patients with CFS/ME. Chlamydiaceae, *Rickettsia*, and *Coxiella* species have such biological attributes to a greater or lesser extent. (86)

Serological tests of the three most debilitated patients verified an earlier infection with *Chlamydia*, but not *Rickettsia* or *Coxiella*. Although many patients have positive serological results for *Chlamydia*, only a small number of them have CFS/ME. To resolve the uncertainty of the working diagnosis, I did a test of treatment. (82) One of the patients with CFS/ME was offered doxycycline as a test of treatment, but there was no clinical effect during 14 days of treatment. For this reason, I rejected my first working diagnosis, although I found it theoretically elegant.

INDUCTION OF WORKING DIAGNOSIS 2.

Viruses have been considered as possible causes of CFS/ME for many years, especially the Epstein-Barr virus. Relying on the work done by researchers who were trying to confirm this hypothesis without any success, I reasoned that the probability of this diagnosis being correct was very low. (87)

For a long time, I was imprisoned in the world of bacteria and viruses as the sole possible causes of CFS/ME, but none of them held biological properties that could explain the symptoms of CFS/ME. However, by reading *Adams & Graham's Introduction to Neuropathology* (88), I became aware of fungi as possible infectious agents of the CNS.

85. Greco A. Brain MR in chronic fatigue syndrome. *Am J Neuroradiol* 1997;18:1265-9.

86. Murray PR, Rosenthal KS, Pfaller MA. Medical microbiology. Mosby Elsevier, 2005; pp. 450, 463.

82. Glasziou P, Rose P, Heneghan C, Balla J. Diagnosis using "test of treatment." *BMJ* 2009;338:b1312.

87. Swanink CM, van der Meer, Vercoulen JH, Bleijenberg G, Fennis JF, Galama JM. Epstein-Barr virus (EBV) and the chronic fatigue syndrome: normal virus load in blood and normal immunologic reactivity in EBV regression assay. *Clin Infect Dis* 1995;20:1390-2.

88. Graham DI, Nicoll JAR, Bone I. Adams & Graham's introduction to neuropathology. Churchill Livingston, 2006.

Working diagnosis 2: CFS/ME might be caused by a fungal infectious agent.

I tested this working diagnosis when the CSF of the most debilitated patient was obtained by lumbar puncture for PCR testing of 18S mitochondrial RNA. The test revealed no signs of fungal infection. As the test is considered to have high sensitivity and specificity, it persuaded me to reject my second working diagnosis.

INDUCTION OF WORKING DIAGNOSIS 3.

Infectious transmission assumption 1: Women are more frequently exposed to the infectious agent causing CFS/ME.

Having escaped from this bacterial and viral mindset, it was much easier to think freely without microbiological prejudices and to seriously consider even the last and smallest chapters of microbiological textbooks. At the same time, I became aware of a remarkable book written by Peter Vinten-Johansen et al. about John Snow. (89) The discovery of the transmission route of cholera is eminently outlined in this book, a central feature of which is that John Snow discovered it by applying clinical thinking to the effects and cause of the disease. The epidemiological evidence was simply a confirmation of his clinical reasoning. (pp. 219–223) Reading this book gave me the idea to enhance my initial clinical assumptions by considering the transmission of the infectious agent causing CFS/ME.

If the aetiology of CFS/ME is an infection in the CNS, men and women should be equally susceptible to it. As every general practitioner who examines these patients knows, however, women are diagnosed with this disease much more frequently than men. According to NICE, CFS/ME affects women at four times the rate of men. (13) The most reasonable explanation is that women are more frequently exposed to the infectious agent than are men. Another possible explanation might be that women are much more susceptible to the infection, but I found this explanation to be less probable.

Infectious transmission assumption 2: The infectious agent causing CFS/ME cannot be transmitted directly between humans.

Patients with CFS/ME seem to represent isolated cases with no discernible indications of direct transmission between members of a family.

Infectious transmission assumption 3: The infectious agent causing CFS/ME is transmitted to the alimentary tract and may be transmitted by contaminated drinking water.

Some small-scale epidemic outbreaks of CFS/ME have occurred throughout history. (83) These epidemics may have been caused by several possible routes of transmission. However—as was the case during the time of John Snow—sometimes

89. Vinten-Johansen P, Brody H, Paneth N, Rachman S, Rip M. Cholera, chloroform, and the science of medicine: a life of John Snow. Oxford University Press, 2003.

13. National Institute for Health and Care Excellence (NICE). Clinical guideline CG53. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children. NICE, 2007. http://www.nice.org.uk/nicemedia/pdf/CG53FullGuidance.pdf

83. Parish JG. Early outbreaks of "epidemic neuromyasthenia." *Postgrad Med J* 1978;54:711–7.