PARASITES OF HEALTH

PARASITES
OF
HEALTH

ON THE
PATHOPHYSIOLOGY
AND
MODE OF COMMUNICATION
OF
NON-COMMUNICABLE DISEASES

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Front cover images: *Taenia* egg left, *Toxocara* egg right. Credit to the Centers for Disease Control and Prevention's Division of Parasitic Diseases and Malaria (CDC–DPDx) and to the Oregon Public Health Laboratory.

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Notice: The book explores the probable aetiology and pathophysiology of non-communicable diseases. The hypotheses suggested need to be verified before the treatment suggested in this book can be incorporated into medical practice. It is the responsibility of practitioners, on the basis of their own experience and knowledge, to make diagnoses, determine the best treatment for each patient, and take all appropriate safety precautions. The publisher, author, and editor assume no legal liability for any injury or damage resulting from the use or application of any products, methods, or ideas presented in this book.

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DEDICATION

Til Mette

Som et rolig vindpust
med orkan styrke.
Det er deg.

Du river meg overende
og aldri har jeg stått stødigere.
Du åpner dører jeg aldri har sett
til rom jeg ikke visste fantes.

Fanget i dine armer
Har jeg aldri følt meg så fri.

To Mette

Like a quiet breath of wind
with the power of a hurricane.
That's you.

You pull me down
and never have I been standing more steady.
You open doors I've never seen
into rooms I didn't know existed.

Caught in your arms
I have never felt so free.

If it is terrifying to think that life may be at the mercy of the multiplication of infinitesimally small creatures, it is also consoling to hope that science will not always remain powerless before such enemies. . . . All is dark, obscure and open to dispute when the cause of the phenomena is not known; all is light when it is grasped.

— Louis Pasteur (1822–1895)

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Preface

> An imaginative conception of what *might* be true is the starting point of all great discoveries in science.
>
> Peter Medawar (1915–1987)

> False facts are highly injurious to the progress of science for they often endure long; but false hypotheses do little harm, as everyone takes a salutary pleasure in proving their falseness; and when this is done, one path toward error is closed and the road to truth is often at the same time opened.
>
> Charles Darwin (1809–1882)

> As a physicist, I wonder why it is that biology and medicine seem to have so few new theories.
>
> Murray Gell-Mann in 2012

My initial intention with the work presented in this book was only to unravel the aetiology of chronic fatigue syndrome/myalgic encephalomyelitis, commonly abbreviated as CFS/ME. However, the clinical reasoning that made me unravel the very probable family of microorganisms that are involved in the causation of CFS/ME turned out to be so fertile that I continued reasoning far beyond my initial intention. As a result, I have ended up writing a book about the probable aetiology of a number of so-called non-communicable diseases.

The book consists of five parts. The first part describes the problem-solving process that I used to unravel the aetiology of CFS/ME. I started my endeavour during the summer of 2006 and reached a preliminary microbiological conclusion during the autumn of 2008. Since then I have reconsidered and refined the conclusion several times and accumulated circumstantial evidence about Taenia larval tissue infection (LTI), with a non-human definitive host as the highly probable fundamental aetiological cause of CFS/ME. The circumstantial evidence consistent with this conclusion comprises the rest of the first part of the book.

During the work of reading, writing, and thinking, combined with observing, examining, and communicating with patients on a daily basis, it was impossible for me to avoid thinking that CFS/ME might not be the only disease caused by this family of microorganisms. In fact, it would have been improbable for the microbiological

agent causing CFS/ME not to cause any other disease entities. Just as the tubercle bacillus proved to be the cause of a number of disease entities, the family of microorganisms that causes CFS/ME probably causes a number of other diseases as well.

The second part of the book is a primer on aetiological thinking on diseases with still unknown aetiology. This section is a theoretical analysis based upon existing biomedical knowledge—a sort of "meta-analysis" of what we actually know about the aetiology of diseases and the potential candidates that may cause diseases with still unknown aetiology. It may be categorized as "theoretical medicine" or "science-fiction medicine" depending on the reader's evaluation. Whatever the reader's evaluation might be, the purpose is to trigger thinking about the biomedical aetiology of diseases with still unknown aetiology.

With the view that Louis Pasteur's "germ theory of disease" should be revived regarding non-communicable diseases, and inspired by the Standard Model of particle physics, I propose a Standard Model of medicine:

> *The deterministic cause of all physical and psychiatric diseases is microorganisms, except for some already known genetically determined disorders, prions, physical injuries, harmful chemical substances, and radiation, as long as the body's metabolic needs are met. The expression of disease is the result of the interaction between the microorganisms, the immune system, and the tissues involved. Susceptibility to disease may be increased as a result of genetic predisposition of the immune system, or manipulation of the immune system by infections.*

My main assertion is that the "goddamn particle" or microorganism causing so-called non-communicable diseases is actually helminth infections, that is to say, taeniid and *Toxocara* LTI, with canine and feline predators as the definitive hosts. These infections are not communicable directly between humans, but are transmitted to humans by faeces from these animals. The infectious reservoirs most important to humans are probably domestic dogs and cats, which—in analogy to the Trojan horse—introduce the infectious helminth eggs to humans who accidentally ingest the eggs. The potential impact of dog and cat helminth zoonoses has been consistently neglected in medical science and increasingly ignored in western lifestyle, as reflected by the advancement of the dog from the doghouse in the garden to the family bed.

The third part of the book presents the result of my efforts to apply Occam's razor to construct a pathophysiological model of taeniid and *Toxocara* LTI that may explain the development of a number of diseases. This model is principally based on disturbances of the immune system due to helminth tissue infection, disturbances due to a localized metabolic acidosis caused by the helminths' fermentative energy metabolism, disturbances of the hormonal environment, and disturbances due to the mechanical impact of helminth cysts and resulting granulomas and calcifications. By these principally simple mechanisms, the model may explain the pathophysiology of a number of so-called non-communicable diseases. I propose disease aetiology hypotheses that together may explain more than a hundred of these diseases.

The pathophysiological model of taeniid and *Toxocara* LTI may also fill some gaps in the discussion about nature and nurture that cannot be explained by genetic, lifestyle, or environmental risk factors alone. The third part concludes with suggestions about studies that can be done to test some of the disease aetiology hypotheses.

In the fourth part of the book, I make the assertion that helminth infections in general are the most important causes of ill health globally partly because of the diseases themselves and partly because of the consequences of impaired innate and adaptive cellular immune responses induced by helminth infections when the individual is challenged by viral, bacterial, and protozoan infections. Globally, a number of medically recognized helminth infections affect billions of people living in poverty. These infections probably contribute to increased susceptibility to infections, increased contagiousness, decreased response to antibiotic treatment, development of drug resistance, impaired response to vaccines, and increased risk of emerging diseases. These effects are detrimental to helminth-infected individuals and to the societies that they are a part of. But the development of drug resistance and emerging diseases puts the health of the rich part of the world at risk as well. Therefore, it is in the interest of the rich part of the world to combat and prevent helminth infections worldwide.

The fifth and last part of the book deals with what to do. First, it is about treatment and prevention of taeniid and *Toxocara* helminth infections and what is needed to combat them. Second, it is about what I think should be the future directions of medical research.

In accordance with the pathophysiological model of taeniid and *Toxocara* LTI, I suggest a number of hypotheses regarding the aetiology and development of a number of different diseases. However strange and speculative the reader might find the hypotheses to be, they all have the great advantage of being falsifiable. To propose falsifiable hypotheses regarding a great variety of diseases based on rather limited medical evidence may not be advisable and will make me an easy target. I realize that I have to be prepared to be met with initial ridicule, assault, dismissal, or silence by my medical colleagues. Hostile responses will, I hope, have a scientific basis and be motivated by a wish to advance medical science. However, my hypotheses may undermine the authority and financial interests of parts of the establishment, and therefore some hostile responses may masquerade as being scientifically motivated. The response I sincerely hope for is something like this: "The hypotheses presented in this book seem reasonable enough to be tested before they are dismissed." Considering the history of medical discoveries, however, it may be too much to hope for.

Even if the reader takes an unprejudiced attitude to my hypotheses, it may be difficult for him or her to seriously consider that tissue helminth infections could have a significant impact on health in the rich part of the world. I can assure the reader that, even for me, such a conclusion was unthinkable when I started my search for the infectious cause of CFS/ME. However, the conclusion turned out to be unavoidable when I applied the same thinking as that of Sherlock Holmes, a character created by our colleague Sir Arthur Conan Doyle, as expressed in his famous quote "when you have eliminated the impossible, whatever remains, *however improbable,* must be the truth." Overcoming belief bias is arduous but absolutely essential in the pursuit of science.

My ultimate goal became little by little to unravel the aetiological causes of noncommunicable diseases. Reaching this goal is fundamental to allowing medical clinicians to help patients who are suffering from these diseases to live as healthy lives as possible and to prevent these diseases in future generations. I realize that I cannot reach such a goal without risk of making mistakes. Furthermore, I realize that the initial response to my suggestions from my medical colleagues, positive or

negative, proves nothing. Only testing of my hypotheses will prove whether they—or which of them—are right or wrong.

The concept that diseases with still unknown aetiology are "non-communicable" shares some fundamental similarities with the old belief in "spontaneous generation" of life: it is based on speculation alone, it functions as a mere excuse to cover processes we do not yet understand, and it holds back the development of biology and medicine. Somewhat rhetorically, one might say that the belief in non-communicable diseases is a belief in spontaneous generation of diseases, though influenced by certain risk factors. I think time is long overdue to examine whether diseases with still unknown aetiology are infectious or not. The driving force that caused the gradual abandonment of the concept of spontaneous generation of life was experimental biomedical research. Similarly, if the concept of non-communicable diseases shall ever be abandoned, it will also be by experimental biomedical research.

This book is a compromise between my ambition to develop and refine highly reasonable hypotheses about the pathophysiology of dog and cat helminth zoonoses in human disease and the necessity of communicating the hypotheses to the medical community for verification or falsification. I could have continued for years to expand and refine the hypotheses but—however reasonable the hypotheses might be—I do not have the resources needed to test them. I have therefore had to limit my ambition to develop biomedical hypotheses and present evidence consistent with them in a way that is reasonable enough to be taken seriously by unprejudiced medical colleagues. In this way, I could say the same about my hypotheses of non-communicable diseases that John Snow said about his hypothesis of cholera in 1849: "These opinions respecting the cause of cholera [*non-communicable diseases*] are brought forward, not as matters of certainty, but as containing a greater amount of probability in their favour than any other, in the present state of knowledge."

All of the references in this book are highly recommended reading and will bring you insights of great importance. Among the many references, I will especially recommend two very important books published by the not-for-profit science-based development and information organization CABI. Each of them addresses parasitology of underestimated medical relevance. The first book is *Taenia Solium Cysticercosis: From Basic to Clinical Science,* edited by Gagandeep Singh and Sudesh Prabhakar. The second one is *Toxocara: The Enigmatic Parasite,* edited by Celia V. Holland and Huw V. Smith.

Another most important book is *International Health and Aid Policies: The Need for Alternatives,* written by Jean-Pierre Unger, Pierre De Paepe, Kasturi Sen, and Werner Soors. The book, or at least its introduction, should be compulsory reading for politicians and bureaucrats who sincerely want to promote the health and wealth of the populations they are supposed to serve.

Among the many article references, I will especially highlight the paper of Peter J. Hotez, David H. Molyneux, Alan Fenwick, Eric Ottesen, Sonia Ehrlich Sachs, and Jeffrey D. Sachs from 2006: "Incorporating a Rapid-Impact Package for Neglected Tropical Diseases with Programs for HIV/AIDS, Tuberculosis, and Malaria." The paper emphasizes the biological and immunological interactions between different chronic infectious diseases, arguing that helminth diseases must be prevented and treated to successfully fight malaria, tuberculosis, HIV/AIDS, and poverty.

Finishing the writing of this book coincides with the bicentenary of the birth of John Snow (1813–1858). His excellent biography, authored by Vinten-Johansen, Brody, Paneth, Rachman, and Rip, explains the fundamental importance of John Snow's

clinical reasoning regarding the probable modes of communication of cholera. This lesson was very helpful to me when I searched for the unknown infectious agent causing CFS/ME in humans. Even though there are many differences between cholera and the so-called non-communicable diseases, the faecal-oral mode of communication is principally similar, though the latter diseases involve non-human species as the infectious source. The subtitle of my book is therefore inspired by the title of John Snow's publications from 1849 on his elegant reasoning and studies of cholera.

Please read the book in your hands *and* the references, use your own intelligence, and allow yourself to adopt independence of mind! If you are in a position to test my hypotheses, I would be most grateful if you will do so. And if you are in a position to do something to prevent the transmission of helminth infections worldwide and you seize the opportunity to do so, people who are now living—as well as future generations—will accomplish healthier lives.

Oslo, August 2014
Torgeir Landvik

Acknowledgements

I would like to express my deep thanks to many individuals and institutions of Norwegian society; without them, this work would never have been initiated or have reached the level of insight presented in this book. First and most of all, I thank each patient I have met during my 34 years of general practice in Enebakk for what I have learned from them. I am especially grateful for the confidence shown by a small group of patients who listened to me and read handouts about my new theories regarding their diseases, and who were willing to try the anthelmintic treatment as a diagnostic method on the basis of these theories. I have done my best to deserve their confidence and support, and writing this book is part of that endeavour.

For 27 years, I worked as a general practitioner without ever thinking seriously about doing anything other than what a general practitioner is expected to do. During these years, I was distressed by the ignorant way that patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) were treated by the health care system and by my own inability to offer these patients adequate treatment for their perceived illnesses. Even though I experienced an increasing distrust about modern medical research, it never occurred to me that the development of medical knowledge could be done by anyone other than professional medical researchers. However, my beloved professor Mette Gulbrandsen opened my eyes to the possibilities in analysing subjective information from patients as an alternative to counting, measuring, and producing p-values to gain new insights. Equally important was that she was sowing seeds of curiosity in me, which was a prerequisite to my ever thinking that I could do the work myself to gain new medical insights. Without her influence, this work would never have been initiated.

In 2006, I attended a conference at the Norwegian Knowledge Centre for the Health Services regarding the publication of a newly released Norwegian report about CFS/ME. All of the speakers at the conference, except for one, expressed that we actually know next to nothing about the pathogenesis or effective treatment of CFS/ME. The singular exception was neurologist Harald Nyland from Haukeland University Hospital of Bergen, who claimed that he knew that CFS/ME was caused by a physical disease in the central nervous system, even though he did not have any definite evidence to confirm the assertion. His statement inspired me, as his claim seemed to be correct because it was the only way to explain the symptoms seen in patients with CFS/ME. Furthermore, I am grateful to Peter Gaustad, professor of microbiology, and Olav Øktedalen, specialist in infectious diseases at the University Hospital of Oslo, for help regarding some microbiological tests and insightful discussions on microbiology.

One of the conditions for my work is knowledge about the biology of living creatures of all sizes. I therefore express my sincere gratitude to medical and veterinary scientists who have procured this knowledge during the last two centuries. However, without free access to it, I would have been unable to try to increase our common knowledge. For the acquisition of specialized medical knowledge, I owe a debt to several institutions of Norwegian society that provided universal access to knowledge. The Norwegian Electronic Health Library, which offers free access to more than 2000 medical journals for all medical doctors everywhere in Norway, and the free medical and veterinary libraries of the University of Oslo have all been invaluable to me. Last, I am deeply grateful to the Labour Party politicians who instituted the welfare system of Norway, providing universal access to higher education and good quality health care independent of social and economic background. These qualities of Norwegian society made it possible for me to get an education and a job that enabled me to do the work outlined in this book.

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)

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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

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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

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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

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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)

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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.

nature itself designs experiments that provide clues to transmission routes. Such a "natural experiment" happened in Bergen, Norway, during the autumn of 2004 when there was an epidemic outbreak of a *Giardia lamblia* (and *Cryptosporidium*) infection. (90,91) The epidemic was caused by contaminated water from the municipal water supply that had not been sufficiently purified before consumption. A remarkable side effect was an alleged epidemic of CFS/ME in the same population—though on a much smaller scale than the *Giardia* epidemic. The extent to which this alleged epidemic of CFS/ME was true was under investigation while I was analysing the aetiology of CFS/ME, but there was no official conclusion on the matter. (91,92) I found the alleged epidemic probable enough, however, to include this clue in my thinking and to conclude, as John Snow did, "that the very matter which produced the attack was swallowed in the water." (93)

Infectious transmission assumption 4: CFS/ME is caused by a zoonosis from cats.

Summarizing the assumptions described thus far, CFS/ME is a focal CNS infection caused by an infectious agent transmitted through the alimentary tract to which women are much more frequently exposed than men. On the basis of these assumptions, a probable transmission route is from animals, which women tend to have more intimate contact with than men do. I found that the most obvious animals to consider were domestic cats. The assumption was supported by the fact that 70% of the members of the Norwegian House Cat Association are women. (94) Generally, female dominance is even greater in special organizations for race cats: in 2007, the female representation among members of the Norwegian Persian Cat Ring was 88%. (95)

Besides the predominantly female preference for domestic cats as pets, one of the most apparent differences in activities between men and women relates to domestic work such as house cleaning, as confirmed by a number of gender studies. (96) Women are probably much more exposed than men to the content of the litter boxes of domestic cats.

Working diagnosis 3: CFS/ME might be caused by *Toxoplasma gondii*.

The most important known zoonosis transmitted from cat faeces to humans is toxoplasmosis. *Toxoplasma gondii* reproduces in the intestine of cats but the oocysts sporulate and become infective 1–5 days after excretion. Because of this, toxoplasmosis may be categorized as a soil-borne zoonosis. Toxoplasmosis is regarded as

90. Nygård K, Schimmer B, Søbstad Ø, Walde A, Tveit I, Langeland N, Hausken T, Aavitsland P. A large community outbreak of waterborne giardiasis—delayed detection in a non-endemic urban area. *BMC Public Health* 2006;6:141.

91. Robertson LJ, Forberg T, Hermansen L, Gjerde BK, Langeland N. Demographics of Giardia infections in Bergen, Norway, subsequent to a waterborne outbreak. *Scand J Infect Dis* 2008;40:189-92.

92. Mørch K, Hanevik K, Rortveit G, Wensaas KA, Eide GE, Hausken T, Langeland N. Severity of Giardia infection associated with post-infectious fatigue and abdominal symptoms two years later. *BMC Infect Dis* 2009;9:206.

93. Snow J. On the origin of the recent outbreak of cholera at West Ham [Letter]. *BMJ* 1857;s4-1:934.

94. Bodil Eikeset, Chairman of the Norwegian House Cat Association, personal communication, October 2007.

95. List of members on the Norwegian House Cat Association website, October 10, 2007.

96. Statistics Norway. Tidsbruk, levekårsundersøkelse [Time spent on different types of domestic work].

harmless for humans except during pregnancy, but the infection has been suspected as a possible cause of schizophrenia. (97,98)

The three patients had negative serological results for *Toxoplasma gondii*. However, the most debilitated patient in my practice had lived with cats almost her whole life and allowed them to hunt birds and mice. Although the serological test is supposed to have high sensitivity, because it is indirect, I was not convinced about its sensitivity for an infection many years after the initial exposure. I therefore offered the patient a test of treatment with pyrimethamine 50 mg once daily (loading dose 200 mg), sulfadiazine 500 mg × 3, and calcium folinate (7.5 mg folinic acid) in January 2008. The treatment was stopped after 14 days without any treatment response. For this reason, I rejected my third working diagnosis.

INDUCTION OF WORKING DIAGNOSIS 4.

Infectious transmission assumption 5: CFS/ME is caused by a zoonosis from dogs.

I found it reasonable to proceed on the basis of a zoonosis being the most probable cause of CFS/ME. More detailed questioning about the history of several male and female patients regarding lifetime contact with animals pointed me more in the direction of dogs than of cats. However, the gender differences in prevalence of CFS/ME could not be explained as easily for a zoonosis from dogs as for a zoonosis from cats. One explanation of the gender difference related to a dog zoonosis might be that girls and women generally seem to have more intimate contact with pets than do boys and men. Another potentially associated factor, though, was that one of the patients reported a worsening of symptoms related to losing weight. There is no reason to think that this fact is related to transmission of an infectious agent, but it may be related to a decreased functioning of the immune system, thereby allowing reactivation of a latent infection. We all know from everyday life that there is a marked gender difference in the tendency to go on a weight-loss diet. This might further explain the gender differences in the prevalence of CFS/ME.

Working diagnosis 4: CFS/ME might be caused by *Toxocara canis*.

The *Giardia* epidemic of Bergen was not one that was expected to take place in Norway. Many outbreaks of gastrointestinal infections have occurred as a result of drinking water that has been contaminated by human faecal material in Norway, but never before has an outbreak of *G. lamblia* occurred, at least as far as we know. (99) According to the official evaluation report, (100) the sewage from a few houses

97. Cetinkaya Z, Yazar S, Gecici O, Namli MN. Anti-*Toxoplasma gondii* antibodies in patients with schizophrenia—preliminary findings in a Turkish sample. *Schizoph Bull* 2007;33:789-91.

98. Hinze-Selch D, Däubener W, Eggert L, Erdag S, Stoltenberg R, Wilms S. A controlled prospective study of *Toxoplasma gondii* infection in individuals with schizophrenia: beyond seroprevalence. *Schizoph Bull* 2007;33:782-8.

99. Nygård K, Gondrosen B, Lund V. Water-borne disease outbreaks in Norway. *Tidsskr Nor Laegeforen* 2003;123:3410-3.

100. Eikebrokk B, Gjerstad KO, Rytter E, Hindal S, Johanson G, Røstum J. Giardia-utbruddet i Bergen høsten 2004 [The Giardia outbreak in Bergen autumn 2004]. Report from the External Evaluation Committee, Trondheim, May 2006.

had contaminated the water supplying 42 000 inhabitants. According to this report, 1400 persons were verified as being ill from *G. lamblia*, with an estimated 5000–6000 people infected. (p. 50) The official conclusion about the cause of the outbreak contradicted my second assumption about the transmission of CFS/ME. So—who was wrong—the members of the official committee or me?

I studied the four different reports (in Norwegian) produced about this epidemic. All of them came to the same conclusion, although insufficient examinations were done to verify their final conclusion regarding sewage as the source of the outbreak. (101) None of the persons living in the houses supposed to cause the outbreak were examined for *G. lamblia*.

The official evaluation report theoretically analysed seven possible sources of contamination from different parts of the surroundings of Svartediket lake. The faecal material in question was from sheep, humans, dogs, deer, and birds. A hiking trail, frequently used to walk dogs, ran along the lake starting at the end where water was taken for the municipal water supply. The analysis eliminated six of the seven possible sources of contamination to come to the conclusion it did. However, the report stated: "Faeces from dogs represent probably the main source of *E. coli* to the water input. The importance of faeces from dogs as the source of the outbreak in the autumn of 2004 is considered not very likely compared to sewage from housing at the border of the area of precipitation." (p. 50, my translation) I found these two conclusions to be inconsistent because *Escherichia coli* is usually considered to be the most important biological marker of faecal contamination of drinking water. Furthermore, in September 2005, after treatment of the suspected sewage, the number of *E. coli* measured in the water before purification was higher than it had ever been during the previous 10 years. (p. 68)

Many among the patients struck by the *Giardia* epidemic had *Cryptosporidium* in their faeces, too. Both *Cryptosporidium* and *Giardia* are common in Norwegian dogs. (102) Genotyping of *Giardia* cysts from patient samples revealed that they were assemblage B cysts. (101) This assemblage of *Giardia* has been reported to infect dogs and cats as well and therefore has a zoonotic potential. (103)

On the basis of these facts, my conclusion was that faeces from dogs might not only be a possible cause of the *Giardia* outbreak in Bergen in 2004, but that they might even be the most probable cause. The study of the outbreak convinced me of the correctness of my fifth infectious transmission assumption because it confirmed the conclusion I had reached on clinical grounds.

On the basis of my second infectious transmission assumption, neither *G. lamblia* nor *Cryptosporidium* could possibly cause CFS/ME. Among the different possible

101. Robertson LJ, Hermansen L, Gjerde BK, Strand E, Alvsvåg JO, Langeland N. Application of genotyping during an extensive outbreak of waterborne giardiasis in Bergen, Norway, during autumn and winter 2004. *Appl Environ Microbiol* 2006;72:2212–7.

102. Hamnes IS, Gjerde BK, Robertson LJ. A longitudinal study on the occurrence of Cryptosporidium and Giardia in dogs during their first year of life. *Acta Vet Scand* 2007;49:22.

103. Ballweber LR, Xiao L, Bowman DD, Kahn G, Cama VA. Giardiasis in dogs and cats: update on epidemiology and public health significance. *Trends Parasitol* 2010;26:180–9.

zoonoses from dogs, I found *Toxocara canis* and *Echinococcus granulosus* to be the most probable candidates, as the larval worms cause a more aggressive illness in intermediate (or dead-end) hosts than the adult worm does during the reproductive stage in the definitive host. (104) According to the textbooks, (105,86) *E. granulosus* causes hydatid disease with cysts most often found in the liver but also in the CNS. Such cysts were not apparent by medical imaging in the CNS among the patients in my practice. I therefore found *T. canis* to be the most probable infectious agent causing CFS/ME. (106)

This nematode of dogs (and cats) is the cause of visceral larva migrans, ocular larva migrans, and covert toxocariasis. (107) The dog nematode *T. canis* is probably more important clinically to humans than is the cat nematode *T. cati*. (108) After ingestion by humans, the eggs of *T. canis* hatch in the gut and the larvae migrate from the gut to the liver, lung, eye, brain, kidney, and muscles. (105)

Serological tests done on some of the patients were all negative. However, this serological test has a low sensitivity for disease that lasts more than a few years. (109) According to the medical literature, these larvae seem to have a limited lifespan in the human host, approximately 10–12 years. Considering this fact in relation to the self-healing power of the human organism, I found that the probability was very low for working diagnosis 4 to be correct, as several of my patients had been debilitated for decades. Hence, I rejected the working diagnosis purely on a theoretical basis and I did no test of treatment for CFS/ME for this working diagnosis. I reached this conclusion in May 2008.

INDUCTION OF WORKING DIAGNOSIS 5.

I next reconsidered *E. granulosus* as a possible infectious agent causing CFS/ME because I was rather sure about the correctness of the assumption about a zoonosis from dogs.

Working diagnosis 5: CFS/ME might be caused by *Echinococcus granulosus*.

Echinococcosis is a cosmopolitan zoonotic infection caused by adult or larval stages of tapeworms (cestodes) belonging to the genus *Echinococcus* and the family

104. Axford J. Medicine. Blackwell Science, 1996; p. 2.15.

105. Goering RV, Dockrell H, Zuckerman M, Wakelin DW, Roitt I, Mims C, Chiodini PL. Mims' medical microbiology. Mosby Elsevier, 2008; p. 347.

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

106. Hotez PJ, Wilkins PP. Toxocariasis: America's most common neglected infection of poverty and helminthiasis of global importance? *PLOS Negl Trop Dis* 2009;3:e400.

107. Despommier D. Toxocariasis: clinical aspects, epidemiology, medical ecology, and molecular aspects. *Clin Microbiol Rev* 2003;16:265-72.

108. Smith H, Noordin R. Diagnostic limitations and future trends in the serodiagnosis of human toxocariasis. In: Holland CV, Smith HV, eds. Toxocara: the enigmatic parasite. CABI Publishing, 2006; pp. 89-112.

109. Garcia LS. Diagnostic medical parasitology. ASM Press, 2007.

Taeniidae. (110,111) This family represents the most medically important tapeworms of humans. (112) Like nearly any other tapeworm with a known life cycle, *E. granulosus* requires two hosts for its completion. The adult tapeworm lives in the small intestine of dogs and other canids, which are the definitive hosts. *Echinococcus granulosus* is hermaphroditic and likely reproduces both by self- and cross-fertilization. (113) Fertilized oocytes mature in the intestine and when leaving the definitive host, the eggs are fully capable of infecting an intermediate host.

The juvenile larval stage of *E. granulosus* develops after ingestion of infective eggs by an intermediate host, primarily ungulates such as sheep, cattle, pigs, and horses. The eggs hatch in the intestine of the intermediate host where the released oncospheres (larvae) penetrate the gut wall and then enter the veins or lymphatics. (114–116) The oncospheres that travel in the portal system lodge in the capillary bed of the liver, which acts as an effective filter for most of the larvae. By a very slow process of growth, an oncosphere metamorphoses into a metacestode or hydatid cyst. The inner germinative layer of the hydatid cyst eventually produces brood capsules, within which an asexual budding process takes place, producing numerous protoscolices, which are infective to definitive hosts. (112,117) Secondary cysts may develop in the intermediate host following the rupture of a primary cyst, dispersing germinal layer material and protoscolices. The life cycle of *E. granulosus* is completed when a canid eats protoscolices of the hydatid cyst.

Humans may become accidental hosts when infected by ingestion of *E. granulosus* eggs as a result of fondling infected dogs or by ingesting food, water, or soil containing eggs. (112) Larval infection (hydatid disease, hydatidosis) is characterized by long-term growth of a metacestode (hydatid cyst) in the intermediate host. (118) Four species of *Echinococcus* are recognized: *E. granulosus*, *E. multilocularis*, *E. oligarthrus*, and *E. vogeli*. The epidemiologically most important *Echinococcus* species outside

110. Thompson RCA, McManus DP. Aetiology: parasites and life-cycles. In: Eckert J, Gemmell MA, Meslin F-X, Pawlowski ZS, eds. WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern. World Organisation for Animal Health and World Health Organization, 2001; pp. 1–19. http://whqlibdoc.who.int/publications/2001/929044522X.pdf

111. McManus DP, Zhang W, Li J, Bartley PB. Echinococcosis. *Lancet* 2003;362:1295–304.

112. Roberts LS, Janovy J. GD Smith & LS Roberts' foundations of parasitology. McGraw-Hill Higher Education, 2006.

113. Lymbery AJ, Thompson RCA. Electrophoretic analysis of genetic variation in *E. granulosus* from domestic hosts in Australia. *Int J Parasitol* 1988;18:803–11.

114. von Sinner W, Lewall D. Hydatid disease (echinococcosis). In: Palmer PES, Reeder MM, eds. The imaging of tropical diseases. Vol. 1. Springer-Verlag, 2001; pp. 205–353.

115. Swiderski Z. *Echinococcus granulosus*: hook-muscle systems and cellular organisation of infective oncospheres. *Int J Parasitol* 1983;13:289–99.

116. Jabbar A, Crawford S, Młocicki D, Swiderski ZP, Conn DB, Jones MK, Beveridge I, Lightowlers MW. Ultrastructural reconstruction of *Taenia ovis* oncospheres from serial sections. *Int J Parasitol* 2010;40:1419–31.

117. Thompson RCA. Biology and systematics of *Echinococcus*. In: Thompson RCA, Lymbery AJ, eds. *Echinococcus* and hydatid disease. CAB International, 1995; pp. 1–50.

118. Zhang W, Li J, McManus DP. Concepts in immunology and diagnosis of hydatid disease. *Clin Microbiol Rev* 2003;16:18–36.

Central and South America is *E. granulosus*, which has at least 10 different strains, or genotypes (G1–G10). (119)

Filtration in the capillary bed of the liver is believed to account for the predominant involvement of the liver (50–70% of cysts). If this barrier is overcome, filtration in the next capillary bed of human circulation is in the lungs, the second most predominant location of hydatid cysts (15–30%). If the larva is not trapped in either the liver or the lungs, or if it travels through the lymphatics and bypasses the liver and lungs, it may lodge virtually anywhere in the body, most notably in the peritoneum, spleen, kidneys, heart, brain, spine, bony skeleton, and muscles. (114) The rate of growth of the cyst is more rapid in the lungs than in the liver, spleen, or other solid organs and slowest in bones. A cyst may be latent for a long period, up to 53 years having been reported. (114) The infectious content of the cyst may die and the cyst wall may be calcified. If the cyst ruptures, it may cause biliary obstruction, infection, dissemination, and anaphylaxis, all of which are more important than the mass effect of the enlarging intact lesion. (114)

Serology

Several tests are available for serum antibody detection in cystic echinococcosis, with an overall sensitivity in the range of 50–80%. (114) Serological tests of eight patients in my practice were all negative. However, serological testing is not very reliable clinically, especially when the brain is involved. (120–123)

Cysts

Another way to find indications of echinococcosis is to look more thoroughly for cysts in the body of the patients. I personally examined old computed tomography/magnetic resonance imaging (CT/MRI) scans of the patients and requested CT examinations of the abdomen and thorax if not already done.

The most debilitated patient had a syrinx from T4 to T9, as described by the radiologist. A syrinx is categorized as a malformation or developmental disease according to the text *Robbins and Cotran Pathologic Basis of Disease*. (124) An alternative

119. Lavikainen A, Lehtinen MJ, Laaksonen S, Agren E, Oksanen A, Meri S. Molecular characterization of *Echinococcus* isolates of cervid origin from Finland and Sweden. *Parasitology* 2006;133:565-70.

114. von Sinner W, Lewall D. Hydatid disease (echinococcosis). In: Palmer PES, Reeder MM, eds. The imaging of tropical diseases. Vol. 1. Springer-Verlag, 2001; pp. 205-353.

120. Bükte Y, Kemaloglu S, Nazaroglu H, Ozkan U, Ceviz A, Simsek M. Cerebral hydatid disease: CT and MR imaging findings. *Swiss Med Wkly* 2004;134:459-67.

121. Salehi M, Soleimani A. Cardiac echinococcosis with negative serologies: a report of two cases. *Heart Lung Circ* 2009;18:59-61.

122. Gavidia CM, Gonzalez AE, Zhang Q, McManus DP, Lopera L, Ninaquispe B, Garcia HH, Rodríguez S, Verastegui M, Calderon C, Pan WK, Gilman R. Diagnosis of cystic echinococcosis, central Peruvian highlands. *Emerg Infect Dis* 2008;14:260-6.

123. Chevalier X, Rhamouni A, Bretagne S, Martigny J, Larget-Piet B. Hydatid cyst of the subcutaneous tissue without other involvement: MR imaging features. *Am J Roentgenol* 1994;163:645-6.

124. Kumar V, Abbas AK, Fausto N. Robbins and Cotran pathologic basis of disease. Saunders Elsevier, 2004.

interpretation of a syrinx might be to regard it as a possible hydatid cyst. Furthermore, I found a possible cyst anterior to corpus vertebra T4 and posterior to corpus vertebrae C7 and T7 in the same patient.

Another patient had asymmetrical lateral ventricles with a greater ventricle on the right side protruding into the left cerebral hemisphere detected on MRI. This was considered by the radiologist to be a cyst of no clinical importance. The images demonstrated a cyst in her right maxillary sinus as well. Furthermore, the same patient had a process in the right lobe of the liver with a diameter of 8 mm on ultrasound and CT, interpreted as a haemangioma by the radiologist. This process might also be interpreted as a cyst. The third of my initial patients of the study had calcifications and cysts in the left kidney and calcified nodes in the mediastinum interpreted as probable sequelae after tuberculosis (Philippine patient). A fourth female patient, 60 years old, with extreme fatigue and extreme chronic pain, located in the area of the liver, had two small cysts in the liver.

Larval metabolism

Echinococcus granulosus metacestodes and protoscolices are multicellular organisms and, like any other living organism, need to produce energy or ATP for their own metabolism. Generally, trematode metabolism is little understood, and the metabolism of larval stages has received scant attention. (112) However, we know that *E. granulosus* and other helminthic parasites can only metabolize glucose and galactose for energy metabolism. Because of the lack of available oxygen, energy metabolism mainly occurs through fermentation. The end product excreted by helminthic parasites in general and *E. granulosus* in particular is lactate, but acetate and succinate are secreted as well. (112,125,126) Lactate is an end product formed in the cytosol of the cell, whereas succinate and probably acetate are of mitochondrial origin. (125)

One of the many different and odd symptoms among some of the patients with CFS/ME is some degree of subjective intolerance to sugar. The symptoms of this intolerance are sweating, nausea, and feeling unwell with a time lag from half an hour to two hours after sugar ingestion. This peculiar symptom seemed more understandable for me in light of the knowledge about the energy metabolism of *E. granulosus*.

Parasite-induced trophic transmission

Tapeworms present many examples of a phenomenon called parasite-induced trophic transmission (PITT), in which parasite infection causes changes in the behavioural, physiological, or morphological characteristics of one (intermediate) host that facilitates transmission to the next host. (112) *Echinococcus granulosus* and *Taenia multiceps* directly disable intermediate hosts and facilitate predation by definitive

112. Roberts LS, Janovy J. GD Smith & LS Roberts' foundations of parasitology. McGraw-Hill Higher Education, 2006.

125. McManus DP, Bryant C. Biochemistry, physiology and molecular biology of Echinococcus. In: Thompson RCA, Lymbery AJ, eds. Echinococcus and hydatid disease. CAB International, 1995; p. 140.

126. Tielens AGM, van Hellemond JJ. Unusual aspects of metabolism in flatworm parasites. In: Maule AG, Marks NJ, eds. Parasitic flatworms. CAB International, 2006; pp. 387-407.

hosts. (111) If an intermediate host were to acquire symptoms that were similar to those of patients with CFS/ME, it would be easily captured by a predator.

TESTING WORKING DIAGNOSIS 5

> When we wish to check a hypothesis, what do we do? We cannot verify all its consequences, since they are infinite in number. We content ourselves with verifying a few, and, if we succeed, we declare that the hypothesis is confirmed, for so much success could not be due to chance. It is always at bottom the same reasoning. (64)
>
> Henri Poincaré (1854–1912)

I could not find anything definitive in the literature to falsify the working diagnosis of echinococcosis as the cause of CFS/ME. However, the evidence for echinococcosis was based only on clinical reasoning and indications of possible cysts in the patients. The next step was to confirm or disconfirm the working diagnosis by means other than those already described.

A case-control epidemiological study might confirm the relation between CFS/ME and contact with dogs, but possible confounders are numerous. The epidemiological methods used by John Snow regarding cholera transmission are perfect options for diseases with a short time span between transmission of the infectious agent and the resulting disease. When the delay between infectious transmission and disease may be several years, however, epidemiological studies will be disturbed by an unreasonably large number of confounding factors. Furthermore, patients may become infected without living with dogs in their own family. Dogs of relatives or friends may also transmit the disease. Direct hand contact with contaminated earth and lawns, in combination with nail-biting or drinking contaminated water, could also transmit the infection to an individual.

PCR examination of the cyst content aspirated from suspected cysts might be an approach, but the procedure may cause rupture of the cyst and risk of anaphylaxis. Furthermore, PCR examination for *Echinococcus* is currently not available in Scandinavia. Another option to confirm or disconfirm the working diagnosis was the test of treatment. (82) My conclusion was that a test of treatment with the anthelmintic agent albendazole would be the most reliable and least risky option to confirm/disconfirm the working diagnosis echinococcosis. (127)

Albendazole was introduced in 1979. It is thought to act by inhibiting the polymerization of helminth β-tubulin and in this way to interfere with microtubule-dependent functions such as glucose uptake. (27) Glycogen stores become depleted, the ability of *E. granulosus* to produce energy declines, and the larvae starve and may die. As

111. McManus DP, Zhang W, Li J, Bartley PB. Echinococcosis. *Lancet* 2003;362:1295-304.

64. Poincaré H. Science et méthode [Science and method]. Forgotten Books (original work published by Thomas Nelson and Sons, 1908). Chapter IV: Chance; p. 89.

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

127. Ntusi NA, Horsfall C. Severe disseminated hydatid disease successfully treated medically with prolonged administration of albendazole. *QJM* 2008;101:745-6.

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

albendazole is fat soluble, it should be taken with a fat-rich meal to increase bioavailability. The World Health Organization (WHO) has issued recommendations for the treatment of echinococcosis with albendazole. (128)

Case 1, female, 60 years old, responder

The two most debilitated patients in my practice with extreme chronic pain and fatigue were offered test of treatment with albendazole on September 8, 2008. They were given verbal and written information about hydatid disease and about albendazole. One of them declined because she found my working diagnosis to be too odd. The other patient thought that my working diagnosis might be correct and wanted to try the albendazole test of treatment. She was 60 years old and had experienced chronic abdominal pain since the age of six. The pain worsened when she was 19 years old and worsened seriously when she was 46 years old. Despite extensive examinations in the most prestigious university hospital of Norway, no causes were found for her symptoms. Her extremely intense pain 24 hours a day was located in the region of the liver/right diaphragm and she scored the pain intensity as varying between 8 and 10 on a scale from 0 to 10. During the last 12 years, she had to use codeine and pethidine daily for pain relief. Her second most debilitating symptom was severe fatigue.

After seven days of albendazole 400 mg twice daily (10 mg/kg/day), accompanied by 40 g of fat, she developed deep venous thrombosis (DVT) in her left leg and was admitted to the local university hospital. Albendazole treatment was discontinued. During her hospital stay, a nodulus in the upper lobe of the right lung was discovered. The nodulus, which was invisible six months earlier on CT, was examined by biopsy. Injection of local anaesthetics into the thoracic wall and pleural cavity during this procedure resulted in nearly total relief of the excruciating pain localized to the liver/right diaphragm. It seems apparent from this fact that the cause of the pain anatomically was related to the pleura adherent to the right diaphragm. The lung nodulus was surgically removed a month later. Histological examination revealed a completely benign tumour that was not a hydatid cyst.

As echinococcosis could not be verified by serological analysis, I thought that *E. granulosus* might instead leave traces of its metabolism in the human body. In the CNS, human nerve cells aerobically metabolize glucose, the end products of which are CO_2 and H_2O, which are evacuated from the body through circulation and respiration. In a healthy brain, there should be no production of lactate. If CSF contains lactate in higher concentrations than normal, it would be an indication of a microorganism in the CNS using fermentation as its metabolic pathway.

On October 30, 2008, I happened to search PubMed for chronic fatigue syndrome and 4387 results were returned. The third among these was an article by Sanjay J. Mathew et al.: "Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with general anxiety disorder: an in vivo 3.0 T (1)H MRS imaging study." (129) It was enchanting to me to see an exact confirmation of my previous

128. Pawlowski ZS, Eckert J, Vuitton DA, Ammann RW, Kern P, Craig PS, Dar KF, De Rosa F, Filice C, Gottstein B, Grimm F, Macpherson CNL, Sato N, Todorov T, Uchino J, von Sinner W, Wen H. Echinococcosis in humans: clinical aspects, diagnosis and treatment. In: WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern, 2001; pp. 21-48.

129. Mathew SJ, Mao X, Keegan KA, Levine SM, Smith EL, Heier LA, Otcheretko V, Coplan JD, Shungu DC. Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with general anxiety disorder: an in vivo 3.0 T (1)H MRS imaging study. *NMR Biomed* 2009;22:251-8.

theoretical assumption about lactate in CSF, which additionally supported my working diagnosis of echinococcosis.

The patient who received albendazole treatment for seven days experienced minor improvement during the last two days of treatment and wanted to try the treatment once more. Her mother and an aunt had also been diagnosed with DVT, although at an older age. DVT was not mentioned as a side effect of albendazole treatment, but I thought it could not be definitively excluded as being related to the treatment. I explained this to the patient and told her that if there was a connection, a worst-case scenario might be fatal cerebral infarction even though she was now on warfarin medication after the DVT. The patient was urged to think matters over again. After doing so, she said that she would definitely try the treatment once more despite possible risks.

For documentation purposes, I videotaped an interview with the patient about her symptoms on November 12, 2008. The patient restarted the test of treatment with albendazole 400 mg twice daily (10 mg/kg/day) the next day. After four days of treatment, the involuntary movements of her extremities decreased and then disappeared completely after 16 days. After a week of treatment, she felt as if her body were 10 kg lighter, she moved more easily, her chronic diarrhoea disappeared, and her nightmares and screaming during sleep were relieved. She used to be bothered periodically by flickering in a part of her visual field, obstructing her ability to read. During the first treatment period of 28 days, her visual disturbances disappeared, as well as her heart palpitations. However, there was no pain relief.

After a week of treatment holiday, her nightmares recurred, although they were milder than before treatment. After 14 days of treatment holiday, as recommended by the manufacturer (GlaxoSmithKline) and WHO, (130) the patient started a new treatment period on December 24, 2008. After a week of treatment, the patient experienced notable pain relief and expressed that she had never had such a good day during her entire adult life.

The patient underwent six treatment periods of 28 days interrupted by 14 days of treatment holidays. The excruciating abdominal/diaphragmatic pain diminished gradually from the middle of the second treatment period. During the fifth treatment period, the abdominal/diaphragmatic pain disappeared completely. The degree of fatigue was markedly reduced as well. However, the patient still had aching pain in her back, shoulders, arms, and hands, in addition to diffuse pain in the right part of her body. There was no pain relief from albendazole treatment for these symptoms.

The patient experienced sweating and felt unwell after sugar intake before treatment. During the fifth treatment period, she experienced decreased intolerance to sugar intake. She used to feel hungry half an hour after dinner before the treatment started. During the sixth treatment period, she felt full for 3–4 hours after dinner. Despite substantial symptom relief and a better quality of life, she felt generally more depressed during and after treatment.

Another albendazole treatment period, now with a dosage of 600 mg twice daily (15 mg/kg/day), started on August 17, 2009 and lasted 10 weeks without interruption, but there was no further notable treatment response. However, after discontinuation of albendazole on November 2, the patient's abdominal pain recurred gradually.

130. WHO Informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. *Bull World Health Org* 1996;74:231–42.

After four months without albendazole, she estimated abdominal pain intensity to be about 50% of what it was before any albendazole treatment.

Theorizing that the pain might partially be caused by an inflammatory reaction, I prescribed prednisolone 30 mg/day for three days in January 2010. She experienced a 50% reduction in pain and therefore continued prednisolone treatment of 5 mg/day and found this dosage to reduce pain by approximately 20–30%. However, because of the appearance of epigastric pain, prednisolone treatment was discontinued after only two weeks.

The abdominal/diaphragmatic pain recurred gradually and at the end of 2011 was approximately at the same level as before albendazole treatment. The patient obtained permanent symptom relief of visual disturbances, heart palpitations, involuntary movements, screaming during sleep, and nightmares.

The patient started methotrexate treatment on March 15, 2012, at a dosage of 7.5 mg once a week, with folic acid six days a week. She responded to the treatment within two weeks and experienced less pain and increased mobility. Most apparent was the improved supination of her left hand and a decrease in the excruciating abdominal/diaphragmatic pain. The methotrexate dosage was increased to 10 mg once a week starting on April 4 and further increased to 12.5 mg once a week on May 2. The patient now estimated the pain to be approximately two thirds of the previous level. She could now reduce the dosages of pain killers. She felt she had more energy and attributed the change to reduced pain.

Case 2, female, 49 years old, responder

The second patient accepting test of treatment was a 49-year-old woman with previously diagnosed fibromyalgia, migraine, and cluster headache. She was a former heroin addict who had been taking methadone since 1994. The cluster headache often seemed to be provoked by lying on her right side. The patient spontaneously reported deviating to the right when walking and that she felt something was wrong with the right part of her body. She had generalized pain, as well as an especially intense pain in her right thigh and anaesthesia on the lateral parts of the right thigh. The pain symptoms responded remarkably to a hot and dry climate. She gradually became free from pain during a week when she stayed in Egypt. During a stay in Turkey with its hot climate and extremely high humidity lasting for two days, the patient experienced more pain than ever.

The albendazole test of treatment started on January 20, 2009, with a dosage of 400 mg twice daily (less than 10 mg/kg/day). The patient responded with the first notable symptom improvement after five days of treatment by experiencing less pain. On evaluation after 11 days of albendazole treatment, the patient reported experiencing markedly less fatigue, pain, muscular stiffness, vertigo, cluster headache, and migraine. She estimated the intensity of the pain to be 8 to 10 before albendazole treatment, now reduced to 6 to 7. She had rarely experienced such low levels of pain before. She felt more refreshed after sleep, her nightmares were reduced in intensity, and she could more easily discriminate between dreams and reality. Her memory was better and she could more easily read as a result of better vision. The improvement in coordination and mobility after just 11 days of treatment was striking when I saw her. She used to get a headache when stressed by something such as seeing a doctor. On consultation after 11 days of treatment, she was free from headache. The patient did not tell her relatives and friends about the test of treatment and they all commented that something remarkable and for the

better obviously had happened to her. (The patient in case 1 experienced a similar response from her friends.)

After 23 days of treatment, she could better climb the stairs because of better balance and increased muscle power. She had fewer nightmares and dreams. The pain in her right thigh and the anaesthesia on the lateral parts of the right thigh were reduced and she now had hypoaesthesia in this area. She used to have diarrhoea, but after four weeks of treatment, it was nearly normalized. Heart palpitations, migraine, and cluster headache were gone. She felt better, more normal, and less depressed. She used to have tics around the eyes, but the tics had disappeared. She was also less bothered by crippling in her right leg.

After 28 days of treatment, she felt less dizzy, especially when rising from a chair to a standing position. Vision, coordination, and balance were better. She could now climb the stairs without pulling herself up using her arms. The sensation of the skin on her right thigh had become better and the delay in sensation on her skin was reduced. She had more energy and took more initiative. Her memory was better and her friends had commented on it. She felt calmer and less depressed, did not start to cry as easily as before, and was less irritable.

A treatment holiday started on February 25, and on evaluation 14 days later, the pain and numbness on the lateral parts of her right thigh had resumed, but not to the same level as before treatment. She was still free from migraine and headache, and her balance and vision were still better. However, she developed infectious bronchitis and was treated with amoxicillin.

After four weeks without albendazole, she again had cluster headache and migraine. Her nightmares also resumed. After another three days (March 26), she developed an abscess in her right thigh and was hospitalized and treated surgically.

Albendazole was again started on April 23. There was no response after a week of treatment. On May 4, she developed an abscess in her right forearm, where she had been unsuccessfully punctured for intravenous treatment during her hospital stay. I evacuated the pus from the abscess. The patient reported less pain in the region of the kidneys and micturition was better. She used to be completely incontinent and unaware of spontaneous urination, but could now sense that she needed to urinate. She was also less oedematous in her legs. Heart palpitations and precordial aching pain was reduced. An abscess on her right thigh was evacuated on two consecutive days. The patient thought the abscess was due to a former sumatriptan injection.

After 12 days of albendazole treatment, the nightmares again disappeared. After 14 days, she slept very well and felt more refreshed and energetic after sleep. Her legs and hands were less oedematous. Ringing in her right ear synchronous with pulse had disappeared a week earlier. She had fewer heart palpitations.

When she had finished 32 days of albendazole treatment, a new treatment holiday was introduced on May 26. She now reported much less abdominal pain, fewer heart palpitations, better balance, less chest ache, far fewer nightmares, better sleep, feeling more refreshed after sleep, more energy, less ringing in the ears, less oedema in the body, and less locking stiffness in the knees. She had less pain in the region of the kidneys and less pain in her right lower limb. Generally, pain was reduced from 8–10 to 5–7 on a visual analogue scale. She used to have no feeling on the lateral part of the right thigh, but now experienced numbness in the area. She could now sense that she needed to urinate, and this feeling was new to her.

A new albendazole treatment period was started on June 8 and ended July 20. After a week of treatment, she again felt better, having less general stiffness in her

body, better mobility, and less pain. She now became aware of increased tiredness and ptosis related to the ingestion of sweet foods, especially when she ate lots of ice cream. During the last year, she had had chronic skin ulcers on the medial part of her heel, on the medial part of her right leg, and on both wrists. All of these ulcers started to heal during this treatment period. The ulcers had started as small, itching vesicles. Generally, traumatic skin wounds used to heal very slowly in this patient.

I found the treatment response in the first two patients to be remarkable and undoubted. As my focus had been on fatigue and pain, the treatment response for other symptoms was rather unexpected. As a result of the observed treatment response for several other symptoms, I now thought that the rather non-specific symptoms relieved by albendazole were probably related to echinococcosis and that these symptoms might exist without severe fatigue and/or pain and represented a continuum of the disease echinococcosis.

The author, male, 59 years old, responder

I tested the hypothesis on myself, at the time of intervention a 59-year-old man. I was healthy but experienced intermittent ventricular extrasystoles. Albendazole 400 mg twice daily was started on February 9, 2009. The ventricular extrasystoles disappeared after eight days of treatment and I stopped treatment after four weeks.

A year earlier when I considered *Toxocara canis* as a working diagnosis, I had treated myself with albendazole 400 mg twice daily for five days as a self-experiment. During the last three months prior to this self-experiment, I had been bothered with aching pain in my left Achilles tendon that increased so much during running that I had to stop after 10 minutes. The pain subsided considerably after five days of albendazole treatment, which was completely unexpected, and I could again run without any problems.

I restarted albendazole treatment on April 21, 2009, because I still experienced some aching in my Achilles tendon now and then, although I did not experience any functional impairment. However, on May 10, I fell down the stairs and had a compression fracture of T9 in the frontal and right part of the corpus vertebra. I was hospitalized for six days and unable to take the medication for two weeks. I restarted albendazole treatment on May 26 and took it for six months. The pain caused by the compression fracture decreased gradually, and I started working again on July 6. I have not had any functional sequelae since the fracture occurred, but I experience a tender sensation of aching and itching corresponding to the fractured vertebra when eating sugar and carbohydrates. When I changed to a low-carbohydrate, high-fat (LCHF) diet in June 2010, I experienced an aching in the vertebra after ingesting carbohydrates, even with small amounts such as 5–10 mg.

The sporadic aching of the Achilles tendon was still there and I observed no apparent change regarding this minor ailment after albendazole treatment. However, I became aware of minor fasciculations in my leg muscles now and then, especially in the evenings. I am not sure whether I had been unaware of the symptom before albendazole treatment or whether the symptom was new to me. Whichever was the case, I tried an intensive short treatment with albendazole 1200 mg twice daily (30 mg/kg/day) starting on January 2, 2010, for eight days, with supplementation of three doses of praziquantel 2000 mg every second hour and a single dose of methotrexate 15 mg the first treatment day. This short-term intensive treatment had an apparent effect on the fasciculations, but the effect was not noticeable until 1–2 weeks after the treatment had been completed. I still have sporadic fasciculations in the leg muscles, but definitely less often.

During the last few years, I had developed skin tags along the upper rim of my right ear where the arm of my glasses rested. These skin tags decreased substantially during the albendazole treatment and have now disappeared completely during my LCHF diet. I also experienced hair growth in new and abnormal places such as the ears and ear lobes, but I did not experience any change during albendazole treatment or the LCHF diet regarding this symptom.

My gums used to be painful and easily bled when I brushed my teeth or had dental treatment. After albendazole treatment and the LCHF diet, my gums were remarkably less prone to bleeding and much less painful during such treatment.

In August 2010, I tried a new self-experiment by testing increasing dosages of albendazole on myself as follows: 1200 mg twice daily (30 mg/kg/day) for nine days, followed by 1600 mg twice daily (40 mg/kg/day) for another nine days and 2000 mg twice daily (50 mg/kg/day) for one and a half days. Every dose was accompanied by 40 g of vegetable oil. I experienced mild nausea and a very slight elevation of the liver enzyme alanine aminotransferase when taking 40 mg/kg/day. The nausea increased at 50 mg/kg/day and for that reason I stopped the experiment. Another side effect of the high doses was a more than 50% decreased growth rate of my hair and beard, which resumed gradually to normal after six to eight months.

I am still following an LCHF diet and I am no longer bothered by ventricular extrasystoles. However, if I eat carbohydrates in the evening, especially glucose in chocolate and cakes, I am usually awakened late in the night by painful leg cramps.

Case 3, male, 28 years old, responder

A 28-year-old man from Pakistan reported severe headache and syncopation (fainting) three times. According to the radiologist, MRI revealed a large arachnoid cyst in the patient's left temporal region (fig. 1). He had had atopy and asthma since he was 23 years old. He had been very fond of dogs when growing up in Pakistan.

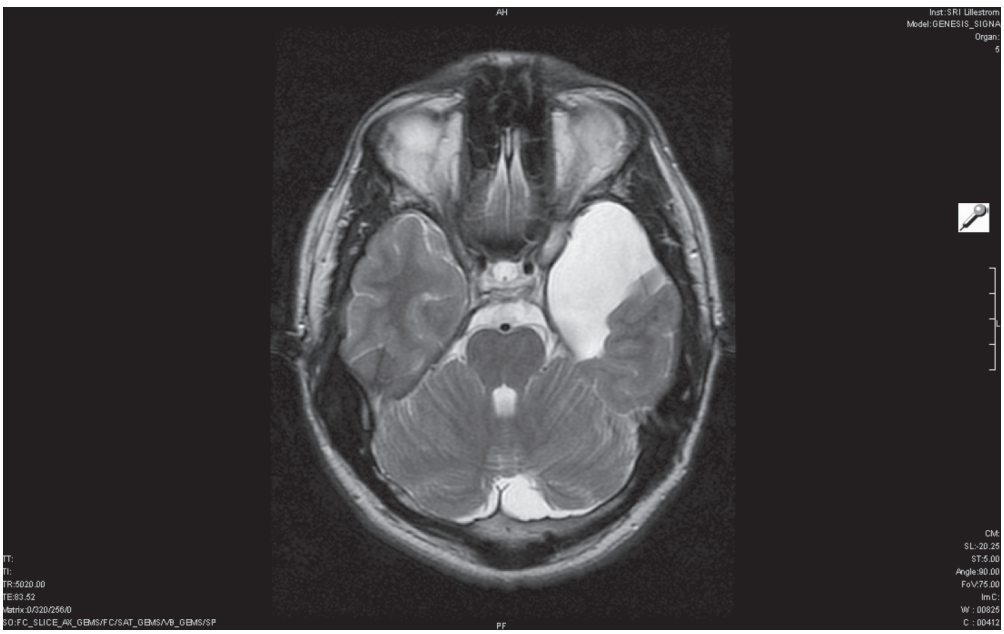

Figure 1. Case 3. MRI T2-weighted scan, January 8, 2009.