Chapter 9
Causality and Dispositionality in Medical Practice

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9.1 Some Background

I am a clinically qualified general consultant physician in general medicine and clinical pharmacology in the UK, with over 20 years of clinical experience. I have held professorial chairs in both subjects, in Zimbabwe and New Zealand respectively. In New Zealand I was also Director of the National Toxicology Group and had 10 years of experience in drug regulation and pharmacovigilance as Medical Assessor for the New Zealand Medicines Adverse Reaction Committee and the Medicines Assessment Advisory Committee. I also had similar responsibilities to the New Zealand Toxic Substances Board for the registration of other chemicals and for advice on chemical safety. I was appointed Chairman of the Advisory Committee to the World Health Organisation (WHO) Programme for International Drug Monitoring whilst in New Zealand. Following the above, for the last 25 years I was the founding Director of the Uppsala Monitoring Centre, which is responsible for the technical support to all WHO supported drug safety monitoring programmes worldwide. In that role, I was the first to develop data mining in pharmacovigilance and risk-benefit analysis. I have written over 350 scientific papers and, whilst I am now retired, I am still actively involved in teaching and projects. In all this work, the challenge of determining causality in individual patients has been paramount.

A very important issue I investigated many years ago were reports of blindness in 7 patients from around Germany, reported as possibly being due to omeprazole, a drug used to treat peptic ulcer. It was a very wide selling drug and the pharmaceutical company was particularly concerned: because of the very high sales, chance associations with blindness were possible, but it was odd that the reports were all from Germany, and besides, they were from intensive care units around Germany. The first issue that I found was that a trial use of the drug (unknown to both the

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R. L. Anjum et al. (eds.), *Rethinking Causality, Complexity and Evidence for the Unique Patient*, https://doi.org/10.1007/978-3-030-41239-5_9

pharma company and regulators) was being conducted on the prevention of peptic ‘stress’ ulcers in patients in intensive care. Then I found that about half the seven patients had taken methanol overdoses, a well-known cause for blindness. The other three were diagnosed as ischaemic optic neuropathy, which is a complication of life threatening trauma or other illness affecting the eye circulation by hypotension, which was the case for these other patients. Since literally millions of patients from around the world had used the drug without reporting blindness, and there was no known toxicological or pharmacological reason for blindness, I thought the other possible causes were most likely, in spite of the one unusual feature about these cases: they were receiving omeprazole intravenously and not by the far more common oral route. About 20 years further on I find that in huge longitudinal patient databases of over a million exposures it is suggested that blindness occurs in a few patients on omeprazole, who are predominantly female, over 60 and have hypertension: but this is another group in which blindness could be due to other causes.

Am I wrong to think that when I can see a more likely cause with a known mechanistic explanation – toxic methanol, prolonged and profound hypotension – that those are more likely the causes? And the damage from hypertension and other changes to eyesight in an aging population is at least as likely an explanation. But why especially women? There is clearly some uncertainty about my causal diagnoses here.

9.2 Considering Causality

Always we need the best information possible; we need to be transparent in our reasoning; we need to follow up and we must be open to new evidence. Clinical medicine uses multiple ways of accomplishing its ends, which are the diagnosis, treatment, amelioration or cure and, if possible, prevention of any dis-ease causing problems in an individual. At the heart of clinical medicine is an empathy with the patient in understanding what ails them in as deep and broad a way as possible. To do this, a practitioner uses, or a coordinated group of practitioners use science, art, learning and experience, and indeed whatever wisdom they can effectively bring to bear on a problem. A practicing clinician is not a scientist per se, but rather *uses* science.

Diagnosis is an essential first step. Some illnesses are easy to recognise, but even with those, there are competing possible diagnoses. Illnesses are shape-changing masquerades. Only a careful case history and examination of the patient will give us a useful picture of a range of clinical conditions for further consideration using observations and tests. A diagnostic assessment usually produces a list of possible causes to explain the patient’s clinical signs and symptoms and their chronology, and that can be listed in order of probability in any given patient and in their particular context. The key challenge is what might be the cause of this patient’s clinical state, but it is not only the various disease states (medically recognised clinical illnesses rather than their phenomenological consequences) that need to be considered, but also how that individual patient will react to a given dis-ease entity

(dis-ease being the symptoms, signs, anxieties and any other personal consequences that are concerning them). A diagnosis must take into account not only context (environmental and familial) and the various disease attributes but also those proclivities of the patient in how they respond to dis-ease challenges.

A classic triad of questions is useful:

Can a disease ever cause this clinical state?
Has it done so in other humans?
Is it responsible for the clinical picture in this particular patient?

The essence of these questions is to understand the phenomenology of the disease and then to consider causality. Some would argue that consideration of the broader phenomenological aspects (their dis-ease) – the overall impact of disease – has little or no place in determining its cause. But this is to disregard the ways in which the patient's personal background and context may influence the ways in which they present the features of their dis-ease to the clinician, and in turn how the clinician interprets those features into different categories (physical, social, psychological, spiritual etc.) and then cares for and manages them. Variations in diseases themselves and their presentations in patients may alone lead to considerable misconceptions, for example about the severity and nature of pain, or indeed the description and localisation of any symptoms within their bodies.

Commonly, we *make* diagnoses. We look for the cause of an illness, or at least for an explanation of the physical signs and symptoms the patient presents. We are limited in interpreting those pieces of clinical information by what we have remembered about disease entities and the ways in which humans respond to them. We are, however, able to use many other information sources to aid our thinking, although it will take time, experience and imagination to find all the relevant material. We may have an easy task with a clearly recognisable pattern we commonly see in our daily experience, but if we find that there are dis-ease components in the pattern (due to individual dispositions) we do not recognise, this leads to confusions. Consider a patient whose family history is one of close members having had coronary artery disease. If that patient should have chest pain, she will naturally first think that her chest pain is due to heart disease and indeed may be more likely to describe her pain as having anginal qualities, perhaps ignoring the exact position of the pain in her chest. In turn, the patient's context is ever changing and needs to be considered while making a diagnosis and subsequently during their treatment. It is at this point that the dispositions of the disease should be considered as being modified by those dispositions of the patient.

Sometimes the patterns are complex and responding to their intricacy can be very demanding. Patients are not just carriers of disease entities, they have their own dispositions which react to disease differently and also to the same disease at different times and in other situations. Dispositionality, as a way of probing the phenomenon of a person's dis-ease seems to be a useful way of analysing a clinical situation. In respect to the example just given, we now know that women with coronary artery disease present a different spectrum of symptoms compared to men.

I and some colleagues were concerned by the roll out of WHO's '3 by 5' Programme in 2003, which aimed to provide AIDS treatment to 3 million people in Africa by 2005. It was a laudable and ambitious programme, but we were concerned about the little attention to monitoring possibilities for effectiveness and safety of the known toxic treatments. I attended a meeting in South Africa soon after the launch and there were several reports of deaths from lactic acidosis, a result of mitochondrial damage. *It was noted that those early South African cases were all women.* The drugs concerned were part of the 'highly active antiretroviral regime'. Stavudine and didanosine were the main suspected drugs that had been noted to cause this problem, which was rarely seen in the US and Europe, *where it was usually only symptomatic and reversible*. Now we know that around 80–90% of cases of lactic acidosis occur in women (in Africa) and that their mortality is as high as 50%. The early experience of these drugs in the western world was largely in men, and an early paper (Brinkman 2001) promoted the idea that there was small incidence with no serious clinical significance. We therefore knew of the potential problem from before the WHO roll out, but epidemiology in males suggested a small risk.

More recent reviews (e.g. Trang et al. 2015) explain more about the mechanisms. But there is more: it is obese African women with a high body mass index that are particularly at risk. Why? Also unknown is whether there is a possible genetic cause in African women. Are there other dispositional reasons why these patients are so badly affected? Are there contextual problems, such as poor availability of lactic acid screening for early symptomatic patients, that makes the mortality so high?

Suppose the clinician elicits a full case history (and this supposes no time constraint) and does a complete relevant physical examination. Each of the findings may be a disposition of a disease entity, or of the patient reacting to their situation, or may indeed be a general disposition of that patient. For example, does one patient always look pale and possibly anaemic, or perhaps another may have so called 'white coat hypertension' (raised blood pressure whenever it is measured in a hospital environment)? We may be faced with a patient that is garrulous and often chatters inconsequentially. I once had such a patient with a large open, varicose ulcer on the leg, and a mild fever. Her son accompanying her was a senior clinician himself, who apologised saying, "She's always chatty like this." I accepted this, but decided to admit her since she needed both analgesia and antibiotics: it was also late in the evening. The following day she had a very high fever, was very drowsy and had a falling blood pressure. This was a septicaemia with delirium and the knowledge of such a possibility should have alerted me to investigate more thoroughly whether infection was starting to cause a delirium. I was swayed by my colleague's reassurances with near disastrous consequences. She had a perilous passage through intensive care with a severe septic shock. Embarrassingly both mother and son were grateful to me.

In the past and now also in the present, many seek a single cause for an effect. It seems, however, much more useful to think of possible causes and to understand their mechanisms, and so consider a range of probabilities of causality based on the situation for a particular patient. A sore throat is likely to be infectious if a person has been enclosed in a crowded space during a winter epidemic but one would be more likely to consider a drug cause (e.g. the much rarer agranulocytosis) than if the

sore throat occurred de novo while the patient was convalescing alone and already taking an antibiotic.

This clinical consideration of patients demands a broader view, deeper thinking and longer timeframes than most epidemiological studies or clinical trials allow in providing evidence useful in clinical practice. Clinical trials tend to focus on a simple connection between cause and effect – the likelihood of drug X being strongly associated with effect Y for a statistically significant proportion of those who take it, compared with controls. But a strong *association* is not proof of causality on its own, it remains a strong probability only. Nor is probability proof of a *cause*: it is essential to couple cause with effect by understanding the various ways in which attributes (or dispositions) of the disease, of the patient, and of the treatment and the context of the patient all interplay. Moreover, perfect, linear, causal relationships are rare in medicine, and the strength and variation of a disposition are as important as the fact of its mere presence or absence.

Causality will also become ever more important as we attempt to make the best use of genetic mechanisms behind the ways our bodies function. The new generation of gene therapies and other such 'personalized' treatments are more targeted to specific basic biomic functions in the body, which result in our dispositions and their strengths of expression. So, a proper, dispositional grasp of causality is a vital tool in helping healthcare professionals reach the best judgements, especially when time, resources and reliable information are in short supply. A keen understanding of all the factors underlying a clinical problem is the path to efficient use of resources, rather than the use of an overly simplistic but rigid 'guideline'; guidelines should reflect nuances of variation rather than simply dictating a pathway to a single algorithmic 'truth'. It is therefore better to consider a *causal explanation* of how a patient's symptoms and signs might appear as they do rather than to concentrate on the ideal of a single direct cause and effect. That is, to consider that the whole phenomenon of dis-ease includes the propensities of other dispositions to have an additive, augmenting effect as well as possible secondary effects.

Consider for instance a hypertensive patient, treated with beta-blockers, who dies from anaphylaxis after a bee sting or another allergen such as penicillin. The beta-blocker may well have contributed to the causal mechanism underlying the fatal event, by reducing the cardiovascular response to the severe hypotension caused by the acute allergic response. Similarly, the known sedative effects of a beta blocker may add to those of a benzodiazepine in a patient with a high blood pressure thought to be due to anxiety, with the result in a secondary effect of a fall with injuries. There would be a degree of speculation in such situations about what was in fact causative. Such speculations would probably not prove practically useful in the acute situation but they may give some chance of avoiding similar occurrences in the second case, and accumulating experiences of this kind might point towards a way to allow avoidance of important problems for patients in the future.

An elderly relative, taking warfarin anticoagulant after a series of minor strokes, developed heart failure and was treated with a frusemide, a diuretic commonly used to remove excess water from the body. He improved and his ankle swelling from the heart failure reduced. Some days later, he had a rash and painful ulcers on his lower

legs and feet. The nursing home staff said they thought it was bed sores since he had been sitting and lying most of the time. I was sceptical because the ulcers were on the front of the feet and legs, not the right place at all. A dermatologist was consulted who suggested that the rash was a vasculitis, and I was able to suggest that frusemide was the cause, and the diuretic was changed. It was all too late; for he found the pain from the vasculitic ulcers so bad he needed morphine which made him sleepy and his breathing was also suppressed. He developed pneumonia and died peacefully from two adverse reactions to his treatments: the frusemide caused vasculitis, which caused pain, which caused morphine, which caused respiratory depression, which caused bronchopneumonia, which caused death. This kind of complex chain is quite common in medicine and illustrates why a causal explanation is valuable for understanding.

Some causal logic	**Implication**
Necessary cause D → E E → D	If D happens then E will happen, if D does not happen E will never happen – necessary cause or condition
Sufficient cause D → E Z → E	If either D or Z happens, E will happen – sufficient cause or condition
Contributary cause D → E Z ↗	If D happens , E may happen, but only with z –contributary cause or condition
Secondary/remote cause D → Z → E	If D happens Z may happen & then E happens – secondary cause

Most clinical healthcare practitioners would like to practice medicine with a detailed and empathetic diagnostic work-up including some of the considerations above, but also most of us know that time constraints do not allow for every patient to have a full assessment. In very many instances, such an approach is unnecessary and even counter-productive: emergency situations and the treatment of acute common diseases with generally good outcomes are examples. It is nevertheless wrong to consider one instance of contact with a patient in isolation as adequate. One meeting with a patient allows a preliminary assessment of immediately important dispositional factors. A patient meeting with her family medical practitioner for the first time for years may be asking for a symptomatic remedy for a persistent cold and cough and then mention a heavy period as an aside. The same patient may refuse an examination on the grounds that she is embarrassed because she is currently bleeding. Treating the symptoms of a cold without making an arrangement to properly pursue the vaginal bleeding would be a mistake indeed. It is very helpful to have continuity of care where a single clinician knows a family's background, and would be alert to behaviour that was unusual.

There are some instances where treatments are routinely commenced with a complete assessment of how an individual patient differs from the norm, followed

by a carefully-balanced choice of medication bearing in mind the variability of the cause(s) and additionally keeping a close eye on how things turn out in the long term. The way of using antiretrovirals for HIV/AIDS is an obvious example. AIDS is a chronic disease which has various phases and states of ill-health (dis-ease), some induced by the changes, sometimes progression, of the disease process and sometimes due to treatments. Because the immune system is negatively affected, it also leaves the body open to various kinds of infections and different kinds of neoplasia. Patients change over time, as do their diseases and treatments, not only because of some disease processes but also because of aging. These patients and all people need careful monitoring in all aspects of *their* lives. Diseases and their management are all unique phenomena. But this sort of premium care is still unusual since it can only be delivered through healthcare systems with extensive personnel and technical resources linked to stable and well-organised health services.

For all patients, however, it seems best to consider *why* a particular clinical effect happens, *what* can be done about it, and *how* best to take action. This points to the need for a far more nuanced and holistic approach, which acknowledges that the way a treatment acts on an individual depends on their constituent dispositions towards different disease effects. It is about who those individuals are, where they are, their circumstances, history, what they eat and any other conditions or substances that affect their body systems. In aging societies, those older people are likely to suffer more illnesses, live with more chronic conditions and take more drugs to counteract them. This has profound implications for understanding causal relationships between dispositions. Successful management of a patient is best achieved by getting detailed information from, and on, an individual's dispositions, then matching it to the known characteristics (dispositions) of the treatment and then following up the patient to ensure that an optimal result has been gained.

Traditionally, medicines that demonstrate a high probability of achieving the desired outcome in controlled conditions are considered safe to market, prescribe and use. But in the real world, we know that even the best drugs typically only work as desired around 70% of the time. Variables driven by misdiagnosis, treatment variables such as dosage and compliance play out alongside environmental, genetic and individual factors to reduce the actual effectiveness, so therapeutics can only be improved by exploring risk and benefit probabilities and carefully monitoring outcomes, particularly of new treatments.

9.3 Diagnosis and Decisions

Causality in individual clinical decision situations is much too important to be left to chance or limited to the broad-brush norms defined by epidemiology. And we shouldn't let the cost or difficulty of pursuing the ideal deter us from doing what's right and good. Patients need and deserve nothing less.

Establishing a working diagnosis is the first major goal. The first focus of a clinician will be on the characteristic dispositions of the possible disease entities,

arraying them in order of likelihood (differential diagnosis). This should also take account of the patient's context (environment) and the ways in which the human body tends to respond to the disease to produce symptoms. There are likely to be uncertainties due to gaps in information, or to variation in the strength or likelihood of features (dispositions) of the disease or of the dispositions of the patient such as response to pain or blood loss or immunity. What is the most likely causal link that explains the patient's symptoms and signs – qualitatively as well as quantitatively? What important data is missing and must necessarily be found before one can decide on a plan of action? What are the key dispositions we can use to follow the progress of the patient and the disease entity? For example, a microbiological identification and presence of bacteria in different body tissues or excreta usually enables us to decide on the dispositions of the likely causative organisms. We might, however, need to act without knowing the precise nature of the infection. But we can start treatment before the microbiological tests are done, then we must follow up the effect on the patient carefully, which includes measuring the temperature and heart rate of the patient and any other key dispositional responses ('vital signs') that may change, as well as measuring the success or otherwise of the patient's response to the infection. We also see that therapy and management have dispositions as well: the chemical structure, pharmacology and toxicology of any medicinal product have their dispositions, good and bad. They too interact with those of the patient and disease entity. Management may include other therapies than drugs such as chest physiotherapy to expel unwanted secretions in acute bronchitis or pneumonia.

A proper, dispositional grasp of causality is a tool to help clinicians reach the best judgements, especially when time, resources and reliable information are in short supply. Dispositional thinking is a dynamic way of sifting evidence about both disease and patient.

Many clinicians will think that talking about dispositions adds nothing to the way they already do their work, and indeed that dispositionality brings confusions. Many clinicians also feel that they have enough experience and intuition to pick up nuances of both patients and disease behaviour that are outside the norm – and many can. The stress, however, of work, of time pressure, of limited resources, can lead to mistakes being made. Thinking dispositionally can provide a way of double checking what we do and highlighting uncertainties that are inherent in diagnosis and management decisions in medicine.

Thinking about the dispositions of both patient and disease leads both to completeness and clarity in management. For example, the patient may be an aging alcoholic (dispositions to check might be liver and kidney function etc.) and the drug might be toxic at higher dose levels (so considering how it is metabolised and excreted might lead to a lower starting dose). Recognising these factors might also lead to the necessity of following up the patient after a given time to check on the patient's progress, perhaps with appropriate tests. Other less obvious considerations may follow from these more obvious ones, such as checking the patient's memory (any early dementia), their eating habits (if the drug should be taken with food) or their daily habits (if the drug is a diuretic they should be informed about the likely time of the diuresis, and plan to be near toilet facilities during that time).

9.4 Overview of Important Dispositional Insights in Clinical Care

1. Personal attitudes toward the patient can influence one's assessment and actions. This is an underused but key matter and a useful test of one own overall disposition in relation to the patient.
   - Do I like this patient? Do I find that the patient smells? Are they condescending and impolite? Or engaging and lively?
   - There are many more sophisticated possibilities and eliciting them will allow a critical view of factors that need to be considered and allowed for in the patient interaction.
2. What are the clinical dis-ease symptoms and signs in this patient?
   - Does the patient look ill or in pain? Are they afraid? Are they embarrassed? Impatient? Are they hesitant or in any way unclear in their responses?
   - These are dispositional features that must be taken into account in the interaction with the patient as well as being of diagnostic import.
3. Checking the clinical findings about diseases against prior clinical knowledge: what is key, what is missing, and what is unusual?
   - Assumptions dependant on scholarly descriptions of diseases and on experience can be limited in scope and misleading. A conscious check on the dispositions presented by the patient can help avoid premature assumptions.

     (i) As the patient's story unfolds and physical signs are elicited, the clinician will be alerted to a range of diagnostic possibilities to check against known features of diseases. Missing data must be considered carefully with each potential diagnosis. The variation in power of disease features needs to be considered against the array of responses possible given the dispositions of the patient. Consider an easily understood example from my own experiences of investigating pain. The *type* of pain is tricky, as it can be challenging to determine across cultures. In Zimbabwe what many would say is a 'stabbing pain' is described as 'pricking', thus raising questions about how severe a pain is. Even when the site of a pain is described, it may confuse a clinical appraisal because of the anatomy of the nervous system where a nerve branches, and disease affecting one branch is felt in an area innervated by another (referred pain). This may cause confusions in dental pathology, for example.

     (ii) The patterns of symptoms and signs elicited may overlap for a number of diseases. The immune responses to infections, to cancers and to other invasions by entities recognised as foreign to the human body can provide examples of this kind of confusing situation. Spontaneous abortions may be due to the mother's body recognising the fetus as a foreign invader, for example. Infections produce a change in the immune system that result in

normal body tissues being seen as foreign, in autoimmune disease (although this may be triggered in other ways, too).

(iii) Consideration of the interplay between various dispositions of the disease and its unwilling host, leads us to analyses of powers of diseases, their modes of expression and their actions. In turn this gives us ideas about useful laboratory tests and further monitoring of the patient's situation including the kinds of treatments that might be useful.

Considering dispositions also leads to considerations about what other evidence might be available to understand the disease and treatments and particularly in understanding cause and effect relationships.

4. Specific help can be obtained from the Bradford Hill proposals (Hill 1965) as well as DoTs (Aronson and Ferner 2003) and EIDOS guidelines (Ferner and Aronson 2010).

5. It is useful to think about dispositions in considering the value of evidence available from other sources, and particularly statistical associations. The choices of keywords in searches are usefully specified using dispositions, for example.

   – Decisions in managing patients such as choosing a medication are critically determined by choosing the correct medicinal product to be active against the disease, but not to do harm to the particular patient, who may be sensitive and consequently harmed by one product and not another.
   – The weighing of effectiveness against risks makes any such decision challenging. A dispositional approach to an individual's possible idiosyncrasies and much more dispositional information on the effectiveness - risk profiles of medicines as they are used in routine clinical practice, as opposed to controlled studies, is needed.

6. Interactions between dispositions is important where multiple diseases might or do coexist in patients, or when multiple therapies are in use.

   – Whilst commonly found in older patients, there is an increasing propensity for multiple disease/ treatment situations to develop as more medical disease situations are recognised.

7. Causal explanations, including possible interactions between dispositions, are of considerable value clinically even if speculative: the speculations are enhanced with other similar occurrences and by prior scientific or clinical evidence of the powers of those dispositions. Any instances of interactions and unusual outcomes should be reported in detail and be made available for others to share.

8. Many individual and rare medical situations fall outside the norms usually considered in controlled clinical trials and even controlled observational studies. Thinking about variations in the disease and patient dispositions possible through theoretical and practical knowledge of mechanisms is important.

- Rare disease presentations and unusual adverse reactions may not occur often in relation to an individual disease or medication, but the totality of such examples over the whole of healthcare is huge. Adverse drug reactions were the 5th most frequent cause of death in the US and similar findings have been seen in several other countries.

9. As we learn more about genomics and biomics, the links to the incidence and powers of dispositions will be very important in diagnosis and therapeutic decisions.
   - Linking statements 6 and 7 emphasises the value of individual case reports with full descriptive detail to allow medicine to progress.
10. *Causal explanation* needs to be more widely practised to allow us to understand better how the propensities of different dispositions of disease, patient and treatment interact for better or worse outcomes.
    - Rejecting the inclusion of subjects with identifiable potentially confounding propensities is a two-edged sword: it allows for clarity in identifying a possible statistical association but removes the potential for multivariate analysis.
    - Statistical association and particularly non-association should always be tempered by what we know about the possible mechanisms by which a proposed cause could produce an effect, plus any other dispositional evidence demonstrating why a particular instance of cause and effect might be rare or unique.

9.5 Conclusion

Humans share many attributes but there are many examples of unusual ('orphan') diseases as well as rare adverse reactions to therapies. These situations need dispositional thinking and not only epidemiological, normative approaches. Having had the privilege of being a clinician as well as working in a scientific setting experimenting with drugs and chemicals, I can conclude that medicine is not a science but the application of described knowledge or knowledge acquired by experience. Medicine is its own discipline in which the essential skills are:

1. For the clinician to match the dispositions of the patient in front of them with all their acquired knowledge of others who have similar dispositions, to find the closest binary match and to understand the probable constitutions of their patient.
2. The clinician must understand the dispositional weaknesses of their particular disease(s) and so, choose a treatment that has the maximum benefit for the patient with the least harm.
3. All of this must be undertaken with a specific aim of treatment that is in agreement with the patient and takes account of the patient's social context using an empathetic and holistic (phenomenological) approach.

4. Clinicians also have responsibility to ensure that all their reasoning from diagnosis and clinical management works in real-life clinical practice. They must pass on to others their knowledge, particularly when outcomes are unexpected.
5. The responsible clinician should also try to identify *why* the unexpected outcome occurred, so adding to global knowledge.

It is clear that the above six points are most difficult to attain, but the vision should remain.

References and Further Readings

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