

Theory and Practice - How do they relate to each other, and why is a practice such as homeopathy theoretically unacceptable?

Prof. Jan P. Vandenbroucke

Department of Clinical Epidemiology, University of Leiden/The Netherlands

Medicine is a «stochastic» art. The aim of medicine is not to achieve cure, but to do everything possible according to established theory to make cure happen. To accept the principle of infinite dilution, for example, goes against established theory of chemistry, physics and biochemistry! Its study by randomized controlled trials would be a simple game of chance. It would be a great waste of time and effort to try all alternative therapies in randomized trials. It is warranted only in the instance of a genuine surprise by a regular physician that something might work.

My contribution will consist of two parts. In the first part I will try to give you a general introduction into the relative role of theory and practice in medicine, and I have entitled this first part «*medicine as a stochastic art*». And in the second part I will try to propose criteria of when to take claims for alternative medicine seriously and when not.

Medicine as a stochastic art

Let me begin with *medicine as a stochastic art*. To explain this idea I have to go back to *ancient Greek* writers. I will not present you *Greek* - if only because I am unable to interpret it - but the texts were interpreted by KATERINE IERODIAKONOU who is a Greek philosopher working at the *London School of Economics* at the department of Philosophy of Science. She studied these texts, in preparation of a doctoral thesis on the history of science. She presented the ideas to a symposium on the history of medicine, thinking that they were only relevant to historians. When I read the abstract of her presentation I told her that her ideas, or at least the ideas of the *ancient Greeks*, were still extremely relevant to modern medicine. This meeting led to us writing a paper together which appeared in *the Lancet* of February 1993. If you are interested in the basic *Greek* texts you will find the references there.

The *ancient Greek* doctors and philosophers - there was sometimes little distinction - said that medicine was a peculiar art which they called a *stochastic art*. A stochastic art because it was not *deterministic*. What did they mean? They meant that a

doctor can treat a patient according to the best principles, according to all the rules of the trade, and nevertheless the condition of the patient may deteriorate. Another patient can be treated somewhat carelessly by another doctor, not treated really according to the rules, and yet the patient improves. So, in medicine, there exists some unpredictability between means and ends. You cannot foretell the outcome from what is being done, or vice versa.

This is peculiar, the *ancient Greeks* said. And this is different from other arts, for example, compared with architecture - or building a wall. From the end product, from a built wall, you can see whether the work was done properly, because you can see if the wall is straight, then the work - the process of building the wall - was done properly. Not so in medicine! The patient can be cured which does not necessarily mean that the right diagnosis was made nor the right treatment given - and vice versa.

The *Greeks* knew of other *stochastic arts*, for example, the art which we are cultivating today [at the symposium]; the art of *rhetoric* was also a *stochastic* art. Why? Because, even if you use all the tricks of *rhetoric* you are not certain to convince all people in the audience. So again, there is unpredictability between ends and means. In that view, they redefined the aim of medicine. They said the aim of medicine is not to achieve cure, not to achieve health, but to do everything possible to make cure happen. And they used the analogy - the famous analogy of the *Stoic ethics* - that medicine is also like someone aiming with a long bow and arrow at the target. You should not judge whether he's a good shot or not only because he hits the target or not. Rather, you should judge whether he aims in the right way; and if he aims in the right way then he is a good shot even if he misses the target; because there might be an occasional wind coming along dragging the arrow off, which has nothing to do with the art of shooting. So there is this very strange idea which is still true in modern medicine; that there can be a wind coming along and whatever you do for the patient, it will fail. It is an idea which is highly relevant when we think about discussions on quality assurance. Over the past two decades we have had discussions about whether we should use outcome or process to measure quality. Now the ancient Greeks would certainly have said that we should use process. And most theoreticians of quality assurance still say so for exactly the same reasons. They say that you cannot tell the quality of medicine from the outcome of medicine. You cannot tell that someone has performed poor medicine because the patient dies. Of course, it is true that, if a surgeon, for example, has a series of very poor outcomes in a row, there might be something wrong with his technique. It might be a warning sign, but not necessarily so. It might simply be bad luck, or he might be a very good surgeon to whom the worst cases are sent. Only direct inspection of the technique, of the process, will tell whether he's a good surgeon or not.

This *stochastic* element is even the reason why, in evaluating new therapies, you use the whole armamentarium of randomization, control groups, modern epidemiology and statistics, because our greatest fear is to compare the incomparable. Like in the assurance of quality or a judgement on quality, judgement of new methods should be done taking stochastic elements into account. The ancient Greeks would not have been a major source of our civilization and much of our thinking if they had not gone yet one layer deeper. They wondered *why* medicine is a stochastic art, and here, they were split. There were two explanations which were offered in the 2nd century AD. The first explanation was by ALEXANDER APHRODISOS in the 2nd century, who said that the *stochastic* element is a fundamental property of medicine. Because, he said, medicine never proceeds by simple syllogisms. We all remember from secondary school what simple syllogisms are. They say: all men are mortals, Socrates is a man, so Socrates is mortal. ALEXANDER says medicine is not like that. Medicine reasons by expressions like «in most cases» or «only in a rare instance», which are statements that are true in general, but not for a particular patient. So, ALEXANDER said, medicine has no universal truths, only empirical evidence. In great contrast, in the same century, GALEN said, «No! Medicine is as good as any other science; there are universal truths, but only the application is fallible because of individual patient variation.» This very old debate was also mentioned by PARACELSUS - who seems to have a quotation apt to any occasion - who said that *there are two approaches to the study of medicine: One in the books and one in nature*. It was greatly expanded by WILLIAM CULLEN in his introductory lectures to medicine at the end of the 18th century, who said that for two thousand years, there had been two plans proposed for the study of medicine, the *dogmatic* and the *empiric*. We still do not know what choice to make.

ALEXANDER's theory could be very fashionably rephrased, for example, by invoking *chaos theory*. Chaos theory propounds the idea that whole systems can become unpredictable, can become undeterministic, even if the component parts are completely known. It is said that long term weather prediction will, in principle, always be impossible for that reason. Even if, from day to day or year to year, or over centuries we can predict events of a solar system; in the end, its behaviour is unpredictable. We might also say that each individual human being, as a whole, might be so complex biologically that we never will be able to logically predict what will happen if we do something like giving a drug. Even if one knew the whole human genome, and how it works, maybe we still would not be able to predict the whole. Part of the culture of randomized controlled trials in medicine is rooted in a similar suspicion. Something might seem perfectly logical from a biological point of view, it might even work in the laboratory, might even work in experiments with animals, and might even work in the first

few patients, but when evaluated systematically with a proper control group - it fails. We might have a very good insight into the etiological role of cholesterol in producing coronary heart disease. Still, all attempts at introducing a cholesterol reducing therapy to reduce mortality have failed, except in extreme subgroups. The theory of ALEXANDER is still relevant, and it even underpins some of our thinking about randomized controlled trials. On the other hand, the theory of GALEN is a great comfort for basic scientists, because GALEN believed that there were universal mechanisms, and basic scientists are studying these. The application might be fallible, but with time, this will be solved. Then there will be direct application, direct reasoning from biological principles to the patients. It is important to realize that most physicians still, and perhaps rightly, reason in a *Galenic* way. If you ask a physician about a particular patient, why he or she has treated a patient in a certain way, then you will get a story about a mechanism, like playing with building blocks. Something goes wrong in the cell, something else goes wrong, and there is a consequence, and if we understand it, maybe we can influence the problem at that level. If we need empirical checks, they are conveniently forgotten. Suppose you ask a cardiologist: Why did you treat that patient with *streptokinase*? He will explain the *coagulation pathway* and explain where *streptokinase* intervenes therein. He will never tell you that it is because of *GISSI-1* or *-2* (the mega-trials). This tendency for explanation is so strong, that even in medicine we use explanations where there are none. Take *aspirin*, for example. Nowadays, we think we know how it works - by influencing *prostaglandin metabolism*. But twenty years ago, if you had asked a doctor, why do you prescribe *aspirin*?, he would have said, Because of an *antipyretic* effect. He would never have said, Because some natives in *America* once cooked a concoction from the bark of a tree, and they say it lowers fever. If one asks the cardiologist, why do you use *digitalis*, he will answer: I use *digitalis* because it has a *positive chronotropic and inotropic* effect - which is a *linguistical tautologically* statement saying «because it works». He will never tell you that there was an old woman who cooked a concoction of foxglove, and saw ankle edema reduced in people who used that concoction.

The empirical base is almost always forgotten and one can wonder why. I do think it is impossible that physicians are reasoning wrongly, since this is so strongly prevalent in their way of behaving and of thinking. Part of the reason might be that medicine must be more than a collection of facts, because by facts alone you cannot treat individual patients. Each individual patient is a slightly different mix of pathophysiologic mechanisms. Randomized controlled trials give only averages. To treat individuals, one always has to reason, to make trade-offs between different mechanisms, in order to make a decision. One has to reason; one cannot use a collection of facts. As CULLEN said at the end of the 18th

century: «At the present state of affairs; we need both, the dogmatic and the empiric, because neither is sufficient.» I can only concur. Medicine is rooted both in theory and in empiricism.

Criteria of when to take claims for alternative medicine seriously

What does this tell us about evaluating alternative therapies? When should we perform randomized controlled trials, when should we bother to be involved? There is a tendency by some to use a «*black box*» approach; to say that the patient is like a black box; I'm not interested what goes on in the patient, I am only interested to see what I put in and then to see what comes out. If such investigators find that there is a claim from alternative medicine, they wish to study it by the best empirical methods, to study it by randomized controlled trials! I strongly object. If there is no theoretical background, if there is no prior information from the laboratory, from animals, or from patient observations, a randomized controlled trial becomes a simple game of chance. In a randomized trial at the 95% confidence level, there is always a one-in-twenty chance to achieve statistical significance in either direction. I'm not prepared to believe the results of a game of chance, because more is at stake. What is at stake is a *judgement* that a therapy works. A judgement that a therapy works is a causal judgement, because one maintains that the therapy produces some deflection in the natural history of the patient. Causal judgements are not made from facts, causal judgements supersede facts. Here, I think *homeopathy* is a very good example. There are randomized controlled trials; some are even published in *the British Medical Journal* or *the Lancet*, saying that it works. When one looks at these randomized controlled trials, there is not too much glaringly wrong with them, because otherwise they would not have been published. There are always «*maybes*», maybes about double-blindness, intention-to-treat, sample size, etc.; but nothing glaringly wrong. Now, I have the choice either to believe the results of these games of chance with all their *maybes*, or there is the other price; to accept the principle of *infinite dilution*, the principle that dilution beyond a certain number might still be effective, and if you dilute even more it would be even more effective. This principle goes against established theory of *chemistry*, *physics* and *biochemistry*! The price is simply too high, because chemistry, physics and biochemistry are incompatible with the concept - so I discard the evidence. This is something that is done routinely by medical doctors, and we admire them for that. When a medical doctor gets one of the glossy advertisements from the pharmaceutical industry telling him or her with bright colours that a randomized controlled trial was performed in 33 patients with a new vasodilator, and that this vasodilator improved the memory of demented people, then that information goes straight into the waste-basket - whatever the methodology, whatever the *p value*! I throw away evidence from

homeopathic trials for exactly the same reason. If the principle that is proposed by alternative practitioners is in opposition to established theory - do not bother to start the trial. Whatever comes out, it will not make sense to believe it.

Secondly, there is the question; if we do not know whether it works or not, then should we test this alternative? Again, I say no, except in one instance. That is when there is a genuine surprise by a regular physician that something appears to work. This is the equivalent of the normal way of doing things in pharmaceutical trials. When a pharmaceutical company subjects a drug to a randomized controlled trial, they have a very good biologic understanding of the drug's effects. They have laboratory work and evidence from the first few patients, and then they submit it to the randomized controlled trial. There is always the possibility of failure. Most drugs that are tested in this fashion come out positive because there is so much preparatory work. The equivalent in thinking about alternative therapy is in the case when a regular physician is surprised that something happens. This happens from time to time in medicine. It happened with the bark of a tree, it happened with the concoction of foxglove, that physicians were surprised by the effects. It still happens from time to time. It happened in the *Netherlands*, a few years ago, where a *randomized controlled trial* was done for an alternative therapy on *psoriasis*. It was invented by what was thought to be a rather crazy chemist. No-one believed that it worked, but it became quite popular with patients. This did not mean too much, until a dermatologist said: «Gee, I have a patient with *psoriasis* in whom I never could establish a cure nor any improvement over the past ten years, and suddenly he improved. I asked him what happened, and he admitted he had used this alternative therapy. I couldn't believe that, it was sheer nonsense. But a week later I saw another patient, and the next week another patient, and my colleague saw another patient. And then we decided, in absolute ignorance of the mechanism, that maybe we ought to give this therapy the benefit of a randomized controlled trial.» So it was done and I think that the results are on their way in the literature.

I have discussed this proposal with a few people and I will relate two reactions. The first reaction was, «This criterion will not work because doctors are so very credulous people, they always believe things when they try something with a patient and it works in the first patient and in the second patient, they will believe anecdotes, they are credulous people!» The second reaction was, «It will not work, as doctors are so conservative; they never change their minds, and the establishment always looks foolish in retrospect.» To make this criterion operational will require discussion, discussion with regular physicians and others; but I contend that we need some criteria since it is impossible to apply our resources to testing all alternative therapies in randomized trials. It would be a great waste of time and effort, except in those cases which show some promise!

Theory and Practice - How do they relate to each other

Further reading

IERODIAKONOU K, VANDENBROUCKE JP. Medicine as a stochastic art. *Lancet* 1993; 341: 542 - 543