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Causality and Mechanisms: Between Statistics and Philosophy

Causality is a fundamental concept both in science and in daily life. We are constantly seeking causal explanations of disease, divorce and conflicts between people. This is something we do in our own lives, maybe especially when things go wrong. We want to understand, to have an explanation, to try to make sure that things go better next time. In some cases seeking causal explanations is part of trying to place the blame for some untoward event.

Causal explanations may be based on an (attempted) understanding of underlying mechanisms, or they may be based on a pure experience without deeper understanding. Clearly, human beings have always had a lot of knowledge about the dangers lurking in the world around us. People have known, for instance, that eating certain mushrooms is dangerous and may lead to illness and death, and consequently they have avoided these mushrooms. For most of human existence there has been little understanding of the mechanisms behind these dangers. Hence, causal understanding has mostly had its basis in simple experience. Only the growth of modern science during the last two or three hundred years has allowed an understanding of the underlying mechanisms in many fields.

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In fact, the great idea of natural science is to uncover mechanisms, to look behind the phenomena, to understand in a rational sense what is taking place. Natural science has been a great success, leading to a tremendous number of innovations that has changed the world. And science marches on, uncovering new understanding of natural phenomena every day. In the field of medicine in particular, this has resulted in treatments for illnesses that used to be the scourge of mankind.

Causality in medicine

In fact, the field of medicine is an interesting place to look for the status of causal understanding today. The development of drug treatments will in many cases be based on a mechanistic understanding of underlying biological principles. One example is Tamiflu which is a treatment for influenza, and is also thought to have an effect against a possible pandemic influenza (in fact the Norwegian government has in 2005 acquired 1.4 mill. treatment courses for the value of 150 mill. NOK in preparation for a pandemic outbreak). Tamiflu acts by blocking the activity of the enzyme neuraminidase, thereby preventing new viral particles from being released by infected cells. The details of this action appear to be quite well understood. However, this mechanistic explanation is not in itself sufficient to be sure that Tamiflu actually works as intended. For a new medication to be registered for general use, it is necessary that clinical trials be conducted so that the medication can prove its efficacy and safety.

The concept of a clinical trial is fundamental in modern medicine. It is carried out in such a manner that it can prove the causal effect of a medication in a purely statistical way. The basic principles are randomization (patients are distributed randomly between treatment groups) and blinding (neither doctor nor patient knows which treatment the patient actually gets). If a sufficient difference between treatment groups is observed in a properly conducted clinical trial, the effect can be ascribed to the treatment. The degree of certainty in this conclusion can be given a precise mathematical value (the statistical p-value). The conclusion is based on the experiment and does not depend on any mechanistic knowledge one has about the treatment effect.

Returning to Tamiflu, there are several clinical trials of relevance. Much of the material was summed up in a *Lancet* paper[1] where considerable uncertainty was demonstrated regarding the effect on a possible pandemic originating with bird flu (avian influenza), although the effect on ordinary seasonal influenza is clear. Hence, in spite of the mechanistic principle underlying the medication, its actual effect has not been clearly demonstrated.

This example demonstrates that there are two types of causal thinking that underlie the development of new medications. On the one hand, there is the mechanistic understanding which is often the creative part, and the reason why the medication was proposed in the first place. On the other hand, there is the strict empirical testing in a clinical trial. This latter part can be seen as a scientific extension of the age-old human experience-based understanding of the world. A clinical trial can demonstrate an effect or lack of same, even in the absence of a deeper understanding of why the medication should work.

In fact, the strict requirements that all new medications be tested in clinical trials attests to a lack of complete trust in a mechanistic biological understanding. The mechanistic view is important, but it has to be checked against experience in a systematic trial to see whether it actually predicts the right effect in sick people. And quite often the effect is not as intended.

The validity of mechanistic understanding in medicine varies a lot. In some cases it is quite good; there is e.g. a detailed knowledge about the function of the heart and its diseases. The mechanism behind cancer is much less understood, although theories abound. In psychiatric disease, mechanistic understanding is mostly non-existent. Many theories concerning psychiatric illnesses do exist, of course, from psychodynamic to biological ones, but they are typically highly controversial. There are some medications in the area that are quite effective, but the understanding of why they work is limited. For example, the original antipsychotic drugs were stumbled upon by chance, and although it is an empirical fact that they work, no one really understands why.[2]

1: Jefferson, T. el al. *Lancet* 2006; 367: 303–313.

2: Preskorn, S.H. *Journal of Psychiatric Practice* 2001; 7: 209–213.

Causality and statistics

The clinical trials referred to above play a fundamental role in developing medical therapy, especially new medications. The tools of randomization and blinding actually allow proof of a causal connection by statistical means. This is one of the major reasons why statistical methods are currently central in medical research; in fact, in an editorial in the millennium year 2000, a leading medical journal, the *New England Journal of Medicine*, presented "Application of statistics to medicine" as one of the eleven most important developments in medicine in the last thousand years.[3]

In studying the medical effects of lifestyle factors such as smoking or eating habits, the principle of randomization cannot be used. However, one sees today the interesting development of new schools of statistics with original and fruitful approaches to analysing causality in more complex situations. One particularly interesting example is the counterfactual school represented by J. Robins at Harvard University and his co-workers.[4]

A statistical view of causality also opens for a more general non-deterministic view of causal relationships. In medicine, it is obvious that risk factors generally do not with certainty lead to disease, they merely increase the risk. The concept of probabilistic causality is an important tool in this area.[5]

Causality in a broader sense

In medicine, causality is all-important because the doctor has to act in relation to the situation of his patient, either suggesting a treatment or a preventive measure, and this should ideally be based on a causal understanding. In the natural sciences, causality is connected to a mechanistic understanding of the underlying principles. In psychology and the social sciences, the causal understanding is a far more difficult issue and often very controversial. For instance, while a malfunctioning heart can be studied in a laboratory with large numbers of specific tests, the same cannot be done with a dysfunctional marriage.

Hence, there is a large variation in the level, or even possibility, of mechanistic and causal understanding. Furthermore, causality is also connected in a deeper sense to our view of the world, and causality has for centuries been one of the major themes in philosophy. Kant asserted that causality is one of the categories, in addition for instance to space and time, that is necessary for our understanding of the world. However, these categories may not be a part of the underlying reality; "das ding an sich" is unknown.

Causality is also closely connected to the issue of free will and consciousness. If everything that happens has a cause, then where does free will come into the picture? The issue may also be phrased in a scientific setting: Scientists often tend to view themselves as independent observers of the external world, drawing conclusions about the principles

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3: Editorial: Looking back on the millennium in Medicine. *New England Journal of Medicine* 2000; 342: 42–49.

4: A good starting point for studying this work might be Robins J.M., Hernan M.A. & Brumback B. *Epidemiology* 2000; 11: 550–560.

5: Suppes P. *A Probabilistic Theory of Causality*. 1970, North-Holland, Amsterdam.

that govern the surrounding world on the basis of their experiments or observations.[6] But if everything is determined by cause and effect, then this must also hold for the statements and beliefs of the scientist. A particular conclusion formulated by the scientist, perhaps a book he writes, must in this world view be the result of a causal chain, originating far back, possibly at the start of the universe in the Big Bang. If this is so, why should the statement of a scientist be a true statement about the world? Of course, this holds for all of us, not just scientists. In a purely deterministic causal world, we would all be automatons and no meaning could be attached to anything we say or do.

It is interesting to note that science itself refutes the most simplistic view of causality. In quantum physics the prevailing view is that causality is not present on the most fundamental level of the physical world. In fact, in a recent essay in Nature[7] it is stated:

> "The discovery that individual events are irreducibly random is probably one of the most significant findings of the twentieth century. But for the individual event in quantum physics, not only do we not know the cause, there is no cause. The instant when a radioactive atom decays, or the path taken by a photon behind a half-silvered beamsplitter are objectively random. There is nothing in the Universe that determines the way an individual event will happen. Since individual events may very well have macroscopic consequences, including a specific mutation in our genetic code, the Universe is fundamentally unpredictable and open, not causally closed."

Returning to the field of medicine, it is interesting to note that even events with potential medical consequences, e.g. a mutation that gives cancer, may happen in a fundamentally non-causal way.

Hence, in spite of all scientific progress, the concept of causality, as well as the associated concepts of free will and consciousness, is full of paradoxes and uncertainties. These philosophical aspects often tend to be ignored by scientists, but considering them would enrich their understanding as well as point to the limitations of present knowledge. In fact, scientific knowledge does not represent a consistent and non-contradictory view of the world in any complete sense. The scientific world view may be a success, but its power of explanation is still fundamentally limited.

6: This idea of an independent observer has been thoroughly challenged in quantum physics where it has been demonstrated that performing an observation changes the whole system.

7: Zeilinger, A. *Nature* 2005; 438: 743.