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Review

Causality in medicine

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ABSTRACT

This article is the result of a symposium organized at the French Academy of Sciences on May 31, 2016, entitled: *Do we need to know the causes to understand and intervene? Questions on causality in the biological and medical sciences*, and published in French in a book entitled: *Causality in the biological and medical sciences* (EDP Sciences, 2017).

1. Introduction

Most everyone would agree that looking for the cause of an event is a natural thing to do. This is particularly so in medicine. Sometimes the response is simple, unequivocal, for instance when there is an obvious genetic or environmental cause. Elsewhere, in more complex situations, it is less straightforward. Emphasis is often placed on chronology—the striking effect of a sequence of events—despite the lack of any link to causality. This attitude often leads to errors, especially if the public is poorly informed, the side effects of vaccinations being a caricatured example. In other situations, no precise cause can be found. Indeed, many diseases have a multi-factorial origin associating factors of genetic, epigenetic, and environmental predisposition. The disease is caused, or its progress favored, by a group of factors that, taken individually, have little or no effect. Such complex situations are difficult to analyze despite the progress made possible by recent advances in genetics and biology, epidemiology, and other disciplines. In many cases, there remains a considerable amount of uncertainty, which is particularly regrettable because it is always preferable to treat causes than symptoms. Here, we propose to examine this complexity, illustrating our discussion with the particularly well-documented search for the cause of a prototype disease, insulin-dependent diabetes mellitus.

2. Background

Causality has always been a major topic in medicine. It is important to know the cause of disease not only to enable the best possible treatment, but also to develop the best possible diagnostic tests. Everyone knows that it is dangerous to treat fever with antibiotics without knowing its cause. But, on the contrary, it is reasonable to withhold treatment because we do not know the cause? That unfortunately, is often the dilemma in many medical disciplines.

The chronology can be striking, for both patients and doctors. We know that history taking is an essential part of the diagnostic process, but must resist the temptation of linking together consecutive events. There is such a thing called coincidence. This point is essential and is well illustrated by the controversy about side effects of certain vaccinations. Cases of multiple sclerosis were observed in individuals who had recently received the hepatitis B vaccine. Certain neurologists rightly expressed concern. But when large-scale epidemiology studies were performed, they demonstrated the absence of any relationship between this chronology and causality. The frequency of multiple sclerosis is no higher in individuals recently vaccinated against hepatitis B than in the general population. This epidemiological fact has been clearly demonstrated [1], but for many people, doubt remains, unfortunately contributing to the current trend to mistrust vaccinations. The same remark can be made about

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macrophagic myofasciitis and neurological disorders attributed to aluminum contained in numerous vaccines.

Before going further, it is undoubtedly important to give a precise definition for certain terms often used inappropriately. Etiology is the search for the cause and not the cause itself. Cause is not pathogenesis or pathophysiology, terms corresponding to mechanisms independent of cause. Predisposition can have a favoring effect, but is not cause, as illustrated by the fortunate fact that all people with a predisposition do not develop disease. The same is true for risk, which is defined as high disease *frequency*, i.e. in some but not all.

3. Apparently simple cases

In certain cases, the situation is apparently very simple, the cause is obvious. Infection is a good example, when the responsible pathogenic agent is known. This is also the case for monogenic diseases when the genetic mutation or anomaly is recognized. However, even in these cases, the situation is not always as simple as it would appear. For instance, in contagious infections, we know that not everyone will get the disease during an epidemic, an observation probably related to genetic factors. Nevertheless, the infectious agent is still the cause of the disease, even though only a certain number of individuals with a mutation inducing a particular immune deficiency become ill, generally severely [2]. But this remains exceptional; most carriers of the mutation in question are not susceptible to infectious diseases other than the one associated with the mutation.

For monogenic diseases, the question is one of penetrance. In certain configurations all individuals carrying the mutation present the disease, while in others, expression is highly variable from one individual to another, both in terms of severity and age of onset. There are even cases where the disease does not develop despite the presence of the mutation. Many often poorly understood factors can affect penetrance. Epistasis, other genes interacting with the disease-causing mutated gene, may be involved. In other situations, environmental factors modulate disease expression.

4. Complex diseases

Very often, diseases are multifactorial. For the simplest situations, this can correspond to the combined effects of several identified factors, somewhat like an airplane accident where many causes, sometimes five or six, have an additive effect: each cause taken individually, or even associated with several others, is insufficient to trigger the accident. This type of situation—the additive effect of external factors—is well known in medicine. For example, in coeliac disease, ingestion of gluten is a prerequisite for disease expression. But, of course, symptoms do not develop in everyone who eats gluten-containing food. In fact, for most patients, the situation is much more complex: poorly understood interactions occur between genetic and environmental factors.

5. Genetics

Genetic factors can be expressed in several ways. Predisposition—let us hazard the term cause in certain cases—can be inscribed in the inherited parental genome. This is hereditary disease, caused by one or many genes. But it must be noted that in the multiple-gene configuration, hereditary familial disease does not occur if the genetic factor is expressed insufficiently. The role of heredity is thus very limited, but nevertheless very significant.

The greatest problem we are facing today is to determine which genes and mechanisms support the genetic control of diseases with a hereditary component. The emergence of modern genomic techniques generated great hope. Considerable effort was devoted to the identification of predisposing genes in large cohorts of several thousands of patients using highly sophisticated methods such as genome-wide association studies (GWAS) [3]. But, for the most prominent complex diseases, GWAS identified more than 50 loci (sometimes as many as 100) or more precisely chromosomal regions, each time with a very low relative risk, rarely greater than 1.5. Technically, this was a major deception, if not a failure, since very few predisposition genes could be directly incriminated, and, in fact, all of the recognized genes taken together probably accounted for no more than 25–40% of the disease heritability. Several explanations were proposed. The first, and simplest, was genetic heterogeneity: but how could each individual patient have a specific if not unique genetic profile? It was also suggested that GWAS methodology might not recognize certain important genes, for instance rare variants making a major contribution to disease expression, or on the contrary potentially frequent genes with weak or moderate penetrance. Certain variants might appear at the first stage of development, as would suggest the observation of different variants (mutations) in monozygotic twins. Single-nucleotide polymorphism (SNPs), such as sequence repeats or structural variants (large-sized deletions or insertions), might also be missed by GWAS. Undoubtedly, gene interaction and epistasis, as mentioned above, were not taken sufficiently into consideration. In any case, we do have to accept the fact that these different hypotheses, put forward over the last few years thanks to the most recent genetic techniques, have not provided sufficient progress to significantly fill in the gap of missing inheritability.

We also know that certain genetic characteristics are not innate and can be acquired. Epigenetic findings are illustrative [4]: the environment can affect gene expression via independent biochemical marks on the DNA sequence. Transgenerational transmission of certain acquired characteristics might be explained by an apparent association with epigenetic marks transmitted from parents to their offspring.

6. Microbiota

Finally, it is important to mention the metagenome, especially the metagenome of the intestinal microbiota. We know for instance that a reduction in intestinal microbiota diversity is associated with diseases such as obesity, type-2 diabetes mellitus, and certain autoimmune

and allergic diseases [5]. A causal relation between changes in the microbiota and disease onset has however not been demonstrated to date. Albeit, there is evidence indicating that in certain situations it is the disease, and in particular inflammation, that contributes to changing microbiota composition, and not the contrary.

7. Environment

The effect of the environment is of course crucial, but also very complex. For the ecologist, the environment refers essentially to the physical, chemical or climatic context in which an individual lives. For the geneticist, many other factors are involved, including the group of factors that lead to an interesting fact: strong heredity in certain polygenic diseases is associated with a rate of concordance between monozygotic twins that rarely exceeds 40–50% despite the fact that monozygotic twins live in a very similar environment, at least during childhood. This results from personal factors including individual behavior, in particular dietary habits and use of addictive substances such as alcohol and tobacco. These factors also include interpersonal relations with other individuals, the educational context, and more generally the cultural context.

The role of environment in the genesis of insulin-dependent diabetes has been the object of extensive study. Over the last 20 years, a large body of work has been devoted to the search for a viral cause. Particular attention has been given to Coxsackie-type enterovirus. Certain epidemiological, serological or even molecular arguments have been brought together, but are not particularly convincing. The evidence is also uncertain for other autoimmune diseases such as multiple sclerosis, despite the fact that the pathogenic process begins very much like a viral infection that triggers autoimmune disease secondarily. The viral infection may have occurred long before the onset of overt disease, explaining why its stigmata would be so difficult to identify. This causal infection might also be non-specific, i.e. widespread in the general population. The pathogenic process would thus involve a specific individual response to a potentially common viral infection.

Infections can also play a completely different role; instead of triggering disease they might protect against its development. A few years ago, we were struck by the rise in the prevalence of autoimmune diseases and allergies occurring concomitantly with a decline in the prevalence of infectious diseases. We gathered together a large volume of data obtained experimentally and clinically that indicated a cause-and-effect relationship between these two observations [6]. In the non-obese diabetic (NOD) mouse, disease (insulin-dependent diabetes) prevalence is moderate if the young mice are raised in less than optimal sanitary conditions. If mice are decontaminated starting with cesarean section for delivery, disease prevalence rises sharply to over 90% in females. These "clean" mice can be completely protected from disease onset with a simple infection caused by bacteria, viruses, or parasites. Moreover, diabetes, like multiple sclerosis and inflammatory bowel disease, exhibits vast differences in prevalence by geographic region. The prevalence observed in children of people who migrate from a low-prevalence country to a high-prevalence country is that of the arrival country [7].

8. Conclusions

Beyond this, we must recognize that there still exists a very large number of diseases for which no cause is evoked. This is notably the case for neurological diseases such as amyotrophic lateral sclerosis (Charcot's disease) or Alzheimer's disease. Is there an explanation? Is it lack of knowledge, insufficient analysis? Perhaps the complexity could simply be beyond the possibilities of our current scientific capacities. But it might be that there really is not a cause, a rather disquieting hypothesis we must consider.

Here, enlightenment from early work by eminent mathematicians could be useful. Pierre-Simon de Laplace and Henri Poincaré demonstrated long ago how a relatively minor event can, in the long run, lead to a chain of predictable phenomena—or at least phenomena that can be explained by the laws of physics and chemistry—that induce events the source of which can no longer be recognized. This is the basis of the chaos theory, or to a certain degree what Edward Lawrence called the butterfly effect. Unfortunately, this theory would be difficult to test in medicine where disease onset can take many years, making it most difficult to identify the remote truly initial event.

Undoubtedly, we are going to have to admit that certain diseases maybe stochastic, due to chance. This possibility has been widely discussed concerning several somatic mutations observed in patients with cancer. But is genetic instability a chance event? Could it be due to causes we have not learned to recognize? Two famous citations come to mind. The first from Albert Einstein is that "chance is the name God uses when he wants to remain anonymous". The second, perhaps less hazardous, comes from Jean Baudriard: "chance is the purgatory of causality".

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