Exposures, mutations and the history of causality

EDITOR,—The editorial by Paolo Vineis is an interesting attempt to clarify various interpretations of causality in the medical literature. The following remarks are to be taken as a mere running commentary of the excellent paper by Vineis.

Causation is a conditional relation such as: if C then D. Ventricular standstill causes death: if the ventricles fail to contract, the patient dies.

What binds causes to their effect? Counterfactual conditionals (or counterfactuals) introduce some sort of necessity in a causal relation. Counterfactuals have the following structure: Assuming that (1) If C then D and (2) C and D occur.

we then have: If C had not occurred (though it did), D would not have occurred. The following conditionals are counterfactuals that are contrary to the facts as the first part of the conditional “if C had not occurred” is false. Counterfactuals translate into predictions and introduce some support of necessity that allows us to separate statements that are accidentally true from those which are regularly true: in the second case, our knowledge extends to the counterfactual cases.

Incidentally, I have serious reservations about the usefulness of Hempel’s or Popper’s hypothetico-deductive models because there are no such things as general laws in medicine: medical explanation is not deductive.

Vineis distinguishes five major interpretations of causality in medicine. After discussing an earlier broad Aristotelian one he brings in a second stream, springing from the success of bacteriology and according to which causality is analysed in terms of agency: a cause is a single, necessary factor of its effect. If C is a necessary cause of D, than D necessitates C in each way of maintaining other causal or interacting factors constant. A necessary factor is a sine qua non determinant on which the effect depends; it usually involves a cause-effect relation over some mixed nature, at once empirical and semantic. Necessary factors depend on the way we carve the universe, a point highlighted by MacMahon. According to the third stream, a cause is a sufficient (that is, necessitating) condition of its effect. If C is a sufficient condition of D, then C necessitates D in each way of holding other causal or interacting factors constant: it hinges on the degree to which C produces D in contrast with the weaker tendencies of alternative causal background conditions.

For Mackie, a cause is part of some sufficient conditions—that is, an INUS condition. Exposed attributable fraction (or Cole’s attributable proportion) is the INUS element namely Mackie’s necessary causal component of a sufficient set; it estimates how necessary the exposure is for the occurrence of the disease or, counterfactually, what is the probability that the disease would not have occurred among the non-exposed, given that exposure and disease actually occurred.

Yet, there is, as it were, no known example in medical science of a condition sufficient for its effect so that when this deterministic model broke down a fourth stream emerged as the ideas of sufficient and necessary causes were being traded away for a probabilistic model. This new account revolves around the transmission of probability distributions: probabilities or propensities replace sufficient causes as metaphysical determinism begins to fade away.

What should we now do with the concepts of sufficiency and necessity? Actually, one of the consequences of the probabilistic turn is that sufficiency and necessity in causal contexts are often not categorical but apt to come by degree.1,2 Thus the question raised by cohort studies is the following one: to what extent is C regularly followed by D? Such studies measure the tendency towards causal sufficiency of C for D or the capacity of C to produce D; or, counterfactually, the probability that unexposed persons in a healthy population would have contracted the disease had they been exposed.

Conversely, case-control studies raise a different question: to what degree can the previous occurrence of C be inferred from the occurrence of D? Such studies estimate the tendency towards necessity of the putative causal factor—that is, (counterfactually) what proportion of the diseased population would not have caught the disease, had they not been exposed, given that exposure and disease actually occurred.

The fifth stream is raised by the papers by Porta et al. and the following discussion by Trichopoulos et al.3,4 Wesley Salmon distinguishes causal processes from causal interactions.5 The latter involve the production of change and are concerned, as discussed above, with causal relations between events; namely the object of epidemiological methods; they involve questions of the type: why A in contrast to B? On the other hand, causal processes bring about “how” questions; they involve the a-temporal-continuous propagation of causal influence from one location to another, so that the basic kinds are here processes rather than events. We know that smoking causes lung cancer long before the details of the links between the smoking and the lung cancer were traced. These two viewpoints identify two approaches in medical research with relevant distinct methodologies: epidemiology on the one hand and experimental medicine—that is, investigation of physiopathological mechanisms of disease processes on the other.

But even though epidemiology and medical science in general, are predicated upon distinctions between streams of facts, causes and causal power are, in Hume’s view, not observable facts of nature: causation vanishes into our grounds for it. Causes are not observable artefacts that are relative to the kind of question that needs to be answered: Collingwood was writing that “the cause of an event in nature is the handle so to speak, by which we can manipulate it.”6,7

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4 Karhausen LR. The logic of causation in epidemiology. Scan J Epidemiol 1996;24:8–13


Author’s reply

EDITOR,—I thank Dr Karhausen for his clear comments to my paper on causality in epidemiology.1 In addition to a summary of the different models of causation that have been used in medical reasoning, he gives some suggestions that deserve further theoretical development.

According to Bayes’s theorem, the probability of disease given exposure is: $P(D|E) = P(D|E)p(D)/p(E)$, that is, the probability of developing the disease, conditional on exposure, is given by the product of the prior (unconditional) probability of disease by the likelihood of exposure among the cases, divided by the prior probability of exposure: $P(D|E) = P(D|E)p(E)/p(D|E)p(E) + P(D|E)p(E)$. The relation aimed at in cohort studies, which are typically targeted to ascertain whether, in the course of time, a given cause tends to induce a certain disease, or even is needed for its occurrence, is $P(D|E)p(E) = 0$ (none of the exposed is healthy), while if the cause is necessary, $p(non-E|D) = 0$ (no diseased person is unexposed).

In addition, while it is clear that causality is rarely sufficient and/or necessary, also in case definition we have to face blurred borders among diseases. Let us consider the following scenario (see table 1). For groups I and II the causal agent is single and well known (a virus for smallpox, a bacterium for tuberculosis). However, even in such cases of monocausality, disease manifestations can be polythetic—that is, based on the following remarks are to be taken as a mere running commentary of the excellent paper by Vineis.

Table 1: Disease manifestations

<table>
<thead>
<tr>
<th>Monothetic</th>
<th>Polythetic</th>
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<tr>
<td>Tuberculosis (I)</td>
<td>Smallpox (II)</td>
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<tr>
<td>Bubonic and anorexia (III)</td>
<td>Lung cancer (IV)</td>
</tr>
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more than one criterion; in the case of tuberculosis, the disease is not always unequivocally recognisable, and complex clinical and immunological criteria have to be used. In other words, while for smallpox clinical diagnosis is unequivocal, tuberculosis is a complex constellation from a symptomatological point of view, and the only way to recognise its different manifestations as belonging to a single entity is to refer to the causal agent. For many infectious diseases (another example is syphilis), the complex and polythetic clinical features can be unified in a single entity only because the causal agent can be identified or its presence can be inferred by immunological means. A univocally defined disease (on the basis of histology) such as lung cancer has several causes. Lung cancer cases have a certain histological appearance in common, but they cannot be unified on the basis of their aetiology. Finally, many psychiatric diseases are polythetic, both clinically and aetologically. For example, bulimia cannot be univocally distinguished from other conditions characterised by compulsive eating or obesity. As for causal hypotheses, they are still extremely vague and apparently at the border between psychiatry, genetics and social medicine.

It should be emphasised that situations such as smallpox are an exception, while the rule is represented by “blurred” borders among different diseases, both on the side of symptoms and on the side of causal pathways.

Authors’ reply: Thinking about interactions and mechanisms

EDITORS.—We enjoyed the comments offered by Dr Karhausen on our two papers, as they discuss several causal issues that may be particularly relevant for research on mechanisms of carcinogenesis, and for the biological, clinical and epidemiological analyses of oncogene-environment interactions.

We are not sure we totally agree with his (perhaps too clear cut) distinction between the roles of epidemiology and “experimental medicine” in analysing mechanistic interactions, and between processes, factors and events. None the less, at this time we have little to add to the aetiological and aetiopathogenic considerations we made in our previous papers, in this journal and elsewhere. When new integrative studies are designed, and as new empirical evidence is accrued on the environmental causes of oncogene activation, we hope the proposals of Karhausen will again be thought out.

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