METHODOLOGY REVIEW

In Support of Clinical Case Reports: A System of Causality Assessment

作为临床病例报告的支持：因果关系评估体系

En apoyo de los informes de casos clínicos: sistema de evaluación de la causalidad

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ABSTRACT

The usefulness of clinical research depends on an assessment of causality. This assessment determines what constitutes clinical evidence. Case reports are an example of evidence that is frequently overlooked because it is believed they cannot address causal links between treatment and outcomes. This may be a mistake. Clarity on the topic of causality and its assessment will be of benefit for researchers and clinicians.

This article outlines an overall system of causality and causality assessment. The system proposed involves two dimensions: horizontal and vertical; each of these dimensions consists of three different types of causality and three corresponding types of causality assessment. Included in this system are diverse forms of case causality illustrated with examples from everyday life and clinical medicine. Assessing case causality can complement conventional clinical research in an era of personalized medicine.

摘要

此评估确定临床证据的构成。病例报告是经常被忽视的证据，因为人们相信这些报告无法解决治疗与结果之间的因果链。这可能是个错误。阐明因果关系及其评估的主题对于研究人员和临床医生将会大有裨益。临床研究的有用性取决于对因果关系的评估。此评估确定临床证据的构成。病例报告是经常被忽视的证据，因为人们相信这些报告无法解决治疗与结果之间的因果链。这可能是个错误。阐明因果关系及其评估的主题对于研究人员和临床医生将会大有裨益。

本文概述了因果关系和因果关系评估的整体系统。推荐的系统涉及两个维度：横向和纵向；其中每个维度都包含三种不同类型的因果关系及因果关系评估的三种对应类型。本系统中所包含的是以日常生活和临床医学的例子来说明病例因果关系的各种形式。评估病例因果关系可在个性化的医学年代中，对常规的临床研究进行补充。

SINOPSIS

La utilidad de la investigación clínica depende de una evaluación de la causalidad. Esta evaluación determina qué constituyen pruebas clínicas. Los informes de caso son un ejemplo de pruebas que suele pasarse por alto con frecuencia, ya que se cree que no pueden resolver las relaciones causales entre tratamiento y resultados. Esto puede ser un error. La claridad en el tema de la causalidad y su evaluación será beneficiosa para investigadores y personal clínico.

Este artículo esboza un sistema global de causalidad y evaluación de la causalidad. El sistema propuesto implica dos dimensiones: horizontal y vertical, cada una de las cuales consiste en tres tipos diferentes de causalidad y tres tipos de evaluación de la causalidad correspondientes. En este sistema, se incluyen diversas formas de causalidad de casos ilustradas con ejemplos de la vida diaria y de la medicina clínica. La evaluación de la causalidad de los casos puede complementar la investigación clínica tradicional en una era de medicina personalizada.

INTRODUCTION

The clinical case report has been a major driver in the advancement of medical therapy. In 2008, for instance, the publication of a few case reports revolutionized treatment for severe hemangioma in infants.[1] In many medical areas, such as pediatric surgery, case reports constitute large portions of the body of evidence.[2] In the field of medicine as a whole, the number of MEDLINE-listed case reports substantially exceeds the number of published clinical studies (unpublished observation). Even so, case reports have an ambivalent reputation. While appreciated as "cornerstones of medical progress,"[3] they are also disregarded as the "least publishable piece of medical literature"[4] and range around the lowest levels of the modern medical evidence hierarchy.[5] Although when done well they can be convincing and valuable to the practitioner, they are dubious to the methodologist because it is unclear how the causal relation between treatment and outcome should be assessed in single cases.

The topic of causality poses difficulties in epistemology. Causality was the source of major conflicts: Aristotle broke with Plato over causality more than 2000 years ago.[6] It was again about the causality issue when David Hume, in the 18th century, challenged the rationality of all empirical science.[7] Three decades later, Immanuel Kant proclaimed the necessity of renewing human thinking, again starting out with the causality debate.[8] And the advent of modern physics made even Kant's endeavor appear to have been in

vain.[9] Bertrand Russell, finally, wanted to strike the word "causality" from the philosophical vocabulary because he was convinced there could be no such thing.[10] Similarly, Ludwig Wittgenstein claimed the belief in causality to be superstition.[11]

Causality-negating verdicts, however, do not mean much in everyday life. When a car breaks down and is taken to a garage, the driver is concerned about the cause of the breakdown and wants a causal repair. Likewise, when a form of medical therapy is being applied, a crucial question is whether it improves or heals the disease or symptom, ie, whether it yields *therapeutic causality*.

There should be little wonder, then, that the causality debate is still alive, perhaps with even more professional input than ever.[12-14] Inspirations come from many related fields: determinism[15] and probabilism,[16] conditionalism[17] and counterfactuals,[18] universals[19] and contexts,[20] logic[21] and formalism.[13] Recent developments have led to the acknowledgment that there are manifold meanings of *causation* and *causality*. As Nancy Cartwright pointed out, "causation" is one word but many things[22]; there is *plurality in causality*.[23]

We wanted to integrate this plurality into an overall system and clarify the position of the clinical case report in that system. With that in mind, we conducted an investigation on two levels.

- *Regarding medicine*, we screened 4 years of the former *Lancet* rubric for case letters, as well as case reports from other journals and from medical textbooks. We also discussed case assessment with many practitioners and analyzed the types of criteria by which the cause-effect relations in individual treatments can be identified.

- *Regarding epistemology*, we searched for an overall system that integrates the major forms of causality and their assessment methods. Such a system would eventually provide a basic framework for all clinical research. Within such a framework we could position the methods for single-case causality assessment and the causality criteria on which practitioners implicitly rely in individual therapeutic situations. This article outlines the system of causality and causality assessment, specifically in relation to medical therapy. The different notions of *what is* causality and *how it can be assessed* are put into this system.

The system does not reflect considerations and hypotheses about any hidden physical foundation of causality.[24] It also does not present an overview of the array of statistical methods of causality assessment[25] because statistics does not organize the system and only covers a fraction of it. Accordingly, the cases used to exemplify the different system aspects are examples from everyday life or are taken from medical therapy.

MAJOR PERSPECTIVES IN CAUSALITY: HORIZONTAL AND VERTICAL, GESTALT-LESS AND GESTALT-BASED

One major constituent of the system is gestalt. Gestalt theory was initiated by Christian von Ehrenfels[26] and Max Wertheimer.[27] "Gestalt" was defined as something that can be recognized independently of the specificity of its parts.[28] The gestalt is what makes a figure, process, quality, or context directly recognizable as such. For example, a melody can be recognized independently of the incidental particularities of its tones, regardless of whether they are in high or low pitch, in fast or slow sequence, or from a piano or trumpet. Similarly, a characteristic figure in the visual field can be identified regardless of whether it is in this or that location, large or small, blue or red. Karl Duncker introduced the gestalt concept to the causality debate,[29] and Paul Michotte elaborated on it.[30] Already the early concepts of causality expounded by Plato and Aristotle had been related to gestalt, as idea and form,[31-33] but the currently dominant contributions to the methodology of causality assessment are those of David Hume, John Mill, and Ronald Fisher, none of which relate to any aspect of gestalt.[7,34,35] As shown in what follows, both gestalt-based *and* gestalt-less causalities, and their assessment methods are relevant parts of the causality system.

The second major perspective of causality involves its horizontal and vertical dimensions (Figure 1). *Horizontal causality* is currently the dominant concept. It refers to a relation in which A (the cause) temporally precedes B (the effect) and thereby somehow causes it. The second concept we call *vertical causality*. It is currently rather neglected. It refers to the cause of a horizontal A-B causality. In other words: What makes A cause B? What causes the A-B causality? This question obviously does not aim at a cause that temporally precedes the A-B succession, but at a cause that exists in another dimension, simultaneous with the A-B succession. This cause we call the *meta-cause*, or *vertical cause*, of the horizontal A-B-causality.

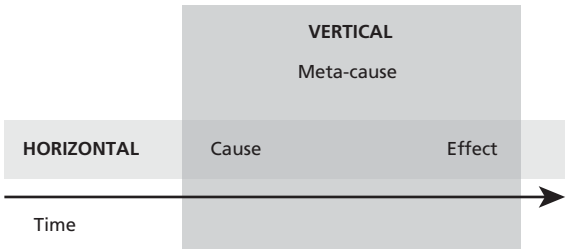

Figure 1 Two dimensions of causality.

As outlined in the following, the horizontal and vertical dimensions each contain three types of causality and three types of causality assessment.

HORIZONTAL CAUSALITY

The concept of horizontal causality can be unfolded by three basic questions. First, do cause and

effect belong together as a unity, or are they separate? According to Kant, they form a unity in which the effect comes *through* the cause and follows *out of* it.[36] However, Hume's and Locke's descriptions make cause and effect appear to be two separate things.[7,37] Second, if they are not one unity, is the gestalt of the cause equal to the gestalt of the effect? Yes, according to Leibniz: "*causa aequat effectum*."[38] However, according to Walch, D'Alembert, and Gatterer, such equality is not a necessity.[39-41] Third, if they do not form a unit and are not necessarily similar, do cause and effect form a one-to-one relationship? According to Hume's model of constant cause-effect relations, one must assume one-to-one connections.[7] However, according to Thomas Hobbes, a cause is constituted by the sum of accidentals that together produce the occurrence of the effect,[42] and Leibniz even wrote (in seeming contradiction to his dictum of similarity) that an effect would be brought forth when not only 2 or 10 or 100 or 1000 but an infinite number of things work together.[38] This is most definitely not a one-to-one relation of cause and effect. Modern approaches speak of multicausality, of interactions among causes, of "acting in concert."[43]

These positions seem to be rather contradictory, but none of them must necessarily be false. Indeed, all of these cause-effect relationships can occur, depending on the appearance or non-appearance of gestalt factors. There are the three major types of horizontal causality, and thus three assessment methods (Figure 2).

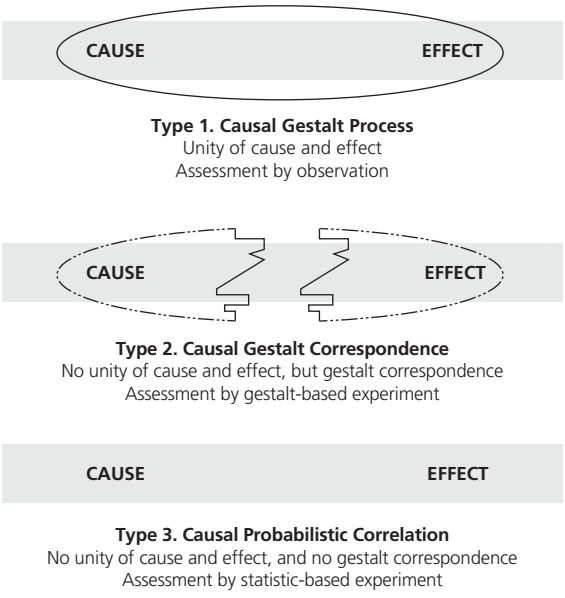

Figure 2 Three types of horizontal causality.

Type 1 Horizontal Causality: Cause and Effect Appear as a Unity

The wetness of the rain becomes the wetness of the street. In this example, taken from Karl Duncker,[29] the rain causes the wetness of the street: first the water is in the air (A, preceding), then it is on the street (B, following); from A to B there is an observable process, an evolvement (the falling of the water drops). The evolvement is the heart of this kind of causation. It embraces A and B, which are parts of it; it forms a bridge between the two.

The cause—the rain—obviously does not only consist of the preceding A, the water in the air, but also of the evolvement process, the falling of the rain water. Without this process, the preceding A (the water in the air) could not cause the following B (the water on the street). To understand this kind of causality, not only must events A and B be taken into account, but perhaps even more importantly the process that stretches from A to B and connects the two. Wesley Salmon highlighted the importance of that process: "One of the fundamental changes which I propose in approaching causality is to take processes rather than events as basic entities."[44] Events would only be secondary entities, produced by interactions or furcations of the processes.

Still, looking at the process alone is not enough. In the rain example, the cause is constituted by both the preceding event, or state, *and* the evolvement process. Only the integration of these two components constitutes the cause. Also important is that the rain process has a gestalt that makes it recognizable as such, regardless of whether the rain occurs over a short or long period, over a large or small territory, and whether the raindrops are big or small, or more or less densely aggregated. What matters is the whole gestalt of the rain, and it is precisely this gestalt that allows the recognition of the rain as the cause of the street's wetness.

These two aspects—the process and its gestalt—need to be emphasized. That is why we call this kind of causation a *causal gestalt process*, or type 1 horizontal causality (Figure 2).

The method of identifying the rain as the cause of the street's wetness is rather simple. It does not require an experiment; plain observation is sufficient. What is necessary, however, is the observer's mental capacity to recognize the gestalt of the rain process. For an adult this is not difficult. He or she can easily comprehend that the water is first in the air and then on the street and that there is an evolvement from the first situation to the second. However, a small child might not as easily comprehend this overall context.

The observational assessment of a causal gestalt process is a *type 1 horizontal causality* assessment. It can be relevant also when evaluating therapy, and examples are given in Box 1.

Type 2 Horizontal Causality: Cause and Effect Appear Separate but With Gestalt Correspondence

The rhythm of finger movements becomes the rhythm of percussion sounds. In this example, also taken from Karl Duncker,[29] it is the movement of the fingers that causes the sounds. The finger movements (A) are the cause and the sounds (B) are the effect. In this case, the causality is obvious because of the similarity

Box 1: Type 1 of Therapeutic Causality Assessment: Examples for Causal Gestalt Processes

Similar to the rain example on this page, there can be causal gestalt processes in therapeutic situations.

- The implantation of a prosthesis (= cause) turns into the new wall of a ruptured aorta and thus prevents further extravazation (= therapeutic effect).
- Endotracheal intubation, arterial stent insertion, or urethral catheterization, etc, creates an artificial lumen (= cause) that allows a normal passage of air, blood, or urine (= therapeutic effect).

(or equality) between the finger movements and the knocking sounds; there is a *gestalt correspondence*.

Consider another example. When a computer mouse is intentionally moved in a lemniscate (A) and the screen cursor also moves in a lemniscate (B), the mouse movement can be identified as the cause and the cursor movement as its effect. Again, the cause-effect relation can be immediately and easily recognized because of the gestalt correspondence between A and B.

In these examples, there is no plainly observable evolvement from A to B (from movement to sound, from mouse to cursor), but rather a correspondence between the gestalt of A and B: a *causal gestalt correspondence*. This is type 2 horizontal causality (Figure 2).

To identify such a correspondence as a causal relation, mere observation is insufficient. The researcher's active intervention is needed. As the researcher can know with certainty that he is causative in his own intentional actions and that he himself is thus causing the finger movements and the movement of the computer mouse, the following is a valid method of causality assessment. If the researcher intentionally creates A through his own action *and* if there is a gestalt correspondence between A and B, there can be certainty that the A-B relation is a causal relation. Both elements are needed: without the researcher's intentional causation, A and B and their correspondence could be affected by a third factor, a hidden cause, and without the gestalt correspondence, any change of B, even when following A, could come about by mere chance. When these two elements—the researcher's causation activity and the gestalt correspondence—are interconnected, one can be certain about the causality. This is *type 2 causality assessment*.

Notably, some gestalt correspondences can be described as mathematical laws: for example, a researcher actively induces an increase in the temperature of a gas (A), and that increase is associated with a proportional rise of gas pressure (B). In this situation, A can be recognized as the cause of B. This proportional or mathematical relation is a special sort of gestalt correspondence, often called *mathematical functionality*. Ernst Mach suggested substituting the concept of causality with the concept of functionality,[45] but it cannot be a full substitute because it is only a part of type 2 causality assessment.

Type 2 assessment is also relevant for therapeutic evaluation. In the examples given in Box 2, the researcher's (the physician's) intentional activity is the treating of the patient, and the gestalt correspondences appear between the gestalt of the treatment course and the gestalt of the symptom course.

Type 3 Horizontal Causality: Cause and Effect Appear Separate and Without Gestalt Correspondence

When cause and effect are connected by neither a gestalt process nor a gestalt correspondence, one is dealing with *gestalt-less* causality (Figure 3).

The lack of gestalt relation makes a direct approach to this kind of causality impossible. However, an *indirect* approach has been developed. A pure chance constellation—the exact opposite of causality—can be constructed by using a multitude of study objects and randomly allocating them to a treatment or to a control group and only treating the treatment group with the test procedure while not treating or differently treating the other group. In other words, one conducts a randomized controlled trial (RCT).[35] If, under these randomized conditions the groups' outcomes differ more than would plausibly happen through mere chance alone (the demarcation line is usually drawn at the probability value of .05), one will indeed have assessed a causal relation between the treatment and the outcome difference. This causal result is called statistically significant when $P < .05$. One can speak here of a *causal probabilistic correlation*.

In a causal probabilistic correlation, the occurrence of A raises the probability of the occurrence of B.[59] The

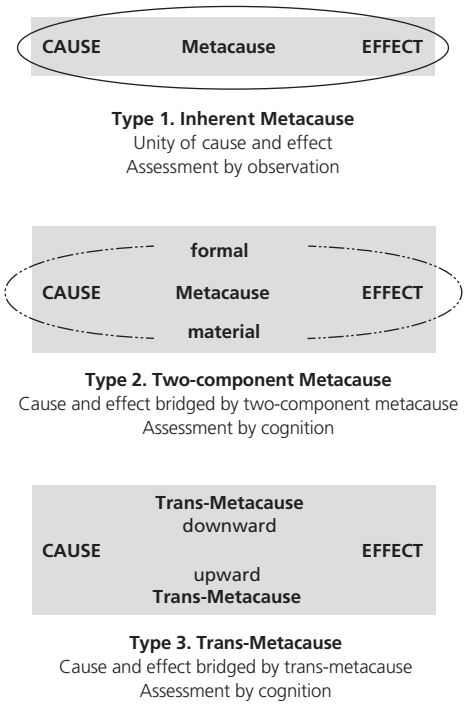

Figure 3 Three types of vertical causality.

Box 2: Type 2 of Therapeutic Causality Assessment: Criteria and Examples for Causal Gestalt Correspondences

Similar to the everyday examples presented in the text—see page 19—there can be causal gestalt correspondences in therapeutic situations between treatment patterns and patterns of symptom improvement. All of the following kinds of correspondence are criteria for therapeutic causality.

Weak criterion

- *Time-correspondence*: Uncontrollable postpartum bleeding due to placenta accreta ceases immediately after vasopressin infiltration.[46] (Time correspondence alone, though reasonably hinting at causality, is a weak criterion. Synchronic factors can be confounders and need extra control.)

Strong criteria

- *Time-pattern-correspondence*: Hiccup present for 8 days stops on day 8 exactly when the patient smokes marijuana, recurs on day 9, and again disappears (persistently) on day 10 right after the patient smokes marijuana once more.[47] Time-pattern correspondence is the basis of the traditional N-of-1 studies.[48,49]
- *Space-pattern-correspondence*: Twenty-four hours after intracutaneous injections of botulinum toxin at 10 sites on a chronically hyperhidrotic palm, corresponding anhidrotic areas develop around the sites, finally flowing together and thus creating a persistent total anhidrosis.[50] This is a correspondence between the space patterns of the treatment and the improvement.
- *Morphological correspondence*: Conduction anesthesia creates an anesthetized area corresponding to the innervation area of a blocked nerve. Further correspondences exist when external fibers of the nerve, which are proximally innervating, are blocked and when the onset of anesthesia starts proximally, spreading to distant areas only later on.[51]
- *Dose-effect-correspondence*: Catatonia ratings in a woman with schizoaffective disorder improve in inverse correspondence with zolpidem plasma concentrations.[52]
- *Dialogual correspondence*: A 5-year-old autistic boy who has never spoken a word and only screamed chaotically his whole life receives Nordoff-Robbins interactive music therapy. Musical elements are presented by the piano therapist. The boy mimics them; he also mimics sung words and thus develops a growing vocabulary corresponding to those words. In this case, one can even hear the causality.[53]
- *Parallel-test-result-correspondence*: A woman, bitten by a swan, presents an infected, swollen and deeply blue finger. After unsuccessful treatment with oral cephradine, a wound swab culture demonstrates *Pseudomonas aeruginosa* resistant to cephradine but sensitive to ciprofloxacin. The treatment is changed to ciprofloxacin and the finger rapidly heals, corresponding to the tested sensitivity.[54]
- *Complex-prediction-and-observation correspondence*: Chronic anal fissures with sustained internal sphincter hypertonia[55] and subsequent reduced perfusion of the posterior midline anoderm[56] are interpreted as ischemic ulcers.[57] External application of isosorbide dinitrate is thus expected to induce a sequential process: first, a reduction of internal sphincter pressure; second, an increased perfusion; third, a reduction of fissure-related pain; and fourth, a healing of the fissure. Corresponding to the expected sequence, this healing sequence is observed.[58]

A can be called a *probabilistic cause* and the B a *probabilistic effect*. For such probabilistic causality, the terminology often is changed from speaking of "causes" to talking of "conditions" or "conditional factors." For further comments, see Box 3.

Notably, the conduct of an RCT requires more intentional activity than the assessment of type 2 causality. In an RCT, the researcher (or the team) is active not only in regard to the cause, ie, conducting the patient treatment, but is also active in regard to the effect, ie, actively controlling the pure chance conditions for the effect observation. Thus, an RCT includes causation activity *and* control activity. Accordingly, the RCT constitutes type 3 causality assessment. For a deeper understanding, it is helpful to see how the RCT design incorporates 4 major methodological paradigms. Box 4 describes these paradigms as well as the difference between the RCT and other type 3 assessment methods.

The RCT is generally considered the gold standard for therapeutic causality assessment: the "most accurate (or valid) answer to a question of causality."[61] This view, however, is not correct. The RCT is the gold standard for only type 3 causality assessment.

The System of Horizontal Causality and Its Assessment

From type 1 to type 3 of horizontal causality there is an increasing loss of the observable connection between cause and effect (Figure 2), moving from unity to gestalt correspondence and finally to no gestalt relation whatsoever. This increasing separation makes it increasingly difficult to achieve a reliable assessment of the causality, necessitating a parallel increase of experimental activity: Type 1 assessment is free of experimental activity, type 2 assessment requires causation activity and type 3 assessment requires causation plus control activity. The type 1 assessment is no experiment; the type 2 assessment is a *gestalt-based experiment*; and the type 3 assessment is a *statistic-based experiment*, ie, an RCT.

Notably, assessments of type 2 and 3 causality, but not of type 1, comply with the interventionist positions of Scheler, Dingler, and Wright, who claimed that for a causal relation to be comprehensible one needs to reconstruct it in the context of experimental activity.[62-64] On the other hand, assessments of type 1 and 2, but not of type 3, comply with the possibilities of single-case situations. Duncker, Michotte, and Ducasse already described possibilities of individualized causality assessment.[19,30,65] Yet because of the dominance of the RCT-

Box 3: Terminological Comments: "Causes" and "Conditions"

For probabilistic causality, the terminology often is changed from speaking of "causes" to talking of "conditions" or "conditional factors." Contextual conditions, however, are also of relevance for non-probabilistic causalities. For example, rain can cause the wetness of the street only when the air temperature is high enough that for the rain not to freeze and turn to hail. On the other extreme, the rain can only wet the street when the street's temperature is low enough so that the water does not immediately evaporate. Similarly, finger movements can cause percussion sounds only when an environment of air allows for the origination and transmission of sound. Such conditions are necessary for the respective causality to occur. Still, in these examples, the causes in question can be clearly identified through the gestalt relations: through the process of the raining water (first in the air and then on the street) or through the correspondence of the rhythm (primarily in the fingers and secondarily in the sound). A different situation arises when there is no gestalt relation between cause and effect and thus the cause in question is not pre-eminently designated above all the other conditional factors. In such a situation, one may as well refrain from the word "cause" and, as in epidemiology, talk of "conditional factors," "impact factors," "effect-modifiers," "confounders," etc.[60]

Among conditional factors, different kinds can be discerned—those that are necessary and those that are unnecessary to produce the occurrence of the effect, and those that are sufficient for it and those that are insufficient. To make matters even more complicated, there can be factors that are neither necessary nor sufficient but can still contribute to the effect occurrence.[43] John Mackie analyzed the interrelations of necessary, unnecessary, sufficient, and insufficient factors and arrived at a conclusion that might seem a little confusing: causal factors can be an insufficient but necessary part of a condition that is in itself unnecessary but sufficient for the result. This situation has been called an INUS condition.[17]

oriented methodological tradition (Box 4) it is necessary to emphasize that neither repeated observation nor parallel comparison are indispensable general elements of causality assessment. This is also true in therapy. Here, too, single-case assessments are a realistic perspective (Boxes 1 and 2). An expansion of the concept of evidence is accordingly necessary and needs to be explicitly established in modern evidence-based medicine.

Apart from determining how to assess a cause-effect relation, questions arise about possible repetitions and about the generalizability of type 1, 2, and 3 assessments. Before these further questions can be answered, the dimension of vertical causality must be considered.

VERTICAL CAUSALITY

While horizontal causality focuses on the temporally preceding cause (A) and its effect (B), vertical causal-

Box 4: Methodical Paradigms Within the Randomized Controlled Trial

The randomized controlled trial (RCT) incorporates four methodological paradigms, formulated during the past four centuries.

17th century. *Experimentation* was posited as the basis of all reliable empirical research by Francis Bacon in his famous Novum Organon Scientiarum.[66] (For the specific assessment of causality, John Locke[37] claimed that experimentation was mandatory). Experimentation goes beyond mere observation and involves actively influencing and manipulating the investigated object. Still, manipulation alone does not guarantee a valid assessment of (type 3) causality without the following methodical elements.

18th century. *Repeated succession* (association, conjunction) is a further methodical key. David Hume drew attention to it when he figured that one only observes space relations, time relations, and correlated associations. The reasons for such associations are not accessible. Hume thus called A a "cause" and B an "effect" when, neighboring in space and time, any repetition of A is always followed by B: "We may define a cause to be an object, followed by another, and where all the objects similar to the first [A] are followed by objects similar to the second [B]".[7] This seminal definition led to the famous problem of induction,[67] but even without that problem the mere association of A and B does not suffice for causality. For example, when every morning, just after Mr Smith leaves his house, the hour hand on his watch moves to the eight o'clock position, it is not his step out the door that causes the clock's hand to move. Malebranche called it a dangerous fallacy to conclude from associations,[68] and modern epidemiology sees it as trivial common sense: associations do not guarantee causality.[69]

19th century. *Comparison* is the next methodological key, prominently established by J. S. Mill.[34] Mill turned his attention to complex settings in which various preceding factors are followed by various outcomes, and when the question arises of how to identify that a preceding factor is indeed a cause of a certain outcome; and, vice versa, how to identify an outcome as indeed an effect of a certain preceding factor. Different from Hume, Mill focused not only on succession but also on comparison, introducing two assessment methods: the method of agreement and the method of difference (and their subspecifications: the methods of residues and variation). Mill talks about *agreement* when out of several factorial sets all contain a factor A and they all are followed by the same outcome B. In contrast, he talks about *difference* when out of several sets only one contains factor A and only that set is followed by outcome B; or vice versa, when only one set contains a certain outcome B, which is the sole outcome preceded by factor A. However, Mills himself criticized these methods. He pointed out that only the method of difference could offer certainty, and only for the identification of effects and not causes. Even then, Mill did not clarify what amount of repetition and what degree of comparativeness is needed for the method of difference to be reliable.

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20th century. *Randomization* was the final element, introduced by R. A. Fisher when conceiving the randomized controlled trial (RCT) in 1935.[35] The RCT includes all three aforementioned elements: experimentation, as the study objects are intentionally manipulated; repeated succession, as the study contains not only a singular object but a group of objects; and comparison, as the study contains both a treatment and a control group and only the treatment group receives the test treatment. In addition to these three elements, the RCT includes an allocation of the study objects to a treatment or a control group by a pure chance procedure, by randomization. With the RCT, Fisher followed the tradition of Bacon, Hume, and Mill, but spun it in a new direction. Whereas the tradition of its predecessors was pure empiricism, the RCT implements mathematics; and whereas Hume and Mill looked for criteria of direct causality assessment (and either totally or partially failed), the RCT uses an indirect criterion, contrasting causality with a mathematical model of anti-causality against pure chance. A remarkable particularity of the RCT lies in the fact that it assesses causality by determining the quantitative difference of the group outcomes. As a consequence, assessing the causality in an RCT also involves assessing the superiority of the group 1 vs group 2 outcome. In an RCT, assessing causality and assessing superiority are the same.

Other epidemiological approaches to causality also employ experimentation (each medical treatment is an experimental action), repeated succession (of treatment and outcome) and comparison (of treatment and control groups). They do not, however, employ randomization but try to compensate for it with methodical elements such as sample restriction, stratification, matching, statistical adjustment, or Bayesian techniques. Still, compared to the RCT design, these approaches suffer from methodological shortcomings, and the RCT is therefore considered the gold standard of therapeutic causality assessment: "the most accurate (or valid) answer to a question of causality."[61] However, it is only the gold standard for type 3 assessment and not for all forms of causality assessment. When the full causality system is taken into consideration, the gold status of the RCT is relative.

Notably, all epidemiological approaches to causality apply cohort comparison.[43,70-77] Even so-called N-of-1 studies compare cohorts, though not of patients but of treatment phases.[48,49]

A curiosity in this context is the well-known list of epidemiological causality criteria published by Austin B. Hill[78] who, after World War II, conducted the first widely renowned RCT in medicine; from this list neither any single criterion nor their sum total is specific for causality.

ity establishes the cause of A-B causality. This shift is particularly relevant when A and B appear to be separate: what makes A cause B, or what causes the A-B causality? These questions address a *metacause*, or a *vertical cause*, of the horizontal A-B causality (Figure 3). The metacause can be defined as the instance that makes A and B follow each other, and which, once known, makes it possible to precisely infer from the cause (A) the effect (B).

The vertical dimension has largely been overlooked in the modern discourse on causality. David Hume, the central reference figure in that discourse, assumed it impossible to assess the reason, or metacause, of a causal relation.[7] This assumption has had a great impact for centuries but is unfounded. As shown in the following, three types of vertical causality exist, with three corresponding types of assessment.

Only when the horizontal cause (A) *and* the vertical cause (the metacause that connects A and B) are taken together, can one talk of the *whole cause*, and *full reason*, of an effect. "Causa, seu ratio," wrote Baruch Spinoza.[79]

Type 1 Vertical Causality: Metacause Is Inherent in the Unity of Cause and Effect

Type 1 vertical causality is identical to type 1 horizontal causality: it is the *causal gestalt process* illustrated by the rain example. Why is the cause (the rain) followed by the effect (the wetness of the street)?

There is a simple reason for the cause (the rain) being followed by the effect (the street's wetness): it is the process of the rain itself. The reason, the metacause, is fully inherent in the causal gestalt process of the rain, and the process is self-explanatory in regard to the causality involved. Thus, not only can the horizontal cause-effect relation be plainly observed in such a causal gestalt process, but also its inherent metacause.

As previously mentioned, this kind of causality assessment is also relevant for medical therapeutic evaluation, and examples are presented in Box 1.

Type 2 Vertical Causality: Two-component Metacause Bridges Cause and Effect

When evolvement from the cause to the effect is not plainly observable, another type of metacause can often still be assessed: the type 2 vertical causality. This kind of causality is surrounded by many misconceptions and misunderstandings, and these are determining the key problems in the philosophy of science.

Particularly problematic was David Hume's premise that it would never be possible to know the reason why a cause (A) is followed by its effect (B). As a consequence, Hume's only chance of assessing causality was to take a constant association of A and B as the criterion with which to identify a cause-effect relation: "We may define a cause to be an object, followed by another, and where all the objects similar to the first [A] are followed by objects similar to the second [B]."[7] This definition became a highly influential directive, and it was the Humean notion of causality that Bertrand Russell attacked at the beginning of the 20th century. Russell disqualified it as an ontological disaster. He further emphasized that the advanced empirical sciences do not at all assume the existence of such regularities and do not in the least aim at discovering them; what they search for are formulas, functional relations. Russell thus wanted to eliminate the word "cause" from philosophy.[10]

In contrast, Karl Popper enhanced the status of Hume's constant association of A and B and made it the

general form of all laws of nature. Popper proclaimed that all laws must be written in the form of all-sentences: "whenever A, then B" or "all A are B."[80] Such laws can, for formal reasons, never be verified, but they can be falsified by single observations. Thus, taking Hume's definition of causality as the general template for the laws of nature, Popper arrived at his famous philosophy of scientific falsificationism.[80-82] However, Popper had chosen a sort of "law" that, according to Russell, is nothing the advanced sciences would ever want to discover or even assume to exist. Their laws are not all-sentences, but functional relations, mathematical formulas.

These laws, these functional relations or formulas of mathematical gestalt, can indeed be a connective tissue between causes and effects. For example, according to the gas law ($P \times V = const \times \frac{m}{M} \times T$) an increase in the temperature (ΔT) of a gas with constant mass and volume induces a proportional increase in the pressure (ΔT) of this gas: $\Delta T \sim \Delta P$. In this case, ΔT is the cause, ΔP is the effect, and the law ($P \times V = const \times \frac{m}{M} \times T$) is what connects the two. Thus, it is the law that enables one to derive that the cause (ΔT) will be followed by the effect (ΔP), and how that will happen. Accordingly, this law can be identified as the metacause of the ΔT-ΔP causality, or at least as a part of the meta-cause. The law establishes a bridge between cause and effect.

Bertrand Russell was correct: the advanced sciences strive to discover laws that are functional relations and not causalities. However, it is precisely these laws that allow the observation of a variety of causal relations that otherwise could not be seen. In particular, these laws allow causality assessment in the single-case situation: If the law, the formula, predicts a causal A-B relation, and if the A-B relation is then observed in reality, the observer is right in identifying the concrete relation as causal. Seen from this perspective, the word "cause" should definitely not be dropped from scientific usage.

Taking an even closer look at the gas example, one can see that the metacause has two components. The first component comprises the material factors that constitute the gas: its mass (m), molar mass (M), volume (V), temperature (T), and pressure (P). The second component is the gas law ($P \times V = const \times \frac{m}{M} \times T$) that interconnects these material factors. Notably, the material factors and the law are equivalent to the Aristotelian causa materialis and causa formalis, respectively. In fact, all four components of Aristoteles' concept of causality can be seen in the gas example[33]:

- the *causa efficiens* is the initial rise in temperature;
- the *causa materialis* comprises the specific constitutive material factors of the gas;
- the *causa formalis* is the gas law that interconnects the material factors; and
- even the *causa finalis* is present when there is an intentional act of increasing the gas temperature to increase the gas pressure.

From these components, the effect (increasing gas pressure) can be precisely inferred. Accordingly, Aristotle's concept of causality encompassed the *total cause*. Subtracting from this total cause the *causa finalis* means subtracting the human intention (which is not always present). Subtracting the *causa materialis* and the *causa formalis* means subtracting the metacause. What then is left is the *causa effiens*, the initial event. It was only *this part* of the total cause that Hume addressed and called "cause." This limited view made it impossible to see any connection between "causes" and their effects.

Why and how are the material factors of a gas associated with the gas law, and how can such a mathematically formulated law, such a functional relation, be validated? The answer lies in the following: The identifications and measurements of the individual material factors (pressure, volume, mass, absolute temperature) are already incorporated in simple laws, and the integration of these simple laws eventually constitutes the complex gas law. Accordingly, an integrative, evolutive method of law assessment can be worked out and made operable. This method will be published in a separate article.

To summarize: knowing a law makes cognitional causality assessment possible, even in single case situations. An example of law-based assessment in medicine is electrolyte substitution steered by formulas and by observable dose-effect relationship.

Knowing metacauses can also facilitate the understanding and assessment of causal complexities. Such complexities, ie, sequences of linearly connected causal relations, and *causal systems*, ie, complexes of functionally interconnected causal relations and causal chains. An everyday example is a mechanic repairing a broken-down car. Due to his professional education and mental capacity he has insight into multiple explanations: why the car's parts were functionally interconnected in their specific way; why the car is now not functioning; and why certain repair actions (A) would lead to a functional restoration (B). It is this insight into the system's working principles that allows an understanding of the A-B relation as a causal relation and thus also allows the prediction that A will be followed by B. Again, as in the gas example, if there is such an insight-based prediction of an A-B succession and if this A-B succession is then concretely observed in a single-case situation, it can be identified as a cause-effect relation.

The certainty comes not from comparing car repairs and non-repairs, not at all from randomization, and not from a gestalt correspondence between the repair actions and the restored function. It comes from knowing the working principles of the system, just as the certainty in the gas example came from knowing the law. Again, single-case causality assessment is possible.

Knowing the working principles of a system also can be relevant for medical therapeutic evaluation. The example in Box 5 is remarkable because it presents highly certain but also highly particular evidence. As in

Box 5: System Assessment in Therapy Evaluation

A 26-year-old man is admitted to a regional hospital with severe chest pain, localized frontal hematoma, raised troponin-T and creatine kinase, and a right bundle branch block.[83] After receiving medical treatment, he recovers from the symptoms. Was the treatment effective?

If only the baseline symptoms and outcome are registered (as in conventional clinical trials), there can be no certainty about the therapeutic causality. The situation changes, however, when a full overview is given. The facts are as follows.

The young man has a high-speed snowboard crash. Echocardiography and magnetic resonance imaging show a rupture of the descending aorta, a false aneurysm of the aortic arch, and a contained rupture of the aortic isthmus with an intussusception of the intimal cylinder into the distal aortic segment. The patient develops arterial hypertension in his arms, which can be explained by a compression of the left carotid artery. As neither a median sternotomy nor a lateral thoracotomy alone would allow full exposure of both lesions simultaneously, a two-step therapeutic procedure is chosen. First, the abdominal rupture of the descending aorta is treated with an endovascular stent implantation. Second, 2 days later a median sternotomy is conducted and the aortic arch is opened. A circumferential intimal tear is sutured, and the aorta is closed with a Vascutec patch. After the surgical procedure, the arterial hypertension in the arms promptly disappears; the patient recovers rapidly, and is discharged 1 week after the operations.

With this information, and based on anatomical and physiological systems insight, the expert knows that:

- The patient's life was highly endangered, and the 2-step intervention successfully saved his life.
- Each of the surgical measures (stent implantation, suture of the intimal tear of the aortic arch, and reclosure with a Vascutec patch) was causally effective, and each repaired a defect of the aorta and restored functionality.

The basis for the causality assessment is as follows. The surgeon is able to make an *insight-based prediction* that there is a good chance the interventions (A) will be followed by a coherent pattern of structural and functional improvements of the organism (B), and he makes achieves an *insight-based observation* of exactly this A-B succession. The conformance of this kind of prediction and observation allows certainty about the causal relation between A and B—even though the operation is a novelty and conducted only in a single case. System transparency is the key to this kind of therapeutic causality assessment.

the car repair example, the evidence can only be realized when there is insight into the working principles (the meta-cause, the reason) of why the treatment eventually leads to the desired outcome. This insight is a necessary presupposition, and without it one would miss the most relevant part of the observation: the therapeutic causality. One is dealing here with *cognitional causality assessment*—which is not conceived in the evidence hierarchies of today's evidence-based medicine and is not reflected in its methodology.

Type 3 Vertical Causality: Trans-metacause Bridges Cause and Effect

There is a hierarchy among the different types of vertical causality: a type 1 metacause can itself have a metacause, which is a type 2 metacause; for example, the metacause of the rain process lies in the laws of gravitation, condensation, etc. Similarly, a type 2 metacause can have a metacause, which is a type 3 metacause. This type 3 metacause is rather different from types 1 and 2. While type 1 is plainly observable and type 2 is assessable with cognitive effort, they still belong to the same level of reality as the horizontal A-B causality. The type 3 metacause, however, comes from outside: from the hidden parts of reality, from deeper or from higher levels (Figure 3). It is a *trans-metacause.*

Type 3 meta-causes have been designed into molecularistic, atomistic, and sub-atomistic models. For example, the behavior of a gas (and the gas law itself) can be derived from the kinetic gas model. Thus the gas molecules can be considered the trans-metacause behind the macroscopic cause-effect relations in a gas. Even deeper-reaching models explain again the properties of the molecules, models that have been designed for the sub-molecular and sub-atomic level and that make these sub-entities appear to be the vertically underlying cause of molecule properties. Finally, quantum theory comes in, and the sub-models are enclouded in stochastics and indeterminism.[84] All of these underlying particularistic meta-causes are of type 3a (Figure 3).

The most classical of all Western thoughts, Plato's concept of the *idea* is in contrast to the particularistic models.[31] Plato considered the idea as that which forms the respective physical reality; not doing this particularistically (as molecular and atomic interactions) but holistically; not coming from a deeper, sub-physical part of reality (as particles do) but from a higher, supra-physical part of reality. This would be the type 3b metacause. Similar concepts are used in the diverse schools of vitalism that assume the existence and effectiveness of non-physical and non-chemical forces (*entelechia*, *vis vitalis*, *nisus formativus*, *morphogenetic field*, *etheric force*, *formative forces*, etc), and the more traditional forms of medicine are often conceptually outlined in this respect. The extent to which these concepts are valid is not a matter of concern here.

An important difference between the particularistic and the holistic concepts is the causative direction. Particularistic concepts imply *upward causality*, ie, the causation comes from the *parts* of the system. In contrast, holistic concepts imply *downward causality*; ie, the causation comes from the *totality* of the system. While the concept of upward causation is immanent in all reductionist thinking, the term *downward causation* was coined (though not with regard to Platonism and vitalism) in psychobiology by Roger Sperry and in the

context of system theory by Donald Campell. It was elaborated by Karl Popper and John Eccles regarding mind-body, and again by James Murphy, Peter Anderson, Anthony Dardis, and others.[85-90]

If taken radically, upward causality comes from below the macro-physical parts, from particles (molecules, atoms, etc), and downward causality comes from beyond the totality of the respective system, from its own construction process or morphogenesis. The radical concept of downward causality thus even considers the existence of non-physical and non-chemical causes.

Different questions arise: On the one hand, they arise about the status of diverse kinds of particles: whether they exist only under certain experimental or observational conditions, or in how far they exist even only as mere model entities.[91] On the other hand, questions arise about the existence of non-physical and non-chemical causative instances: whether they exist at all, and if so how they could possibly be assessed. Apart from these difficulties, the radical upward route of causation (from the subatomic level to the atomic, molecular, and cellular levels, to tissues, organs, and organisms) eventually disseminates in indeterminism, and the radical downward causation, currently at least, is not clearly understood. Neither one thus provides a broadly applicable contribution to the possibilities of cognitional causality assessment in single-case situations.

The System of Vertical Causality and Its Assessment

As with horizontal causality and its assessment, there are three major types of vertical causality. The meta-cause is increasingly externalized and is differently assessed (Figure 3):

- the type 1 metacause is fully inherent in the respective A-B succession and can thus be plainly observed;
- the type 2 metacause also belongs to the A-B succession level but cannot be plainly observed, and its assessment needs cognitional activity; and
- the type 3 metacause is located at a deeper or higher level of reality, and its assessment requires an even greater surplus of cognitional achievement.

Several of the classic causality concepts can be characterized by how they relate to the system of vertical causality: Hume's concept contains no verticality at all. Aristotle's concept contains the interrelating vertical aspects of *causa materialis* and *causa formalis*. The Atomist concept adds an extra upward causality. And the Platonist concept adds an extra downward causality.

GENERALIZATION

Inherent in the assessment methods is the potential for generalization, either based on repetition (the power of custom) or insight (the power of reasoning). The *repetition* of an A-B causality suggests *that* there will be similar causalities in the future; and *insight* into the reason for the causality makes it obvious *why* A will be causally followed by B. Insight thus provides a stronger basis. However, the topic of insight—of cognitional causality assessment—is neglected in the dominant Hume-Popper methodological tradition and has not been sufficiently clarified, neither for RCTs nor for case assessments.

Regarding RCTs, two points must be stated. First, an RCT result does *not* provide the reason for the causality it assesses. Second, a single RCT is only *one* causality assessment and does not differ in this respect from a single case assessment. Even with a large number of participants, one RCT represents only one causality assessment. Hence, an RCT result offers no basis for the prediction that such a result will be generated from a similar sample in the future. Generalizability, on the statistical level, would require that the study sample (treatment plus control sample) and the future sample both be randomly selected from the total present and future population of subjects, which can never be realized.[92] Still, most RCTs have the potential for generalization, yet it comes not through the RCT itself but through other background research that provides some, though insecure, insight into the reason for the therapeutic causality, ie, into the intervention's working principle. If this insight is then supplied with a claim of general validity, the RCT is an exemplary test. Hence, both are needed: the (insecure) insight into the working principle that is per se general and thus the *basis* for the generalization, and the confirmative RCT that is per se a singular test and thus an *exemplary validation* of that basis. Further support for the generalizability of an RCT result can come through its replications.

Take-home Messages

1. Case causality: It is possible to assess therapeutic causality in single-case situations. There exist criteria for case causality.
2. Case reports: Case reports should explicitly reflect on the case causality.
3. Causality system: Different types of causality require different assessment methods: cognitional, observational and experimental; for cohorts and for cases. The system of causality puts the different types and methods into order.

Regarding case assessments, the insight into the working principle is the most relevant. If such insight is present and transparent, it is, by its nature, always a *general insight*. Hence, it has a tripartite potential: for generalization, for individualization, and for causality identification in the single-case situation. Our example is the snowboard case in Box 5. The surgeons were able to achieve that triple task: Their insight into the patient's injury and into the possibilities of surgical intervention allowed them to *generalize* how any such patient could be treated, *individualize* this general perspective to the concrete incoming patient, and *identify* in this particular patient the concrete succession of treatment and recovery as a causal relation. All three achievements were based on the same capacity for cognitional insight.

An important aspect of insight-based generalization is that it does not imply a machine-like necessity. Confounders may well disrupt the A-B succession, but often those confounders can be cognitively understood. *Reflection in action*[93] can often be realized, and the causative actions can be adapted accordingly; this applies also to medicine.

The possibilities of insight into the working principle and the resulting generalizability depends on the type of horizontal causality involved. In the *causal gestalt process*, the working principle is openly assessable and generalization is thus easy. In *causal gestalt correspondence*, insight into the working principle is often easily achieved; and if not, generalizability can be supported by case repetitions. In the *causal probabilistic correlation*, the insight in the working principle is mostly weak and validation by statistical methods is necessary.

CONCLUSION: THE NEED TO EXPAND THE CONCEPT OF CLINICAL EVIDENCE

The system of causality and its assessment is particularly important for clinical case research because it identifies a variety of methods and criteria for the assessment of case causality. Accordingly, the system suggests expansions of the current concept of medical evidence in regard to the possibilities of assessing causality in individual therapeutic situations. The criteria of causal case assessment can be used in clinical research, upgrading case reports.

Clinical case research will have to be fostered in the future in the same way that clinical trial research is currently promoted. With this goal ahead, more subtypes of causality assessment may need to be differentiated; the methods of assessment further elaborated; semi-standardizations for case research determined; the generalization topic further analyzed; guidelines for the conduct and publication of case studies and case series improved and professionalized; and cross-design syntheses of cohort evidence and case evidence developed. In all of this, the theme of causality will need thorough and critical attention. Case reports may easily induce bias and illusion if the methods and criteria for the assessment of causality are not handled with sufficient care.

The conventional ideal in therapeutic evaluation is to identify the best therapy available—"best" in the sense of comparative cohort studies. RCTs often are optimal for achieving this goal because they simultaneously assess causality and comparative superiority. However, the individual patient does not always need the proven best cohort therapy. Often, the challenge is to find and apply just the right and individually appropriate treatment for the concrete personal situation. This is the task of *individualized, personalized medicine*. Yet it can hardly be mastered without a methodology that truly supports the assessment of therapeutic causality in the individual case.

The causality system presented here embraces both cohort assessment (eg, RCT) and case assessment and opens a perspective on case causality as an asset complementary to conventional clinical research. This approach has been called *cognition-based medicine* [94]; it can also be considered as *expanded evidence*. If medicine is to become individualistic, this expansion is a highly urgent undertaking—conceptually, methodologically, and practically.

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