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CAUSALITY IN EPIDEMIOLOGICAL RESEARCH

PRZYCZYNOWOŚĆ W BADANIACH EPIDEMIOLOGICZNYCH

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STRESZCZENIE

Artykuł przedstawia we wstępie krótki zarys historyczny koncepcji przyczynowości. Następnie analizowane w nim są problemy dotyczące współczesnych interpretacji związków przyczynowych w nauce ze szczególnym uwzględnieniem badań epidemiologicznych. Bardziej szczegółowej analizie poddano teorię *D. Lewisa (counterfactuals theory*) oraz współczesne teorie probabilistyczne, w tym graficzne przedstawianie układu zależności między zmiennymi w postaci wykresów DAG (*directed acyclic graphs*). Acykliczne grafy kierunkowe są w ostatnim dziesięcioleciu wykorzystywane coraz częściej do obrazowania złożonych układów badawczych w epidemiologii.

Autor doceniając wyjaśniającą rolę graficznego przedstawienia zależności między zmiennymi w badaniach epidemiologicznych oraz rolę warunkowych prawdopodobieństw zdarzeń z uwzględnieniem przesłanek *Markowa* i podejścia bajesjańskiego, wyraża pogląd, że metody statystyczne nie są wystarczające do określenia zależności przyczynowych i wszelkie rozumowania przyczynowe zawierają w sobie element subiektywnej oceny badacza. W opinii Autora ujmowanie zjawisk w kategoriach przyczynowych stanowi ważną podstawę do podejmowania działań terapeutycznych oraz interwencji z dziedziny zdrowia publicznego i dlatego byłby przeciwny konsekwentnemu podejściu indeterministycznemu.

Słowa kluczowe*: przyczynowość, determinizm, indeterminizm, prawdopodobieństwo warunkowe, acykliczne grafy kierunkowe*

ABSTRACT

The article presents short historical review of the concepts of causality. Then it deals with contemporary concepts of causal dependence with special reference to epidemiological studies. In particular Lewis counterfactuals theory and contemporary probabilistic theories were analyzed including applications of DAG's (directed acyclic graphs), which in the last decade are frequently applied for presentation of complicated study designs in epidemiology..

Authors high appreciation explanatory role of graphic presentation of relationships between variables and the role of conditional probability of events respecting Markov conditions and Bayesian premises, does not change his opinion, that statistical methods are insufficient for final assessment of causal dependence and some subjective element of learned judgment of the scientist has to be always present.

In Authors opinion causal approach to associations between are crucial as a base for therapeutic approach and for public health interventions. This is why he is against consequent indeterministic approach.

Key words: *causality, determinism, indeterminism, conditional probability, DAG's (directed acyclic graphs)*

HISTORICAL DEVELOPMENT OF THE CONCEPT OF CAUSALITY

To put problem of causality in epidemiological research in perspective, we cannot avoid one basic question: in what extend it is specific to the domain of epidemiology, and how it reflects more general epistemological problem of causality in natural and social sciences. The short historical introduction may be justified by the fact, that the most fundamental questions of causality were formulated first by philosophers, who later, with narrowing focus of the scope, called themselves sometimes epistemologists or methodologists.

Theory of four causes created by Aristotle takes special place in history of causality. Starting from the analysis how sculpture was created, he described four components of the process:

- The material cause: "out of which statue was build", eg. marble or bronze
- The formal cause: "the form". In case of statue it was its shape.
- The efficient cause: "the primary source of change or rest" – the work of an artisan.
- The final cause: "the end, that for the sake of which a thing is done"

Such causal description matches well conscientious activity of humans. Aristotle widened this notion to causality in the science of nature, but in this field accuracy of his description was not so obvious. Fundamental meaning of Aristotelian notion of causality is in its role as reference point for later analysis and criticism, which paved the road to contemporary views on the subject. Exemplifying the efficient cause by work of an artisan Aristotle did not take strictly deterministic stance. His determinism was placed rather in limitations of the creator.

First strictly deterministic view of the world was formulated by Stoics, for whom universe was imbued with divine reason. It left no room for chance or possibility, which in their opinion reflects only human ignorance of the causal connections between events. Apart from the "divine reason", such an interpretation of causality survived to this day among quite many epidemiologists (1,2,3).

Strong endorsement of extreme determinism came in middle ages from Christian philosophers for whom causality was direct consequence of omnipotence and omniscience of the God. Fifths proof of the existence of God in the Summa Theologiae of Aquinas was based on unbreakable chain of causes and effects which followed backwards always lead to the final cause - the God (4).

In strictly deterministic view "cause" appears as primary notion, which did not require definition: All material things, situations and events have their causes. Nothing happen without a cause. Chances or unexplained incidents are effects of causes which strictly determine their occurrence, but are unknown to us.

XVI Century founders of modern philosophy: Descartes, Hobbes, Spinoza and Leibnitz also presupposed causal determinism based on the existence of God, but differ in their contribution to the modern notion of causal inference (1).

Four causes of Aristotle, were accepted by founders of scientific empiricism Galileo and Bacon, but were rejected by Descartes who accepted only efficient cause, as most scientists do in the contemporary times.

With marked differences in ontological description of causality both Hobbes and Spinoza stressed necessity of the causal relation. As his fundamental contribution, Leibnitz introduced principle of sufficient reason. Though precise formal description of necessary and sufficient conditions which may be applied to interpretation of causes came later with the development of contemporary logic.

Important contribution of Locke was strictly empiricist approach, free from metaphysical premises. Although he accepted notion of causality and explained it by the action of "power", but he never referred to uniformity or necessity of causal connection.

Even stronger rejection of the principle of universal causation came from Newton. On the basis of his laws of motion he introduced fundamental distinction between causation and law-like behavior. According to Newton, there are two classes of events: those which happen according to law, and those which are effects of causes. Newton distinction is difficult to sustain. Even if it would be acceptable to interpret free movement with constant speed as a movement which occur according to law and is independent on any external causes, it is not so obvious regarding other types of movement. For example uniformly accelerated movement also occurs according to one of Newton laws, but it evidently may be described as an effect of applied force.

Especially profound analysis of causal connections was done by David Hume, eighteen century Scottish philosopher (1,5). Hume started his analysis from scrutinizing three basic principles which in his view are essential to the causal connection. They are:

- continuity in space and time,
- priority in time of cause to effect,
- necessity of the connection between cause and effect.

Hume conclusions were devastating to all previous justifications of causal relations. He refuted presumption of earlier rationalists, who accepted a priori concept of universal causality. He focused on empirical circumstances associated with events, that people perceive as causally connected. He showed difficulties in finding any justification for causal necessity, which could be as stringent as logical necessity. Therefore he concluded that interpretation of necessary causal relations is illusory and based on habit emerging from finite number of previous similar perceptions. He also rejected references to power of God, because, according to him, such claims do not give "insight into the nature of this power or connection". Hume's criticism of the views of his predecessors is also based on analysis of the terms used in description of causal relations: "the terms efficacy, agency, power, force, energy, necessity, connection, and productive quality, are all nearly synonymous and therefore it is absurdity to employ any of them in defining the rest". Hume's criticism retain its validity in the contemporary era. All the later attempts to define causal connection based on empirical material failed. After rejecting metaphysics of causality, Hume started completely new approach to the problem. He took the

effort to describe rules which could serve "to judge of causes and effects". This approach opened the path for assessment of causation by selecting sets of criteria.

CRITERIA OF CAUSAL INFERENCE IN DETERMINISTIC MODEL OF MILL

With few exemptions in later studies causal inference was described not by outright definition, but rather by formulating more or less specific lists of conditions which has to be fulfilled in order to declare that the events are causally connected.

The first general list of five causal criteria was elaborated by J.S. Mill, and now is known as Mill's canons (or methods) of induction. Mill leaves distinction between cause and effect to independently observed temporal sequence of events and does not include it in the definition (6).

- Method of the only agreement:
  If in a series of cases in which event B is present, only event A_i is also present, but none of the other events is present in all of those cases, then event A_i is the cause (or effect) of the event B.

With such research setup, in which in all instances when A_i occurs, also occurs B, we may conclude that A_i is sufficient cause of B. It would be also necessary cause if it would be specific cause of B, which means that no other event different than A_i if it would occur, would be followed by B.

Most probably Mill himself, at least at the time of first edition of his System of Logic, interpreted method of agreement as a tool to proof necessary cause. But for contemporary methodologist it is obvious, that any attempt to control all the variables is grossly unrealistic. In all research designs scientist has to select variables for analysis on the basis of his knowledge, intuition, common sense, and last but not least available financial means.

- Method of the only difference.
  If with a set of events $\{A_1, A_2 \ldots A_n\}$ event B occurs, but if with set of events $\{A_1, A_2 \ldots A_n\}$ which does not contain event A_i, but contains all the of the other, event B does not occur, then event A_i is the cause or part of the cause of B.

For the set of events listed in design of the study, event A_i is necessary cause of the occurrence of the event *B*. It is also alone or in combination with some other events (part of the cause) from the set $\{A_1, A_2 \ldots A_n\}$ sufficient cause of the event *B*.

First version of the method of the only difference was postulated by Hume. It is also worth to note that counterfactual reasoning is based on the same principle.

- Combined method of the only agreement and the only difference
- Method of residues
  In a setting of known causal relation, observed modification of this relation, which is associated with presence of the new event, which did not occurred when causal relation was not modified leads to conclusion that this new event is a cause of the observed modification. If, for example, we observe movement of iron pendulum which is different from observed before, and there is magnet in the room where pendulum moves, we may conclude that presence of magnet is a cause of distraction of pendulum movement from this, which is caused by the force of gravity and the effect of Coriolis.
- Method of concomitant variations

This method is best illustrated by analysis of the dose response curves. Increased (or decreased) strength of the cause induces concomitant quantitative changes in the effect.

The methods of only agreement and of only difference provide strongest evidence of causal inference among Mill 's cannons. But all his methods bear general burden of induction. It is limited number of events (variables) which investigator may control and unlimited of those which are beyond the control and even beyond his knowledge. Presupposition of Mill 's analysis is strong causal connection.

Scientific and also common observation of daily life provide many examples of association between events, which people used to qualify as causal. With great variety of those associations there are two features which dominate attention of observers: one is temporal sequence, that cause precedes of effect or at least it starts before effect occurs, other is regularity of the association. This perspective was adopted by philosophical approach to the problem of causation forming group of "regularity theories". Strong deterministic presumption is frequent base of those theories, but they may also be neutral to the problem of determinism.

Regularity theories had serious problems with irregularities observed in causal relations. Some effects occur after many different causes, some require special circumstances to occur. Throwing stone is insufficient condition to break the window: it has to be thrown in the proper direction and no screen has to be present on its way. But if certain sets of circumstances occur, throwing stone suffices to brake the window. Still it is not necessary condition to brake the window since it may be broken by hitting it with hammer. John Mackie tried to meet those problems with introduction term "inus" , acronym for: insufficient, but necessary part of sufficient but unnecessary condition". Example with throwing stone is good example of the "inus" cause (7).

COUNTERFACTUALS THEORY

David Lewis created special philosophical system to explain causality on the base of counterfactual statements (8.9,10). Counterfactuals theories of causation gained vast popularity among epidemiologists in 70 ties and 80 ties of the XX C, but the concept is quite old.

Idea, that cause is necessary for effect to occur, was first formulated by D Hume: *„ ...where, if the first object had not been, the second never had existed"*.

It is also embedded in the Cannon of Only Difference of JS Mill: *„If an instance in which the phenomenon under investigation occurs, and an instance at which it does not occur, have every circumstance in common save one, that one occurring only in the former, the circumstances in which alone the two instances differ, is the effect or is the cause, or an indispensable part of the cause, of the phenomenon"*.

What is really new in counterfactuals theory is its special ontological background. Lewis stated his theory in terms of „possible worlds" one of which is said to be closer to actuality than the other, if the first resembles the actual world more then the second does.

According to Levis: *„ „ If A were the case, C would be the case" is true in the actual world if and only if (i) there are no possible A worlds; or (ii) some A-world where C holds is closer to actual world then is any A-world where C-does not hold"*.

In Levis counterfactuals theory primary relata of causal dependence have to be events. Levis construes events as classes of possible spatiotemporal regions. (Others found later that differently defined events and even facts may be compatible with the basic definition). According to Lewis, in order to be qualified as causally related, events have to meet certain criteria:

1. They have to be distinct from each other. It means that effect cannot be identical with its cause, and cannot be part of the cause. Saying "hello" loudly cannot be a cause of saying "hello".
2. Standard interpretation of counterfactuals excludes backtracking ones (two events having third common cause).
   Temporal asymmetry of causal dependence . According to Levis it is typically true that events causally depend on earlier, but not on later events. Though Lewis claims that time-reversed causation is a conceptual possibility and cannot be ruled out a priori. In general asymmetry of causal inference is quite difficult to model on the ground of counterfactuals theory.
3. Transitivity. According to Levis causation is transitive.

Lewis theory raised criticism based on philosophical presumptions, but also on the problems with direct application of his theory to empirically observed events. Transitivity and existence of causal chains may be observed in many instances, but it is possible to find numerous counter examples to it. Kvart gave the following counterexample: worker in a factory cut off his finger, physician reinstalled this finger to worker's hand, after operation finger regained its full function. Cutting finger was a cause of performing operation. Performing operation was a cause of regaining function of the finger, but it is hard to accept that cutting finger was a cause of regaining of all finger functions (11,12).

Another problem for Lewis model is preemption. Two sufficient causes would occur, but one occurs before another. Suzy and Bill are throwing stones at the bottle, both with perfect accuracy. Bill throws first and brakes the bottle. If he wouldn't throw, the bottle would be broken by Suzy. According to counterfactuals criteria throwing stone by Bill was not the cause of braking bottle, since if Bill wouldn't throw the stone, bottle would be broken anyway by Suzy (13).

Counterfactuals theory assumes that causation is an absolute relation whose nature does not vary from one context to another so context sensitivity was difficult to model on its grounds.

In its initial version from 1974 counterfactuals theory of causation functioned under assumption of determinism[1].

In the realm of epidemiology we rarely have so strong ties between cause end effect. Statistical methods used in contemporary epidemiology hardly match this model. Many of the associations studied in epidemiology are not necessary nor sufficient and what we presume to be causes or risk factors simply change probability of the occurrence of effect. This is why strongly deterministic model of Mills and other "regularity theories" do not suit most of the modern epidemiological studies. Increased numbers of epidemiologists turn to models of probabilistic causation.

1 In the later version from 1986 Lewis accepted chancy causation as a conceptual possibility and defined more general notion of causal dependency in terms of chancy counterfactuals: *„ Where c and e are distinct actual events, e causally depends non c if and only if c were not occurred, the chance of e's occurring would be much less then its actual chance"* Last version of Lewis counterfactuals theory was presented in Harvard Witehead lectures in 2000. In this version he used as central notion „influence" and tried to deal with problems which were raised by critics of 1974 version. In his concept probabilities are unconditional (in the possible worlds) contrary to other probabilistic causation theories

PROBABILISTIC CAUSATION

Strictly deterministic description of natural events met insurmountable problems in XX ties century quantum physics. Physicists were first, who started describe results of scientific observations in indeterministic perspective. Many of them claimed that referring to causes which are beyond our empiricist cognition is pure metaphysics. The only thing which we are able to observe and measure is probability of occurrence of events and conditional probability of associations between them. In their opinion, so called „sufficient causal connection" is temporal sequence of events which conditional probability equals „1", and necessary causal connection" is defined by conditional probability of effect in the absence of the event called "cause" equals „0" (14,15)

Definition of causation based on probability rising (PR) states: "A is a cause of B if, and only if conditional probability of B, given A is bigger then conditional probability of B given non-A.

A causes B if and only if P(B/A)>P(B/non-A)

This definition requires further elaboration, since his formula brings some problems:

- It is symmetric: If ***P(B/A)>P(B/non-A)*** occurs, also occurs ***P(A/B)>P(A/non-B)***
- Spurious correlations (A and B are caused by the same third factor C)

In a typical, frequently quoted example, drop of atmospheric pressure C is a cause of a storm B, but also causes drop of barometer reading A. Barometer reading may correlate with occurrence of storm, but it may hardly be accepted as the cause of a storm.

To eliminate problem of spurious correlation Hans Reichenbach's introduced „screening off concept": If P(B/A&C)=P(B/C), then C in his terminology C screens A off from B. In other words C renders A probabilistically irrelevant to B (16).

On this reasoning is based "no screening off" – NSO condition, which Reichenbach included in the definition of probabilistic causation:

- A is the cause of B if and only if occurrence of A increases probability of B occurrence.
- There is no factor C different from A and B, which occurs earlier or simultaneously with factor A, which screens A off from B.

Another approach to the problem of spurious correlations is test situation –TS, in which all potential screening factors are fixed:

A causes B if P(B/A&T)>P(B/not-A&T) for every test situation T

Problem with this criterion is in premises that all the events T may have some causal influence on appearance of B. So in the procedure of testing, when choosing variables to fix, we presume that they are causally or probabilistically related to the effect. Such elements of circularity may rise serious criticism against inclusion of TS procedure in general definition of probabilistic causality, but it doesn't depreciate its value in practical studies of causal associations between variables.

PROBLEM OF ASYMMETRY IN PROBABILISTIC DEFINITION OF CAUSATION

Another problem relating to probabilistic causation lays in symmetry of conditional probabilities used in the definition. Most of our intuitions regarding causal dependence presume that relation between cause and effect is somewhat different then relation between effect and the cause and by so it is asymmetrical. The simplest solution would be to include in the definition additional precondition that causes precede their effects in time. This was included in Suppes definition, but it not always is completely true eg. smoking and cancer, river current and bank erosion. But in most of those cases in which it would be applicable, temporal sequence provides sufficient criterion for asymmetry.

In a search for more universal criteria for asymmetry of causal inference, philosophers look for specific probabilistic features of relationships between causes and effects. Some of those criteria require specific set-ups and bigger number of analyzed variables. So their universality is also doubtful.

One of the arguments for asymmetry is based on Reichenbach's „common cause principle": common causes may screen different effects from each other, but common effects do not screen their causes.

Occurrence of storm (S) is correlated with drop of atmospheric pressure (P) and is also correlated with dependent of atmospheric pressure reading of barometer (B). But we may reject causal dependence of the storm from barometric reading, because atmospheric pressure screens occurrence of storm from barometric reading:

P(S/P&B)=P(S/P)

Common effects do not screen their causes from each other. Pulmonary cancer (C) may be caused by smoking (S) and also by working with asbestos (A). (The fact that they are different types of cancer does not invalidate this reasoning). Though among asbestos workers smoking increases probability of having cancer, as among smokers does working with asbestos:

P(C/S)<P(C/S&A)

Some authors believe that asymmetry may be secured by manipulation with a cause in a condition of fixing all other variables. To test whether A is a cause of B we should hold fixed other independent causes of B and A. In such a situation cause rises probability of

effect, but effect is not able to rise probability of a cause. Already cited arguments on circularity and limited applications of manipulation criteria suit also here (17) .

DIRECTED ACYCLIC GRAPHS (DAG) AND MODELING OF CAUSALITY

Causal reasoning in many examples may be quite simple and easy to intuitive understanding. In multifactorial setup, numerous interdependencies among variables may be difficult to overview and require methods of further clarification. Graphical presentation is particularly useful for that purpose.

Pioneering work in this field was done by Sewall Wright, geneticist and epidemiologist who in 1920-ties used graphs to „fill gaps" in representation of causal mechanisms in genetics (18).

Graphs were applied for analysis of interdependence between variables in 70-ties and 80-ties by economists and sociologists who used graphs to compare statistical models. In this same period statisticians used directed and undirected graphs to study independence of relationships among random variables usually without reference to causality.

Two ambitious research programs of J. Pearl and group of scientists from the University of Pittsburgh P. Spirtes, C. Glaymour and R. Scheines (SGS) were aimed on making algorithms which would find causal inferences on the basis of statistical data (19-22). They choose directed acyclic graphs as most suitable tool for graphic modeling. Directed graphs with edges pointed with arrows serve for modeling asymmetry of relations between variables and acyclicity of graphs prevents circuitry of dependences – no variable may be presented as a cause of itself. DAG's form a subset of Bayesian networks: probabilistic graphical models that represent random variables and their conditional interdependencies (23). Important presumptions of DAG's presentations is that they have to satisfy Markov Condition: parents of X screen X from all other variables (Y), except for the descendants of X

P(X/PA(X) &Y**)= P(**X/PA(X)**)**

DAG's graphs are applicable to analysis of causal dependencies if they satisfy the Causal Markov Condition, which asserts that Markov Condition holds of a population if DAG's and probability distributions are given causal interpretation.

Detailed description of theory of DAG's and its applicability to analysis of causal relations in epidemiology is included in vast, easily available, literature. So I will limit myself to few comments.

DAG approach provide a useful and powerful tool for visualization and interpretation of causal inferences. It clearly represent complicated interdependences in study design. It also helps to discover and analyze complicated instances of confounding and selection bias.

With all respect to robustness of DAG presentation of epidemiological data, belief of the authors and promoters of this approach, that DAG's may open the pathway to crating algorithms of causal inferences, would require further explanation and analysis of premises which stand behind such a statement.

All variables which are included in DAG presentation, have to be selected on some earlier accepted criteria, which may include presumptions on associations between variables. So creating DAG is based on prior knowledge of the investigator. Causal interpretation of DAG requires meeting by the graph earlier defined criteria of causality. DAG graph may shortcut the path to causal interpretation, but it is difficult to imagine that it may to do so without prior acceptation of requirements which allow us to interpret statistical association as causal one.

SUBJECTIVE ELEMENTS IN CAUSAL REASONING

Centuries of scientific and philosophical efforts on the problem of causality in natural and social sciences failed to find analytical solution, which would provide undeniable tool to separate all causal dependencies from acausal associations. It rises a question whether we really need causal model of relationships between events and facts in science and in common life. Problem is, that even if it would be possible to describe associations between all observed events in purely indeterministic way, most of the people doesn't do it in intuitive approach to common life situations and even to many scientifically studied ones. Mother who is quantum physicists and uses indeterministic presumptions in her professional life, rarely accepts indeterministic explanation of the mess in her child room.

Causal interpretation of events is a base for most of our practical activities in medicine and in public health. If knowledge is a tool for efficient practice, one have to expect that the knowledge would point to the things, events or facts, whose modification leads to achievement of desired aims. With all the reservation of philosophers toward manipulation theories of causality, we may agree, that even if creating theory of causality on the basis of manipulation is circular, manipulation is a powerful confirmatory tool of previously presumed causal dependence. High esteem of experimental design in the opinion of most epidemiologists shows how strong is their consensus on the role of manipulations in causal reasoning. Similarly the effects of public health interventions assessed by epidemiological studies may

serve as pragmatic argument for accuracy of causative premises.

Closely related to epidemiological practice probabilistic theories of causation leave the room for individual interpretation of causal mechanisms which lay behind probability rising principle. Numerous solutions of the problems associated with application of probabilistic theory of causality like common cause, colinearity, confounding and selection bias may be interpreted as means of adopting our statistical tools to our prior knowledge and causal intuition. W somehow know that barometric reading should not be a cause of a storm, so we expect from methodologists to find statistical tools "to screen" barometric reading as causally irrelevant. And we are willing to use that tool in other setups in which similar common cause situation may occur, but in which we do not have this prior knowledge as in a case of barometer and storm.

Statistics is causally blind or at least it's casual vision is impaired. In the case of perfect colinearity assessment of the difference between feasible and infeasible causes has to be based on other sources of knowledge than purely statistical test. One of children's toys is a box with holes, to which match blocks of particular shapes. If such a box would have circular and triangular holes to which match circular and triangular blocks and all triangular blocks would be blue, and circular would be red, through circular holes would pass only red blocks and through triangular only blue. Child knows that painting triangular blocks in red would not make them passing through circular holes. And child obtained knowledge, that for matching holes by blocks shape is important and color is not, out of statistical sources.

Most of statistical and epidemiological tools are directed to eliminate potential sources of fallacies, which may lead to false causal reasoning and leaving those statistical associations for which we were not able to find source of error. Robust effectiveness of DAG's is especially good example of that approach, which is closely related to Poper's methodology of falsification (24). But to turn statistical connections into causal interpretation, we have to rely on learned interpretation, which may have many different sources, some of which are difficult to define and may be even classified as subjective or intuitive.

Well known Hill's criteria and earlier formulated criteria included in the Report of the Advisory Committee to the Surgeon General, are examples of pointing to potential sources of causal reasoning in epidemiology (25,26). Those criteria do not provide proof of causal dependence nor even increase its measurable probability. The purpose of those criteria is to provide basic framework for intersubjective communication of our causal intuitions.

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