

## WHEN UNCERTAINTY IS NOT THE PROBLEM: SCIENCE, COMPLEXITY, AND THE EVALUATION OF RESEARCH

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### Abstract

Uncertainty has traditionally been regarded as a transient limitation of scientific knowledge, expected to be resolved through methodological refinement or the accumulation of evidence. However, when research is conducted at the frontiers of knowledge and addresses complex, non-linear biological systems, uncertainty ceases to be a methodological flaw and becomes a structural condition of scientific progress. Drawing on epistemological, historical, and clinical perspectives, this article revisits the productive role of uncertainty in knowledge generation and highlights its relevance for understanding complex medical phenomena. From this standpoint, illustrative examples from clinical practice and the history of biomedical research are discussed, showing that many significant advances emerged from contexts of conceptual exploration rather than strict predictability. Finally, the article examines the implications of this perspective for contemporary systems of research evaluation and funding, emphasizing the tensions that arise when criteria of predictability and methodological security are applied to inherently uncertain problems. Recognizing uncertainty as a legitimate component of the scientific process is essential to promote research practices that are more consistent

and better aligned with the complexity of current medical challenges.

**Key words:** uncertainty, complex systems, biomedical research, research funding, program evaluation

### Resumen

*Cuando la incertidumbre no es el problema: ciencia, complejidad y sistemas de evaluación*

La incertidumbre ha sido tradicionalmente considerada una limitación transitoria del conocimiento científico, destinada a resolverse mediante mejoras metodológicas o acumulación de evidencia. Sin embargo, cuando la investigación se desarrolla en la frontera del conocimiento y aborda sistemas biológicos complejos y no lineales, la incertidumbre deja de ser un defecto del método para convertirse en una condición estructural del progreso científico. A partir de aportes epistemológicos, históricos y clínicos, este artículo propone revisar el papel productivo de la incertidumbre en la generación de conocimiento, destacando su valor en la comprensión de fenómenos médicos complejos. Desde esta perspectiva, se revisan ejemplos ilustrativos provenientes de la práctica clínica y de la historia de la investigación biomé-

ca, que muestran cómo muchos avances significativos surgieron en contextos de exploración conceptual más que de previsibilidad estricta. Finalmente, se discuten las implicancias de este enfoque para los sistemas actuales de evaluación y financiamiento de la investigación, señalando las tensiones que emergen cuando se aplican criterios de previsibilidad y seguridad metodológica a problemas intrínsecamente inciertos. Reconocer la incertidumbre como un componente legítimo del proceso científico resulta clave para promover una investigación más consistente y mejor alineada con la complejidad de los problemas médicos contemporáneos.

**Palabras clave:** incertidumbre, sistemas complejos, investigación biomédica, financiamiento de la investigación, evaluación de programas

Uncertainty has traditionally been regarded as a transient limitation of scientific knowledge, expected to be overcome through improved study designs, greater methodological precision, or the progressive accumulation of evidence. However, when research is conducted at the frontiers of knowledge—and particularly when it addresses complex biological systems—uncertainty ceases to be a correctable flaw and becomes a structural condition of scientific progress. In this context, it is pertinent to rethink the idea of uncertainty not as a failure of method, but as a constitutive component of scientific advancement. This reconsideration is not merely conceptual; it has direct implications for how research projects are currently evaluated, funded, and prioritized, particularly within competitive calls and systems for the allocation of research grants—an issue addressed later in this article.

A useful point of departure for this reflection is provided by the now-classic essay by Martin A. Schwartz, who argued that “feeling stupid” is an inherent experience of good scientific research<sup>1</sup>. Far from being a rhetorical provocation, Schwartz described a common situation faced by those working on genuinely novel problems: the explicit awareness of not knowing, of operating in conceptually unstable territories without clear maps or guaranteed outcomes. This cognitive discomfort, rather than indicating incompetence, signals that the researcher has moved beyond the safety of the known into questions that truly matter.

## Uncertainty and scientific progress

This seemingly subjective observation gains greater depth when placed within a broader epistemological framework. In this regard, the methodology of scientific research programs proposed by Imre Lakatos offers a particularly suitable structure for legitimizing uncertainty as an integral part of scientific work<sup>2</sup>. According to Lakatos, science does not progress through the simple refutation of isolated hypotheses, but through programs composed of a relatively stable hard core of assumptions surrounded by a protective belt of auxiliary hypotheses that are adjusted in response to empirical anomalies. What distinguishes progressive from degenerative programs is not the absence of anomalies, but their capacity to expand explanatory power and to open fertile lines of inquiry. In other words, science advances not by eliminating uncertainty, but by organizing it.

## Complexity, nonlinearity and clinical experience

This perspective becomes especially relevant when the object of study consists of complex, non-linear biological systems. In such systems, relationships between variables are rarely linear or unidirectional; instead, they involve multiple levels of organization, feedback loops, and emergent phenomena that cannot be inferred from the isolated analysis of their components. In this context, the expectation of precise and stable predictions is, in many cases, epistemologically unjustified, as early anticipated by Weaver and later developed by Cilliers. Contemporary medicine has also conceptualized clinical practice through the lens of complexity, emphasizing that many care processes do not follow simple causal pathways or predictable trajectories<sup>3</sup>.

Clinical medicine—across multiple domains, and particularly evident in fields such as pulmonology, respiratory physiology, and intensive care—routinely confronts this type of complexity. The relationships between ventilatory responses to CO<sub>2</sub>, pulmonary mechanics, and daytime hypercapnia, the effects of hypoxic and hypercapnic loads in sleep-related breathing disorders, and the evolution of advanced chronic diseases constitute paradigmatic examples

of non-linear systems. These phenomena are sensitive to initial conditions and modulated by multiple physiological, environmental, and contextual variables. Attempts to reduce them to simple linear models may create a false sense of certainty at the cost of impoverishing system understanding<sup>4,5</sup>.

At this point, the history of biomedical research becomes particularly illustrative, as exemplified by the work of Julius H. Comroe Jr. In his retrospective analyses of the origins of numerous medical advances, Comroe demonstrated that many discoveries now regarded as fundamental did not arise from research aimed at immediate clinical objectives, but rather from basic studies driven by curiosity, loosely defined questions, or even accidental findings<sup>6,7</sup>. In works such as *Retrospectroscope* and *Pay Dirt*, he challenged the tendency to retrospectively reconstruct linear trajectories where contingency, uncertainty, and open-ended exploration had in fact predominated. This historical reconstruction suggests that uncertainty not only accompanies scientific progress, but often precedes it and makes it possible. A classic example is Semmelweis, whose work on puerperal fever shows that some decisive advances do not arise from linear trajectories or strict predictability, but from attention to anomalies and conceptual exploration under conditions of uncertainty<sup>8</sup>.

In a convergent vein, Alfredo Lanari described genuinely creative researchers as those capable of advancing even within contexts of “conceptual fog,” recognizing a possible path and an attainable goal despite the absence of precise definitions at the outset<sup>9</sup>. Genuinely innovative research rarely follows a highway mapped out in advance; more often, it advances across open country, finding and correcting its own path as it goes. This exploratory mode—closer to trial, reformulation, and iterative understanding than to the execution of a closed plan—represents another expression of the productive value of uncertainty, as later noted within the field of Argentine respiratory medicine<sup>10</sup>.

From a *Lakatosian* perspective, the historical examples analyzed by Comroe can be interpreted as research programmes that, despite persistent anomalies and the absence of immediate applications, demonstrated a remarkable capac-

ity to expand the available conceptual space. Their value did not lie in short-term predictive accuracy, but in their potential to enhance understanding of complex biological phenomena. In this sense, the history of medicine reinforces the notion that clinical science progresses not solely through hypothesis confirmation, but through sustained engagement with uncertainty.

### Evaluating Science in Contexts of Uncertainty

This approach is particularly pertinent in the contemporary context, where many of the most relevant problems in medicine—from complex chronic diseases to global health crises—are characterized by high levels of uncertainty, non-linear interactions, and outcomes that are difficult to predict. In such scenarios, attempts to eliminate uncertainty may lead to excessive simplification or to decisions based on fragile models. By contrast, explicitly acknowledging the limits of available knowledge enables the design of strategies that are more flexible, adaptive, and resilient.

This conceptual framework, however, stands in tension with the criteria that currently dominate many systems for evaluating research projects, allocating funding, and awarding grants. These systems often demand precise formulations of objectives, hypotheses, and expected results, leaving little room to recognize “not knowing” as a legitimate point of departure. Paradoxically, this demand for predictability may discourage research oriented toward complex problems, where uncertainty is not a design flaw but an inherent feature of the object under study<sup>11</sup>. From a complementary perspective, it has been argued that certain evaluation systems tend to select for methodologically safe but conceptually conservative practices, fostering dynamics that may impoverish scientific development in complex domains<sup>12</sup>.

The implications of this perspective for both research and clinical practice are significant. First, it invites a more humble epistemological stance, one that acknowledges the provisional nature of models and the inevitability of anomalies. Second, it suggests that the value of a research line should not be judged exclusively by its immediate predictive capacity, but also by its

potential to expand understanding of complex systems. Finally, it promotes a scientific culture that tolerates uncertainty without abandoning rigor, and that values critical exploration over illusory certainty.

In a medical context increasingly pressured to deliver rapid and immediately applicable results, revisiting these historical and epistemological lessons becomes particularly relevant. Working

at the edge of knowledge entails accepting that uncertainty is not an enemy to be eradicated, but a territory to be inhabited with intellectual discipline, conceptual openness, and epistemic honesty. As the history of medical science repeatedly shows, it is precisely at this edge that the most meaningful advances tend to emerge.

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## Bibliography

1. Schwartz MA. The importance of stupidity in scientific research. *J Cell Sci* 2008; 121: 1771.
2. Lakatos I. The methodology of scientific research programmes: Philosophical Papers. Worrall J, Currie G, eds. Cambridge University Press; 1978.
3. Plsek PE, Greenhalgh T. Complexity science: the challenge of complexity in health care. *BMJ* 2001; 323: 625-8.
4. Weaver W. Science and complexity. *Am Sci* 1948; 36: 536-44.
5. Cilliers P. Complexity and Postmodernism: Understanding Complex Systems. London: Routledge; 1998.
6. Comroe JH. Retrospectroscope: Insights into Medical Discovery. Menlo Park: Von Gehr Press; 1977.
7. Comroe Jr JH, Dripps RD. Scientific basis for the support of biomedical science. *Science* 1976; 192: 105-11.
8. Kadar N, Romero R, Papp Z. Ignaz semmelweis: the "savior of mothers": on the 200th anniversary of his birth. *Am J Obstet Gynecol* 2018; 219: 519-22.
9. Lanari A. Reflexiones sobre investigación y creación científica. Buenos Aires: Sigma SRL; 1995.
10. De Vito EL. De la actividad asistencial al abstract y al artículo original. *Rev Argent Med Respir* 2006; 3: 120-5.
11. Saltelli A. Why science's crisis should not become a political battling ground. *Futures* 2018; 104: 85-90.
12. Smaldino PE, McElreath R. The natural selection of bad science. *R Soc Open Sci* 2016; 3:160384.