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Scientific Hypotheses: Writing, Promoting, and Predicting Implications

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ABSTRACT

Scientific hypotheses are essential for progress in rapidly developing academic disciplines. Proposing new ideas and hypotheses require thorough analyses of evidence-based data and predictions of the implications. One of the main concerns relates to the ethical implications of the generated hypotheses. The authors may need to outline potential benefits and limitations of their suggestions and target widely visible publication outlets to ignite discussion by experts and start testing the hypotheses. Not many publication outlets are currently welcoming hypotheses and unconventional ideas that may open gates to criticism and conservative remarks. A few scholarly journals guide the authors on how to structure hypotheses. Reflecting on general and specific issues around the subject matter is often recommended for drafting a well-structured hypothesis article. An analysis of influential hypotheses, presented in this article, particularly Strachan's hygiene hypothesis with global implications in the field of immunology and allergy, points to the need for properly interpreting and testing new suggestions. Envisaging the ethical implications of the hypotheses should be considered both by authors and journal editors during the writing and publishing process.

Keywords: Bibliographic Databases; Peer Review; Writing; Research Ethics; Hypothesis; Impact

INTRODUCTION

We live in times of digitization that radically changes scientific research, reporting, and publishing strategies. Researchers all over the world are overwhelmed with processing large volumes of information and searching through numerous online platforms, all of which make the whole process of scholarly analysis and synthesis complex and sophisticated.

Current research activities are diversifying to combine scientific observations with analysis of facts recorded by scholars from various professional backgrounds.[1] Citation analyses and networking on social media are also becoming essential for shaping research and publishing strategies globally.[2] Learning specifics of increasingly interdisciplinary research studies and

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acquiring information facilitation skills aid researchers in formulating innovative ideas and predicting developments in interrelated scientific fields.

Arguably, researchers are currently offered more opportunities than in the past for generating new ideas by performing their routine laboratory activities, observing individual cases and unusual developments, and critically analyzing published scientific facts. What they need at the start of their research is to formulate a scientific hypothesis that revisits conventional theories, real-world processes, and related evidence to propose new studies and test ideas in an ethical way.[3] Such a hypothesis can be of most benefit if published in an ethical journal with wide visibility and exposure to relevant online databases and promotion platforms.

Although hypotheses are crucially important for the scientific progress, only few highly skilled researchers formulate and eventually publish their innovative ideas *per se*. Understandably, in an increasingly competitive research environment, most authors would prefer to prioritize their ideas by discussing and conducting tests in their own laboratories or clinical departments, and publishing research reports afterwards. However, there are instances when simple observations and research studies in a single center are not capable of explaining and testing new groundbreaking ideas. Formulating hypothesis articles first and calling for multicenter and interdisciplinary research can be a solution in such instances, potentially launching influential scientific directions, if not academic disciplines.

The aim of this article is to overview the importance and implications of infrequently published scientific hypotheses that may open new avenues of thinking and research.

DEFINITION

Despite the seemingly established views on innovative ideas and hypotheses as essential research tools, no structured definition exists to tag the term and systematically track related articles. In 1973, the Medical Subject Heading (MeSH) of the U.S. National Library of Medicine introduced "Research Design" as a structured keyword that referred to the importance of collecting data and properly testing hypotheses, and indirectly linked the term to ethics, methods and standards, among many other subheadings.

One of the experts in the field defines "hypothesis" as a well-argued analysis of available evidence to provide a realistic (scientific) explanation of existing facts, fill gaps in public understanding of sophisticated processes, and propose a new theory or a test.[4] A hypothesis can be proven wrong partially or entirely. However, even such an erroneous hypothesis may influence progress in science by initiating professional debates that help generate more realistic ideas. The main ethical requirement for hypothesis authors is to be honest about the limitations of their suggestions.[5]

EXAMPLES OF INFLUENTIAL SCIENTIFIC HYPOTHESES

Daily routine in a research laboratory may lead to groundbreaking discoveries provided the daily accounts are comprehensively analyzed and reproduced by peers. The discovery of penicillin by Sir Alexander Fleming (1928) can be viewed as a prime example of such discoveries that introduced therapies to treat staphylococcal and streptococcal infections

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and modulate blood coagulation.[6,7] Penicillin got worldwide recognition due to the inventor's seminal works published by highly prestigious and widely visible British journals, effective 'real-world' antibiotic therapy of pneumonia and wounds during World War II, and euphoric media coverage.[8] In 1945, Fleming, Florey and Chain got a much deserved Nobel Prize in Physiology or Medicine for the discovery that led to the mass production of the wonder drug in the U.S. and 'real-world practice' that tested the use of penicillin. What remained globally unnoticed is that Zinaida Yermolyeva, the outstanding Soviet microbiologist, created the Soviet penicillin, which turned out to be more effective than the Anglo-American penicillin and entered mass production in 1943; that year marked the turning of the tide of the Great Patriotic War.[9] One of the reasons of the widely unnoticed discovery of Zinaida Yermolyeva is that her works were published exclusively by local Russian (Soviet) journals.

The past decades have been marked by an unprecedented growth of multicenter and global research studies involving hundreds and thousands of human subjects. This trend is shaped by an increasing number of reports on clinical trials and large cohort studies that create a strong evidence base for practice recommendations. Mega-studies may help generate and test large-scale hypotheses aiming to solve health issues globally. Properly designed epidemiological studies, for example, may introduce clarity to the hygiene hypothesis that was originally proposed by David Strachan in 1989.[10] David Strachan studied the epidemiology of hay fever in a cohort of 17,414 British children and concluded that declining family size and improved personal hygiene had reduced the chances of cross infections in families, resulting in epidemics of atopic disease in post-industrial Britain. Over the past four decades, several related hypotheses have been proposed to expand the potential role of symbiotic microorganisms and parasites in the development of human physiological immune responses early in life and protection from allergic and autoimmune diseases later on.[11,12] Given the popularity and the scientific importance of the hygiene hypothesis, it was introduced as a MeSH term in 2012.[13]

Hypotheses can be proposed based on an analysis of recorded historic events that resulted in mass migrations and spreading of certain genetic diseases. As a prime example, familial Mediterranean fever (FMF), the prototype periodic fever syndrome, is believed to spread from Mesopotamia to the Mediterranean region and all over Europe due to migrations and religious prosecutions millennia ago.[14] Genetic mutations spearing mild clinical forms of FMF are hypothesized to emerge and persist in the Mediterranean region as protective factors against more serious infectious diseases, particularly tuberculosis, historically common in that part of the world.[15] The speculations over the advantages of carrying the MEditerranean FeVer (MEFV) gene are further strengthened by recorded low mortality rates from tuberculosis among FMF patients of different nationalities living in Tunisia in the first half of the 20th century.[16]

Diagnostic hypotheses shedding light on peculiarities of diseases throughout the history of mankind can be formulated using artefacts, particularly historic paintings.[17] Such paintings may reveal joint deformities and disfigurements due to rheumatic diseases in individual subjects. A series of paintings with similar signs of pathological conditions interpreted in a historic context may uncover mysteries of epidemics of certain diseases, which is the case with Ruben's paintings depicting signs of rheumatic hands and making some doctors to believe that rheumatoid arthritis was common in Europe in the 16th and 17th century.[18]

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WRITING SCIENTIFIC HYPOTHESES

There are author instructions of a few journals that specifically guide how to structure, format, and make submissions categorized as hypotheses attractive. One of the examples is presented by *Med Hypotheses*, the flagship journal in its field with more than four decades of publishing and influencing hypothesis authors globally. However, such guidance is not based on widely discussed, implemented, and approved reporting standards, which are becoming mandatory for all scholarly journals.

Generating new ideas and scientific hypotheses is a sophisticated task since not all researchers and authors are skilled to plan, conduct, and interpret various research studies. Some experience with formulating focused research questions and strong working hypotheses of original research studies is definitely helpful for advancing critical appraisal skills. However, aspiring authors of scientific hypotheses may need something different, which is more related to discerning scientific facts, pooling homogenous data from primary research works, and synthesizing new information in a systematic way by analyzing similar sets of articles. To some extent, this activity is reminiscent of writing narrative and systematic reviews. As in the case of reviews, scientific hypotheses need to be formulated on the basis of comprehensive search strategies to retrieve all available studies on the topics of interest and then synthesize new information selectively referring to the most relevant items. One of the main differences between scientific hypothesis and review articles relates to the volume of supportive literature sources (**Table 1**). In fact, hypothesis is usually formulated by referring to a few scientific facts or compelling evidence derived from a handful of literature sources.[19] By contrast, reviews require analyses of a large number of published documents retrieved from several well-organized and evidence-based databases in accordance with predefined search strategies.[20-22]

The format of hypotheses, especially the implications part, may vary widely across disciplines. Clinicians may limit their suggestions to the clinical manifestations of diseases, outcomes, and management strategies. Basic and laboratory scientists analysing genetic,

Table 1. Characteristics of scientific hypotheses and narrative and systematic reviews

Characteristics	Hypothesis	Narrative review	Systematic review
Authors and contributors	Any researcher with interest in the topic	Usually seasoned authors with vast experience in the subject	Any researcher with interest in the topic; information facilitators as contributors
Registration	Not required	Not required	Registration of the protocol with the PROSPERO registry (https://www.crd.york.ac.uk/prospero/) is required to avoid redundancies
Reporting standards	Not available	Not available	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (http://www.prisma-statement.org/)
Search strategy	Searches through credible databases to retrieve items supporting and opposing the innovative ideas	Searches through multidisciplinary and specialist databases to comprehensively cover the subject	Strict search strategy through evidence-based databases to retrieve certain type of articles (e.g., reports on trials and cohort studies) with inclusion and exclusion criteria and flowcharts of searches and selection of the required articles
Structure	Sections to cover general and specific knowledge on the topic, research design to test the hypothesis, and its ethical implications	Sections are chosen by the authors, depending on the topic	Introduction, Methods, Results and Discussion (IMRAD)
Search tools for analyses	Not available	Not available	Population, Intervention, Comparison, Outcome (Study Design) (PICO, PICOS)
References	Limited number	Extensive list	Limited number
Target journals	Handful of hypothesis journals	Numerous	Numerous
Publication ethics issues	Unethical statements and ideas in substandard journals	'Copy-and-paste' writing in some reviews	Redundancy of some nonregistered systematic reviews
Citation impact	Low (with some exceptions)	High	Moderate

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molecular, and biochemical mechanisms may need to view beyond the frames of their narrow fields and predict social and population-based implications of the proposed ideas.[23]

Advanced writing skills are essential for presenting an interesting theoretical article which appeals to the global readership. Merely listing opposing facts and ideas, without proper interpretation and analysis, may distract the experienced readers. The essence of a great hypothesis is a story behind the scientific facts and evidence-based data.

ETHICAL IMPLICATIONS

The authors of hypotheses substantiate their arguments by referring to and discerning rational points from published articles that might be overlooked by others. Their arguments may contradict the established theories and practices, and pose global ethical issues, particularly when more or less efficient medical technologies and public health interventions are devalued. The ethical issues may arise primarily because of the careless references to articles with low priorities, inadequate and apparently unethical methodologies, and concealed reporting of negative results.[24,25]

Misinterpretation and misunderstanding of the published ideas and scientific hypotheses may complicate the issue further. For example, Alexander Fleming, whose innovative ideas of penicillin use to kill susceptible bacteria saved millions of lives, warned of the consequences of uncontrolled prescription of the drug. The issue of antibiotic resistance had emerged within the first ten years of penicillin use on a global scale due to the overprescription that affected the efficacy of antibiotic therapies, with undesirable consequences for millions.[26]

The misunderstanding of the hygiene hypothesis that primarily aimed to shed light on the role of the microbiome in allergic and autoimmune diseases resulted in decline of public confidence in hygiene with dire societal implications, forcing some experts to abandon the original idea.[27,28] Although that hypothesis is unrelated to the issue of vaccinations, the public misunderstanding has resulted in decline of vaccinations at a time of upsurge of old and new infections.

A number of ethical issues are posed by the denial of the viral (human immunodeficiency viruses; HIV) hypothesis of acquired Immune deficiency Syndrome (AIDS) by Peter Duesberg, who overviewed the links between illicit recreational drugs and antiretroviral therapies with AIDS and refuted the etiological role of HIV.[29] That controversial hypothesis was rejected by several journals, but was eventually published without external peer review at *Med Hypotheses* in 2010. The publication itself raised concerns of the unconventional editorial policy of the journal, causing major perturbations and more scrutinized publishing policies by journals processing hypotheses.

WHERE TO PUBLISH HYPOTHESES

Although scientific authors are currently well informed and equipped with search tools to draft evidence-based hypotheses, there are still limited quality publication outlets calling for related articles. The journal editors may be hesitant to publish articles that do not adhere to any research reporting guidelines and open gates for harsh criticism of unconventional and

untested ideas. Occasionally, the editors opting for open-access publishing and upgrading their ethics regulations launch a section to selectively publish scientific hypotheses attractive to the experienced readers.[30] However, the absence of approved standards for this article type, particularly no mandate for outlining potential ethical implications, may lead to publication of potentially harmful ideas in an attractive format.

A suggestion of simultaneously publishing multiple or alternative hypotheses to balance the reader views and feedback is a potential solution for the mainstream scholarly journals.[31] However, that option alone is hardly applicable to emerging journals with unconventional quality checks and peer review, accumulating papers with multiple rejections by established journals.

A large group of experts view hypotheses with improbable and controversial ideas publishable after formal editorial (in-house) checks to preserve the authors' genuine ideas and avoid conservative amendments imposed by external peer reviewers.[32] That approach may be acceptable for established publishers with large teams of experienced editors. However, the same approach can lead to dire consequences if employed by nonselective start-up, open-access journals processing all types of articles and primarily accepting those with charged publication fees.[33] In fact, pseudoscientific ideas arguing Newton's and Einstein's seminal works or those denying climate change that are hardly testable have already found their niche in substandard electronic journals with soft or nonexistent peer review.[34]

CITATIONS AND SOCIAL MEDIA ATTENTION

The available preliminary evidence points to the attractiveness of hypothesis articles for readers, particularly those from research-intensive countries who actively download related documents.[35] However, citations of such articles are disproportionately low. Only a small proportion of top-downloaded hypotheses (13%) in the highly prestigious *Med Hypotheses* receive on average 5 citations per article within a two-year window.[36]

With the exception of a few historic papers, the vast majority of hypotheses attract relatively small number of citations in a long term.[36] Plausible explanations are that these articles often contain a single or only a few citable points and that suggested research studies to test hypotheses are rarely conducted and reported, limiting chances of citing and crediting authors of genuine research ideas.

A snapshot analysis of citation activity of hypothesis articles may reveal interest of the global scientific community towards their implications across various disciplines and countries. As a prime example, Strachan's hygiene hypothesis, published in 1989,[10] is still attracting numerous citations on Scopus, the largest bibliographic database. As of August 28, 2019, the number of the linked citations in the database is 3,201. Of the citing articles, 160 are cited at least 160 times (*h*-index of this research topic = 160). The first three citations are recorded in 1992 and followed by a rapid annual increase in citation activity and a peak of 212 in 2015 (**Fig. 1**). The top 5 sources of the citations are *Clin Exp Allergy* (n = 136), *J Allergy Clin Immunol* (n = 119), *Allergy* (n = 81), *Pediatr Allergy Immunol* (n = 69), and *PLOS One* (n = 44). The top 5 citing authors are leading experts in pediatrics and allergology Erika von Mutius (Munich, Germany, number of publications with the index citation = 30), Erika Isolauri (Turku, Finland, n = 27), Patrick G Holt (Subiaco, Australia, n = 25), David P. Strachan (London, UK, n = 23), and Bengt Björksten (Stockholm, Sweden, n = 22). The U.S. is the leading country in

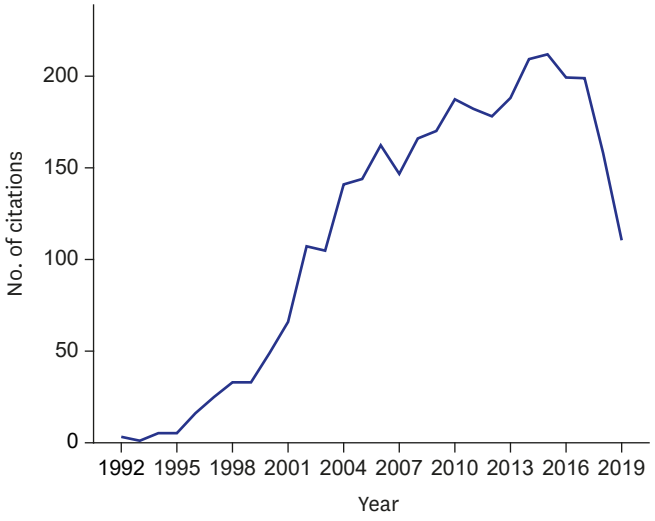

Fig. 1. Number of Scopus-indexed items citing Strachan's hygiene hypothesis in 1992–2019 (as of August 28, 2019).

terms of citation activity with 809 related documents, followed by the UK (n = 494), Germany (n = 314), Australia (n = 211), and the Netherlands (n = 177). The largest proportion of citing documents are articles (n = 1,726, 54%), followed by reviews (n = 950, 29.7%), and book chapters (n = 213, 6.7%). The main subject areas of the citing items are medicine (n = 2,581, 51.7%), immunology and microbiology (n = 1,179, 23.6%), and biochemistry, genetics and molecular biology (n = 415, 8.3%).

Interestingly, a recent analysis of 111 publications related to Strachan's hygiene hypothesis, stating that the lack of exposure to infections in early life increases the risk of rhinitis, revealed a selection bias of 5,551 citations on Web of Science.[37] The articles supportive of the hypothesis were cited more than nonsupportive ones (odds ratio adjusted for study design, 2.2; 95% confidence interval, 1.6–3.1). A similar conclusion pointing to a citation bias distorting bibliometrics of hypotheses was reached by an earlier analysis of a citation network linked to the idea that β-amyloid, which is involved in the pathogenesis of Alzheimer disease, is produced by skeletal muscle of patients with inclusion body myositis.[38] The results of both studies are in line with the notion that 'positive' citations are more frequent in the field of biomedicine than 'negative' ones, and that citations to articles with proven hypotheses are too common.[39]

Social media channels are playing an increasingly active role in the generation and evaluation of scientific hypotheses. In fact, publicly discussing research questions on platforms of news outlets, such as Reddit, may shape hypotheses on health-related issues of global importance, such as obesity.[40] Analyzing Twitter comments, researchers may reveal both potentially valuable ideas and unfounded claims that surround groundbreaking research ideas.[41] Social media activities, however, are unevenly distributed across different research topics, journals and countries, and these are not always objective professional reflections of the breakthroughs in science.[2,42]

CONCLUSION

Scientific hypotheses are essential for progress in science and advances in healthcare. Innovative ideas should be based on a critical overview of related scientific facts and

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evidence-based data, often overlooked by others. To generate realistic hypothetical theories, the authors should comprehensively analyze the literature and suggest relevant and ethically sound design for future studies. They should also consider their hypotheses in the context of research and publication ethics norms acceptable for their target journals. The journal editors aiming to diversify their portfolio by maintaining and introducing hypotheses section are in a position to upgrade guidelines for related articles by pointing to general and specific analyses of the subject, preferred study designs to test hypotheses, and ethical implications. The latter is closely related to specifics of hypotheses. For example, editorial recommendations to outline benefits and risks of a new laboratory test or therapy may result in a more balanced article and minimize associated risks afterwards.

Not all scientific hypotheses have immediate positive effects. Some, if not most, are never tested in properly designed research studies and never cited in credible and indexed publication outlets. Hypotheses in specialized scientific fields, particularly those hardly understandable for nonexperts, lose their attractiveness for increasingly interdisciplinary audience. The authors' honest analysis of the benefits and limitations of their hypotheses and concerted efforts of all stakeholders in science communication to initiate public discussion on widely visible platforms and social media may reveal rational points and caveats of the new ideas.

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