an ongoing basis to new regulations, an increasingly stressed pharmaceutical industry, and to having more and more responsibility placed on their time and skills. It is an exciting and thrilling time to be a medical writer—increasing demands bring with them increasing opportunities—but training for this "new world" cannot be done with training courses and mentorships alone.

Good medical writers are born … but excellent medical writers are created through apprenticeships.

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Writing the Basic-Science Hypothesis: A Practical Guide for Medical Writers

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Why can't anyone write a hypothesis? During my relatively short tenure as a medical writer and editor, I've asked myself this question one too many times. My own background is in the basic sciences, in which research is guided by a hypothesis—a scientific statement that guides experiments and is supported or rejected by the experimental outcomes.[1–3] The hypothesis is a key concept in the scientific method,[1–3] visualized here as a continuous process (Figure).

Despite the prominent place of the hypothesis in basic-science research, it is my experience that PhD-level investigators often struggle to write one (although their research is inherently hypothesis driven). Several things could explain this—deficits in mentoring and graduate-level education in research methods, as well as lax publishing standards, for starters. Although medical writers and editors can't fix these issues at the root, we can help investigators communicate their hypotheses clearly and concisely.

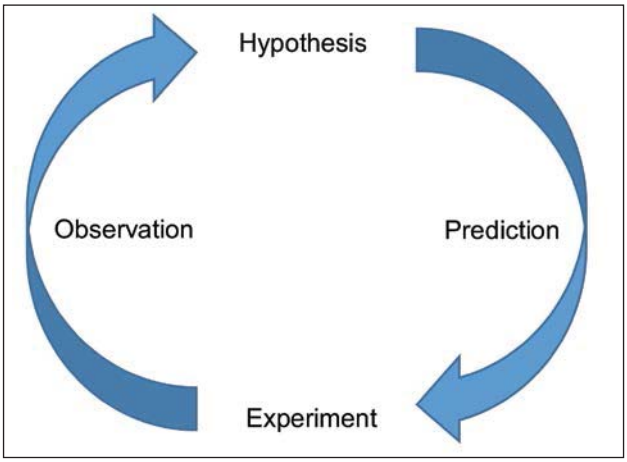

Figure. The scientific method is a continuous process. A hypothesis informs predictions, which inform experiments. Experiments produce observations, which are used to modify the hypothesis.

Anatomy of a Hypothesis

Basic-science research deals with how things work. Clinical research, on the other hand, aims to draw inferences from basic-research findings.[4]

This article focuses only on basic-research hypotheses. Although it is beyond the scope of this article, I could argue that all hypotheses share the same anatomy and essential purpose; because clinical research often benefits from the application of basic-science findings,[5,6] meaningful communication of clinical research also benefits from a working knowledge and appreciation of the process of basic science.

In basic science, a hypothesis is a statement of explanation for an observation[1–3]—elegantly described by Francois Jacob as the *invention of a possible world*.[7] Let's say that you make the observations that bacterium X makes mice sick and that many genes in this bacterium appear to code for toxins. A very broad hypothesis is that *toxins made by bacterium X make mice sick*. A more specific (and more directly testable) hypothesis is that *gene A* (a suspected toxin gene) *in bacterium X produces a toxin that makes mice sick*. A number of predictions and experiments follow logically from this hypothesis (Figure). For example, you could predict that in the absence of gene A, bacterium X will not make mice sick. The experiment then is to inactivate gene A and infect mice with this altered form of bacterium X; the hypothesis would be supported if the mice did not get sick. For a more philosophical discussion on validating hypotheses, I recommend Francisco Ayala's "Darwin and the scientific method."[1]

In the rest of this article, I hope to demonstrate how the term *hypothesis* is misused in publications and to offer some concrete suggestions and best practices for how medical writers and editors can help authors effectively communicate their hypotheses.

A Hypothesis Is Not a Prediction

In my experience, many authors phrase their hypothesis as a prediction. However, remember that you make predictions and perform experiments based on a hypothesis, which is based on observations[3] (Figure). Consider this example from an article in the *Journal of Bacteriology*:

> *The pleiotropic effects of* ybeY *loss on cellular RNAs have been well documented in other bacteria [references], and as such, we hypothesized that deletion of* ybeY *would lead to changes in mRNA levels in* B. abortus. *Therefore, we employed microarray technology to identify mRNAs that are influenced by YbeY.*[8]

Here, the sentence opens with an observation that, in other bacteria, the loss of *ybeY* affects RNA. Next is the prediction that deleting *ybeY* from *B. abortus* would affect mRNA levels, followed by a description of the experimental approach. In fact, I argue that this passage doesn't contain a hypothesis at all.

As an editor, I can transform this prediction into a hypothesis with the following revision (underlined):

> *The pleiotropic effects of* ybeY *loss on cellular RNAs have been well documented in other bacteria [references], and as such, we hypothesized that YbeY modulates mRNA levels in* B. abortus. *Therefore, we employed microarray technology to identify mRNAs that are influenced by YbeY in* B. abortus.

In this case, I inferred the hypothesis based on the stated observation, prediction, and experimental approach. However, I would also query the author to make sure that my interpretation is correct.

In the next example, from *Free Radical Biology and Medicine*, the authors predict an experimental outcome based on a hypothesis that is not stated until later in their paper. Here is the prediction disguised as a hypothesis:

> *We hypothesized that the AS52DKO cells, which lack the ability to repair oxidative lesions, would be more sensitive to PQ [paraquat] exposure.*[9]

The phrase "would be" makes this statement a prediction about the outcome of an experiment testing sensitivity to PQ exposure. Here is their actual hypothesis:

> *… the hypothesis that the PQ mutagenesis is dependent on the generation of ROS and oxidative-stress induced DNA damage.*[9]

The real hypothesis is easy to identify because it describes a mechanism by which cells are damaged by PQ—via reactive oxygen species (ROS) and oxidative-stress–induced DNA damage. In this case, accurately stating the hypothesis from the start helps guide the reader through the narrative. Here is one possible revision:

> *We hypothesize that PQ-induced mutagenesis depends on the generation of ROS and oxidative-stress–induced DNA damage. Therefore, we predicted that the AS52DKO cells, which lack the ability to repair oxidative lesions, would be more sensitive to PQ exposure.*

Write in the Present Tense

A hypothesis explains an observation—something that is occurring here and now. Therefore, phrase hypotheses in the present tense.[3] Here is a good example from the *Journal of Bacteriology*:

> *We hypothesized that* S. aureus *utilizes fatty acids present within lipoprotein particles. To test this hypothesis, we monitored the sensitivity of* S. aureus *cultured in the presence of human LDL to the FASII inhibitor triclosan.*[10]

In the first sentence, the authors state their hypothesis—their explanation of how *Staphylococcus aureus* can source fatty acids when its own fatty acid synthesis pathway is inhibited by triclosan. Note their use of "utilizes" in the present tense. In the second sentence, the authors describe their experimental approach that follows from this hypothesis.

Here is a second example, also from the *Journal of Bacteriology*:

> *Analysis of the known SpoVG-binding sites has not revealed any obvious consensus sequence; therefore, we hypothesize that SpoVG may interact with certain nucleic acid structural motifs rather than a particular nucleotide sequence.*[11]

The authors first describe their observation that SpoVG-binding sites do not contain specific nucleic acid sequences. This observation leads to the hypothesis that SpoVG instead interacts with specific nucleic acid structural motifs.

Be Confident

The second example just above raises another point—be confident in your hypothesis (regardless of the outcome). The authors stated that "SpoVG *may* interact." Although "may" is a modal verb that can express the possibility of something occurring (likely the authors' intention), it can also communicate a lack of confidence. If the authors don't appear confident in their hypothesis, why should the reader be confident in it? Likewise, why should the reader be confident in the experimental design and results? Here's an example from *PLoS Pathogens*:

> *Given that neutrophil recruitment is a major effect of IL-17, we hypothesize that the role of this cytokine in host defence against a particular pneumococcal strain may critically depend on the resistance of the strain to neutrophil phagocytosis, and hence on its degree of encapsulation.*[12]

The authors hypothesize that "the role of this cytokine … may critically depend." Again, the word "may" leaves me feeling uneasy. Rewriting this as "the role of this cytokine … depends critically" conveys confidence on the part of the researchers. Most likely, authors write this way to hedge their predictions. This is understandable and appropriate when drawing conclusions about experimental results, but remember that a hypothesis is made to be tested. In fact, disproving a hypothesis is an important part of the scientific process—not something to fear.

When authors tell a story with confidence, the reader has more confidence in them and their data—and thus in how they interpret their results. Isn't that a good thing?

Don't Hypothesize About Impact

I find that authors often hypothesize about the impact of a study. The following example is from the abstract of a paper about Duchenne muscular dystrophy (DMD) published in *Medical Hypotheses*:

> *We hypothesize that precise genetic editing in IPSC [induced pluripotent stem cells] using CRISPR-Cas9 technology, coupled with MPC [myogenic progenitor cell] differentiation and autologous transplantation, can lead to safe and effective muscle repair…*[13]

This is clearly not a hypothesis (an explanation for an observation); rather, it is a prediction about the outcomes of the proposed work. One strategy is simply to remove the term "hypothesis" and rewrite the beginning of this sentence as "we predict that precise genetic editing …" This abstract goes on to state that

> *With future research, our hypothesis may provide an optimal autologous stem cell-based approach to treat the dystrophic pathology and improve the quality of life for patients with DMD.*

At first glance, the statement seems reasonable, but isn't it actually illogical? The hypothesis itself cannot *provide* a therapeutic approach. Instead, it is the experimental results that may guide research to develop treatments for patients with DMD.

No Hypothesis? That's Okay

Finally, it's not always possible to state a hypothesis—take hypothesis-generating research as an example.[14] In my experience, there seems to be an unwritten (undeserved) rule that such work is not valuable, possibly prompting authors to state a hypothesis that is not really there. Here is an example from a paper in *Microbiome* in which the authors surveyed the caecal microbiome of chickens to identify microbes that might influence the animals' health and productivity:

> *Our hypothesis was that the caecal lumen microflora would vary significantly between chicken breeds and lines, offering opportunities for targeted genetic improvement by selective breeding.*[15]

The authors are doing this work to make an observation—to define a phenotype that can be investigated further. Essentially, their hypothesis is that they will make an observation, but doesn't that go without saying? It is only after they make their observations that they could generate a hypothesis to test experimentally (Figure).

The Medical Writer's Role

If the hypothesis is important to people doing research, then it should be important to people writing about it. In my experience, one can usually infer the author's hypothesis and revise the text accordingly (with a comment that the author check for

accuracy). If the medical writer does not feel comfortable with the subject matter, it is nevertheless possible to restructure the text so that the author can fill in the gaps.

We medical writers are not experts in every subject, but we can judge whether a stated hypothesis is *really* a hypothesis (independent of whether it is a *good* hypothesis). This skill can go a long way in helping authors report clear, robust research to their audience. After all, isn't that our goal?

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