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Editorial

How to write up a hypothesis: the good, the bad and the ugly☆

Summary *Medical Hypotheses* exists to give ideas and speculations in medicine a fair hearing. Doing this is not easy. Most conventional journals would regard some of what is published here as questionable, most referees would reject it as 'unproven'. We have more liberal standards, for reasons we have presented before. But we still require 'good' science — logical argument that is supported by fact and comes to interesting, even useful, conclusions.

Alas, not everything received comes close to even this liberal standard. Since I joined the Editorial Board I have read about 130 submissions to *Medical Hypotheses*. They range from exciting and insightful papers that might be substantial advances in their field, to complete rubbish. I want to lay out what I believe to be the essence of the former so as to avoid having to read so much of the latter.

Clear argument

A hypothesis is, by definition, something that is not yet proven. So you, the author, cannot lay out tables of data or pictures of tissue to prove your case. You must lay out an argument in a clear and convincing way.

The simplest way to do this is to make the steps explicit. Usually, there are several statements in even the simplest syllogism. Each step should either show that your conclusions are the only ones consistent with the facts and with basic logic, or, if there are other conclusions, why you prefer the ones you have drawn. Do not simply ignore the other conclusions. Your readers are not stupid, and will take your dismissal of the obvious as evidence that you are.

So, lay out your argument in small, simple steps. You think cream cakes are a cure for cancer? The argument might be:

1. Cream cakes contain high levels of oxidized lipids (particularly cholesterol).
2. The oxidized lipid is absorbed like other food ingredients.
3. Oxidized lipids are taken up by cells.
4. Within cells they cause cellular damage.
5. Slowly dividing and non-dividing cells do not take up oxidized lipids: only rapidly dividing cells take them up.
6. Cancer cells are the only cells in the body which divide rapidly.
7. So eating cream cakes will load up rapidly cancer cells with cell-killing oxidised lipids, and so kill them.

This allows the reader to see where you started from, and come along with you every step of the way. It also allows you to focus on the key elements. Steps 1–3 might be quite uncontroversial, so you can skip over them quickly. Step 4 is well established in the literature, but might not be known so well outside a specialist community, so it needs a paragraph and some good references to establish it as true (see below on references).

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Step 5 however is quite unexpected. Why do I say that? What is the evidence? Is there counter-evidence? Is it open to question? Maybe *this* is the central unknown in your hypothesis, in which case pointing it out is of critical importance, because measuring cellular uptake of oxidised lipid becomes a key test of your idea.

And Step 6 is just plain wrong, so what am I going to do about that? Remove it, that's what, and if that bursts my bubble, well, what distinguishes science from pseudoscience is the sound of bursting bubbles.

Most of the really ugly arguments I come across can be un-masked by this approach. Is there a step that cannot be supported by a direct quote from a standard text-book? Then you need to provide evidence. The further it is from what is taught at undergraduate-level science (today, not when you were an undergraduate), the more you have to support it. Stating that the majority of chemical transformations occurring in living systems are catalysed by enzymes needs no further amplification (indeed, it does not really need to be stated). Stating the opposite needs major back-up, as it flies in the experience of something like 10,000,000 person-years of biomedical research over the last century.

This may seem like teaching grade school logic, what my children learned in their 'what is a fair test' sessions at six years of age. But literally dozens of submitted papers flit over steps in their arguments that are simply wrong, either because they do not recognise their own assumptions, or (less charitably) because they are hoping I will not recognise them.

Bad evidence

A critical part of this is *evidence*. You start from a base of fact, take some logical steps, make a conclusion, and then see if the world fits with your conclusion. The first and the last of these need evidence. This is the main failing of many other submissions.

First, a long list of examples which are consistent with their hypothesis is not evidence that the hypothesis is true, unless the evidence is *not* consistent with the alternative hypothesis, and particularly with the 'mainstream' hypothesis you are trying to supplant. This is because there are innumerable facts in the world, and nearly all of them are consistent with nearly everything. I could provide a list of things that are consistent with the hypothesis that water is poisonous: everyone who drinks water dies, no one has done a safety assessment on water, very few insoluble compounds are poisonous, the elements making up water are in the most reactive 10% of the periodic table, and so on. But each statement is either irrelevant (like the last), or consistent with other hypotheses (that the *toxins* are poisonous, not the water). So none of them make a useful contribution towards suggesting your hypothesis is more likely to be true that any other wild speculation.

Related is ignoring well-known facts that are *not* consistent with your hypothesis. I recall a long argument about an alternative structure for DNA with one hypothesiser. The structure was very beautiful, but suggested that DNA should fall into its component bases when you heated it. But it does not — I have done the experiment, and human DNA gets more viscous as you heat it, not less. For me that demolished the hypothesis.

Secondly, the argument 'X is correlated with Y, and so must be linked to Y' (although it is rarely stated this honestly). This is usually followed by a long and tortuous 'mechanism', which has been worked out *post-hoc* to explain the correlation. This is also a rubbish argument, if only on numerical grounds. The world has uncountable facets. You can trawl databases of numbers until the most improbably correlations turn up: this is what 'improbable' means — something that *will* turn up eventually by chance. One can, for example, show an excellent correlation between the cumulative deaths

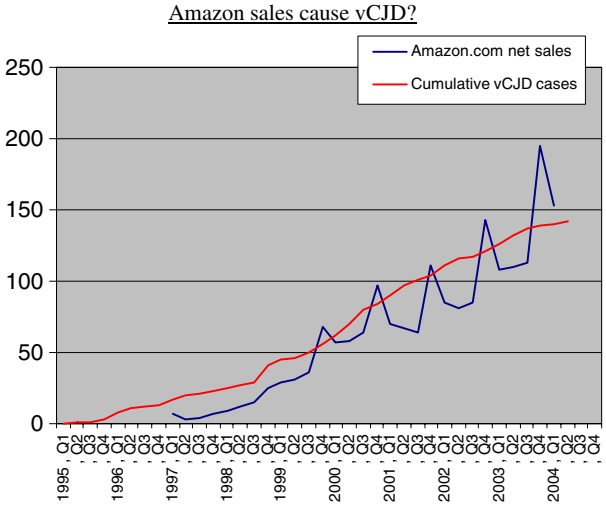

Figure 1 Amazon sales and cumulative vCJD deaths as a function of time. Amazon data from www.amazon.com. vCJD data from http://www.cjd.ed.ac.uk/vcjdq.htm. *X*-axis — date by quarter. *Y*-axis — vCJD cumulative cases/Amazon net sales in $10 Ms. Amazon data prior to 1997 is not available, as Amazon was a private company then. *Note:* the answer to the title is 'no, of course not.'

from vCJD and sales at internet bookseller amazon.com (Fig. 1). But this is meaningless unless there was a reason to look at Amazon.com to start with as a potential cause of vCJD (and I emphasise, for the lawyers, that there is absolutely no such reason). Otherwise all you are showing is that if you look at enough statistics you will find two lines that look the same (which is what I did to find Fig. 1 — it took me about 30 min.).

Both of these types of arguments turn up regularly in newspapers and pressure group leaflets to 'prove' that vaccines cause autism, that microwaves cause cancer, that vitamins from plants are different to vitamins from chemists. You might be able to batter a journalist or a politician into submission with such arguments, but readers of Medical Hypotheses are made of sterner stuff. And so are the editors, so please do not waste my time! (Any or all of these propositions might be true, but this is not the way to prove it.)

Thirdly, there is the argument that goes ''science cannot explain X, I have an explanation for X, therefore my explanation may be right''. I hope this does not need to be debunked further here.

Wrong evidence

Lastly, there is evidence that does not even exist, which brings me to references. Papers have references in them to save space when you present your evidence and your arguments. If Smith et al. did wonderful work, rather than describe everything they did, you just state their conclusions and refer to Smith et al. The reader can then go and read what Smith et al. actually said if they want to.

But your statement of what a paper is about must be accurate — to say anything else is deception. Saying ''Bains et al. (2006) showed that cream cakes cure cancer'' is misleading if the paper just correlates cream cake consumption with cancer. Saying ''Wood is a well-known toxin (Smith and Jones 1942)'' when Smith and Jones were talking about the number of people killed by falling trees is downright dishonest. This example might seem ludicrous, but I have read several manuscripts that make a striking assertion, and then cite a reference that does not support it all — on one occasion it actually proved the opposite! Finding just one such horror in a paper means that you do not trust a single thing the author says, and thus it destroys the whole point of our good publishers felling trees (entirely safely, of course) to get your opus into print.

Good evidence

There are therefore four kinds of evidence you can use to support your argument.

Evidence that the problem you are talking about is real

An amazing number of manuscripts fail to do this. A paper titled ''Cream cakes as a curative treatment for the effect of low frequency electromagnetic fields on human cognition'' rather assumes that there is an effect of electromagnetic fields on brains. This is by no means established fact — so establish it. And not just by reference to your last paper in Medical Hypotheses (see below). More mundanely, some recent evidence that the problem is still outstanding is useful — a paper theorizing on the cause of AIDS must first argue why HIV is not a cause of AIDS, or it has nothing to argue about.

Evidence that the foundations for your argument is solid

This must refer to *fact*. Your previous speculation that cream cakes cure cancer cannot now be cited as evidence that it is true. There is no problem with you saying ''I previously speculated that the preferential uptake of toxic oxidised cholesterol by rapidly dividing cells might make cream cakes a cure for cancer.'' But that was a speculation. Hypotheses built on speculation is called 'philosophy' or 'fiction', and is not what we are about.

Evidence that your argument is logical

Do this by showing what it is, as above.

Evidence that your conclusions are right

It is easy to get mesmerised by a chain of arguments that leaves you stranded in a logical cull-de-sac. Your hypothesis has some implications. Do they agree with the real world? If not — trash the hypothesis, please, because the real world is the ultimate judge. If oxidised lipids cured cancer, then hamburgers should be even better than cream cakes, and the rise in fast food consumption should be paralleled by a near-abolition of cancer. This has not happened. Ooops. Amazon.com trades mainly in the US, but nearly all vCJD cases are in Europe. And so on. It sounds obvious. But the

hypothesis that leads to an absurd conclusion is, well, absurdly common.

So what?

Lastly, I believe strongly that hypotheses must be testable, otherwise they are just waffle. Is there, *even in principle*, any way to see if water is toxic? If not, you are wasting my time — you might as well say that water is *vootick*, (a property I just invented, which has no measurable characteristics at all). So, suggest a test. Maybe you would expect mice raised on grain alcohol instead of water to live longer? Then that is a potential test. If someone does the experiment and it works, you will be famous.

It would be nice, in a journal called 'Medical Hypotheses', for at least some of the implications of your hypothesis to have relevance to the practice of medicine. Otherwise it is 'just' theory, an under-rated part of biology but not really appropriate for this journal.

None of this is prescriptive. There are excellent papers in Medical Hypotheses that read like letters from home, and frankly appalling ones that read like, well, like every other paper. But if you could eliminate papers with no structure, no argument, no evidence and no appropriate references, I, and I believe you, would be much happier.

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