Has Hippocrates Had His Day?

‘Have some sense of proportion!’ she would say, sometimes as often as thirty-eight times in a single day.

—Douglas Adams

After an interlude of well over a year, I wish to return in this space to matters concerning the ethical and social context of life extension. Whereas in previous editorials I focused on the overall pros and cons of postponing aging, here I will consider a topic central to the speed with which such therapies may be made available. The topic I refer to is complex, overlapping not only the range of ethical issues that this journal periodically highlights, but also issues of a mainly political flavor, another key component of RR’s scope.

The Hippocratic oath plays as central a role in the conduct of the medical profession as one can possibly imagine. As all readers surely know, it is a set of tenets to which medical students must swear allegiance in order to become qualified to conduct medical practice. However, in this editorial I will not in fact discuss the pros and cons of these tenets, but rather the pros and cons of an injunction that Hippocrates is touted to have made separately, and that does not occur in the Hippocratic oath (although it is often presumed to, since they have the same author).

I refer, of course, to the phrase “Primum non nocere” or “First do no harm,” which is probably better known than any component of the Hippocratic oath itself. Much has been written concerning the relevance of this principle to modern medical practice, and I will not attempt a remotely thorough survey of that debate here. Instead I will highlight three examples—one a survey of the recent past, one an isolated incident in 1999, and one possibly in the not-too-distant future—that appear to suggest, at least to me, that it is the source of an inappropriate degree of caution in the development and introduction of new medical advances.

My first example arises from a report produced last year by Dr. Mary Ruwart, a specialist on government regulation of the drug industry. Ruwart’s central criticism of the prevailing regulatory framework in the United States is that it is more cautious than is justified by the lives saved and lost—in other words, that the number of lives lost as a result of the unavailability of drugs that could have been approved sooner exceeds the number saved by the non-approval of drugs that would have been approved by a quicker process.

A reasonable reaction to these findings is that maybe there is merit in erring modestly on the side of caution in this regard. After all, the negative effects of a dangerous drug may shorten lives by more than the benefits of a safe drug lengthens them. One must also consider the anxiety aspect: People’s emotional responses to risks are notoriously far from proportional to the probability of the feared event; therefore, patients and their loved ones may prefer the devil they know.

The operative word in the preceding paragraph, however, is “modestly.” However
strong the arguments just given (and others like them) may be, there must be some threshold ratio of lives lost to lives saved that is too high—in other words, that justifies adjusting the regulatory procedure so that new treatments are approved more speedily than now, despite the acknowledged downside of a raised risk that side-effects will be missed. What is that ratio? Two? Ten?

Dr. Ruwart’s account draws on a large body of information in deriving the figures she reports. Rather than attempt to summarize it in this short editorial, I recommend that readers consult it themselves for the full story; I will restrict myself here to the bottom line. Despite bending over backward at several steps in her analysis to give the status quo the benefit of the doubt, Ruwart concludes that a minimum of over 50 times as many lives have been lost as a result of the increase in time to market resulting from the tightening of Food and Drug Administration (FDA) procedures over the past 40 years than are saved by the increased stringency that those procedures confer. Specifically, at most 90,000 lives have been saved and at least 4.7 million lost. As Ruwart’s report goes on to explain, even this is a gross underestimate of the true ratio, because it ignores major factors such as the increased cost (and consequent reduced takeup) of such treatments that the increased time to market inevitably causes.

My second example involves no statistics, because it concerns a single patient. Jesse Gelsinger was 18 years old when he died of anaphylactic shock in 1999 as a result of receiving a gene therapy treatment for ornithine transcarbamylase deficiency as part of a safety trial. It later emerged that he only received the treatment because of errors made in selecting patients. Nonetheless, that trial and numerous others across the globe were suspended for many months while procedures were tightened.

I contend that this story is closely related to the situation that Ruwart described. In this case the treatment in question was at a far earlier stage of development than Phase III, at which most of the delay in drug approval occurs, but the impact on lives lost is probably comparable. Let us suppose, in view of the long way to go before gene therapy becomes safe and effective, that each month for which all such trials worldwide are halted translates into a day’s delay in the final arrival of approved treatments—a conservative estimate, I would argue. Then let us consider how many people die each day of conditions that could in principle be alleviated by gene therapy. These include a large and increasing number of single-gene defects, together comprising at least a few percent of all deaths—a few thousand deaths per day worldwide, in other words. Additionally, we must take into account the treatability of late-onset conditions that kill a large proportion of Westerners: Work is vigorously proceeding to develop gene therapies against cancer and diabetes, to take just two examples. Thus, the lives that will eventually be lost as a result of our knee-jerk reaction to Gelsinger’s death very probably exceed by a factor even greater than 50 the lives saved by suspending trials rather than tightening procedures while the trials continued.

Finally, as you might expect, I want to consider the impact of primum non nocere on life extension in future decades. At present, the FDA does not consider aging a disease, so it would actually be impossible to get a life-extension treatment approved with that claimed function, only as a treatment for specific conditions. Further, many of the interventions that I have brought together within the SENS scheme (and which, therefore, I of course think likely to contribute to the first true antiaging therapies) are highly novel and, thus, likely to endure an extended period of refinement and elimination of side-effects. As things stand, my estimate of the time it would take in today’s regulatory context to advance the entire SENS panel from preclinical proof of concept (in mice) to actual clinical availability is around 50 years. Some that I speak with think it could be even more. I should clarify that some of this time will of course be irreducible by regulatory changes, because there will be a great deal of science still to do to translate the SENS therapies from mice to humans, but I estimate that there is a 50% chance that that will take only 15 years. Therefore, we must confront the distinct possibility that an entire generation will be lost to aging as a result of our allegiance to Hippocrates’s doctrine.
I do not, in fact, expect that the preceding will occur. I predict that once mice are given two extra years of healthy life with treatments begun when they only have a year to live, society will revise its sense of proportion in these matters rather rapidly. However, that revision will be most rapid if we start to agitate for it now: hence, this editorial. A moment’s hesitation is in order, though. Because his edict has served us for so long, might Hippocrates not have been right? I feel that he was indeed right at the time, but has become progressively less right as medical knowledge has advanced.

What has changed, simply, is the amount we know about how to treat health conditions, including what we know about how to monitor the progress of that treatment as it proceeds. Thus, the balance of probability between successful and unsuccessful treatment has changed. In Hippocrates’s time—indeed, until quite recently—sick people would quite often recover spontaneously when the best medical opinion regarded such recovery as very unlikely, simply because diagnosis was so primitive in earlier eras that a severe symptom that today would be reliably identified as temporary often would be judged life-threatening. Nowadays, by contrast, the probability of recovery in the absence of treatment (or in the context only of well-established treatment) is much more accurately predictable: by no means infallibly so, to be sure, but we are interested in the numbers here. It is those who would recover without therapy who are most at risk of harm from a well-intentioned but unsafe therapy: Those who would not be not harmed if the therapy fails, they are simply not helped. (Of course, this binary description of the situation is only an approximation—a full statement would need to go into degrees of help and harm and ranges of alternative therapies—but you get the idea.) In other words, the probability of doing harm with a well-meaning therapy is much lower now than in centuries past, because the confidence with which a physician can determine whether a therapy is needed at all is higher. This is the core of my reason for feeling that *primum non nocere* has diminishing force in the modern medical world and should be progressively deemphasized in the procedure by which new treatments are regulated.

**REFERENCES**


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