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EMBO reports

Overselling hysteria

The role of the media and medical journals in promoting questionable risks—a case study of the testosterone controversy

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On February 4, 2014, *The New York Times* published an editorial "Overselling testosterone, dangerously", in which it alleged that the rise in testosterone prescriptions was medically unwarranted, and that scientific studies suggesting an increased risk of cardiovascular disease (CVD) provided "the most compelling evidence yet that many American men have embarked on a perilous course of overtreatment" [1]. This editorial was the most prominent among a flood of similar stories, and it provided an authoritative position by virtue of the reputation of the *NY Times* as a leader in mainstream media. In this article, we use this case—the studies on the alleged risk of testosterone treatment and the ensuing media coverage—to discuss how the media often promote a false narrative that negatively impacts public health and policy.

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The public has a great appetite for health-related information; indeed, one of the most frequent uses of the Internet is to obtain information about medical conditions and health care. This demand provides a fertile ground for high impact medical news stories, often based on the publication of new study results. Not surprisingly, media reporting of medical studies has been shown to influence not only popular opinion, but also the opinion of healthcare providers and regulatory authorities [2]. What has not been adequately appreciated, however, is how distorted reporting of medical risks promotes false concepts that may persist for years, thereby negatively impacting medical care and public health [3,4]. The infamous study that claimed a link between the MMR vaccine and autism has had a massive impact on vaccination rates in Western countries and is still being cited as evidence by the anti-vaccination movement despite the fact that it has been thoroughly debunked. We here use the term "medical hysteria" to describe widespread media coverage of alleged treatment risks that interferes with rational, evidence-based health care.

Does medical hysteria exist?

The best recent example of medical hysteria is the wholesale changes in medical attitudes and practices regarding the use of hormone replacement therapy (HRT) in peri- and post-menopausal women after intense coverage of the Women's Health Initiative (WHI) study. In 2002, the mass media breathlessly reported that this large study had been prematurely halted after it showed greater risks of stroke, death, and invasive breast cancer for women who took estrogen and progesterone compared with those who received placebo [5]. Medical experts called for immediate curtailment of the use of HRT in women. Prescriptions for HRT products fell by more than 80% and remained at that level for years. Today, healthcare experts still routinely reference this study as demonstrating the dangers of HRT.

This was a gross distortion of the WHI results, however. The study reported increased risk of adverse events of only 19 events per 10,000 person-years of exposure for the estrogen–progesterone arm compared with placebo. This means that if one woman in every generation of a family used estrogen–progesterone for 10 years, it would take 50 generations, or approximately 1,000 years, to observe one extra adverse event in that family. The result may have been statistically significant, yet it is clinically meaningless.

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Importantly, both the public and the medical community appear unaware of the results published in a 2013 follow-up study with seven additional years of monitoring that reported no significant difference between HRT and placebo for mortality or a long list of other adverse events. Remarkably, although the estrogen–progesterone arm did show a minor increase in breast cancer cases compared with placebo, breast cancer cases were significantly *reduced* by more than 20% in women who received estrogen treatment alone (no progesterone) compared with those who received placebo [6]. To this day, it is taught to medical students and trainees that the WHI showed estrogen increases the risk of invasive breast cancer even though this reverses the actual

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results. The impact of the distorted reporting of the WHI results and its acceptance by the medical community cannot be overstated. It has deprived women for nearly 15 years of an effective and safe medical treatment for the symptoms of menopause, including osteoporosis [7]. Research funding for this important topic was also devastated and has not recovered. This is an important example of medical hysteria.

The testosterone controversy

Testosterone therapy has been used to treat testosterone deficiency (TD) in men since the 1940s. TD is a common disorder that profoundly impacts men's health and quality of life [8,9]. It contributes to erectile dysfunction (ED), decreased sex drive, diminished lean body mass, decreased bone mineral density, increased fatigue, depression, and cognitive impairment. TD is an independent predictor of the development of metabolic syndrome and contributes to visceral obesity in men. It is also associated with increased mortality, atherosclerosis, and coronary artery disease. Clinical evidence suggests that testosterone therapy offers a host of cardio-protective benefits, including improved endothelial function, reduced inflammation, improved lipid profiles, improved systolic and diastolic blood pressure, and reduced glycated hemoglobin A1c and insulin resistance. Moreover, a February 2016 study [10], based on a large randomized clinical trial, showed significant improvements for sexual activity and desire, physical activity, and mood.

> *"... the power of narrative is such that once a story is established, it is difficult to change it, no matter the strength of the contradictory evidence."*

In late 2013, T therapy suddenly became highly controversial after a study published in the *Journal of the American Medical Association (JAMA)* asserted increased risk of CVD. It was followed 2 months later by a second study that appeared to confirm increased CVD risks. The FDA followed 2 days later with an announcement that it would investigate CVD risks with testosterone products. Each of these stories received prominent media attention, nearly all with comments noting that prescription rates had dramatically increased over the prior decade, and that the treatment was often initiated for sexual concerns in older men as well as unsubstantiated comments that it was used by many men as an anti-aging elixir. The public's perception of the issue was confounded further in the USA by ubiquitous television advertisements by plaintiff attorneys asking men to contact them if they had suffered heart attacks or strokes while using testosterone.

In September 2014, the FDA held an advisory committee meeting, at which panelists voted in favor of adding a warning to the label of testosterone products, despite recognizing there was insufficient evidence to conclude there was increased CV risk. The warning has since been added, and reads: "To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use". Despite this cautious language, the addition of this warning has caused many in the medical field to believe the FDA did in fact conclude there was increased CV risk with testosterone products. An additional warning regarding the possibility of venothrombotic events, such as deep venous thrombosis and pulmonary embolus, has contributed to the general belief that testosterone therapy is associated with increased CV risk.

How strong was the evidence?

For researchers in the field, assertions of increased CV risk with testosterone products based on these articles were difficult to understand, for several reasons. First, there was a rich literature spanning more than two decades suggesting that higher endogenous testosterone concentrations and also testosterone therapy appeared to be cardioprotective. Second, the literature suggesting increased CV risk consisted of only four studies in total, each one remarkably weak.

The first of these studies, by Basaria *et al* published in 2010 in *NEJM,* was a 6-month placebo-controlled study of testosterone gel in older, frail men designed to assess muscular and functional responses to testosterone treatment. Among men who received testosterone, the authors reported 23 adverse events categorized as cardiovascular, compared with only five events in men who received placebo. This resulted in termination of the trial prior to full recruitment, which was reported in all major media outlets. Yet, there were only four MACE, a figure too low to draw any conclusions. The remaining "events" were of questionable clinical significance, such as syncope, non-specific EKG changes, palpitations, and premature ventricular contractions. None of these were defined prior to the study nor was there an attempt to identify these systematically. Interestingly, the study demonstrated substantial muscle and functional benefits of testosterone in older, frail men, yet those results received scant attention.

The article by Vigen *et al* published in *JAMA* was what really established the testosterone controversy, yet the authors misreported their primary results. This was a retrospective analysis of 8,709 men with low levels of testosterone who had undergone coronary angiography in the Veterans' Administration health system. Some of these men went on to receive a prescription for testosterone and the remainder represented the untreated group. The authors reported that 3 years after angiography, the absolute rate of adverse events (no. of individuals experiencing an adverse event/no. of individuals in the group), consisting of death, MI, or stroke, was 25.7% in men who received T prescriptions compared with 19.9% who did not.

> *"... medical literature has frequently been at the root of gross errors in medical beliefs that have harmed public health."*

However, the correct absolute rate of events for testosterone-treated men was 10.1% (123 events in 1,223 men) compared with 21.2% (1,587 events in 7,486 men) in the untreated group, meaning that the testosterone group had a lower rate by half. The article was revised within 1 week of publication, replacing "absolute rate of events" with "estimated cumulative probability of events". However, the correction was not officially noted for 2 months and

received no media attention. A second correction published months later revealed large data errors involving more than 1,000 individuals, with the additional revelation that nearly 10% of the all-male study population was comprised of women! Twenty-nine medical societies and more than 150 leading testosterone experts from around the world petitioned *JAMA* to retract this article, arguing that the data were "no longer credible". *JAMA* declined.

The study that followed quickly on the *JAMA* study, by Finkle *et al*, was also a retrospective study that compared rates of non-fatal MI in the period up to 90 days following receipt of a testosterone prescription with MI rates in the 12 months prior to prescription. The authors reported an increased MI rate after receipt of a testosterone prescription of 36%. However, there was no control group of testosterone-deficient men who did not receive testosterone, so it is unknown whether this reported MI rate was higher, lower, or unchanged compared with an untreated similar group. Curiously, the reported MI rate following the prescription was only approximately one-third as high as expected, based on the NIH Heart Attack Risk Calculator for a similar population. The last of the studies allegedly indicating increased CV risk with testosterone was a meta-analysis that was contradicted by six other meta-analyses, none of which showed increased risk, and the largest of which suggested *decreased* CV risk in men with metabolic conditions such as diabetes and obesity.

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The FDA's own pharmacovigilance team appeared unimpressed with these studies. They wrote "...several significant limitations ...precluded a definitive assessment of the role of testosterone therapy in the cardiovascular events noted in the [*NEJM*] study". "Given the described limitations of the study by Vigen *et al*, it is difficult to attribute the reported findings to testosterone treatment". And, "...it is difficult to attribute the increased risk for non-fatal MI seen in the Finkle study to testosterone alone...". Notably, the European Medicines Agency conducted its own review of the literature and concluded there was no evidence of increased risk that merited addition of a CV risk warning to the label of testosterone products.

In contrast to these four studies, more than 100 other studies have shown no increased CV risk, or even reduced risk, among men with higher endogenous testosterone concentrations or who received testosterone therapy. High-level evidence demonstrates an inverse relationship for serum testosterone and mortality, incident coronary artery disease, severity of coronary artery disease, atherosclerosis, and carotid intima-media thickness. More than a dozen studies have been published since the CV controversy arose, and none has provided supporting evidence. Several placebo-controlled studies have actually shown benefits with testosterone in men with known CV disease, including those with angina and with heart failure. Importantly, in 2016 the results of the largest clinical testosterone trial to date were published, involving 790 men 65 years and older. In this study, the number of MACE was the same in first year for men who received testosterone or placebo gels ($N = 7$) and was lower during a second follow-up year of monitoring (two events in the T arm, nine in the placebo arm). Although this last study did receive moderate media coverage focused on the magnitude of reported benefits for sexual function, mood, and physical activity, there was little mention of the reassuring data regarding CV events.

The role of medical journals

Despite our best efforts to assess medical topics with dispassionate objectivity, errors in beliefs occur, errors that may carry substantial negative health implications once the information spreads. Yet, the power of narrative is such that once a story is established, it is difficult to change it, no matter the strength of the contradictory evidence. As Winston Churchill has been quoted, "A lie gets halfway around the world before the truth has a chance to get its pants on". As with the unwarranted fear of the MMR vaccine or of HRT, the current fear of the alleged risks of testosterone use has deprived patients of beneficial treatment and has blinded the scientific community from the possible benefits of treatment that merit further investigation.

It is not a coincidence that the hysteria related to HRT and now to testosterone therapy both involved studies reporting unexpected medical risks. The question then is how such studies turn into medical hysteria and which factors contribute to the spread of erroneous claims of risk. After long careers in medical research, we still highly value medical literature, but we also recognize that it may mislead us. Indeed, medical literature has frequently been at the root of gross errors in medical beliefs that have harmed public health. We believe it is critical to recognize this phenomenon and to understand its origins in order to avoid similar mistakes in the future.

> *"Although there may be legitimate concerns regarding the pharmaceutical industry, it is egregious to distort the science regarding a pharmaceutical product in the service of a political view."*

It is not widely known that medical journals provide journalists with pre-publication copies of studies they deem likely to generate public interest in order to encourage comprehensive coverage on the day of publication. For example, we received from a journalist a pre-publication ("embargoed") copy of the article by Vigen *et al* nearly 1 week before its publication date, with request for analysis and commentary. This practice allows journalists to file a complete story about a major study as soon as it is released to the public. Journalists and the invited experts agree not to disclose information about the embargoed manuscript until its publication date. This collaboration may seem beneficial to a health-conscious population hungry for the latest information. However, the dark side of this intersection of popular media and scientific journals is that the media's competitive appetite for its own ratings might lead journals to choose articles for publication and for distribution to the media based on consumer appetite rather than scientific rigor. This may lead to widespread dissemination of distorted information that in turn may contribute to irrational fears among the public and physicians alike.

"If it bleeds, it leads"

Media stories are often weighted toward issues that engage emotion, in particular, fear or outrage. Review of the most sustained health care stories of the last 15 years reveals that stories of unexpected risks are among the leaders. During the 2014 Ebola crisis in West Africa, media stories suggesting the virus could create a similar epidemic in the USA were repeated daily for weeks, creating such fear that "two-thirds of Americans [were] expressing worry about a large-scale domestic Ebola outbreak". An immense amount of resources were misappropriated to address Ebola in the USA, despite the fact that the risk of an American becoming infected was "less than the risk of being killed in an airplane crash, from a lightning strike, from a bee sting, or by a shark".

The media also promotes simple narratives, often with a good/bad dichotomy. With medical stories, studies that suggest unexpected risk in a widely used product generate the biggest headlines, such as "Testosterone is dangerous!" However, research studies rarely lend themselves to such simplistic conclusions, and, like the WHI results, it may take time and analysis from multiple angles to finally gain the appropriate perspective. However, once a narrative is established by initial reports, public opinion—including those of physicians—is unlikely to change regardless of new evidence.

Another, more recent factor is the competition among medical journals for high impact factor, a metric based on number of citations. Journals with a high impact factor find it easier to entice articles from authors and attract advertising revenue. However, the explosion in the number of medical journals has created a much greater competition for both authors and advertising revenue. This competition makes journals more interested in gaining publicity through the lay press by publishing controversial articles to generate media attention. It is worth noting that two of the four articles suggesting increased CV risk (compared with more than 100 articles reporting direct or indirect CV benefits) were published in two medical journals with the highest impact factors: *JAMA* and *NEJM*. The title of the first of the CV risk studies is instructive. This study set out to investigate whether testosterone therapy provides functional and muscular benefits compared with placebo in frail men with compromised mobility, yet the title as published in *NEJM* was "Adverse events associated with testosterone administration".

Medical politics are powerful

Medicine is not immune to beliefs that color the interpretation of science. One such powerful belief is that pharmaceutical companies aggressively promote non-existent medical conditions to influence prescribing physicians and the public to create a large market for their products. In 2013, Woloshin and Schwartz published the article "Low "T" as in "Template": how to sell disease". The authors identify themselves as members of the steering committee of a conference on preventing overdiagnosis. In their commentary, they write of marketing of testosterone products as "a mass, uncrontrolled experiment that invites men to expose themselves to the harms of a treatment unlikely to fix problems that may be wholly unrelated to testosterone levels". They add, "Ignoring the lessons of estrogen therapy is scandalous".

A similarly themed op-ed decrying the increasing use of testosterone therapy and listing various risks noted in the product insert was published in the *Chicago Tribune* by Adriane Fugh-Berman of PharmedOut, a non-profit group which states its goal on its website as to "(d)ocument and disseminate information about how pharmaceutical companies influence prescribing". These types of articles, together with "scandalous", yet erroneous references to the WHI and the risks of estrogen, contribute to a sense of moral outrage in the medical community that was finally satisfied by reports of alleged increased CV risk. In these cases, the facts regarding testosterone treatments were trampled by a decision to use weak reports of CV risk as ammunition in a broader political stance against the pharmaceutical industry. Although there may be legitimate concerns regarding the pharmaceutical industry, it is egregious to distort the science regarding a pharmaceutical product in the service of a political view.

Physicians do not read scientific articles

Physicians have become inundated with clinical responsibilities and documentation requirements. The limited time available to keep up with the literature is therefore reduced to reading summaries or media reports rather than actual articles. However, it is difficult to critically assess the quality and reliability of a study based on summaries or media reports.

Moreover, a new science of statistics and methodology has become prominent in medical literature, most of which is unfamiliar to clinicians. The study by Vigen *et al* that precipitated the testosterone "controversy" utilized a methodology called stabilized inverse propensity weighting with time as a covariate, applied to Kaplan–Meier curves. Soon after it appeared, a gathering of approximately twenty testosterone experts from prestigious academic centers were asked whether any had previously heard of this methodology. Not one raised a hand.

The introduction of increasingly complex methods and statistical analyses in scientific papers has made it challenging for the average clinician to understand what was done, let alone assess whether the authors' conclusions are supported by the data. Clinicians thus often defer judgment to what they believe to be trusted authorities, such as the journals—"it must have been reviewed by people who understood it, so I guess it's right"—or commentators in news stories with impressive academic affiliations.

It is disconcerting to recognize there is no longer a place where healthcare professionals can turn for dispassionate, considered opinion, including top medical journals. Marcia Angell, who served as an Executive Editor of *NEJM* in 1988, and Editor-in-Chief from 1999 until June of 2000, was quoted as saying that *NEJM* would not publish retrospective studies unless the effect size was threefold due to the likelihood of unrecognized confounders creating a false-positive result. For comparison, the study by Vigen *et al* reported an increased adverse rate of only 0.29. Professional societies may offer guidance, but are often reluctant to take strong positions, particularly controversial ones. The FDA has been regarded as an impartial arbiter, especially by the public, yet the FDA's mission is to protect public health by regulating the pharmaceutical industry and it has no claim or standing to regulate the practice of medicine. For this reason, the FDA may decide to add warnings regarding treatment risks even in the absence of strong evidence. The warning added to

testosterone products regarding venothrombotic events, for example, was added before there was a single study showing increased rates of VTE. Subsequently, a large study showed no increased risk.

The awkward truth is that no one is in charge of assessing medical information. The European Medical Agency (EMEA) called for Pharmacovigilance Risk Assessment Committee and issued a similar response to that of the FDA. Of note, NIH and CDC and the European Center for Disease Prevention and Control (ECDC) have no regulatory authority. Institutions such as the National Institute for Health and Care Excellence (NICE) in the UK and Federal Institute for Risk Management (BfR) in Germany are risk assessment bodies and do not get involved in the regulation of drugs and did not appear to take an interest in the testosterone controversy.

A good narrative trumps facts

Assessment of risks of treatments have always been a part of medical practice, as evidenced by the phrase, "First, do no harm". Yet, the current emphasis on risks, no matter how small, creates an unbalanced situation. Many benefits may be worthwhile, even when they entail some risk, and failure to treat may also be associated with harm.

However, once a narrative suggests treatment is risky, this association is very resistant to change. Studies have shown that individuals with strongly held positions on issues such as global warming will hold onto those beliefs even when confronted with strong evidence contradictory to their position. In the case of testosterone therapy, the narrative has been that pharmaceutical companies were making lots of money selling useless products to unsuspecting patients, and now suddenly we find that the treatment is associated with CV risks. Never mind that these results were outliers, and that twenty years of accumulated data strongly indicated that higher endogenous testosterone levels and testosterone therapy appeared cardioprotective, the media-created narrative won the day.

One reason that distorted viewpoints persist is the practice in journalism of having one or two voices representing each side of an issue, regardless of the relative number of experts supporting a position. "Balanced" reporting thus leads to what is called false equivalence [4]. The US television satirist John Oliver in his show *This Week Tonight* hilariously demonstrated this by showing two experts for each side sitting at a table discussing whether human activity contributed to global warming. This gave the impression of an even divide. However, he then brought in another 96 individuals in white laboratory coats, noting that 98% of weather scientists believed humans do contribute to global warming. This created a powerful visual impact in which 98 individuals sat across from a paltry two individuals.

> *"The blame for misleading the public should be shouldered equally by journalists, scientists, journal editors and research institutions."*

In addition, the credentials of the experts should matter, but generally do not. Nearly every strong critical voice in the news coverage of testosterone therapy has come from individuals without research or clinical experience in the field, who have tended to label treatment as misguided attempts at preventing aging when it is in fact a deeply distressing and long-established medical condition that occurs as a result of a hormone deficiency. This contrasts with the unanimous agreement by a group of international experts from 11 countries that the evidence does not support increased CV risk [8].

Who shoulders the responsibility?

This analysis prompts consideration of the nature of medical science. Clinical studies merely provide results, which are colored by experimental conditions, choices of populations studied, and personal interpretation of findings, among other variables. The "truth" generally requires a variety of studies, each providing a slice of information that when taken together, ideally results in a consistent picture. Ioannides reviewed highly cited original research articles from high impact general medical and specialty journals and reported that in one-third of these the original results were either contradicted by subsequent studies or the effect size was diminished.

In cases where a single study has been hailed as true, there is frequently a retrenchment over time. The near-universal discontinuation of HRT in women following the WHI study in 2002 is one recent example: Although initial conclusions were that HRT was dangerous for women, more analyses and data from the WHI itself eventually showed that breast cancer was significantly reduced by more than 20% in women who received estrogen alone versus placebo. As pointed out by Shapiro *et al*, "We conclude that over-interpretation and misrepresentation of the findings in the WHI study have resulted in major damage to the health and well-being of menopausal women". The WHI was not "a victory for women and their health" [6], and the claim that the findings "do not support the use of this therapy for chronic disease prevention" is not defensible. Nor can the pejorative editorial statement that "the WHI overturned medical dogma regarding menopausal [HT] be defended".

With this in mind, it would be prudent to regard any single study result with considerable caution. Yet, it is the business of the media to promote healthcare studies as "news", which today means numerous repetitions over a 24-hour period, after which the "old" news is replaced by new news. This pattern of dissemination of information is in obvious conflict with the slow process of digesting new scientific information, which may take considerable time to sort through the results, to analyze the methodology and interpretation of results, and determine how to place the new information within the existing framework of what is known.

Why is this issue important? Firstly, patients become less adherent to their treatment when they are exposed to fear, hysteria, and conflicting information about alleged risks. Secondly, physicians need to make an effort to understand and evaluate the relevance and the magnitude of a new study with regard to improving the healthcare of their patients. However, burdened by increasing patient volume and frivolous paperwork, they have less time to read the medical literature and are consequently relying more on the lay press to stay up to date on medical research. At one stage of the 2009 H1N1 pandemic, the mass media were the most common source physicians used to gather information. Thirdly, the outcomes reported by the media influence clinical decision-making. A 2013 study showed that

Sidebar A: Further reading

The role of medical journals and the media

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oxycodone prescribing patterns followed changes in media coverage.

In summary, when flawed clinical research is reported in the media with hype and sensationalism, as in the case purporting a link between testosterone therapy and CV risk, it will have a devastating effect on patients, physicians, and the scientific community and eventually a damaging effect on the whole of society. The blame for misleading the public should be shouldered equally by journalists, scientists, journal editors, and research institutions.

What is to be done?

A number of strategies could help to reduce the medical profession's vulnerability to distorted study results and their coverage in the media. First, the collaboration between medical journals and the media must be recognized, as it tends to promote stories that emphasize risk and lead to fear and outrage. Physicians should also be wary of pronouncements from individuals who are unlikely to have clinical experience with a drug or treatment. Second, the limitations of any one study must be recognized, particularly since as many as 70% of the most highly cited studies eventually prove to be unreproducible. Third, studies with large populations may demonstrate differences between groups that are highly statistically significant, but of such a small magnitude that their clinical meaningfulness is negligible. Fourth, even if ever-more sophisticated statistical methods may attempt to reduce differences between groups, residual confounding is difficult to eliminate. Large, retrospective studies must therefore be regarded as hypothesis-generating rather than definitive. Fifth, the current trend to use increasingly complex statistical methods obfuscates how a study was performed and detracts from the ability of clinicians to assess the credibility of results, thereby reducing their value.

Finally, certain topics carry emotional baggage. These include hormone therapy for men and women, as they relate to emotional issues such as aging, sexuality, and over-medicalization. Studies alleging increased treatment risks may fit conveniently into pre-existing belief systems that

our society overdiagnoses and overtreats many conditions. Well into the twenty-first century, we are not immune to irrational, unsupported fears of medical treatments. Recognizing our vulnerabilities to hysteria, and taking steps to avoid them, should improve medicine, science, and the care of our patients. The more emotional we are regarding a medical story, the more likely we are to be wrong about it.

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