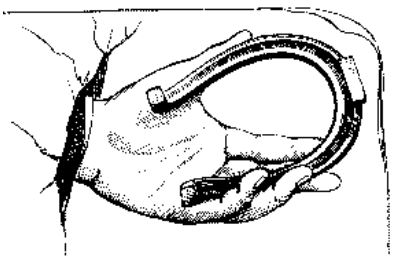
Commentaries



Choosing a Treatment

I am writing this before the *New England* *Journal of Medicine* has published letters responding to its editorial on two independent studies of vertebroplasty versus "sham" vertebroplasty. The articles, from different continents, concluded that vertebroplasty was no more effective than injecting lidocaine, which had lower morbidity and cost. The author made the bizarre statement that he didn't know whether doctors should now advise vertebroplasty or not for compression fractures, and that the patient should simply be given the evidence, thus allowing them to make an informed decision. I am sure that there will be letters denouncing the editorial and still others pointing out the weaknesses in the vertebroplasty studies. While the evidence should point to a clear choice: a procedure with complications that costs a lot and doesn't work, versus something cheap and low chance for bad outcome, the reality is that patients with friends who did well with vertebroplasty are likely to be more influenced by their friends' results than the doctor's ambivalent recommendation. But how can the doctor suggest a treatment that doesn't work? Probably because it works in his hands.

No studies are free of weaknesses. All study designers make choices. What should be measured? When should it be measured? Which tests are the best for measuring these outcomes? How many subjects are required? Given multiple options for each question, one always can argue that a different choice would have been better, possibly producing a different outcome. What exclusionary and inclusion criteria were made "too lax" in order to not inhibit enrollment or too "strict" in order to narrow the focus? At what point does the "KISS" (Keep It Simple, Stupid) principle outweigh the tremendous desire to accrue as much data as possible?

It is one thing for a doctor to allow a patient to make an informed decision when there is no data and quite another to be offered the option of an expensive procedure with proven lack of benefit.

Many years ago, a procedure in which the external carotid and internal carotid were anastomosed, bypassing constricted carotids, was occasionally performed, with the goal of preventing stroke. It was intended to bypass completely blocked carotid arteries since the blocked vessels could not be re-opened. It was thought to be especially helpful when both carotids and the basilar were blocked, since this meant there was too little flow through the Circle of Willis to compensate for the carotid blockage. It seemed a match made in heaven. The operation was technically easy and impressively safe. There was virtually no risk of stroke associated with the operation. The external carotid was outside the skull, sitting almost directly on top of a distal, but moderate sized branch of the middle cerebral artery. Not only was the morbidity low but the anastomosis remained open in a very high percentage of cases. The only problem was that when the study was performed to prove efficacy, it was found not to help. Placebo-treated patients did just as well. What was most surprising to me was what happened next. The surgeons who were the principal investigators at each site challenged the results by pointing out that the study was flawed by recruitment bias. They wrote that the "best" subjects, the ones most likely to improve with the procedure, were not offered entry into the study. They were operated on since it was common knowledge that the operation worked. Therefore the study really should have concluded that the procedure was not useful only in this selected group of patients who were poor candidates.

I am not sure what made those subjects worse than the patients who were kept from participating, but all studies have stringent inclusion and exclusion entry criteria, and there weren't differences between the placebo and actively treated subjects. So one can only wonder how and why someone would undermine his own study by steering potential subjects away, and what sort of sophism would allow someone then to throw out all the results. Or why doctors would participate in a study that they thought was unethical to perform.

{Not to bad-mouth the surgeons, we should keep in mind that hormone replacement therapy trials were postponed for many years because most authorities in the field thought them unethical since it was "clear" that they reduced coronary artery disease and hip fractures. This proved, once again, the importance of evidence-based medicine.}

As far as I'm aware the external-internal carotid operation is no longer done, and, I can see by the NEJM editorial on vertebroplasty, that this may be because it isn't paid for, not because it doesn't work. Efficacy doesn't seem to matter to everyone even in this alleged era of evidence-based medicine.

What are we physicians to do when evidence contradicts our everyday experience? We gave up blood-letting many years ago. We gave up operating on Bell's palsy about 30 years ago; putting people with subarachnoid hemorrhages into a sedative-induced stupor and stimulus-reduced environment where they became psychotic while waiting for their vasospasm to resolve, about 20 years ago; using anticoagulants for stroke within the past few years, and so on. We sometimes learn from our mistakes especially when we "know" something to be true. It is not a new insight to say that we must be ever vigilant against our own prejudices, for we harm others as we fail to examine ourselves.

Evidence-based medicine is not the gospel, but it provides a surer footing than the old approach that we have all been guilty of, as distilled by a teacher of mine: "if you've seen one case you can say, 'in my experience.' If you've seen two cases you can talk about 'my series.' But

when you've seen three cases, it becomes, 'in case after case after case.'"

At some point we must draw a line and pull back from our instincts and make data-driven recommendations. As difficult as it is, we can try to track our results, do our own private research projects to challenge other conclusions and say, not "in case after case," but rather, "in my last 10 patients;" maybe even publish our results. That's what clinical journals are for.

– **Joseph H. Friedman, MD**

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Racism and the Threat of Influenza

We humans have never lived in a bacterially sterile world, a world free of disease-causing germs. Nor dare we envision a future time when infectious disease will have retreated to history books lest we join those past civilizations that relied solely on fanciful illusions.

During the last millennium there have been three lethal pandemics, killing millions of souls. The great bubonic plague commencing in 1346, sometimes called the Black Death, altered the economy of 14th Century Europe, presaging the end of its feudal economy and witnessing the hesitant beginnings of more diversified farming, and in cities, cottage industries. The plague killed perhaps one fourth of the European population.

The second communicable disease tragedy was the awesome influenza pandemic commencing in the summer of 1918 and killing in excess of 50 million people within 18 months. And we are in the midst of a third global pestilence, AIDS.

How, in general terms, do communicable disease threats, such as influenza, arise? Are they merely random phenomena, part of what mathematicians call chaos theory and hence unpredictable? Are they, perhaps, capricious happenings, proof of humanity's maladaptive status in the overall scheme of things and therefore both tragedies and warnings that we repent? Are they, alternatively, manifestations of divine punishment, the predominant belief until the last century? Or, perhaps, are there underlying trends, secular patterns, etiological relationships in these various pestilences which, with more careful scrutiny, serve to clarify the dynamics and origins of pandemics?

And why, parenthetically, do these global perils always seem to take origin in distant, exotic places? We hear of Spanish flu, Asian flu, Hong Kong flu, Ebola fever, Lassa fever, tsutsugamushi, Siberian tick fever. But almost never do we hear of Jersey City influenza, Barrington encephalitis or Woonsocket fever.

And we who are privileged to give geographic names to newly encountered pestilences live under the naïve impression that we Americans prosper in an idyllic, pestilence-free community; and were it not for those alien pathogens from distant, unclean communities such as rain forests with strange names, we would thrive in a contagion-free society. Why, Oh why, said Henry Higgins, can't the rest of the world be just like us ?

Hyperbole perhaps, yet our American society truly contends that through clean living – and some marginal help from medical science – we have arrived at what the Pilgrims had called that shining city on the hill, essentially free of nasty pestilences.

Underlying this innocent perception of the contaminated and uncontaminated segments of the world, between the "them" (the teeming masses infested with communicable disease) and the "us", essentially disease-free but now needlessly threatened by the unclean world beyond our borders, rests a subtle form of racism which simplistically divides the world by ethnicity and is prompted by the inchoate fear that the third world is intent on sending both its uneducated young and its threatening pathogens to seek shelter on our pristine shores. It is the 21st Century variant of Hearst's 19th Century Yellow Peril.

It is an old tradition to assign blame before seeking constructive explanations. What person, tradition or institution can we blame for the unremitting threat of influenza? Epidemiologists, tracing the origins of new pandemics, tell us that China's vast population of humans living in close proximity with two billion swine and ten billion domesticated poultry has generated many of the past influenza pandemics – and will likely do so again in the future. The biological crucible for mixing human, avian and swine influenza genes is there, and for reasons other than malice, China is therefore the likeliest location for a new and communicable influenza virus to be generated, emerging into the neighboring human population and then spreading to the other continents.

In truth, since 1974, this nation has been challenged by 29 new or resurgent human pathogens including HIV infection (AIDS), Lyme disease, legionnaire's disease, cryptosporidiosis, SARS, avian flu, swine flu and more than a score of others; most, but not all, originating from less developed regions of the globe.

But it is well to recall, lest we think that the United States is a virologically privileged territory without its share of inciting world pandemics of influenza, that the tragic 1918 influenza pandemic, inaccurately called the Spanish flu and still the most lethal pestilence in human history, originated in the American prairies of Haskell County, Kansas.

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Stanley M. Aronson, MD, has no financial interests to disclose.

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