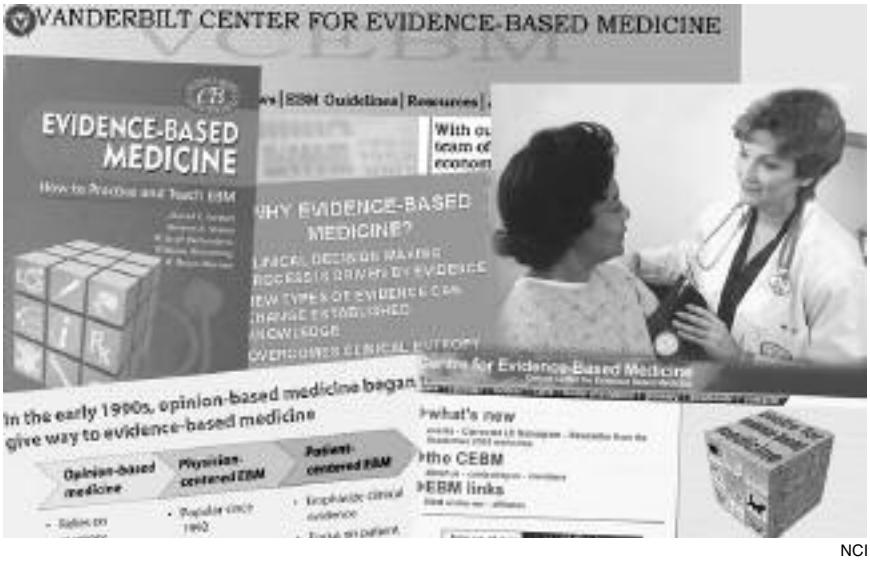

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An obsolete image of doctor and patient? In the not too distant past, medicine was an art and the doctor based decisions on a combination of experience and diagnostic information.

How Statistics Fail Medicine: The Strange Case of Aspirin

by Cathy Helgason, M.D.

Most persons are not familiar with the paradox facing the physician when trying to apply the results of medical scientific discoveries to the individual patient. In the not too distant past, the decision to apply a new diagnostic test or treatment to a patient was based on the expertise of the physician gained from treating other patients, and his training and knowledge of biology and physiology. Thus, medicine was an art. But this was to change with the advent of what is called evidence-based medicine (EBM).

Around the early 1980s, medicine took a bizarre turn, and physicians lost their credibility with their patients and each other. The buzzword for medical decisions was *objectivity,* and the expertise of the physician was to become mistrusted. Objectivity meant that any diagnostic or treatment decision must be founded in the results of large, double-blind, randomized clinical trials, and any creative interpretation of unique patient characteristics is proscribed. This would ensure that any outstanding physician was put in his place, and that special expenditure of money regarding any patient presenting with unusual symptoms would not occur. Thus, the HMO system gained control over the activities of both physicians and patients in an effort aimed toward shareholder profits.

Even stranger became the mass support for, and brainwashing of, academic physicians into this system of EBM. These physicians promote this approach arguing that it will ensure common terms of discourse, consciously denying creative or competing approaches to scientific inquiry. After all, science has been taken over by the assumptions, postulates, and axioms of probability theory. Evidence-based medicine is founded in probability theory-based statistics (PTBS), the sure road to "objectivity," because its methods and results are separated from the context of any unique patient or physician. This is because PT deals only with known variables in its analysis, ignoring unrepresented and unknown context.

In addition, in order for variables to be statistically handled, they are separated from one another and their context—the patient—when they are placed into distributions. But, anyone who faces a situation where diagnosis and treatment of a patient is concerned knows that that person has special characteristics and that unknown factors can influence how his medical condition evolves over time.

The very foundation of probability theory-based statistics is a total denial of the concept of causation, for the supposed benefit of certainty. But, what physicians adhering to evidence-based medicine refuse to recognize, is that that certainty is false when it is applied to decisions regarding the individual patient: False because of failure to acknowledge invisible factors that may affect the clinical course, and refusal to acknowledge the unique complexity and interaction of known and unknown variables in the individual patient. But, where expertise is not recognized, it is not needed, absolving the physician of any causal responsibility for his patient.

The Case of Aspirin

An example of how EBM has affected the use of a common drug, aspirin (acetylsalicylic acid), for the prevention of heart attack and stroke, illustrates the paradox. In 1993-1994, our group sought to better understand why certain patients, in spite of taking their dose of aspirin, returned to the hospital with another stroke.

While EBM was asking what common dose of aspirin for the population was effective in statistically preventing stroke, we wanted to know why a particular patient failed to obtain its supposed therapeutic effect. We wondered if it was necessary to individualize the dose of aspirin to the patient, while recognizing that other possible explanations for aspirin failure included, but might not be limited to, non-compliance, a disease process that could not respond to aspirin, and multiple causes for stroke of which aspirin was only one necessary drug for treatment where others had not been prescribed.

This approach was creative because it

sought to find out the answer to a clinical problem for each individual patient without using PTBS. It resulted in two publications, which under the current reign of EBM, would have never been printed today.[1,2]

To better understand our approach to the problem, one must understand the biological effect of aspirin. Aspirin has many possible mechanisms by which it could interrupt the cause of heart attack and stroke, but the one effect considered all important at the time was its effect on a blood cell called the platelet. Platelets participate in blood clot formation, a process called thrombosis, by becoming activated to secrete certain substances and aggregating or sticking together.

When someone cuts himself, this is a mechanism for repair. When the process causes a blood vessel to become blocked, as in heart attack or stroke, the platelets do this at the site of vessel wall damage, usually where atherosclerosis exists. Aspirin inhibits this process by inhibition of an enzyme called cyclooxygenase, which in turn inhibits platelet stimulation by agonists such as epinephrine and collagen. Aspirin is not expected to inhibit adenosine diphosphate-stimulated platelet aggregation, a process interrupted by clopidogrel, another so-called anti-platelet drug commonly used for prevention of heart attack and stroke.

Aspirin can have some effects which might be considered negative for prevention of vessel occlusion, such as its inhibition of an enzyme called prostacyclin in the vessel wall. Prostacyclin itself inhibits platelet aggregation and causes the vessel to dilate, thereby increasing blood flow to the organ it supplies.

These facts suggest that to achieve the desired effect of aspirin for prevention of thrombus formation in any one person, the dose of the drug must be carefully tailored to inhibit platelet aggregation, but allow prostacyclin to work. The beauty of the situation is that, through a simple blood test, one can measure what is going on in a patient's blood in this regard. Thus, we tested *ex vivo* the effect of aspirin over time in patients who were taking the drug for prevention of stroke. The classic test for this is the method of Born, which has been used clinically for years by ours and other groups, and is described in our publications of 1993-1994.[1,2]

The Dose Counts

The results of our study were displeasing. We found that different persons required a different dosage of aspirin to achieve the desired biological effect, and that this effect could change over time, requiring repeated testing and dosage adjustment. These results caused displeasure because they showed that aspirin was like any other drug, and required the attention of the physician, the patient, and the lab.

The results were not surprising. All other drugs used for prevention of stroke and heart attack need dosage adjustment over time, according to the results of repeated testing; for example, antihypertensives used for blood pressure control, lipid-lowering agents for control of cholesterol, insulin or oral diabetes drugs used for blood glucose control. Correct dosing of aspirin for the individual patient was going to require the vigilance of the physician, compliance of the patient, and expenditure of time and money to maintain the goal effect.

Our story ends with the admission that, instead of considering the conclusion that aspirin must be dosed like any other drug, multiple large double-blind randomized clinical trials requiring millions of dollars were launched to test what common dose of aspirin was right for all patients, what the common dosage of aspirin was for all that would achieve the desired biologic effect, and which common biological effect was right for all persons.[3-7] While none of these trials has disputed our findings, and indeed the trials have confirmed our findings for the population, the results of these trials still cannot answer the question: Is the dose of aspirin, that I as the physician am prescribing, the correct one for the unique biology and medical disease to prevent a heart attack or stroke in this particular patient?

The complexity of the biology of the patient cannot be addressed by PTBS and EBM. Beyond the changing ability over time of aspirin to affect platelet aggregation, there are many other reasons for the failure of aspirin to prevent heart attack and stroke. Some other reasons include: (1) noncompliance of the patient, (2) decreased effect on inflammatory factors at the arterial wall, (3) aspirin modulation of thrombolysis (dissolving thrombus), (4) red blood cell aggregation and its inhibition, and (5) genetic polymorphisms.

Each of these causal methods by which aspirin can inhibit thrombus formation may be required to a certain degree in any one individual patient. The methods may interact in a certain way in the individual patient. How they are affected by aspirin may change over time in any given patient.

Other tools of science, not limited to neural networks, such as fuzzy logic, cellular automata, and, of course, methods created by the talent of an individual with unique insight, could be used to better understand and control this process. But these methods are forbidden in spite of the fact that the complexity of the biological processes involved in thrombus formation in individual patients is neither portrayed nor interpretable by probability-based statistics and the large double blind randomized trial.

Dr. Helgason's primary area of research interest is the topic of causation, which was an outgrowth of her studies on individualized diagnosis and therapy for patients with stroke. She is Professor of Neurology at the University of Illinois College of Medicine at Chicago.

Notes

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