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COMMENTARY

The Myth of Mechanism

By T.V. Rajan

I recently sat on a grant review panel to evaluate a proposal seeking to determine if nonlinear electrical fields, whatever they are, have any role in the development and progression of osteoporosis. The hypothesis underlying the proposal was that in our primal state, we humans were exposed to these cosmic nonlinear electrical fields. With the emergence of housing, motor cars, and perhaps even clothing, the premise is that we have insulated ourselves from them, leading to the proliferation of the ills of modern human including osteoporosis, hair loss, asthma, and, doubtless, cancer.

The investigator wanted to test a new device that has apparently been designed to capture (and perhaps even generate) nonlinear fields even within a modern dwelling. The device: a mattress that can be easily camouflaged, enabling a placebo-controlled study. The investigator proposed to compare the bone structure of a group of individuals who were asked to sleep on these mattresses in comparison to others who slept on regular mattresses that otherwise looked the same.

Needless to say, a proposal such as this generates a certain amount of skepticism among traditional scientists as myself. I shared with many of my colleagues this sense of a certain level of incredulity about the premise. However, I found myself parting company with them on one crucial issue. A question that I've wrestled with, and to which I do not know the answer is whether there are two fundamentally different aspects to any research undertaking and whether these two aspects are not more or less independent of each other.

The first issue is to determine whether a phenomenon exists, and to document either possibility in a scientifically rigorous manner. The second is whether a phenomenon operates by a mechanism that can be comprehended in the context of our current knowledge of human physiology and behavior. The point of divergence between myself and many reviewers on this and other review panels has been my

belief that the determination of the mechanism by which a phenomenon acts is not primary to documenting whether a phenomenon exists, and whether it is useful.

I would argue that by and large, clinical medicine has developed through empiricism and phenomenology, and the understanding of mechanism(s) has not necessarily been a prerequisite for enormous usefulness. For instance, Whipple in his humility heeded the belief of lay people in his general practice that a certain plant was helpful in the treatment of dropsy. In 1765, he wrote his canonical monograph on its use. Over the past 200 years, digitalis and its glycosides have been the mainstay of therapy in cardiac disease. It is only recently, within the last 20 years, with the discovery of the ouabain sensitive sodium potassium ATPase that we had begun to understand that mechanism by which digitalis might act. I have little doubt but that a modern National Institutes of Health reviewer would dismiss out of hand a modern Whipple who chose to use a mattress to treat osteoporosis.

Nor is this divergence between mechanistic understanding and clinical usefulness only limited to phenomena discovered 200 years ago. For instance, at the end of the World War II, about 30,000 young American GI's were stationed in islands of the Pacific Ocean. A large number of these contracted lymphatic filariasis, a disease caused by a parasitic nematode and transmitted by mosquitoes. They developed fevers, chills, and the unique symptoms of this disease: inflammation of the spermatic cord, or funicitis. The symptoms were frightening and many of these young individuals were evacuated back to the United States. This episode prompted feverish research into possible treatments for the disease, since none was available at that time.

This crash program resulted in the discovery, in 1947, of diethylcarbamazaine, which has remained the mainstay of therapy against lymphatic rises for the last 50 years. One cannot even begin to estimate the number of human doses of this drug that have been distributed. Indeed in many countries such as China and India, the drug has been added to cooking salt as a public health measure to reduce the incidence of this disease in large rural populations. Despite its documented efficacy over 50 years and billions of human doses, we have absolutely no idea how the drug works. Similarly chloroquin, the mainstay of anti-malarial therapy until the recent emergence of resistant strains, remains a drug in search of a mechanism. The recent discovery that it might inhibit heme polymerase may provide clues about its action, even though it is doubtful whether we fully understand how it works.

I believe, in the ultimate analysis, that it is hubris to think that no phenomenon is valid unless we understand its mechanism of action. We seem to understand so little about human biology and physiology that a vast majority of what happens to us can simply not be understood, at least with today's knowledge base. Should we therefore dismiss as quackery even something that does work merely because we don't know how it works? The idea that the only kind of research that should be supported by NIH is "mechanistic" seems to me as a premise that is deeply flawed and potentially inhibiting to the development of novel therapies not envisioned by our intellectual constructs. If nothing else, humility dictates that we appreciate that there are more things in heaven and earth than are dreamt of in our philosophy.

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