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A Systematic Approach to Alternative Medical Procedures

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In 2007, medical costs in the United States were estimated at \$2.4 trillion (Keehan et al. 2008). If one included the costs of time lost as a result of illness and of insuring those now uninsured or underinsured, the total would be closer to \$3 trillion. Most of the non-time-lost costs are incurred for diagnostics, treatments, drugs, and other therapies.

There are ways to lower the costs of health care, such as changing payer-and-profit structures and improving infrastructure efficiency. The largest potential source of savings, however, is minimizing the need to access the health care system, especially for chronic and infectious diseases. A more strategic, proactive approach to health care could drastically reduce the need for initial access. In this article I give examples of instances in which synergistic efforts along several fronts could have important implications for the treatment of degenerative and infectious diseases. Indeed, synergistic effects of individual discoveries could help determine optimal treatments, which could eventually help close the gap between the low-cost alternative treatments and preventatives described in the literature and the high-cost approaches the mainstream medical community now uses. Without closing this gap, we cannot realistically hope to reduce the high costs of health care and make the treatment of diseases more efficient.

In the course of studying this gap, I developed a systematic approach to identify potential treatments and preventative actions for patients with a number of diseases. Using what I call literature-related discovery (LRD), I performed an initial proof-of-principle study on Raynaud's phenomenon. The study's goal was to identify potential treatments and preventive measures for Raynaud's by linking disparate concepts

from the medical literature to provide a value-added treatment. My collaborators and I then extended LRD to Parkinson's disease (PD), multiple sclerosis (MS), and cataracts (Kostoff 2008), incurable, degenerative diseases that are treated in many different ways to differing effects.

For each medical condition, we read all the recent reviews of the disease published in respected medical journals, as well as online reviews of the disease and treatment options generated by major medical clinics. We then examined the medical literature for alternative approaches to treating or preventing the disease. We generated two types of results. The first encompassed substances and behaviors that had been demonstrated to have a positive therapeutic or preventative impact on patients with the disease of interest; we labeled these "potential innovations." The second category comprised substances and behaviors that may have a positive therapeutic or preventative impact; we learned of these substances and behaviors by directly or indirectly linking previously disjoint literatures. We called these "potential discovery candidates." Before we published our findings on potential discoveries, we vetted them against major databases (Science Citation Index, Medline, Patents Index) to ensure that these linkages had not been published previously.

We found a total disconnect between mainstream medical practice and the potential innovations and discoveries we uncovered. One could perhaps rationalize this situation if the mainstream approaches offered curative treatments, but, judging from the published medical reviews of the conditions, none of the procedures reversed the degeneration. For PD (Kostoff and Briggs 2008) and MS (Kostoff et al. 2008a) in particular, mainstream approaches consist of a handful of

drugs, then surgery when the drugs are no longer effective. The drugs often substitute one set of symptoms for another set, perhaps extending functionality and mobility, but they do nothing to halt the degenerative processes.

The alternative approaches we identified through LRD offered some hope of reversing some symptoms and the progression of the diseases, although clinical trials (and further research in some cases) would be necessary for validation. We examined alternatives reported only in reputable journals and backed by solid evidence and research.

For example, we researched studies of UCP4, a mitochondrial protein found in the brain. "Messenger RNA expression of UCP4 is increased in brain cells of rats maintained on caloric restriction. Neural cells with higher levels of UCP4 exhibit reduced production of reactive oxygen species (ROS) and decreased mitochondrial calcium accumulation; that is, the UCP4-mediated shift in energy metabolism reduces ROS production and increases the resistance of neurons to oxidative and mitochondrial stress, producing antiaging and neuroprotective effects" (Liu D et al. 2006). The side effects of caloric restriction, as exhibited in rodent and primate studies, are positive on many fronts, and include longer life spans (Kostoff 2001). There is an accumulating body of evidence in both the core and noncore literature concerning Parkinson's and MS for the positive effects of caloric restriction on UCP4 and other coupling proteins, but this potential innovation is not yet used in medical practice.

Another example of a potential innovation that we gleaned from our LRD came from Durukan and colleagues (2006), who found that "IH636 grape seed proanthocyanidin extract effectively suppressed cataract formation in rats.

Routine consumption of grape seed proanthocyanidin extract in the form of food or dietary supplement may offer a prophylactic measure against onset and progression of cataract" (p. 1041).

After Kostoff (2008) was published, I did a very short study on treatments for extensively drug-resistant tuberculosis (XDR TB). We used LRD to search the Medline database in an attempt to discover potential treatments for XDR TB, West Nile virus, HIV/AIDS, and SARS (severe acute respiratory syndrome). One interesting finding was that higher type II interferon (interferon gamma, or IFN-gamma) levels tended to be associated with higher immunity to these diseases. For example, clinical trials of inhalation therapy with IFN-gamma showed some improvement for drug-resistant TB. However, this cytokine treatment often had deleterious side effects.

In a separate study, laboratory experiments on tumor-bearing animals clearly demonstrated that sulforaphane effectively inhibits the spread of metastatic tumor cells through the upregulation of IFN-gamma (Thejass and Kuttan 2007), suggesting that administration of sulforaphane could help mitigate the severity of these major infectious diseases. One potent source of sulforaphane is broccoli sprouts, in which the sulforaphane concentration is more than an order of magnitude higher than in mature broccoli. No adverse side effects have been reported from the use of broccoli sprouts.

Although individual extracts, substances, or behaviors are significant in their own right, synergistic effects may be critical to realizing the full value of individual discoveries. What leads me to this belief? Appendix B of the final paper in Kostoff and colleagues (2008b) contains medical articles we identified that display evidence of dramatic effects resulting from synergies that would not have resulted from individual substances taken in isolation. One of the articles describing the beneficial effects of phytochemicals on cataracts stated: "We propose that the additive and synergistic effects of phytochemicals

in fruit and vegetables are responsible for their potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruit and vegetables is attributed to the complex mixture of phytochemicals present in whole foods" (Liu RH 2003).

Judging from the thousands of abstracts and full-text articles we examined, I believe such findings to be endemic to all of the medical literature. Appendix C in Kostoff and colleagues (2008b) contains a few examples of powerful synergies extracted from other segments of the medical literature. Thus, the synergistic effects of individual discoveries could be very important in determining optimal treatments.

We are currently completing a study on SARS (the 2003 pandemic). The SARS situation is no different from the chronic diseases and the XDR TB case discussed in this article. According to all recent, credible SARS reviews, none of the drug treatments for the syndrome works. What was particularly interesting was that 90 percent of those hospitalized for SARS recovered, and 10 percent died. We are focusing on exploiting that finding to identify numerous potential treatments for SARS. Incidentally, the ratio of those who present with SARS to those who succumb from SARS is identical to that for influenza. The difference is that flu occurs annually, and is three orders of magnitude more prevalent every year compared with the one-time outbreak of SARS.

There is a major gap between the potentially low-cost alternative treatments and preventatives described in the literature and the high-cost mainstream approaches now in use by the medical community. Until this gap is closed, prospects are dim for either substantial health care savings or substantial improvements in chronic and infectious disease outcomes. Biomedical journals, the medical community's fourth estate, should be advocating and promulgating this gap's closure. If health care is the financial straw that breaks the proverbial camel's back and bankrupts the nation, we have no one to blame but ourselves.

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