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Editorial

Revisiting causality in psychosomatic research

Circa 1884, the study of infectious disease was a still-emerging science. Only 30 years previously, Louis Pasteur had performed his famous experiments disproving spontaneous generation and promoting germ theory [1]; however, debate still raged over the best way to prove that certain germs really did cause specific diseases. Robert Koch presented a set of criteria for establishing etiology [2], which in time formed the cornerstone of microbiological research, and brought much-needed scientific rigor to the field. By conducting a set of experiments that prove that (1) an organism is present in every infected individual, (2) that organism could be isolated from an infected individual and grown in culture, (3) that organism, when introduced into a healthy individual, would lead to the development of the same disease, and (4) that the same organism could again be recovered from the experimentally infected individual, a researcher could confidently assert that she/he had found the causative agent.

Undoubtedly, the four postulates set the bar high. Fulfilling all four of the postulates is often impossible and not required for achieving a working consensus on etiology [3]. Acquired or genetic immunity to microbes commonly prevents disease in certain individuals. *Mycobacterium leprae* cannot be cultured in the lab. And there is no animal model for HIV, making any attempt at experimentally fulfilling Postulates 3 and 4 for AIDS ethically unacceptable.

Although originally created for infectious disease, Koch's systematic approach can usefully guide in verifying any claims or accusations of causality. In essence, the postulates caution us to investigate temporal relationships between known associates and rule out alternate explanations before deducing causality. Now, a century and a quarter since Koch published, the postulates seem obvious, and deeply ingrained in any systematic thinker; yet, we see merit in going back to the basics.

One of the most poignant questions in psychosomatic medicine is whether psychiatric disorders cause general medical conditions such as heart disease and diabetes; a related, perhaps more important question is whether prevention or treatment of psychiatric conditions reduces the risk for general medical conditions. The evidence for associations is indisputably ample. However, establishing temporal relationships has been hard, and ruling out alternative explanations even harder.

The issue of temporal relationships can often be addressed by prospective studies. Alternative explanations, however, can only be ruled out by conducting truly controlled studies. But how does one conduct truly controlled studies when one continually learns about new moderators and mediators of risk?

One problem with prospective studies stems from the long "lead-in" time before most general medical conditions progress enough to be detected. Growing understanding of the autonomic, immune and endocrine surrogate markers that predict disease is certainly making it easier to study conditions with long lead-in times. There are other positive developments too. Advances in neurosciences are leading to a resurging interest in psychosomatic medicine. Frontolimbic structures such as the insula, prefrontal cortex, orbitofrontal cortex, and amygdala, which are increasingly being regarded as having a central role in emotion regulation and pathogenesis of common psychiatric illnesses, also seem to have to role in the regulation of autonomic, immune, and endocrine systems. Furthermore, some of the genetic polymorphisms, such as those within the COMT gene that have interested psychiatric geneticists for some time, have started to capture interest of others investigating the pathogenesis of general medical conditions.

Findings from neuroimaging and genetic studies are indeed promising, but challenges remain. The neuroimaging studies are expensive and, consequently, less suitable for large groups. And the associations evident in genetic studies have been weak and often do not withstand conservative statistical adjustments for multiple comparisons.

Despite the limitations of existing data on the relationship between mental health and physical well-being, availability of safer and more user-friendly medications is shifting the risk–benefit balance towards effective and timely treatment for individual patients. Nevertheless, from a policy point of view, further studies are still needed to determine where to allocate limited resources. The aforementioned challenges mean that data gathering will have to be painstakingly "brick by brick." Once we accept the limitations and the possibility that certainty of causation may never be achieved, we will have greater appreciation for incremental progress.

One approach is to break down the complex constructs of "depression" and other psychopathology into simpler, more specific risk factors that can be more directly investigated

[4]. In this way, we can perhaps pinpoint which aspects of mental health issues are in and of themselves atherogenic, or diabetogenic. This edition of the *Journal of Psychosomatic Research* contains several studies that are in this vein: Kornerup et al. [5] look at the construct of vital exhaustion and its value in predicting stroke; Doyle et al. [6] deconstruct commonly used depression rating scales to investigate which aspect of depressive symptomatology is most strongly correlated with major cardiac events; Brydon et al. [7] investigate whether trait hostility is associated with physiological changes that predispose individuals to cardiac events, and suggest that the sympathetic activation and inflammatory pathways mediate the relationship; and Grabe et al. [8] present evidence that alexithymia is an independent risk factor for hypertension and atherosclerosis. Loponen et al. [9], taking a different approach, investigate the combined effect of sleep problems and metabolic syndrome on the risk for coronary heart disease.

As a reminder that mind–body interactions are not limited to the domain of cardiovascular disease, other studies in this edition explore these relationships in asthma and arthritis. Vazquez et al. [10] note that trait anxiety is greater in patients who have had a near-fatal asthma attack than in those had less severe attacks. van't Land et al. [11], noting a previously documented correlation between arthritis and psychiatric conditions, look at a longitudinal population dataset to establish the temporal relationship between the two. Their results indicate that arthritis does predict later development of a mood disorder, while having a mood or anxiety disorder does not increase the risk for later development of arthritis. The investigators took an important step in establishing a causal relationship. We now look to them and others to rule out alternative explanations, and, if the relationship is indeed causal, determine mediating variables.

Though we continue to turn to Koch's postulates for guidance, in reality the questions that interest us now are more complex and sophisticated. For example, Kim et al. [12] examine if age acts as a moderator on the association between depressive symptoms and "eveningness," a marker of phase delay in circadian rhythms. Goodwin et al. [13] further explore the relationship between asthma, mental illness and psychosocial functioning, suggesting that asthma and mental illness may impact functional outcomes synergistically. The cross-sectional nature of their study limits what we can infer, but we do wonder if one of these variables actually mediates the relationship between the other two. Studying interactions between risk factors is obviously more challenging than studying single risks but is likely more reflective of the complex nature of disease pathology.

Two other studies in this edition, although thematically distinct from the rest, are of no less public health consequence. In one, Chilcot et al. [14] show that lower consequence perception predicts non-adherence with the recommendation to restrict fluid intake in patients with end-stage renal disease. In the other, Sim et al. [15] report the results of their investigation into the psychosocial and coping response during the 2003 severe acute respiratory syndrome (SARS) outbreak.

To conclude, the mind–body connection is not one amenable to straightforward empirical investigation. The general medical conditions under investigation in this edition of *Journal of Psychosomatic Research* are known to be multifactorial in etiology, likely resulting from a complex interplay of genetic predispositions and lifestyle factors. When asking if psychiatric conditions, even less clear in terms of their own etiology, have an etiological role in these illnesses, we may have to settle for less than certain answers. Ultimately, everyone decides for themselves how much evidence is enough to guide an action. Andre Gide saw skepticism as an integral part of honest exploration when he said, "Believe those who are seeking the truth; doubt those who find it."

In the spirit of skepticism: believe if you must, but we do hope you enjoy reading this February edition of the journal.

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