

# Pandemic of idiopathic multimorbidity

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*There are two ways to be fooled:*

*One is to believe what isn't so; the other is to refuse to believe what is so.*

Søren Kierkegaard

Sitting among colleagues in the private room of a swank eatery, I recently had the pleasure of participating in a pharmaceutical industry-sponsored medical education event allegedly exploring the management of patients presenting to their health providers with multisystem health complaints. The amateur for the evening—an eloquent orator with impressive credentials—raised the issue of the rising prevalence of patients who present with a laundry list of ongoing and seemingly unrelated persistent complaints often including headache, joint pain, fatigue, brain fog, bloating, chemical intolerance,<sup>1</sup> muscle aches, itchy skin, and so on. In an almost synchronized response, a hum of affirmation rose from the ranks. Yes, the doctors in attendance agreed that they were seeing more and more patients from all age groups with diverse health complaints,<sup>2</sup> with little or nothing to find on physical examination and apparently unremarkable laboratory results. The early chatter suggested that the impartation of any wisdom about the assessment and care of such individuals would certainly be welcome.

The stirring presentation, with moments of humour, anecdote, and flair, was long on style but short on science, concluding that such patients are psychiatrically disordered and, predictably, in need of urgent pharmacologic intervention. Although not specifically classified in the sacrosanct *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, this affliction—we were told—is a manifestation of depression and requires antidepressant therapy whether or not melancholy is evident. Furthermore, failure to treat early and vigorously would likely be “depressogenic” via neuroplastic mechanisms of laying down pathophysiological pathways biochemically destined to induce chronicity and ongoing somatic health complaints.<sup>3</sup> In addition to clinical depression, some of these patients apparently also qualify for the forthcoming *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, new diagnosis of somatic symptoms disorder,<sup>4</sup> which, unsurprisingly, might be treated in some situations with antidepressant medication.<sup>5</sup> When asked about the underlying origins of this clinical presentation,

we were apprised of a likely genetic source—a perplexing supposition considering the marked increase in the prevalence of multimorbidity and, to my knowledge, the lack of a widespread mutation of the population gene pool. However, at my table, one particularly erudite medico imbued with the wisdom of vino simply said of such patients, “I think they’re all nuts.”

## Background

The simultaneous coexistence of ongoing multisystem health complaints in a single person—sometimes referred to as *multimorbidity*—often presents a difficult clinical situation for physicians.<sup>6,7</sup> In this month’s issue of *Canadian Family Physician* (page 533), Tymchak and I discuss the assessment and management of patients who present with otherwise inexplicable multisystem health complaints.<sup>8</sup> Patients with these challenges often have repeated visits to their primary practitioners, high rates of attendance in emergency departments, poor health outcomes, and chronic complaints.<sup>7,9</sup> Associated health care costs are usually enormous,<sup>9,10</sup> with calls in recent literature for concerted action to confront the widespread multimorbidity problem.<sup>11,12</sup> However, with no obvious cause and a paucity of research on this escalating phenomenon,<sup>13</sup> it is often eventually assumed that many idiopathic multimorbidity presentations are psychogenic in origin,<sup>14</sup> and use of psychoactive pharmacologic interventions is common. How do individual patients with such presentations respond to the medical care they typically receive?

The expanding challenge of this type of multimorbidity is profoundly important for patients and the medical system.<sup>7,10</sup> When primary care practitioners find nothing to account for the various symptoms and have little to offer in terms of solutions, patients typically experience frustration and do not know how to proceed. Follow-up visits often result in referral to assorted specialists who generally focus on one component of the patient’s problem—the neurologist explores recurrent headaches and brain fog, the gastroenterologist assesses abdominal discomfort, the rheumatologist evaluates the fibromyalgia, and so on. When serial consultations result in a lack of objective findings, psychiatric referral is often suggested. Presented with this recommendation, disgruntled patients sometimes lose faith in the acumen of their physicians and often end up frequenting the establishments of alternative practitioners, which accounts for the sobering reality that there are more visits in the United States to nonconventional health practitioners than to primary care physicians.<sup>15</sup>

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## Exploring the origins of disease

Within the recent medical literature, there is increasing discussion of a paradigm shift in the understanding of the underlying origins of disease. Rather than genomic predestination, considerable research over the past decade has begun to explore aberrations in the epigenome and exposome<sup>16</sup> as potential source causes of a wide array of chronic afflictions and multimorbidity.<sup>14,17,18</sup> With recent evidence in the past few years that 70% to 90% of disease is likely related to environmental determinants,<sup>19</sup> the term *exposome* has emerged to refer to the totality of environmental exposures from conception onward that might be influencing health. Exploration and appreciation of this domain is critical for assessing the origins of disease and understanding the source of the multimorbidity pandemic.<sup>19,20</sup>

Just as accrued toxic compounds originating from cigarette exposure are a well established cause of various health conditions, myriad toxicants originating from many other day-to-day exposures are now bioaccumulating in people and causing a multitude of health conditions.<sup>21</sup> To facilitate convenience, comfort, safety, and efficiency, there has been the manufacture and release of many thousands of untested synthetic chemicals over the past few decades. Extensive evidence published in various scientific and public health journals has recently verified that individuals from many population groups have experienced exposure to and bioaccumulation of numerous chemical toxicants from the air they breathe, from the food and drink they ingest, from vertical transmission, from dermal exposure, and from compounds injected or implanted into the body. Furthermore, the emerging field of nanotoxicology, a new discipline exploring the potential biochemical havoc resulting from exposure to some nanoparticles,<sup>22,23</sup> has served to bring further attention to the expanding realm of potential toxicants. But just as the exposure problem from cigarettes, which was initially described by Delarue in the 1940s,<sup>24</sup> was ignored for many years, the current exposure problem from innumerable domestic and occupational sources is also being ignored by many clinicians despite irrefutable and extensive evidence.

The Centers for Disease Control and Prevention, for example, publishes biennial reports highlighting the reality that most demographic groups within American society possess varying degrees of human toxicant pollution.<sup>25</sup> Furthermore, cord blood research and breast milk studies have verified widespread prenatal, as well as postnatal, exposure and contamination, respectively.<sup>26-28</sup> Recent science confirms that some toxic agents resist efficient elimination<sup>29</sup> and thus persist in the human organism with enormous potential at low levels<sup>30</sup> to disrupt a plethora of physiological processes and to induce metabolic error by mechanisms including hormone disruption,<sup>31,32</sup> epigenetic change,<sup>33</sup> immune

dysregulation,<sup>34</sup> cytotoxicity,<sup>35</sup> enzyme interference,<sup>36</sup> and others.<sup>37</sup> The literature confirms that the result has been a widespread chemical erosion of human health,<sup>21</sup> prompting the Pediatric Academic Societies to state that “low level exposure to environmental toxicity may be impacting the functioning of the current generation.”<sup>38</sup> But how does this translate into multimorbidity?

A foray into the recesses of the scientific literature reveals discussion of a condition called *sensitivity-related illness*<sup>34</sup> (SRI), with description of a credible causal mechanism<sup>39</sup> to account for much of the emerging pandemic of multisystem health problems.<sup>40</sup> This condition results when toxicant accrual within the human organism—typically from exposure to adverse chemicals—induces a state of immune dysregulation and hypersensitivity resulting in physiological disruption within various organ systems.<sup>41-43</sup> The pathogenesis relates to an intriguing phenomenon called *toxicant-induced loss of tolerance*,<sup>41,44</sup> a finding that represents a considerable advance in medical science pertaining to the origins and mechanisms of disease.

When the toxicant burden within an individual reaches a certain threshold, the immune system often provokes a low-grade systemic inflammation with substantial changes in the cytokine profile.<sup>45</sup> This hypersensitive state magnifies and responds to inciting exposures with the release of a storm of bioactive compounds, often including pro-inflammatory cytokines.<sup>34,41,44</sup> These cell-signaling and, in some cases, gene-regulating molecules can induce a cascade of dysregulated physiology in many organ systems, causing multisystem manifestations with consequent health complaints.<sup>34</sup> The abnormal immune response might be triggered by inciting exposures such as certain foods, inhalants, chemicals,<sup>46</sup> and even electrical incitants.<sup>39</sup> The reaction is often most prominent in the first 12 to 24 hours after incitant exposure and will typically settle after 3 to 5 days if not retriggered. Early evidence suggests that this toxicant-induced hypersensitivity is the underlying source of the allergy epidemic that has occurred in the past few decades.<sup>34</sup>

## Idiopathic multimorbidity discussion

Accordingly, what presents with a range of morbidities and the acquisition of a collection of diagnostic labels<sup>7</sup> might in fact be the consequence of a common underlying cause. As such, does the term *multimorbidity* really apply to this kind of multisystem clinical presentation? Although precise definitions are lacking,<sup>47</sup> *multimorbidity* is generally defined as the co-occurrence of 2 or more ongoing or “chronic” medical conditions within 1 person.<sup>48</sup> Single-source cause does not necessarily negate use of the term *multimorbidity*, as an individual with liver disease, cardiomyopathy, stomach cancer, osteoporosis, and neurologic impairment from alcohol

abuse, for example, is still considered to have multimorbidity. Most individuals with ongoing multisystem complaints go from doctor to doctor over many years desperately trying to find solutions; these people certainly fall into the World Health Organization category of having *chronic conditions*, described as “health problems that require ongoing management over a period of years or decades.”<sup>49</sup> But is this SRI condition always chronic?


No. Application of appropriate interventions to avoid incitant triggers and to facilitate elimination of the toxicant burden reverses the state of toxicant-induced loss of tolerance and consistently results in remarkable recovery from SRI.<sup>29,34,39</sup> Therefore, with unfolding understanding of the source and management of multisystem health complaints, further consideration and subclassification of the term *multimorbidity* might be in order to achieve consensus and common understanding of this diagnostic label.<sup>50</sup> However, use of antidepressants and other psychoactive medications to treat SRI might exacerbate the underlying problem. As some individuals with cytochrome P450 single nucleotide polymorphisms in their genetic constitution are particularly vulnerable to toxicant exposure because of inefficient bioelimination of foreign substances,<sup>51</sup> continued drug dosing might add to their toxicant burden, rendering them more sensitive.

## Conclusion

As the chemical revolution with resultant toxicant bioaccumulation is new, we are the first generation to experience and recognize this pathophysiological response to stockpiled contaminants. However, the tardiness with which knowledge translation occurs in health care is nothing new.<sup>52</sup> Despite the reality that many researchers, health bodies,<sup>32</sup> governments,<sup>53</sup> and legal institutions<sup>54</sup> are cognizant of the problem of environmental and epigenomic determinants of illness,<sup>17,18</sup> such as human toxicant bioaccumulation and the attendant health sequelae,<sup>21</sup> many clinicians are not yet aware of the evidentiary science behind this emerging challenge. It is problematic that those charged with providing health care are sometimes slow to become acquainted with evolving scientific and health information. Research discussing the link between environmental toxicants and declining public health is increasingly manifest in the recent scientific literature, but it is not yet routinely taught in medical schools and remains unfamiliar territory in the busy everyday world of many clinicians.

Despite the deference afforded to values such as creativity and critical thinking in science, it is also apparent that few medical professionals tolerate iconoclastic ideas. In fact, medical history shows that the conventional medical community is frequently recalcitrant in its opposition to findings that threaten the status quo.<sup>52,55,56</sup>

No matter how compelling the scientific evidence, most will reject the truth in favour of what they are comfortable or familiar with.<sup>52,56-58</sup> The rejection of Delarue's observations connecting smoking to lung cancer in the 1940s and 1950s<sup>24</sup> and the resistance to Warren and Marshall's evidence linking ulcer disease to *Helicobacter pylori* in the 1980s<sup>59</sup> are recent examples of what one medical author metaphorically refers to as the “barriers to teaching old dogs new tricks.”<sup>56</sup> With an apparently reflexive tendency to attribute unfamiliar presentations to psychogenic origins, many disorders in the past including Parkinson disease, asthma, ulcerative colitis, migraine headaches, multiple sclerosis, autism, and various other clinical entities have been dismissed as pathopsychological rather than pathophysiological.<sup>43</sup>

Despite the entertaining educational soiree with my colleagues, I wondered whether industry-sponsored medical education was the best means to keep physicians apprised of emerging scientific information. If this approach to knowledge translation and the historical pendulum from research to clinical practice continue, we can expect it will take the usual 1 to 2 generations before health practitioners are familiar with the documented pathophysiological mechanisms and restorative approach to many cases of multimorbidity. If so, countless individuals with apparently inexplicable multisystem complaints will needlessly suffer and receive an incorrect label of being psychiatrically disordered. By the end of the evening, 3 things were evident: that the pandemic of idiopathic multimorbidity was real, that health care costs were escalating, and that the share price of antidepressant manufacturers would likely continue north for years to come. 

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### Competing interests

None declared

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