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On the face of it, the notion that sitting can be harmful to health seems absurd. Sitting is the default human body posture—modern office workers are often seated 15 hours per day (2) and at home are entertained, socialize, learn, and shop all whilst seated. How can a ubiquitous body posture—sitting—be harmful? There are other common physiological functions that can be harmful too. For instance, eating is a physiological necessity, but eating in excess is harmful. Persistent sitting is harmful because we have designed a chair-based world. It was a mistake.

Epidemiological data, from almost one million people, link excess sitting to 34 chronic diseases and conditions (13), including obesity (6) and metabolic, cardiovascular, joint, sleep, and psychological disorders. Homo sedentariness seeks answers: How did this happen? How did chair addiction sweep through the world without anyone noticing?

Humans started their evolutionary quest two million years ago, leaving African forests walking with a bent-over, knuckledusting gait. As Homo evolved, people populated the new world on their legs. Early forms of Homo were not only legbased but manual too. All critical tasks such as hunting, agriculture, building a home, nurturing young, evading inclement weather, escaping predators, conducting warfare, and ensuring security were all performed through physical exertion. This energetic way of life changed about 200 years ago with the Industrial Revolution, which precipitated the migration of people from agricultural communities to cities to work in factories and offices.

Before the Industrial Revolution, 90% of people were energized agriculturalists; presently, more than half of the world's population lives in cities, and the number is increasing. Urbanization was not only accompanied by automated seated work but also by the pervasive use of automobiles

to replace walking and, more recently, by the adoption of screen-based leisure and play. Over the last 200 years, ambulatory Homo sapiens became sofa-seduced, sedentary, and slothful. Homo sapiens became Homo sedentarius. The transition occurred unnoticed, slowly, over four generations in people blinded by the constant promise of prosperity and oblivious to their lethal new persistent posture—sitting.

Almost every daily activity can now be conducted from a chair, but is this physiologically important? When sitting time was compared between agricultural workers and urban dwellers (7), the impact of urbanization on sitting time was found to be great. People who work in agricultural communities sit 3 hours per day (7), whereas urban dwellers sit for 10-15 hours per day (3). As a consequence, the energy expenditure of daily activity called non-exercise activity thermogenesis (NEAT) is 1,000 kcal/day less in people with chair-based occupations compared with those working in agriculture (1, 6). The magnitude of the chair sentence is great and thus likely to be physiologically important.

It is remarkable that some people, despite the omnipresent chair-based environment, are active and resist lethal sitting. These active people were dubbed by Andre Mauroi, "Thinifers" (10). Thinifers stay lean by maintaining high NEAT both at work and at home (11). Thinifers, without entering a gym, walk 2.25 hours per day more than people who have obesity (6). Thinifers remain thin even when challenged with experimental overfeeding. After 1,000 kcal/day of excess food, Thinifers do not slump onto their sofas but activate their NEAT even more (5) by spontaneously getting out of their chairs and walking-off the extra food. Other people are predisposed to weight gain; they do not activate NEAT, they are stuck in their chairs, and after overeating they gain body fat.

If Thinifers can elude the Chairman's seduction, whereas other people are overweight or obese, it suggests that differentiating regulatory mechanisms are at play. A neurological circuit explains this dichotomy. Neuromodulators, such as Orexin and Neuromedin U, function through the paraventricular nucleus of the hypothalamus to reverse sedentariness and promote spontaneous activity. Animals inbred for obesity have neuronal resistance to the effects of these activity-promoting factors. Just as poor environmental air quality can precipitate wheezing in asthmatics, so too sitters are predisposed to sit in chair-based environments.

Growing evidence suggests that the health impact of sitting may overall be greater than that of smoking. This is because the human harm associated with excessive sitting is extensive and includes obesity, metabolic disease, cardiovascular disease, cancer risk, and psychological harm. There is mechanistic evidence that can explain these associations; for example, an exaggerated increase in blood glucose after meals (postprandial glycemic excursion) is a key predictor of Type 2 diabetes. By taking a slow walk for 15 minutes after a meal, people can halve their postprandial glycemic excursions (9). Similarly, breaking up sitting time throughout the day can improve a person's plasma glucose (4). At a molecular level, getting out of your chair, even for a short time, activates multiple molecular mechanisms in the musculature (12) that improve insulin handling. Overall, these data explain why excess sitting contributes to diabetes. The association between excess sitting and carcinogenesis can be explained, in part, by the aforementioned associations between sitting, adiposity, and metabolic dysfunction; however, excess sitting also disrupts sex hormone function, inflammation, and vitamin handling (8). Inactivity is associated with low bone density, dulled intellectual function, and low mood, and in all cases putative molecular mechanisms exist. Excess sitting impacts many physiological systems, which explains why Chairaholics have so many negative health outcomes.

In conclusion, there is historical, pathophysiological, and mechanistic evidence

to explain why people who become chair sentenced bear the lethal consequence. The solution is paradoxical; it is so simple yet requires disruptive innovation and societal reinvention (7a). Homo sedentarius arise: the solution to lethal sitting is to get up!

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