



Commentaries

Reducing Risk Factors



A FEW WEEKS BEFORE I WROTE THIS AN article got a lot of press attention because it discussed seven “risk factors” for Alzheimer’s disease, and stated, or at least inferred, that half of future cases could be avoided by reducing these risk factors. Thinking more and exercising more were the two that stick out in my mind, although smoking and weight loss were also on the list. This was in the newspapers, and the TV news.

Today I read a review article in *Archives of Neurology*, an esteemed publication with a high impact factor, reporting that there were no known modifiable risk factors for Alzheimer’s disease. Being a half-empty kind of guy by nature, and, if I hadn’t been born a skeptic certainly have had it pounded into me over the past few decades of clinical research, this review article made much more sense to me. It also brought to the fore the problems with the interpretation of risk factors.

The first issue is the misunderstanding many have of what the term risk factor means. We think of risk factors as properties that an individual has which increase the risk of that person having a certain outcome. We have learned that cigarette smoking is a risk factor for certain types of cancer. If people stop smoking they are less likely to develop various cancers. Cigarette smoke has chemicals that alter DNA and cause cancer. There is a causal relationship. Epidemiology pointed to potential causes, and at least one was found. Too often, as is the case with the Alzheimer work, one leaps from “associations” to “risk factors.” To have a risk factor puts you at greater risk to develop the problem. This does not mean that there is actually any direct risk. For example, people who are heavy alcohol drinkers are at increased risk of lung cancer. In this case, the risk is directly attributable to the link between alcohol consumption and cigarettes. The risk of lung cancer is not increased in alcohol imbibers who do not smoke. If you live in the Azores you are far

more likely to develop Machado-Joseph Disease, an inherited neurological disorder, than if you live in Kansas, because the illness has a nidus in the Azores. Simply living on one of the islands confers a “risk” but, of course, this is a nonsensical association.

I prefer the term “associations” to “risk” when the connection is only epidemiologic. I think that the term “risk” suggests to most readers a causal relationship. People who have AD were more likely to have been overweight, less well educated, less exercised, used their “thinking skills” less, and to have smoked more. This often suggests that overweight people who smoke and don’t think are more likely to develop Alzheimer’s disease, from which one deduces that losing weight, stopping smoking and solving physics problems will reduce the risk. The epidemiological studies do not, of course, suggest this. What they’ve found is that when one compares people with AD to those without and one analyzes data on their younger years, there were differences in behavior or weight, or blood pressure or something else. Too often these associations are interpreted as causal risk factors. Being overweight is associated with developing AD so you should lose weight. While this may be true, it is far more likely to be like suggesting smoke removal to stop a fire. It has been demonstrated that Parkinson’s disease patients are less likely to have smoked than people who do not have PD. Does this mean that smoking cigarettes prevents PD, or might it mean that people who are fated to develop PD are less likely to want to smoke because of brain differences that are present many years before the disease is known to have taken hold?

There have been many epidemiological studies and, no matter what sophisticated statistical analyses used, the more questions you ask, the more likely you are to find “significant” correlations. Correlations are not risk factors. They

are associations. And, although they clearly showed the connection between cigarettes and lung cancer, they mostly produce associations later found to be spurious. In current times they may lead to expensive clinical trials as clinical trialists run out of good ideas and the demand for solutions increases. Witness the many studies showing vitamin D deficiency associated with a multitude of disorders, few of which improve with vitamin D supplements.

The second problem I have, as a neurologist, is what it means to “think” and what the effect of thinking is on brain structure and function. With the exception of people with certain brain diseases, I believe that everyone thinks all the time, although, perhaps Zen masters may not, but there aren’t enough of them to alter any statistical analyses. What many people believe constitutes the sort of thinking that reduces Alzheimer’s disease is solving problems, translating Homeric Greek and listening to classical music. I like to listen to classical music and to solve problems, but I doubt this is “better” in the sense of protecting me against Alzheimer’s disease, than thinking with the same intensity about dinner or my car or what movie I want to watch on Netflix.

I am unsure if anyone believes that spending time solving differential equations is more protective than studying Greek, or thinking about when to plant your bulbs for next year. If one posits the notion that learning increases synaptic connections, and that the more synaptic connections one has, the greater the brain power you’ve stored up for the decline that comes later when Alzheimer’s starts to draw down the account, then the idea of thinking as a protective exercise makes sense. But is it at all plausible that such a simplistic hypothesis could be true? And if so, what would constitute the type of thinking that would accomplish this? Should we rig up instruments to detect how much energy our brains are using?

Perhaps it would be better to use *less* energy to protect the brain from oxidative byproducts of too much thinking? There's an old joke about the futuristic person who goes to the brain store to buy a new brain. He finds Mozart's brain available for a huge amount of money, and Einstein's for even more, so he asks the manager if there aren't even more expensive brains to consider buying. He's taken to the locked vault where he's shown a brain that costs 10 times as much as Einstein's. He's told that this brain belonged to (pick your own name to put here). It costs more than Einstein's because it's never been used.

Perhaps there are differences in types of thinking. Perhaps problem solving is a different type of thinking than trying to

guess how the ballgame will end. Perhaps daydreaming is good and physics is bad, or vice versa. And is abstract thinking (algebraic geometry) better or worse than non-abstract thinking (differential equations)?

Does anyone believe that because higher levels of education are associated with a lower risk of developing AD that everyone should go to college and that the cost will be offset by the reduced rate of AD 60 years later?

The closer we look at diseases, the more complex and challenging they become. Epidemiological studies to determine true risk factors, provide questions, not answers.

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Where Are the Spirits of Yesteryear?

WHAT IS THE DYNAMIC FORCE BEHIND CIVILIZATION? PATRICK McGovern, a contemporary archeologist, declares that it is the quest for intoxication. Certainly a spirited response; and while it may sound hyperbolic in the eyes of the temperance movement, it is nonetheless a sadly accurate presumption.

The first mention of intoxicating fluids in the Bible occurs when post-diluvian Noah plants a vineyard at the base of Mount Ararat, consumes the wine and becomes drunken (Genesis 9:20-21.) And thus, according to Scripture, a man who had found singular grace in the eyes of the Lord is quickly besotted by a wine derived from the berries of his own vineyard. G. K. Chesterton (1874 – 1936), reflecting upon the abating floods, has then elaborated on the biblical tale:

And Noah he often said to his wife
when he sat down to dine,
I don't care where the water goes
if it doesn't get into the wine.

The origins of wine and other fermented intoxicants are lost in a swirl of legends, heroic myths and apocryphal fairy tales. One of the most vivid of these tales speaks of the mythical king of Persia, Jamshid, the fourth ruler of the great Pishdadian dynasty of greater Iran. The legend declares that Jamshid banished one of his harem wives who, in despondency, then sought a poison for suicide. In her search for a lethal substance she came upon an abandoned vat of old, fermented fruit juice; and thinking it a poison, she drank of it, thus discovering, instead, that the drink provided a form of unanticipated exultation. In haste she returned to King Jamshid, shared her inebriant discovery with him and was promptly returned to her harem status. And thus, one legend tells us, the discoverer of a principal form of addictive slavery was rewarded by hastening her return to another form of slavery.

Unromantic chemists, however, have provided science with a means of determining the age of recovered artifacts by a radioactive measuring process called carbon-dating; and secondly by infrared spectrophotometry they possess a procedure that can analyze small amounts of dried residue clinging to the interior of ancient pottery and thereby identify some substances found in wines and thus may infer that the vessel had once stored wine in the past; and further, they are then able to identify the regions from whence wine-making had originated.

And so, scientists tell us that the first evidence of wine consumption is found in the Neolithic settlements in the Caucasus foothills, some 9,000 years ago. It is likely that the berries were foraged from wild grape vine or other fruits. The development of terracotta pottery, during the late Neolithic age, allowed for the storage of excess wines and hence provided modern-day chemists with ancient specimens in the form of wine-stained shards which were amenable to modern analysis.

Gene-mapping of the numerous grape cultivars, currently employed in the extensive wineries of the Mediterranean and Asia Minor has verified that they are traceable to the wild grape species of that southern Caucasus area situated between the wine-dark waters of the Black and Caspian Seas.

Domestication of the grape vine was the next step in the evolution of viticulture; and there is evidence that this agricultural advancement simultaneously evolved in many Mediterranean and Middle East sites including Macedonia in northern Greece and in Mesopotamia. Physical evidence of viticultural specialization, a necessary phase in the evolution of the industry (with wine presses and facilities for the storage and shipment of the ultimate fermented product), is found throughout the southern Balkans, Mediterranean and many regions in the Middle East.

With the notable exception of Islam (the Prophet had declared that there is the devil in every grape), the many religions that took origin within this nursery of civilization readily incor-