The Four Humors *(Updated for Neurologists)*

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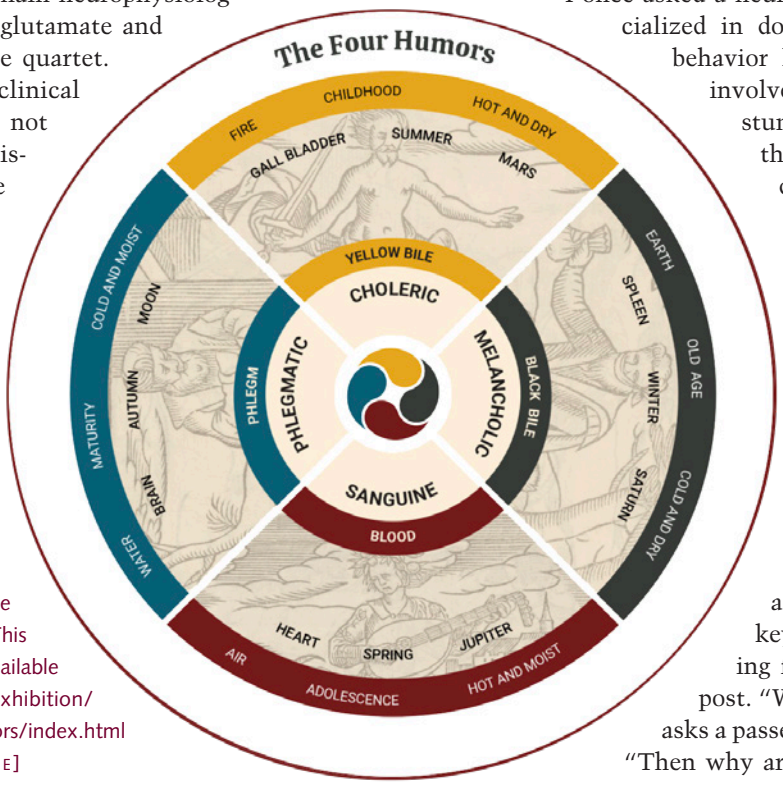
The four humors of ancient Greek medicine, often credited to Hippocrates (460 BCE to 370 BCE), were: blood, yellow bile, black bile, and phlegm. Two thousand years ago, doctors used them to explain pathophysiology. Cancer was caused by an excess of black bile. What caused the black bile to build up may have been an ill-advised diet, excess work, a passing comet, or not enough sunlight. These days a shortage of vitamin D is seemingly involved in everything from falls, to autoimmune disorders, neurodegenerative disorders, and some cancers. The microbiome has also attracted a lot of attention and, plausibly, may be involved in a large number of disorders, too, or possibly none.

In neurology we have returned to that original ancient Greek conception of the foundation of pathophysiology, the four humors. There is a certain symmetry to this line of thinking and we are inclined to believe that nature likes symmetry. The current four humors are quite different than those our Greek predecessors invoked. With a far more superior sophisticated veneer, we invoke dopamine and serotonin as the two main neurophysiological basics. A soupcon of glutamate and acetylcholine complete the quartet.

I don't think I've read a clinical neurology paper that has not invoked dopamine in the discussion section, where the authors feel obligated to explain the physiology of whatever it is that was observed. In many, if not most, cases, there is little reason to think that their explanations hold water, which is, luckily, not a humor.



The National Library of Medicine has an online exhibit of The Fours Humors, seen through the work of William Shakespeare. This image if from the collection, available at: https://www.nlm.nih.gov/exhibition/shakespeare-and-the-four-humors/index.html [NATIONAL LIBRARY OF MEDICINE]

The authors don't think so either, but feel they must come up with some hypothesis. "Although dopamine levels were increased in rat brains after a 3-month exposure to drug X, they were decreased after 2 months in mouse brains, perhaps explaining why the findings in our rabbit experiments were highly varied…"

Dopamine is ubiquitous in the brain. Of course, it is crucial in Parkinson's disease, my own niche, but has also been a focus in schizophrenia, since drugs that block dopamine activity have been found to be helpful in treating some psychotic symptoms. However, it is also apparently involved in obsessive compulsive disorders, addiction, depression, learning, and virtually anything else you can name. Consider a recent statement in an unpublished manuscript under review: "Patients with Parkinson's disease (PD) may be at a higher risk of developing neuropsychiatric symptoms because they have difficulties adapting to a drastic change in the environment due to impaired functioning of the dopaminergic system."

I once asked a neuropharmacologist who specialized in dopamine if there was any behavior he knew of that did not involve dopamine and he was stumped. Not one could he think of, which is not to say dopamine isn't involved in every one of them. I suspect it is. The brain is, in some ways, like a clock, but instead of stopping when one piece in a thousand stops working, it speeds up or slows down. Whenever I see dopamine invoked to explain some outcome, I always think of the joke about the inebriated man who lost his car keys at night and is searching fruitlessly under the lamp post. "Where did you drop them?" asks a passerby. "Over there," he says. "Then why are you looking over here?"

"Because the light is better."

I am not saying dopamine isn't involved in most, if not all, behaviors. I think that we often fool ourselves into thinking we know more than we do by using technical jargon and applying principles that are terribly over-simplistic. When I read that perturbations in one part of the nervous system are associated with, or provoke changes in dopamine somewhere else, I think of the very old children's song, "The Skeleton Dance": "The thigh bone's connected to the hip bone..." In the brain, as in the skeleton, everything is connected to everything else.

I am not trying to demean my research colleagues. Well, yes I am, but only a little. As a clinician and clinical researcher, who now does more peer reviewing than writing, I think it important for us clinicians to understand the famous warning from former Secretary of Defense Donald Rumsfeld about distinguishing the known unknowns and the unknown unknowns. He was talking about the military and defense, but the warning applies to all questions. My concern is avoiding the complacency that comes with thinking you understand something that you don't, because you use technical jargon to obfuscate that lack of knowledge. I have rarely reviewed a paper that made a clinical observation, put that observation into an appropriate, and possibly important context, usually something along the line of "be aware of this rare problem in this disorder," and did not then state that they had no factual basis for inferring a pathophysiological explanation and refrained from doing so. Most papers will, instead, write more about the various theoretically possible explanations, usually based on a case report, an animal experiment, and/or a biochemical study of something different but related. I generally recommend acceptance or rejection of the manuscript based on the material before the discussion hypotheticals and ask the authors to markedly reduce their esoteric but imaginative speculations. Unfortunately, this isn't the usual outcome.

There was a neurological paper published decades ago that became famous, not so much because of its importance, although it certainly provided enormous help to a very small number of people, but because of its humility. In describing the first, and still only, effective symptomatic treatment for the rare inherited disorder, Episodic Ataxia type 2 (EA2), the author wrote that he had been contacted by phone, at night, about a child admitted with presumed hypokalemic periodic paralysis. The child was treated with acetazolamide, as was appropriate, and improved. The next day, the pediatric neurologists met the child for the first time, changed the diagnosis to the correct one, EA2, and described their discovery as "serendipitous," based on a mistake. I wonder how many of us would do this today, and would a journal welcome such an admission? ❖

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