The medical microbiome paradigm and its parallels with humoural medicine

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Abstract

The working concepts that have emerged in microbiome research bear an uncanny resemblance to one of the most ancient traditions of Western medicine: humoural medicine as promulgated by the medical practitioner and philosopher Galen in the second century CE. In particular, both Galenic medicine and medical microbiome research rely heavily on notions of imbalance and balance, with undesirable unbalanced states called 'dyskrasia' and 'dysbiosis' respectively. Therapeutically, both systems aim at restoration to a balanced state. Both traditions also hold that the composition of the focal entities (humours or microbiomes) determines not just every bodily state but mental ones too. Causality for each is conceived teleologically, meaning that parts of bodies 'function for' the maintenance of the whole. And ultimately, each framework asserts that external environments are part of the balance equation, thereby situating the humours or microbiomes in a unified multilevel theory that purportedly explains the very nature of health and perhaps even humans. As well as describing the parallels between these systems, we seek to explain them: Should we think of these resemblances as due to direct historical continuity, or due to incidental convergence? Finally, we address the implications of these abundant similarities. Should medical microbiome researchers be concerned that their field currently shares conceptual parallels with Galenic medicine, or is it something to celebrate? Ultimately, this is an evaluation all medical microbiome researchers will need to make for the future of their field.

Introduction

Medically oriented microbiome research is a far more technology- and data-driven field than much microbial ecology and evolution. Theory and concepts have yet to be developed, in part because there is still so much room for descriptive discovery. The working concepts that have emerged in the microbiome literature, however, bear an uncanny resemblance to one of the most ancient traditions of Western medicine: humoural medicine as promulgated by the medical practitioner and philosopher Galen in the second century CE. In particular, both Galenic medicine and medical microbiome research rely heavily on notions of imbalance and balance, with undesirable unbalanced states called ‘dyskrasia’ and ‘dysbiosis’ respectively (1). Therapeutically, both systems aim at restoration to a balanced state. Both traditions also hold that the composition of the focal entities (humours or microbiomes) determines not just every bodily state but mental ones too. Causality for both is conceived teleologically, meaning that parts of bodies ‘function for’ the maintenance of the whole. And ultimately, each framework asserts that external environments are part of the balance equation, thereby situating the humours or microbiomes in a unified multilevel theory that purportedly explains the very nature of health and perhaps even humans.

Usually, Galenic medicine is thought to persist in contemporary medicine only in the form of alternative approaches. Our perspective will show, however, that Galenic concepts permeate current biomedical research on human microbiomes. As well as describing the parallels between these systems, we seek to explain them: Should we think of these resemblances as due to direct historical continuity, or due to incidental convergence? Finally, we address the implications of these abundant similarities. Should medical microbiome researchers be concerned that their field currently shares conceptual parallels with Galenic medicine, or is it something to celebrate? Ultimately, this is an evaluation all medical microbiome researchers will need to make for the future of their field.

Medical microbiome research

Although microbiome research is often discussed as if it were cohesive and unified, it actually covers a range of strategies and aims. We are using ‘microbiome’ generally to refer to the large-scale molecular investigation of microorganismal communities, many of which have yet to be cultured and examined by more focused methods. Although these communities are studied in multiple environmental settings (e.g., oceans, soils, atmospheres, buildings) much of the focus has been on the microbes that occupy hosts such as animals, especially humans. The vast majority of human microbiome research is concerned with how the microbiome affects human health, and what these interactions mean for the prevention, diagnosis and treatment of disease within a modern medical context.

There is probably no disease or illness or human condition that has not been linked to microbiome composition and function. All systems, organs and activities of the body have

been deemed to be directly and indirectly influenced by the microbiome, especially the gut microbiome. Brain function, mood, mind, personality and behaviour have been linked by study after study to microbiomes. While there may be questions about the pathways, proportionality, generalizability and reproducibility of these connections (e.g., 2, 3, 4), even the most hardened sceptic would not deny that there is something important about the associations between each human and their microbiome.

But how are these relationships cashed out theoretically and conceptually? Microbiome research has its origins in microbial ecology, which although discovery-driven does draw on ecological and evolutionary theory. But in human microbiome research, ecological theory has limited application (for exceptions, see 5, 6). Instead, a much more medically oriented vocabulary is in use, in which some key terms crop up consistently no matter the disease or health state under investigation.

'Dysbiosis' is one of the favourite terms in medical microbiome research (7). Although its meaning is vague, this very vagueness actually seems to ensure the term's ongoing popularity. Dysbiosis is usually taken to mean some sort of difference in microbiome composition that in at least one study, no matter how small, has been associated with a disease state. The implications are that this is a negative change that if reversed would lead to a better health outcome. Backing up this loose hypothesis is a cluster of other concepts that are thought to provide the relevant explanatory mechanisms. Dysbiosis, the putative cause of many diseases, is itself deemed to be the product of an imbalance in microbiome composition. Health, on the other hand, is the product of 'eubiosis' (also 'homeostasis') – the good state of the microbiome – which is brought about by a balanced composition. So ultimately, balance is the underlying explanation of microbiome and host health states.

Despite the fact that balance has proved immensely difficult to quantify or assess in any non-circular way (7), it is the conceptual lynchpin of what counts for a theory in medical microbiome research. And that is what brings us to a far more ancient tradition of medicine in which balance also played the central conceptual role.

Galenic medicine and the four humours

Galenic medicine is a medical philosophy based in part on the humoural theory of disease first described by Hippocratic physicians in the fifth century BCE (8; 9). In the second century CE, the Roman physician Galen elaborated this humoural theory into a sophisticated philosophical system of medicine that would dominate Western medicine into the nineteenth century. In spite of the often-abstruse minutiae of Galen's medical philosophy and its diverse permutations through history, the conceptual basics of this medical system have an intuitive appeal that is sometimes thought to persist in the background of present-day medicine (8).

Health and disease in Galenic medicine is standardly related to the mixture of four humoural fluids (or humours) thought to exist in every human body: phlegm, yellow bile, black bile, and blood (distinct from venal blood, which contained all four humours) (8). This humoural system was understood within Aristotle's philosophy of nature, in which the the natural world comprised primary elements (earth, water, air, fire). These form four combinations of contrary physical qualities (hot and cold, wet and dry). Galen integrated the four humours into his medical philosophy by associating them with these elemental qualities, which produced a conceptually satisfying system by granting all features of the natural world their place in a complex network of interdependent parts (Fig 1).

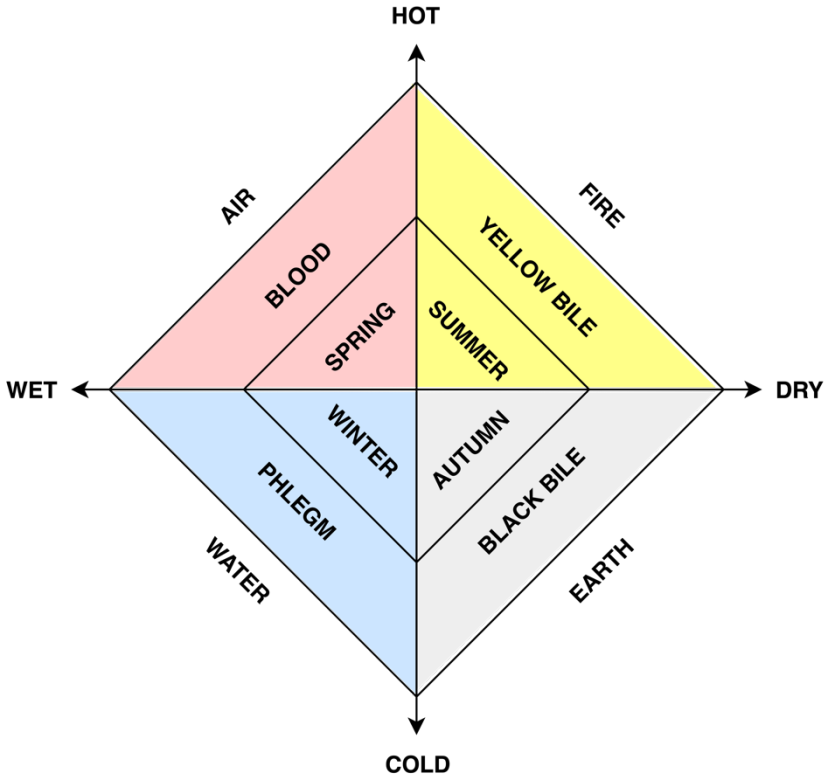

Figure 1:
A simple diagram depicting the oppositions of the four physical qualities and the elements, humours and seasons associated with their possible combinations in Galenic medicine. Some of the associations based on shared qualities may still seem intuitive, like the one between phlegm and wintry weather.

In Galenic medicine, each person was understood to possess their own individualized, natural balance of the four humours in unequal proportions, according to their governing elemental qualities (10). This unique mixture was referred to as their complexion or *krasis*, which was reflected in their physiognomy and behaviour. However, the composition of humours in the body constantly fluctuated in response to internal and external influences, which could easily result in humoural imbalance. While the right balance of humours constituted a healthy state in Galenic medicine, imbalance constituted a state of disease

(11). The goal of medicine was to obtain or maintain the proper balance (*eukrasia*) and to avoid or correct imbalance (*dyskrasia*) through a combination of prophylaxis and therapy.

Since the humours that determined health and illness were connected to change in the world at large, changes in lifestyle and environment became the focus of medical intervention. Rest, exercise and diet presented crucial opportunities to regulate the qualities that governed the humours. Dietetics became particularly significant, because of the presumption that the four humours were concocted from the contents of the stomach. Food was destined to become humoural fluid, and thus possessed considerable medical relevance in Galenic medicine.

The basics of this medical system were common-sensical enough to meet the needs of people who mostly addressed their medical issues at home. An individual's appearance and disposition could be understood through inferences about the four humours and their various mixtures in the body. As part of a world system, the humours helped fit the human body into nature by explaining how health and illness responded to lifestyle and environment. Challenging diseases could be made tractable by Galenic physicians, even if they had difficulties treating them. All these conceptual and practical features have strong echoes in contemporary microbiome research.

Parallels

As microbiome research has developed, several features shared with Galenic medical philosophy have become increasingly articulated in the scientific literature and its public dissemination.

Dyskrasia/Dysbiosis vs Eukrasia/Eubiosis: One of the most obvious resemblances between Galenic medicine and medical microbiome research is the terminology used to refer to healthy and diseased states. We find it unlikely that early microbiome research directly drew on the Greek terminology of Galenic medicine (see 7 for the historical background to 'dysbiosis'), but we do suggest that connections between these terms go far deeper conceptually.

Balance is without a doubt the central conceptual mechanism of both Galenic medical philosophy and microbiome research. It underpins diagnoses and treatments in both fields, and even the interpretation of the most basic data in microbiome research. Certainly, there are differences in how Galenic medicine and microbiome research deploy the concept of balance, especially when it comes to finer-grained details, but the echoes of the past in contemporary microbiome science are hard not to hear.

Theoretical features of treatment: Both systems describe proportions of focal entities or substances in the body that are highly dynamic but capable of being regulated to avoid pathological states of imbalance. Both traditions assume an ideal natural state of health that

is determined by these proportions. Indeed, in microbiome research, it is becoming standard to suggest there is an ancestral state of balance in human history, and that until we restore it, we are doomed to be unhealthy (12). For both systems, even though each person has a natural individualized balance of microbial or humoural proportions, there are nevertheless pathological proportions that affect everyone in predictable ways and this leads to the possibility of standardized treatments.

Practical features of treatment: Both systems emphasize the importance of diet, but for different reasons. Microbiologists consider the impact of diet on the composition and metabolic output of the microbiome, while Galenic physicians considered how the elemental qualities of food impact the resulting mixture of humoural fluids. And although both traditions share a diagnostic focus on excrement, Galenic medicine emphasized analysis of urine samples to gain insight into the state of the body as a whole. More generally, however, the tractable practices of both these systems enable domestic or 'DIY' medicine. Patients under a Galenic regimen could stock medicinal ingredients and make medicines at home; microbiome DIY-ers might try faecal transplantation or probiotics. But whatever the treatment, it is done with the idea that there are causal interventions that can be made in humours or microbiomes to bring about better states of health.

Causality: Both Galenic medicine and microbiome research go beyond straightforward cause-effect relationships. Microbiomes are frequently interpreted as if they function collectively for or against the health of their human hosts (13). This idea of 'functioning for' is usually understood as teleological, in that activities are carried out for the ongoing maintenance of the whole system, in this case the human and its microbiome. This same notion of function is also hard at work in Galenic medicine, which takes Aristotle's notion of 'final cause' (causation that has a goal) and interprets it medically (11, 14). It is not clear at all that it is legitimate to interpret microbiomes as 'functioning for' their human hosts (5), and even basic claims about microbiome causation of disease are problematic to justify with current methods (2, 15). But causal claims of every sort play a central role in extending both microbiome and humoural claims beyond bodies.

Holistic, unified theory: One outcome of understanding causality in a teleological way is thoroughgoing holism. In Galenic medicine, the causal interplay between humours in the body went beyond any skin barrier into the environment itself. That broader environment, while being influenced by bodily humours and human activities, also shaped the humours determining human health. Many early modern medical treatises posited a cosmology of mutual influence between seasons, heavenly bodies and humours (8, 9; Fig 1, Fig 2-A). As microbiome research extends its popular reach into the humanities literature and public spheres, it also has begun to encompass not just the bounded body of single humans, but also the environments that the human body and its microbes inhabit (e.g., 16, 17; Fig 2-B). In comparison to modern medicine, medical microbiome research and Galenic medicine aim to offer a much broader explanatory framework. Usually, scientists are sceptical of unifying theories like this, because they encompass anything and everything. But these unifying powers also give broad theories some of their popular and enduring appeal.

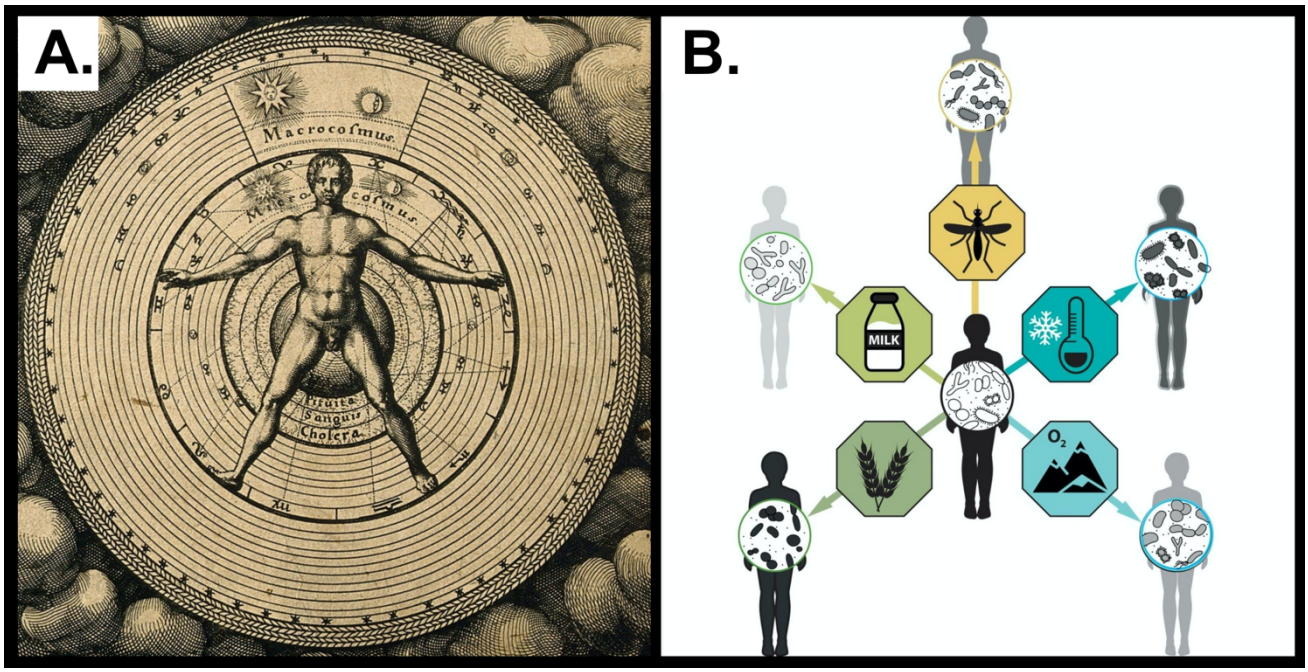

Figure 2:
A. A famous early modern example of the 'microcosm/macrocosm' analogy, depicting correspondences between the human body (microcosm) and the cosmos (macrocosm) that it mirrored (18). This image and the relations it depicts carry strong alchemical (and magical) influences, elaborating beyond elemental mixture alone to make sense of the body as fully integrated within the external world.
B. Just one example of a depiction of the interactions between microbiomes, hosts and the broader environment (19). We are not suggesting these causal links do not exist or that they are not important. Our point here is merely to show how microbiome accounts are expanding beyond individual bodies to capture much more global phenomena, in the same way that humoural theory did.

Explanations of the parallels

What might these parallels mean? How deep do they go and how have they come about? We see three possible explanations for the existence of these conceptual parallels: convergence, continuity, and commonality.

Convergence is the most obvious explanation. Galenic medicine, with its roots in Ancient Greek philosophy and medicine, formed in a particular historical context to serve a set of social goals. Its conceptual machinery provided a unified framework that took advantage of existing diagnostic and treatment technology. 1800 years later, microbiome research arose in a different historical and social context, and its medical application is based on modern technological capacities. It is thus more or less coincidence that these two very different

historical lines of inquiry share congruent conceptual frameworks. In evolutionary terms, the similarities are analogies not homologies.

Continuity is the explanation that is akin to a homology account of similar features: the two traditions share affinities because they are part of a historical continuum. While modern medicine readily accepts its historical debts to Galenic medicine, Galen's direct influence on contemporary practices is usually recognized only in alternative medicine. The continuity thesis, however, suggests that Galenic medicine persisted below the surface of modern medicine. Microbiome research would have to be understood as providing the favourable conditions for these outmoded yet persistent medical beliefs to flourish in the scientific mainstream.

Commonality is a more complicated explanation of the parallels, and might be compatible with both convergence and continuity. This type of explanation suggests that the similarities are not a direct continuation (from Galenic medicine to microbiome research) but that some common causes have produced comparable medical frameworks despite the vastly different contexts in which these medical systems developed. One commonality explanation, for example, would be that these systems adopted similar frameworks to make the challenges of medical research tractable and practical. Galenic medicine had a relative paucity of data and yet huge demands to make sense of human illness and find ways of intervening in it. Medical microbiome research, on the other hand, has a dire need to integrate vast amounts of complex data, with insufficient theory and tools to make sense of it. Given the datasets and social pressures that exist in microbiome research, a simple – even simplistic – conceptual framework that could make intuitive sense of overwhelming data would be very attractive.

The three theses are merely explanatory sketches. Making a case for any of them would require much closer analysis of the parallels, looking in particular for differences underneath the broad similarities. Doing so would require proper historical analysis that compared the contexts in which both sets of concepts arose. For now, we are merely raising these explanations as possibilities to be explored further.

Implications

Whatever the explanation, the main reason most scientists will be interested in these parallels is to understand what they mean for medical microbiome research. To put it far too simply, do similarities to Galenic medical philosophy have negative or positive implications for microbiome research?

One issue that might worry some researchers is that parallels between medical microbiome research and Galenic medicine create an unavoidable association with alternative medicine. For the majority of today’s biomedical researchers, making this connection is undesirable because of standard views that exclude alternative medicine from mainstream

medicine (e.g., 20). Consequently, there could easily be interpretations that medical microbiome research is dependent on outdated medical concepts (i.e., Galenic ones) that many scientists might be tempted to describe as self-evidently wrong or 'prescientific' (1).

Despite these negative implications, it is also possible to conceive of advantages to adopting a Galenic framework. For many centuries Galenic medicine was *the* major medical paradigm – able to diagnose, explain, and treat disease states within an empirically supported, theoretically unified paradigm. Historically, traditional medical philosophies have proven to be long-lived, easy to communicate to the public, and translatable to domestic medical practices, which modern medicine does not easily achieve. Given the conceptual development of today's microbiome research, future observers might even conclude that the adoption of a Galenic framework was a deliberate strategy that did in fact reap these very advantages.

Conclusions

It is undeniable that today's medical microbiome research shares significant conceptual features with an ancient medical philosophy, commonly thought of as outmoded and outside contemporary medicine. We suggest that these similarities raise some important questions for the future of microbiome research. In particular, it is worth thinking more about the significance of balance as an organising principle in medical microbiome research: how does it impact experimental design, interpretation of results, and translation of findings to application and the public sphere? Although we do not have the answers ourselves, we do believe that this whole topic requires detailed philosophical, historical and scientific study. We also suggest that microbiome researchers think about the implications of these parallels every time they invoke concepts such as balance and dysbiosis.

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