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1 **The gut microbiota: an amazing technicolour dream coat or the**
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The gut microbiota: an amazing technicolour dream coat or the emperor's new clothes?

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Something has been bugging me for some time—the gut microbiota! More precisely, the persistent hyperbole in mainstream research commentary keen to preach it seems that the gut microbiota control—well, lots of things! Previously forgivable as the hype of hope it has become for me, to twist the vernacular, gut-wrenching.

First, in the spirit of transparency, some confessions. I have entered the temple of the microbiome and have explored potential links between the gut microbiota and cardiorespiratory control in rodents (Lucking et al., 2018; O'Connor et al. 2019; O'Connor, Lucking, Cryan et al., 2020; O'Connor, Lucking, Bastiaanssen et al., 2020). More recently, we have a newfound interest in the gut-muscle axis (Lahiri et al., 2019) and have embarked on studies in a mouse model of muscular dystrophy (Marullo & O'Halloran, 2023). My university is home to a world-leading microbiome institute. Therefore, my growing malaise, a disbelief of sorts or disquiet at least, could be considered by some as hypocrisy or heresy, or both! I feel compelled however to play Thomas, declaring my doubts, which are grounded in a well spirited sense of scepticism. Research is not a faith-based enterprise after all. Importantly, however, I wish to remain constructively critical and well short of cynical, though at times it proves difficult.

Let's start with the obvious. There is no doubt that microbiome science is on to something. It has clearly been established that the bugs are not just along for the ride, and their capacity to produce metabolites directly relevant to host physiology lends credence to the suggestion we harbour an organ within an organ. Scientific enquiry has provided an evidence base to strongly enrich long-standing recognition of the importance of gut health for whole body health. Who now would deny the importance of the bi-directional interplay between host and microbiome? A wealth of studies has drawn focus to the importance of diet and a 'happy' microbiota signature for everything and anything you might care to do awake or asleep across the life cycle. We have learnt too, that the microbiota populations are different in disease states, but importantly that the gut environment is readily malleable, dynamic, indeed volatile, to the extent that gut microbiota signatures are essentially unique in everyone and indeed variable along the length of the intestine (The Integrative HMP (iHMP) Research Network Consortium, 2019; Fan et al., 2021; de Vos et al., 2022; Hou et al., 2022; Gao et al., 2024). Consequently,

it has proven difficult and may prove intractable to define a normal, healthy microbiota profile (Joos et al., 2024). I applaud this revelation by the field, but by inference a considerable brake should apply to overly enthusiastic interpretation of any state in which the microbiome is adjusted. In essence, we do not know the physiological consequences of an altered microbial signature, which even extends to circumstances in which there is an abundance of 'bad' bugs. The gut microbiome is a profoundly complex ecosystem. Therefore, changes in the microbiota (which in 'test' versus control groups should be considered almost inevitable) should be viewed cautiously and contextually. To my mind, these limitations should favour conservative judgement of outcomes unless a slew of additional *relevant* information is available. Yet, the field at large with some 30,000+ publications related to microbiome in 2024 alone (>16,000 related to gut microbiome) often behaves as though it is the wild west!

I enthusiastically acknowledge the many high quality, mechanistically focussed, evidence-based studies, mostly in animal models, that implicate disrupted microbial populations and/or the downstream microbially-derived metabolites with proposed or known delineated signalling axes and target receptors as relevant disease-modifying factors in the elaboration of several diseases. Moreover, it is impressive that interventional strategies that demonstrably reverse disrupted microbial populations or shape the microbiota in some way either by diet, or with various pre- and probiotic strategies can mitigate or even prevent the elaboration of one or more aspects of major disorders. Notably, there are so many of these studies that it is not practicable to cite them here, a point worth contemplating, for it is compelling. Intriguingly, and a factor that has very much shaped my own mostly arms-length interest in microbiota-related research, is the evidence from several important studies showing that faecal transplant from disease models (or patients) can manifest disease phenotypes in naïve recipient animals. That there is a faecal soup capable of driving outcomes such as hypertension, obesity, anxiety, depression and many more maladies is at once fascinating and deeply frightening! Some strong evidence too that a 'healthy' transplant can be efficacious in restoring order in some models of disease. However, even in high-impact studies appearing in high-impact journals, the devil is in the details.

So, what is the problem?

Some concerns have been raised recently. Multiple myths and misconceptions, prominently perpetuated in the literature have been flagged (Walker & Hoyles, 2023). Whereas these might be considered by some in the field as trivial or incidental misnomers, at worst a faux pas that should not distract from the central message, they do highlight a worrying point: mainstream science is perpetuating 'facts', without fact-checking. And the explosion of interest in all-things microbiome means it is increasingly difficult to separate good and bad science, fact from

fallacy, especially for the converted in the parish. The scale of the enterprise is extraordinary. Moreover, microbiome science has become intimately coupled with industry and the wellness movement such that research findings very often proliferate in various guises through mass media outlets where they are especially prone to exaggeration and where often outlandish claims are made. I acknowledge that much of that is beyond the control of authors (and is not unique to microbiome science), but the seed is often evidently planted by authors fond of colourful declarative conclusions that set a scene for majestic control of mind, mood and body by one or more microbial species, or all the more worryingly, that a disrupted microbiota is the de facto cause of distress, from A to Z.

A vast majority of studies contributing to this narrative are studies in animal models in which there is an association between a disease marker and an altered microbiota. Extrapolation of an explicit role for the microbiota from such a study construct is, quite frankly, not good enough! The microbiome revolution is partly propagated by presumably well-intentioned zealots spreading the gospel. The sea change has been impressive; a tsunami of influence. But we are drowning in this new religion. We need refuge in the safe harbours of empirical science. Yet, there is the rub. Many studies are inadvertently designed to ensure a winning outcome. The science provides the doctrine!

Consider, for example, a common approach employed as follows. Compare control and test groups, distinguished *a priori* in some way (e.g. genetic or induced model of disease). Step 1, compare a multitude of behaviours (some differences may already be known or strongly expected). Step 2, compare the microbiota signatures. Step 3, perform ancillary measures, let's say gene expression profiles (or to be fair perhaps more sophisticated approaches) in one or more brain areas demonstrably linked to the behaviours, but typically well short of interrogation of complex circuitry.

Each roll of the dice produces the opportunity to link a behavioural difference, with an altered signature, and a 'molecular mechanism' to explain the outcome. For a critique of this approach, one need not even be overtly critical of the design per se, but a conclusion from these studies that posits a direct role for the microbiota in mood, anxiety, depression and so on is a stretch, as the study design does not provide for a determination of causality. Yet, this a common template. Moreover, some authors have no concerns it seems when a follow up study, let's say an intervention, now reveals new (unexpected) differences. Further complexity (or perhaps that is better read as opportunity) emerges when young and old, male and female and other relevant groups are added to the mix. On the face of it, this appears to be inclusive, a better attempt to increase generalisability of the data. However, now, the sheer number of

observations guarantee the apparent win, which is of course a terrible loss, if accurate reproducible observation is the prize sought after.

The microbiota revolution is apt given the circular nature of the problem the field faces in interpreting outcomes. Chicken and egg conundrums are common. Interventional studies (particularly in animals) allow for more meaningful delineation of the effect of a disruption (or correction) of the microbiota signature on measures of interest. But commonly in disease models, the co-presentation of microbiota disruption and physiological dysfunction quickly provides for circular argument. Given the proclivity for dynamic change in the gut environment it is plausible, and indeed probably most likely, that any disorder we choose from the whole tragic panoply available to us will be characterised in part by altered lifestyle factors, including diet, which modulates the highly sensitive microbiome. It is entirely plausible that the microbiota signature is a barometer of host health, a useful biomarker. However, does it really surprise us that the microbiome is different in ageing, elite performance, social anxiety disorders, obesity, depression and so on? Would we be surprised to learn that the microbiota signatures differ in people from Genoa and Guadalajara? Or in you or me should we have occasion to travel from one place to the other! Is it adequate that health or performance measures that might differ in these populations can be confidently attributed to different microbial signatures based on correlations? At the very least, shouldn't researchers start with the most plausible considerations in every study, whether their own or work by others? If an argument to the contrary is to be made, shouldn't the burden of proof sit squarely on the shoulders of those who reasonably should be expected to demonstrate why a more obviously plausible premise can be overturned, discarded based upon the strength of the data? With upmost respect to the many fine researchers in the field who adequately address these concerns or at least acknowledge the limitations and act in some way bound by them, we are nevertheless awash with thousands of published research studies open to this basic criticism. Too often, barn door association studies conclude with 'the gut microbiota affect/control/cause XYZ'. Indeed, many studies declare with pomp and confidence this profound conclusion in the title, which then alas proves good enough for others to echo. In this way, we are fooled that there is consensus. We are fooled that the evidence is over-whelming. We are fooled that the emperor is colourfully clad. And the merry-go-round spins on and on.

Circular arguments are inescapable, and so it is tempting in our desire for order to attribute cause and effect. A flawed pattern that presents commonly in the field is as follows: 1) describe the co-presentation of microbial disruption and physiological dysfunction in the disease of the day (so far so good), 2) intervene with a microbial-directed strategy (no beef with that!), 3) effect change in the microbial populations (described conservatively or celebrated as a correction of a dysbiosis) and 4) provide evidence of mitigation or recovery of one or more

functions (a laudable outcome). The flaw is to establish a linear sequence of events for the reader, that microbial populations (sometimes with resolution to species and even strain) *control* the physiological process under examination, amenable to intervention by the directed strategy. The interpretation of studies often does not provide for an alternative reality. And there are many! Take for example, that it is possible that elevated blood pressure in a model of hypertension is mitigated to some extent by a microbial-directed strategy that elevates say, short-chain fatty acids, which are established modulators of several tissues at multiple sites relevant to the determination of blood pressure. Consider, however, that the positive intervention (which is an important observation and not to be dismissed) could be unrelated entirely to the mechanism *causing* hypertension but nevertheless mitigates it through a separate action. Such consideration provides for critic and celebrant. In this example, we might better conclude that microbial metabolites mitigate hypertension rather than the gut microbiota control blood pressure. Say what you mean, mean what you say!

I wish to emphasize that in these studies that one might be overtly critical of, there are very many interesting, nuanced observations that might well point to a role for microbial metabolites in shaping physiology or disease trajectory. However, a one-eyed view by authors can erroneously twist the tale. We must also acknowledge the obvious. In studies limited by their inherent design to interpretation of associations, correlations can be constructed and readily sold. But there remains the distinct possibility that there is no connection at all!

An additional chapter to the microbiome story appears to be glossed over by many. And yet, in some ways it is where the story begins. There is growing recognition of impaired epithelial barrier function as a common feature in a multitude of non-communicable diseases (Sun et al., 2024), drawing focus to a 'leaky gut' theory. A common denominator in the gut microbiome-disease axis might be systemic microinflammation. A disrupted microbiota signature as a cause or consequence of disease, may lead to gut inflammation and epithelial barrier dysfunction with resultant gut barrier breach. As such, altered gut health contributes to altered whole body health. Microinflammation is a plausible driver of physiological malaise (Sun et al., 2024) and it is reasonable to suggest it should be a starting point in attempts to delineate mechanisms contributing to dysfunction in models with known or suspected gut dysbiosis. A potential distraction from this mechanism arises for researchers, borne of an embarrassment of riches in opportunity afforded by the many potential avenues of fertile research, each in turn greatly facilitated by technological advances in deep sequencing of microbial genomes and an explosion of bioinformatic tools, that include AI approaches, that increasingly allow for complex computational approaches to tackle interesting questions. These are of course warranted. But it might also be helpful to start with the premise that a disease manifests a disruption to the microbiome, perturbing the host-microbe interface causing barrier disruption,

exacerbating the primary disease due to systemic inflammation. Deviation from this plausible narrative, which is testable, should carry with it a high standard of proof attainable by means of evidence that is strong and compelling.

The science, real science, of the microbiome is fascinating. It does not need to be dressed up! The field would benefit in the long-term from tempering of the rhetoric and exploration of mechanisms in a meaningful way, with scope to reveal and revel in the innumerable alternative realities. Scientific correspondence should make use of precise language to convey the message borne of the data. Alas, there is too much interest in the story. The microbial world within and our interplay with it is not straightforward or easy to comprehend. Why are so many scientists openly confident in the ‘evidence’ that a bug controls a particular physiological process? Causal evidence is often lacking. The bugs have no voice in the matter, so let the science do the talking! The microbes need not be in control of a process for us to leverage their capacity to modulate a process via metabolites. Let’s strive to be more exact in the language we use.

So, what to make of it all? Should I be in awe of the amazing technicolour dream coat? Or should I see the naked truth of the emperor’s new clothes? As ever, it need not be one or the other. For now, on many claims of a central contributory role for the gut microbiota in aspects of health and disease I am agnostic, keen for more evidence. In advice on health, an aphorism emerges declaring we should consider all things in moderation. Perhaps that also applies to the gut microbiota!

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References

de Vos WM, Herbert T., Van Hul M. & Cani P.D. (2022). Gut microbiome and health: mechanistic insights. *Gut* 71, 1020–1032.

Fan, Y., Pedersen, O. (2021). Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol* 19, 55–71.

Gao W, Lin W, Li Q, Chen W, Yin W, Zhu X, Gao S, Liu L, Li W, Wu D, Zhang G, Zhu R, Jiao N. (2024). Identification and validation of microbial biomarkers from cross-cohort datasets using xMarkerFinder. *Nat Protoc.* 2024 (9), 2803-2830.

240 Hou, K., Wu, ZX., Chen, XY. *et al.* (2022). Microbiota in health and diseases. *Sig Transduct*
241 *Target Ther* 7, 135.

242 Joos, R., Boucher, K., Lavelle, A. *et al.* Examining the healthy human microbiome
243 concept. *Nat Rev Microbiol* (2024).

244 Lahiri S, Kim H, Garcia-Perez I, Reza MM, Martin KA, Kundu P, Cox LM, Selkrig J, Posma
245 JM, Zhang H, Padmanabhan P, Moret C, Gulyás B, Blaser MJ, Auwerx J, Holmes E, Nicholson
246 J, Wahli W, Pettersson S. (2019). The gut microbiota influences skeletal muscle mass and
247 function in mice. *Sci Transl Med.* 11(502), ean5662.

248 Lucking EF, O'Connor KM, Strain CR, Fouhy F, Bastiaanssen TFS, Burns DP, Golubeva AV,
249 Stanton C, Clarke G, Cryan JF, O'Halloran KD. (2018). Chronic intermittent hypoxia disrupts
250 cardiorespiratory homeostasis and gut microbiota composition in adult male guinea-pigs.
251 *EBioMedicine.* 38, 191-205.

252 Marullo AL, O'Halloran KD. (2023). Microbes, metabolites and muscle: Is the gut-muscle axis
253 a plausible therapeutic target in Duchenne muscular dystrophy? *Exp Physiol.* 108(9), 1132-
254 1143.

255 O'Connor KM, Lucking EF, Golubeva AV, Strain CR, Fouhy F, Cenit MC, Dhaliwal P,
256 Bastiaanssen TFS, Burns DP, Stanton C, Clarke G, Cryan JF, O'Halloran KD. (2019).
257 Manipulation of gut microbiota blunts the ventilatory response to hypercapnia in adult rats.
258 *EBioMedicine.* 44, 618-638.

259 O'Connor KM, Lucking EF, Cryan JF, O'Halloran KD. (2020). Bugs, breathing and blood
260 pressure: microbiota-gut-brain axis signalling in cardiorespiratory control in health and
261 disease. *J Physiol.* 598(19), 4159-4179.

262 O'Connor KM, Lucking EF, Bastiaanssen TFS, Peterson VL, Crispie F, Cotter PD, Clarke G,
263 Cryan JF, O'Halloran KD. (2020). Prebiotic administration modulates gut microbiota and faecal
264 short-chain fatty acid concentrations but does not prevent chronic intermittent hypoxia-induced
265 apnoea and hypertension in adult rats. *EBioMedicine.* 59, 102968.

266 Sun N, Ogulur I, Mitamura Y, *et al.* (2024). The epithelial barrier theory and its associated
267 diseases. *Allergy.* 79, 3192-3237.

268 The Integrative HMP (iHMP) Research Network Consortium. The Integrative Human
269 Microbiome Project. *Nature* 569, 641–648 (2019).

270 Walker, A.W., Hoyles, L. (2023). Human microbiome myths and misconceptions. *Nat*
271 *Microbiol* 8, 1392–1396.