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History of medicine: Origin of the term microbiome and why it matters

Susan L. Prescott *

School of Paediatrics and Child Health, University of Western Australia and Princess Margaret Hospital for Children, P.O. Box D184, Princess Margaret Hospital, Perth, WA 6001, USA
In-FLAME Global Network, Worldwide Universities Network (WUN), USA

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ABSTRACT

Contemporary science writing suffers from errors in quotations and misattributions. Given the importance of the microbiome to virtually every branch of science and medicine, its early origins and historical references are vital. Regardless of technological applications – culture technique or next-generation metagenomics – accurate referencing is essential to the scientific pursuit of truth. Despite claims and inferences to the contrary, the rich history of the study of microbiota and the microbiome didn't begin in 2001; many lessons can be learned by closely examining the history of the gut-brain-microbiota connection, including the undervalued role of early pioneers in this field.

"Let food be thy medicine and medicine be thy food"

Who among us hasn't read the famous quote concerning the medicinal aspects of food within science writing and on the big screen at conferences? The oft-cited quote above is continuously attributed to Hippocrates within peer-reviewed writing. However, there isn't a shred of evidence that Hippocrates conveyed this message verbally or in writing. Moreover, all of the available evidence indicates that such a quote – conflating diet and medicines – was developed more recently, and in any case, would be completely at odds with Hippocratic thinking [1]. Since Hippocrates is revered in western culture, the quote is often oriented to a slant such that it is possible to forgo "medicines".

The factual origins of terms and phrases are important for a variety of reasons, including the ways in which they can be insinuated into culturally-determined science writing. Stating that an individual coined a term isn't a vague claim – it should stand up to scrutiny no less than the data presented in the Results Section of an original article. The science writer is informing the reader of facts; in the case of 'coining', the writer should be 100 percent sure that, indeed, person X was the first to use and/or formulate a word or phrase. Coining is completely distinct from defining or popularizing a term.

Such is the case within the microbiome zeitgeist. For example, it is continuously claimed that the term microbiome was 'coined' by Nobel laureate-microbiologist Joshua Lederberg in a 2001. This statement of coinage is presented as fact in 100 s of recent research papers, including those in journals devoted to pediatrics [2], allergy/immunology [3] and even in papers originating from the United States National Institutes of Health, Human Microbiome Project [4,5]. In an article purporting to set the record straight on microbiome terminology, it is even claimed that the term *microbiota* was defined for the first time by Lederberg in 2001 [6]. Remarkably, a 'History of Medicine' article in a recent *Annals of Internal Medicine* issue makes this same claim that Lederberg *coined* the term in 2001 [7].

Despite these claims, the evidence is crystal clear – Lederberg did not coin the term microbiome, nor did he define or coin the term microbiota. Indeed, microbiota is a basic microbiology term in common use for at least 50 years. For example, when germ-free and specific pathogen free animal models were incorporated into common laboratory practices in the 1960s, it was with the specific aim to determine the "*selected microbiota compatible with sustained health*" [8]; Lederberg didn't need to define microbiota, the word never even appeared once in his oft-cited 2001 article [9]. Prior to 2001, the term microbiome was also in use, mostly to infer a very small ecological niche incorporating plant and animal life. Using the search engine Google Books and holding the search to pre-2001 entries will reveal the flavor of usage. Most notably, one particular discussion of the microbiome – in 1988 – provided a specific definition that is directly in line with its current usage in microbiology:

"*A convenient ecological framework in which to examine biocontrol systems is that of the microbiome. This may be defined as a characteristic microbial community occupying a reasonably well*

* Address: School of Paediatrics and Child Health, University of Western Australia and Princess Margaret Hospital for Children, P.O. Box D184, Princess Margaret Hospital, Perth, WA 6001, USA.
E-mail address: susan.prescott@uwa.edu.au

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defined habitat which has distinct physio-chemical properties. The term thus not only refers to the microorganisms involved but also encompasses their theatre of activity." [10]

This history was brought to light by Alan C. Logan (who has written extensively on the history of microbiota and mental health [11–13]) and is discussed in further detail at the blog of noted microbiome expert, University of California Professor Jonathan A. Eisen [14]. Collections such as Google Books and Google Scholar allow for relatively simple ways to determine some of the early origins of terms and who said what, when. This is not a matter of semantics and cannot be confused with administrative referencing/citation errors that inevitably find their way through manuscript proofing stages; misquotes and misattributions are a plague in modern science writing, with 15–20% of articles containing major quotation errors [15,16].

It matters because, as described in reference to the Hippocrates non-quote above, the consequences can lead to 'scientific myth' [17]. At the extreme end this could influence policy and practice [1]. However, even at its most fundamental level, factual science referencing is a matter of ethics. Providing credit where credit is due. When an erroneous attribution is afforded to one researcher, especially a term or quotation in common parlance, the individual or group of individuals – the legitimate source – will remain in the scientific shadows [18].

The oversight of scientists Linda R. Hegstrand and colleague Roberta Jean Hine in the annals of the gut-brain axis, mental health and allergy, provides a clear example of why referencing matters. In 1986, the pair published a groundbreaking study wherein they demonstrated significant differences in hypothalamic histamine levels between germ-free and conventionally raised animals. Put simply, they proved that microbes influence brain chemistry [19]. Enormous implications; total citations to date = 3. The gut-brain-microbiota axis is a rich topic of conversation at the moment. Claims that the term 'microbiome' was coined in 2001 lead to inferences surrounding 'discovery' and by extension, obscure the wellspring of ideas and original findings. It's past time to fix this.

The contemporary reader might be unwittingly led to believe that a rich history in the study of microbiota didn't exist prior to 2001. Of course the cost reduction of high throughput sequencing technology and the application of proteomics, metabolomics, and epigenomics has propelled the microbiome revolution into a truly exciting era for pediatric allergy and immunology. These advances provide hope for prevention, and precise, personalized medical treatments. However, lack of factual referencing can obscure important and highly-relevant findings from the past. Young scientists may be unaware that Rene Dubos studied germ-free and specific-pathogen-free mice for over a decade, determining the interactions between microbiota and factors such as nutrition, stress, maternal care, housing conditions, social interactions and sanitation, on immune function and health over the life course [20].

As pointed out by psychiatrist Iago Galdston: "*The essential deficiencies in academic medical history derive from its commitment to the "great man, great discoveries view of medical history*". [21]. The erroneous claim that a Nobel laureate coined the term microbiome feeds into this historical commitment. Is there no legacy for the thoughtful definition of the microbiome by those less well-acclaimed? Hippocrates gets credited for saying things he didn't say, while Hegstrand and Hine remain unreferenced. Science is itself a compass oriented toward seeking truth. This direction-finding needle is compromised when scientific articles include rinse-and-repeat claims concerning coining of terms and the fountainheads of discovery. The Introduction/Background sections of all articles – reviews and original work – include choices of referencing. Those choices are a matter of ethics. And truth.

Conflict of interest

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