



## Letter to the Editor

# Reply to Silber: on discoveries in science

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I would like to thank Dr. Michael Silber for his thoughtful commentary [1] and for raising an important question about who discovered rapid eye movement (REM) sleep. Dr. Silber (1) expertly narrates the interesting backgrounds of Aserinsky and Kleitman and their studies of REM sleep [2, 3] in the 1950s, (2) discusses their work [2, 3] in the context of my translation and qualitative analysis [4] of the 1926 study [5], noting that Denisova and Figurin “delineate many of the characteristics of REM sleep” [1], and (3) applies several criteria to help judge which set of investigators might be considered the “discoverers” of the phenomenon we now call REM sleep. I concur that data in the 1926 study [5] is remarkable and I am pleased that my translation and qualitative analysis [4] comparing 1926 findings [5] to later work by Aserinsky and Kleitman [2, 3] adds a “deeper dimension to our understanding of the rich history of the complex way that sleep science and medicine have evolved” [1]. Dr. Silber suggests that Denisova and Figurin’s findings are only a “partial identification of a phenomenon” because a “broader understanding of the underlying mechanisms” of the phenomenon is necessary to be “credited with the discovery of REM sleep” [1].

As I argue, while a broader and mechanistic understanding of the phenomenon is critically important for scientific progress in a discipline, it is a mandate for future research and not a concomitant and necessary requirement at the time of the phenomenon’s discovery. For example, the term “autism” was coined by Eugen Bleuler in 1916 [6] while the cluster of symptoms was first systematically described by Leo Kanner in 1943 (“early infantile autism” [6]) and independently by Hans Asperger in 1944 (“autistic psychopathy” [6]). However, mechanistic studies of the pathophysiology of autism were not undertaken by Kanner or Asperger (or Bleuler). Indeed, neurobiological studies investigating the underlying brain basis of this condition are still ongoing and are conducted by many research groups worldwide. As another example, Gregor Mendel systematically investigated, in the 19th century, the dominant and recessive patterns of inheritance of a trait, deriving the rules of inheritance. However, the molecular structure of deoxyribose nucleic acid (DNA) responsible for encoding and transfer of genetic material was characterized much later in the 1950s by James Watson and Francis Crick, Maurice Wilkins, and Rosalind Franklin, on the basis of an X-ray crystallograph

[7–9]. Incidentally, when a genetic mutation is dominant- or recessive-acting, neuroscientists refer to the genetics underlying a brain disorder as Mendelian-type [10]. Discoveries in science can occur at different levels of inquiry.

In my reply, I outline precise criteria for judging an empirical finding as a novel phenomenon, and provide evidence from the 1926 paper—briefly comparing it against these criteria. I end by addressing specific points made by Dr. Silber. I reframe the question about who “discovered” REM sleep to one about who provided the first systematic description of eye movements appearing with increasing rapidity during the rapid breathing phase and recognized these findings as a new phenomenon.

Major scientific discoveries help us better understand nature and create a paradigm shift. Generating questions that are rigorously informed by prior research and testing them within a systematic framework allows observations to have predictive power. This approach can move the field forward with impact because eventually, some hypotheses will be rejected, and new theories will be built to accommodate new facts. Furthermore, consideration of the neurobiological processes that underlie phenomena is a critical element in scientific inquiry. It requires making initial assumptions about potential processes in order to build plausible theories or models that might account for observed phenomena in a causal manner.

The 1926 paper is distinguished by these necessary features: hypotheses carefully investigated within a systematic framework and rigorously informed by previous work, data acquired via quantitative and observational techniques in a well-characterized study population, and a compelling report of a new phenomenon, or more accurately, a set of phenomena. Denisova and Figurin reported horizontal and vertical eye movements of increased rapidity that were time-locked to periods of concomitant increases in body motility and respiration during sleep, and explored the influence of additional factors on these motility cycles. Denisova and Figurin *recognized* the importance and novelty of their finding. As the authors staked claim to a new phenomenon, they (perhaps modestly) acknowledged that there was no precedent in the previous literature as of 1926, including among earlier studies by German colleagues, relative to “the periodic phenomena during sleep in children described by us.”

Significantly, the authors *were* concerned with a deeper understanding of the processes underlying their observations, providing anatomical explanations for the cluster of activities observed during the rapid breathing phase. Denisova and Figurin appreciated the importance of follow-up mechanistic investigations that might confirm or rule out their proposed explanations—writing that it “will be shown in the future.”

The following sections address specific points made by Dr. Silber:

- (1) Dr. Silber writes that “the investigators identified the phenomenon only in infants” [1]. While Denisova and Figurin’s body of research focused on infancy and early childhood, they also included older subjects in the 1926 study. Indeed, they found “periodicity of the same type” [4, 5] in children older than 2 years of age, although the findings were not as clearly defined as in infants. In contrast, as they were unable to observe uninterrupted sleep in adults ( $N = 4$ ) greater than 3–4 hours, the “periodic phenomena in clear form were not seen” [4, 5]. This weaker finding may be due to the shorter length of the session in adults compared to infants (up to 6 hours). Nevertheless, with new questions arising for adult sleep cycles, the 1926 study highlights the fundamentally iterative nature of scientific inquiry and scientific progress.
- (2) Dr. Silber notes that they “did not have EEG or EOG available” [1]. Availability of more advanced techniques per se including electroencephalography (EEG)/electrooculography (EOG) would not allow one to “discover” a phenomenon, unless one has a theory and testable predictions informed by empirical knowledge—here, that different sleep states do exist. In turn, such knowledge would compel the use of a specific tool (e.g. EEG/EOG) to confirm or rule out the presence of eye movements and to characterize sleep states according to the different types of neural oscillations. An absence of a more advanced technique does not detract from the scientific basis of an original discovery.
- (3) Dr. Silber mentions that Denisova and Figurin “did not identify crucial relationship to dreaming” [1]. However, a well-designed, rigorously conducted empirical study addresses a well-defined set of questions (i.e. it need not consider all possible hypotheses), although it may lead to new questions for future testing. Moreover, the link between eye movements during sleep and dreaming has been made as early as 1892 by Ladd, a professor of mental and moral philosophy at Yale, using introspection method [11], and as such, this association is not novel per se.
- (4) Dr. Silber states that “they did not understand physiologic processes underlying their observations” [1]. When reporting a novel finding, researchers might discuss an underlying mechanism in the context of prior knowledge and published literature. When explaining potential neurobiological basis for the association between the increased rapidity in breathing, eye motility, and general movements during the rapid breathing phase, Denisova and Figurin write: “reticular formation (in which so-called breathing centers are located), is linked via the dorsal longitudinal fasciculus with the centers of eye-movement muscles, as well as linked with nucleus n. facialis” [4, 5]. It is not obligatory for a given empirical study both to report a new phenomenon and investigate its underlying mechanism(s).
- (5) Dr. Silber notes that “there is no evidence that they pursued that research further” [1]. As there are many untranslated

articles and monographs, and more unpublished studies by Denisova and Figurin, it is possible that these investigators were involved in further studies on this topic. However, whether they or other researchers undertook further studies bears little weight on the fact that a completely new phenomenon was identified in 1926.

Two additional elements in Dr. Silber’s letter are important to clarify; both pertain to the 1953 study [2]. First, Dr. Silber writes that one of the reasons that Aserinsky and Kleitman do not cite the 1926 paper [5] in their 1953 adult account of REM sleep [2] is “possibly because they were unaware of it at that time” [1]. Yet, at least one of the authors, Kleitman, was aware of the Denisova and Figurin study as early as 1939, citing the work and its 50-minute cycles in the first edition of his book *Sleep and Wakefulness* [12].

Second, Dr. Silber notes [1] that Aserinsky and Kleitman set out to study “rapid, jerky” [2] eye movements, in contrast to the previously detected “slow” [2] eye movements. Yet, these 1953 quotes [2] reveal a lack of rigor in the prior literature supporting the scientific rationale of their study. A crucial point is how in 1926 Denisova and Figurin describe the qualitative nature of movements observed during the rapid breathing phase: as “concentrated” and with “increases in rapidity and movements of eyelids.” In fact, Denisova and Figurin [5] further distinguish these movements from the slow, uncoordinated eye movements during sleep detected by earlier researchers [13] in Germany in the 1870s, and which Denisova and Figurin label as an example of “improper” periodicity [4, 5].

To conclude, when considered against rigorous criteria necessary to assert that an impactful breakthrough has been made in empirical research, Denisova and Figurin’s 1926 data represent a discovery of a phenomenon currently termed REM sleep.

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