PERSPECTIVE

David Agus (left) and Murray Gell-Mann

Meeting of minds

David Agus and Murray Gell-Mann show that the élites of physics and medicine can spur each other to fresh insights.

When cancer researcher and physician David Agus met particle physicist Murray Gell-Mann in 2009, they soon discovered that they occupied different worlds. Agus says their interaction showed him that “borrowing from the world of physics could help my field in unimaginable ways” and that their interaction has “shifted not only how I work and approach medicine, but also how I ask questions, how I solve problems, and how I do science”. *What follows is a conversation between the biologist and the physicist about an issue that may be blocking progress in cancer research.*

Gell-Mann: As a physicist, I wonder why it is that biology and medicine seem to have so few new theories.

Agus: Unlike physics, biology and medicine are reductionist: we first look for an experiment to answer a question, then we conduct the experiment, analyse the results, and try to find a way to explain it. We'll ask: what happens when I activate this particular receptor on that cell? But the experimental results do not always reflect what goes on in a complex human system. Cells are part of a large, intricate network, much of which we're still trying to decipher. The practice of looking at each scale — the cell, the organ, the disease and the organism, for example — and understanding how each fits into a multi-scale model is not done often enough in medicine.

Gell-Mann: Yes, and we should be encouraging speculative conjectures. In physics, we postulated the existence of quarks as fundamental constituents of particles such as the proton and neutron. Quarks have some unusual properties that make them hard to accept in theory — for example, they are permanently bound inside the neutron, proton, and so on, and cannot escape. But without them, the system of elementary particles doesn't make sense. The quark idea turned out to be correct. Is it possible to publish such broad theories in medical journals today?

Agus: Unfortunately, the literature is filled with individual conclusions — and not that many theories that aim to tie these conclusions together. Why do you think theorizing happens more in physics than in biology or in medicine?

Gell-Mann: Physics is a lot simpler. I used to wonder how close we were to a real theory of the elementary particles and their strong, weak and electromagnetic interactions. Some of us were studying symmetry properties of those particles and interactions, giving rise to simple predictions that could be verified. But the magic of ‘gauge field theory’ led us from symmetries to an actual dynamical theory, the standard model, which describes the situation in detail. It is very rare for that sort of thing to happen in biology. Deciphering the genetic code is one of the few examples.

Agus: The genetic code accounted for the existence of DNA base pairs, which led to the discovery of the molecular structure that represents the genetic code. But even if I know your DNA, I cannot use

it to determine what is going in your body at a particular moment. Similarly, I can scan your brain but it won't tell me how smart you are.

Gell-Mann: We don't even know enough about the rest of the DNA — the non-coding DNA that seems to play an important role in regulating gene expression.

Agus: Right. Along the same lines, the first molecular characterization of the human microbiome has recently been described in detail. Our body's microbial communities fulfil an important dimension in regulating what is going on at any one time in the human organism.

Gell-Mann: I have heard you refer to the microbiome when we discuss why people in the Far East don't have the same incidence of prostate cancer as those in the West. But if those same people move somewhere else, say to the United States, the rate slowly goes up towards a value near what you would find normal in their new home.

Agus: Yet a real experiment to show this would require thousands of people and decades of time. So instead, what if we make a model and the question becomes: can you look at all the available data, and do they fit the proposed model?

Gell-Mann: Can the microbiome provide the simplest explanation for the variation? Can that idea be tested?

Agus: It certainly could be an explanation. But back to the bigger picture: why is this conversation not happening in every biologist's laboratory? Why is this not the common way we are studying diseases, including cancer?

Gell-Mann: It should be. We need to develop a new generation of scientists that take observations like these and bring them together by formulating a theory. We also need policies that encourage the publication of such theories. In addition, I think we would do well to pay more attention to outliers. They're generally

neglected because it is easy to look at common cases and figure that someday, someone will explain away those pesky outliers. Looking at outliers is tiring but important.

Agus: But imagine what focusing on them could do. Suppose I treat 100 patients with cancer and only one-third of them respond well to treatment, yet in one fortunate individual the disease vanishes altogether. There's an important clue in that outlier — the single anomaly that escapes death. Studying such outliers can provide an invaluable foundation for broad new understandings. To learn new ways of understanding the human system, we must use simplified descriptions of our observations and develop theories that help us improve health care. ■

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