

“The evidence speaks for itself,” or so many people say. That would contribute to an image of science as yielding unambiguous certainty. Once observations are made and the data collected, the conclusions unambiguously follow.

But should we accept this common belief, this Sacred Bovine, uncritically? For example, data are inert. They do not “speak.” People speak. In addition, people often disagree about the “facts,” even when they have observed the same thing. They conflict about how to *interpret* the evidence. Personal context matters. If science depends on something beyond just the evidence itself, then that exposes an important component of understanding for making any informed decision that relies on scientific claims.

Consider the case of Archibald Garrod and the discovery of inborn errors of metabolism (Gabel & Allchin, 2017). Garrod was a physician working in London in the 1890s. Imagine his surprise when he encountered a patient with *red* urine! What did that mean? Garrod had a background in chemistry, so he interpreted it as a chemical indicator. Could it help him decipher the nature of the patient’s nervous disorder, known as chorea? He identified the pigment as hematorporphyrin. Ultimately, however, he found that it was not related to the disease.

But alert now to the color of urine, his attention was drawn to another patient a few years later whose urine was *black*. The condition, called alkaptonuria, was already documented—as early as 1822. The black color had been traced biochemically to the presence of homogentisic acid, which oxidizes in air or alkaline solutions and changes color. The compound’s presence was apparently the result of a disruption in the breakdown of the familiar amino acid, tyrosine.

Alkaptonuria seemed not to harm the person’s health. At the same time, no underlying cause was known. One researcher, during the early years of germ theory, had suggested that it was due to a bacterium. But Garrod knew personally of patients with the condition their whole lives. It was congenital and lifelong. How could it be just a temporary infection? So, with his particular experience, Garrod began to think of the condition as inborn, reflecting an alternative body metabolism.

Then Garrod encountered a family with several children with alkaptonuria. The mother was having another child soon. Primed with the new idea, Garrod had the nurses monitor the diapers. A few days after birth the telltale black stains appeared. The disease thus seemed *genetic*. Garrod found many other cases of siblings sharing the condition. In the same way, he knew, many families showed

high frequencies of rheumatoid arthritis. So, he concluded further, the unique body chemistry of the condition must be inherited.

As Garrod collected more information about cases from doctors in Europe and the United States, he was now able to analyze many pedigrees. In many cases, cousins had married. Not only did the condition seem heritable, it was also more frequent due to *consanguinity*.

As Garrod’s work in hospitals continued, other biologists were rediscovering the work of Gregor Mendel, marveling at the consistently predictable ratios of some inherited traits. In England, Mendel’s principles were championed by William Bateson, who eventually learned of Garrod’s results. They corresponded and became friends. With his special Mendelian perspective, Bateson saw something else in Garrod’s results. Alkaptonuria was not only genetic. It seemed due to a recessive allele, which recombined when cousins married. Bateson commented:

Now there may be other accounts possible, but we note that the mating of first cousins gives exactly the conditions most likely to enable a rare, and usually recessive, character to show itself. If the bearers of such a gamete mate with individuals not bearing it the character will hardly ever be seen; but first cousins will frequently be the bearers of similar gametes, which may in such unions meet each other and thus lead to the manifestation of the peculiar recessive characters in the zygote. (quoted in Garrod, 1902, p. 1618)

Dramatically, alkaptonuria was the first human trait known to exhibit Mendelian patterns, which Bateson announced in 1901.

Connecting alkaptonuria to Mendelism was an opportunity to appreciate the link between genes and their biochemical expression in cell metabolism. Indeed, Bateson had also studied Mendel’s traits in peas. He learned that wrinkled versus smooth seeds (the outwardly visible traits) correlated to biochemical features: varied starch content and the size of starch granules in the cells of the seeds. Genes and Mendelian traits were intimately related through cell biochemistry.

But Bateson did not stress the significance of this view of gene action, so vivid to us now. Rather, he became embroiled in controversies over Mendelism and whether it could fully describe inheritance. Other biologists looked at traits across whole populations and were impressed by continuously variable traits. For them, discrete ratios and simple either-or factors seemed far too simplistic. For the critics, the plain facts spoke very differently. So, historically, geneticists did not at this time develop a potentially transformative

understanding of the role of specific biochemical reactions in gene expression, illustrated so vividly in Garrod's case of alkaptonuria.

Garrod, for his part, soon drifted away from debates about Mendelism. The concepts of genes were too vague to help him in treating his patients. His passion instead was understanding how, from a medical perspective, each person expressed his or her own chemical individuality. Today, this awareness has fueled the rapidly growing practice of personalized medicine.

Garrod went on to document the role of chemical factors in other genetic conditions. He addressed albinism, whose hereditary nature was already widely accepted. He underscored that the striking white hair, pale untinted skin and pink eyes—so different from the general population—had a very simple biochemical basis. Melanin was missing, of course. But the absence of pigment, Garrod now argued further, resulted from the “lack of a specific intra-cellular enzyme” that produced the pigment from precursor molecules. Moreover, that enzymatic anomaly was inherited.

Garrod also discussed cystonuria. In some rare cases, individuals deposit urine with hexagonal crystals of cystine. Sometimes the resulting stones can be life-threatening. Cystine, of course, is part of the body's normal chemistry. But ordinarily it is not excreted; its sulfur is usually eliminated in other forms. Garrod reasoned that cystonurics (like alkaptonurics) lacked a specific metabolic step and thus accumulated cystine in abnormally high amounts.

As the years passed, Garrod added pentosuria, hematuria, congenita, and congenital steatorrhea to his list of sample cases. Biochemical differences, he proposed, probably underlie other familiar hereditary diseases, such as diabetes, gout, and obesity.

Garrod profiled the common theme in all these conditions. Each exhibited a deficit of a specific biochemical reaction in the cell: “the most probable cause is the congenital lack of some particular enzyme, in the absence of which a step is missed, and some normal metabolic change fails to be brought about” (1923, p. 16). Garrod called them “inborn errors of metabolism.” In the original case of alkaptonuria, “when, for any reason, the ordinary paths are blocked, normal intermediate products are excreted without further change” (p. 6). As a result, through the chemical analysis of urine, one could observe indirectly the working of the body's cells. Garrod had not observed anything previously unknown. He did, however, help the evidence “speak.” It was a remarkable discovery.

Garrod also acknowledged that while all these conditions were extremely rare, they could nonetheless indicate something fundamental about the human body. Namely, the visible traits, such as albinism, had a biochemical basis that determines the individual's unique character. Each successive step in the build up and break down of cellular molecules seemed “the work of special enzymes set apart for each particular purpose” (1909, p. 6). The disease state is the clue to understanding the structure and function of chemical pathways in healthy bodies. Further, one could extend this understanding to externally visible traits, such as eye or hair color, blood types, personal dietary reactions, and responses to certain drugs. The study of a few diseases provided a window into how the body works more generally. Ironically, because Garrod focused on rare diseases and offered no clinical remedies, physicians largely disregarded his profound insights linking genetics and biochemistry. Geneticists, too, hardly gave them notice, because they were narrowly focused on hereditary ratios, chromosomes, and the chemical nature of the genetic material.

Decades later, the conceptual landscape had changed. In 1958, George Beadle and Edward Tatum received a Nobel Prize for their study linking genetic mutations in bread mold to the inactivation of specific enzymes. The award credited “their discovery that genes act by regulating definite chemical events.” The principle has since become known popularly as “one gene, one enzyme”—just what Garrod had claimed earlier. In accepting the award, Beadle referred to Garrod's work:

In this long, roundabout way, first in *Drosophila* and then in *Neurospora*, we had rediscovered what Garrod had seen so clearly so many years before. By now we knew of his work and were aware that we had added little if anything new in principle. . . . We were able to demonstrate that what Garrod had shown for a few genes and a few chemical reactions in man was true for many genes and many reactions in *Neurospora*.

Beadle reflected further on the reason for the neglect:

Biochemists . . . , especially medical biochemists, knew of Garrod's inborn errors of metabolism and no doubt appreciated them in the biochemical sense and as diseases; but the biological world was inadequately prepared to appreciate fully the significance of his investigations and his thinking. Geneticists, it should be said, tended to be preoccupied mainly with the mechanisms by which genetic material is transmitted from one generation to the next. (Beadle, 1958, pp. 596, 598)

In Garrod's case, the evidence had not spoken for itself to everyone. Understanding its meaning required appreciating other concepts. Context mattered.

Molecular biologist Gunther Stent once asked whether a scientific discovery could be “premature.” Sometimes we say an idea is “ahead of its time.” For Stent, that indicated that a concept so clearly understood by one scientist, could not be easily connected to other commonly accepted ideas. For example, Gregor Mendel's work on genetics was published in 1865, but was not regarded as foundational until 1900. Why not? During that interval, other discoveries opened the way to give particular significance to Mendel's modest results. His claims were not rejected originally based on willful ignorance or prejudice (as some assert), but because at that time they had no context. Science relies in part on the integration of concepts. Garrod's case, too, seems to reflect that same problem, of theoretical connectedness (Motulsky, 2002). All the key evidence was available in 1901. Did the evidence speak for itself? No. Bateson did not seem to fully appreciate the biochemistry; or Garrod, the genetics; or physicians, the theoretical scope. Again, for the “plain” evidence to be meaningful, it needs proper context.

In modern society, we often encounter scientific claims relevant to public policy or personal choices. Advocates of one position or product often present a fragment of evidence and portray their conclusion as, accordingly, unassailable. “The evidence speaks for itself,” they say. But the well-informed citizen or consumer might know, by contrast, that evidence is always interpreted, and wonder how context has shaped any particular conclusion.

Teachers may find an interactive classroom inquiry activity on the case of Archibald Garrod & Inborn Errors of Metabolism online at: <http://shippeducation.net/modules/biol/garrod.htm>

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