Archibald Garrod & the Black Urine Disease
TEACHING NOTES

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Overview

This case study focuses on Archibald Garrod and his identification of several "inborn errors of metabolism," which linked Mendelian factors to physiological chemistry at the turn of the 20th century. Nobel Prize winner George Beadle later heralded Garrod's work as an early expression of the "one gene, one enzyme" concept. The case begins with Garrod's analysis of patients with alkaptonuria, whose urine turns black. This was the first human trait recognized as exhibiting Mendelian inheritance patterns. Yet Garrod himself remained aloof from the debates that followed the rediscovery of Mendel's work, and his subsequent work was largely unappreciated by geneticists for several decades. Major nature of science elements include:

- the nature of unknowns (and the border between the known and the unknown)
- evidence and alternative explanations
- theoretical contexts in interpreting evidence
- professional responsibilities of scientists
- the role of persuasion
- conceptual change

THINK Exercises

The primary purpose of these questions is for students to develop scientific thinking skills and to reflect explicitly on the nature of science. The questions are open ended, and the notes here are only guides about the possible diversity of responses. In many cases, there is actual history as a benchmark (which can be shared after the students' own work), but by no means shoudl the history indicate an exclusively "correct" answer. Accordingly, avoid overt clues or "fishing" for answers, implying that a particular response is expected or considered "more right."

The case study should illustrate the blind process of science-in-the-making. To help promote thinking skills, the teacher should encourage (and reward) thoughtful responses, well articulated reasoning, and respectful dialogue among students with different ideas or perspectives.

Where the case study here echoes NOS features students have encountered in other case studies, the relationships should be noted and perhaps contribute to deeper discussion. This form of repetition and integration with prior knowledge significantly deepens the NOS lessons.

THINK (1): Given this clue, how would you approach interpreting or treating this [red urine] disease?

> This case illustrates the conundrum of exploring the unknown, and sometimes even framing the appropriate problem. How can you know *how* to look specifically for something, if you do not yet know *what* it is that you are looking

for? Genuine discovery is always somewhat blind.

Here, is the problem the color itself, or is the color an indicator of something else (a view highlighted by Garrod's background)? Is the *chemical* that causes the color the likely problem (toxin?) or is it a byproduct of another process (for example, the waste product of an infectious agent)? The color may make it easier to extract and isolate the disease compound, but one must still identify it and relate it to some body process related to the disease.

Without explicit connections, trial and error seems inevitable. Sometimes, one must hope to notice something that looks familiar, or wait for an unplanned event to find a connection to something already known. Other times, search can be more deliberate. So open-ended imagination can play an important role in scientific discovery. But should one follow just the first hypothesis? Or should one delve futher and consider multiple possible hypotheses simultaneously? A surplus of hypotheses can sometimes be helpful in suggesting the most relevant information to collect. Here, search can be fostered by considering a variety of possibilities — for example, might the red compound in the urine indicate a specific physiological, biochemical, genetic, nutritional, immunological, or environmental cause?

THINK (2): Describe how the biochemical finding might help in investigating the cause of alkaptonuria.

As in the previous case (through Garrod's special perspective), although the color itself may not be important, it can indicate the presence of an unusual compound. One can try to isolate and identify the black chemical, then trace it back (again, using Garrod's chemical orientation) to chemical processes within the body. Again, one might need a variety of explicit hypotheses. Note that The lack of explicit clues is a typical problem for addressing any new disease.

(This question allos one to review and reinforce the discussion from THINK 1.)

THINK (3): What evidence would help support or rule out the Woklow and Baumann hypothesis on microorganisms? What evidence would help Garrod show that alkaptonuria is due instead to a congenital chemical anomaly? If possible, identify other alternative explanations for alkaptonuria that should be considered.

In the mid-1880s microbiologist Robert Koch presented several postulates for determining the microbial cause of any disease. That might involve testing injections of blood into other organisms (to see if they too get the same disease). One should also be able to culture, and perhaps observe, the disease agent. Confirmation might involve visual microscopic scanning of blood or tissue samples, especially aided by various stains.

A congenital cause would presumably be present and observable from birth. So, interiewing patients and their families might provide clues. Looking for a pattern across many patients would involve (in an era before massive data collection and storage) gathering information from numerous cases, with numerous physicians in numerous places. A congenital cause might *also* be hereditary, and that would involve examining the incidence of the disease among siblings and in whole families, and generating pedigree charts.

Other possible explanations (as above) might include diet or nutrition, anatomical injuries, parasites, or environmental exposure to certain chemicals or other factors.

In each case, the key challenge is to find evidence unique to that cause that would not be found if other causes were working. Because there are alternative explanations, one is looking for evidence that not only confirms one hypothesis, but that also helps rule out (or disconfirm) other possible hypotheses—although this is not always possible.

THINK (4): In what ways does this new data about consanguinity provide significant information beyond the table of siblings in the same family?

Individuals in the same family tend to experience the same environment also. So it can be difficult in such cases to distinguish genetic from environmental factors. Pedigrees and information about earlier generations exhibit critical additional information about the genetic, or hereditary, dimension. Tracing genetics can be especially challenging when parents do not exhibit a condition and thus it is hard to establish a direct link from several siblings to one or both parent(s), rather than to some other shared familial factor. Demonstrated cases of intermarriage by cousins raises the strong possibility of recombination of genes that are unexpressed in parents (see also THINK 5). A connection through multiple generations is further evidence for a genetic, not just a congenital, cause. Here, additional evidence does not merely confirm earlier ideas. It narrows the possible list of explanations.

THINK (5): Explain how Bateson might interpret the evidence of siblings and consanguinous families with alkaptonuria as fitting Mendelian patterns. What kinds of proportions, or ratios, would he expect among offspring?

For Bateson, this could be explained by recessive alleles recombining (as expressed in the quote that follows). One could discuss recombination according to many possible schemes fo heredity, but the Mendelian pattern would be very definite about expecting 3:1 ratios (or 1/4 of children) from two parents who were carriers of a single, unexpressed alkaptonuria allele.

THINK (6): As Bateson, how might you plan to capitalize on Garrod's findings? As Garrod, how might you plan to capitalize on Bateson's work on Mendelian genetics?

The key element for student reflections here is higlighting the role of the social interaction of scientists, especially those with differing theoretical perspectives. The modest interdisciplinary connection in this instance could potentially open new trajectories for each. Bateson could begin to explore more deeply the biochemical dimension of genes (as he did for starch in pea seeds). That might lead him more deeply into the chemical and cellular nature of "traits," mostly viewed in physical terms (eye, seed or hair color; or distinctive size or morphology). This would help to define more clearly what is meant by a "trait" and its corresponding gene.

Garrod, for his part, could expand his study of chemical anomalies to the genetic level, perhaps calculating telltale ratios for the cases of biochemical diseases he already suspects are genetic (such as gout, obesity and diabetes). More sensitive to the possibilities, he (or others) might find more biochemical anomalies with genetic foundations, and reveal more how physiology is reduced to biochemical reactions as units, and then to genes.

All of this relies, of course, on a desire to cross such boundaries and take advantage of such theoretical intersections. As the narrative shows, commitment to existing theoretical orientations seemed to play a very important role in discouraging innovative approaches.

THINK (7): Is Garrod justified in avoiding the debate or should he take an active role in it? Does he have a professional responsibility to participate? What is the consequence of participating or not participating?

> This question introduces considerations about professional ethics and the responsibility of research scientists. Does making a discovery carry with it the responsibility of sharing that new knowledge? The question is more poignent when knowledge has important consequences, especially for public policy. In some cases, others may be aware of the claims, but fail to appreciate their significance or believe the evidence. (Also see THINK 9 on the problem of persuasion.) These issues are hard to resolve, but a discussion can highlight the role of scientists as members of a profession, with certain responsibilities toward others.

THINK (8): Garrod emphasized biochemical individuality, with virtually no discussion of genetics. What do his findings imply in terms of the nature of genetic traits or genes?

> This is the opportunity for students to conslidate their understanding of an inborn error of metabolism — linking (1) genes to (2) enzymatic reactions to (3) cellular processes and ultimately to (4) organismal physiology and other visible traits. Students might consider how traits that they know to be genetic might be expressed in terms of biochemistry or enzymatic reactions.
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> The students' abilities to make these connections will help deepen their understanding of the historical disregard of Garrod's ideas (THINK 10).

THINK (9): What might you do to increase the chances of a more positive or active reception to the ideas?

> Note, as a general principle of the nature of science, that science involves not just assembling evidence and making conslusions on one's own. Science is a social enterprise that involves communication, argumentation, and persuasion of peers.
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> Garrod published large books. But perhaps smaller, more numerous and more widely distributed articles might have reached a wider audience? We do not know what Garrod did in terms of personal communications or correspondence, but this is another important vehicle of conveying results to others.
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> Garrod also faced an additional challenge here of bridging divergent theoretical perspectives. Contrary to popular expressions, the evidence does not speak for itself. Effective communication involves an effort to "translate," or re-contextualize conclusions in terms that are significant or meaningful to other audiences. Thus, for geneticists, Garrod needed to underscore the role of genes, as in the case of alkaptonuria, to show that his information was relevant to *their* interests. For physicians, Garrod needed to draw out the medical and clinical implications more fully.

THINK (10): What would it mean to say that Garrod's work was "ahead of its time"? How should one interpret the similarity between Garrod's early work and Beadle and Tatum's later prize-winning work?

> Molecular biologist Gunther Stent has claimed that certain scientific discoveries are "premature," in that they cannot be connected by ordinary reasoning to widely accepted concepts of the day. Garrod seems to fit that characterization in part, although Bateson was certainly able to appreciate the basic reasoning. In retrospect, we can see that the foundational concepts that underly understanding and appreciating Garrod's conclusions

were present among his contemporaries. However, the predominat trends of research and thinking led in other directions, making Garrod's claims seem far less than central than they became later. Many discoveries do not just add to our knowledge. They transform our perspectives, and in the process disrupt older perspectives. Concepts needs to be reorganized in a new gestalt. Cognitively, that switch can be very difficult. Beadle was well justified in seeing, in retrospect, his own conclusions mirrored in Garrod's earlier work. But the intervening time has also seen a large shift in theoretical perspectives that made them easier to see.

THINK (Review): What does the case of Archibald Garrod and the black urine disease indicate about the following aspects of how science works:

- **the nature of unknowns** (and the border between the known and the unknown) (THINK 1, 2)
  In retrospect, in particular, it seems easy to suggest where scientists *should* have looked for answers. But that relies on information that was not yet available at the time. This inderscores the blindness of "science-in-the-making," so different from the finished version of science that is found in textbooks.

- **evidence and alternative explanations** (THINK 3, 4)
  Evidence may agree with multiple explanations — microbial vs. congenital; congenital vs. hereditary; hereditary vs. Mendelian. Thus, confirmatory evidence alone is not enough. One must look for evidence that helps one discriminate between alternative explanations.

- **theoretical contexts in interpreting evidence** (THINK 5, 6, 8, 9, 10)
  In this case, alkaptonuria was viewed through at least three major theoretical contexts: biochemical, medical/clinical, and genetic. Each tended to highlight certain pieces of evidence as significant and indicate certain further investigations as relevant. Thus, the same evidence could have different meanings for different scientists. Although in the long-term interpretations from the various contexts could be brought together, in the short-term, they seemed at odds. Bridging different theoretical contexts proved to be exceptionally important, and suggests one important role for imaginative interpretive skills in advancing science.

- **professional responsibilities of scientists** (THINK 7)
  Scientists develop specialized skills and this opens consideration of their role in society and of pursuing relevant questions and sharing their knowledge. Much sicentific work is supported by public funding, and this adds another possible dimension of responsibility to the community.

- **the role of persuasion** (THINK 9)
  One often hears that "the data speak for themselves." This case shows that this assumption is not well informed. Data are interpreted differently in different theoretical contexts. In addition, one must communicate the results. The history shows the difficulty of bridging conceptual contexts and sometimes convincing colleagues that certain results are meaningful or signfiicant. It does not happen on its own.

- **conceptual change** (THINK 10)

  New evidence does more than just add to the collection of facts. Sometimes, it leads to a major change in theoretical perspective. Again, theoretical contexts may have a signfiicant role in promoting or inhibiting reception of new findings. Was Garrod's discovery "premature" or "ahead of its time," due to some rare genius? Garrod's conclusions were certainly insightful, but emerged concretely from his personal experience and professional relationships. The discovery depended mostly on appreciating a particular constellation of concepts. For Garrod, that was natural. For others, it required a substantial shift in background knowledge, which only happenad later.