Addressing Nature-of-Science Core Tenets with the History of Science: AN EXAMPLE WITH SICKLE-CELL ANEMIA & MALARIA

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For the past two decades, there has been increasing emphasis in science education to facilitate learning of the nature of science (National Research Council, 1996; Osborne et al., 2003). The issues that fall under the domain of nature of science are wide ranging, and while there is some disagreement about the importance of various nature-of-science issues, recent science education literature demonstrates that some issues are regarded as more fundamental or core to student understanding of science (Lederman et al., 2002; McComas, 2005a). These nature-of-science core tenets include such things as (McComas, 2005b):

- Science demands and relies on empirical evidence.
- Knowledge production in science shares common methods and shared habits of mind, norms, logical thinking and methods (such as careful observation and data recording, truthfulness in reporting, etc.).
  - Experiments are not the only route to knowledge.
  - Science uses both inductive reasoning and hypothetico-deductive testing.
  - However, there is no one step-wise scientific method by which all science is done.
- Laws and theories are related but distinct kinds of scientific knowledge.
- Science has a creative component.
- Scientific knowledge is tentative, durable and self correcting (meaning that science cannot prove anything but scientific conclusions are still valuable and long-lasting because of the way in which they are developed).
- Science has a subjective component (theory-laden character).
- There are historical, cultural, and social influences on the practice of science.
- Science and technology impact each other, but are not the same.
- Science and its methods cannot answer all questions.

Episodes from the history of science are particularly useful for helping students understand the nature of science, and at least partially for this reason, stakeholders have often advocated using the history of science in science teaching to promote student understanding of one or more of these core ideas. Though the development of NOS core tenets has been an important step in establishing targeted benchmarks for NOS instruction, teachers need examples that they can use instrumentally in the classroom to give students meaningful contexts from which they can interpret the relevance of NOS issues. At the same time, it is important that teachers who are receptive to the use of NOS be knowledgeable of how to interpret other NOS episodes in light of their potential worth for teaching NOS.

The following is an example of this instrumental approach in using the history of genetics on heterozygote protection in sickle-cell anemia to help students to connect to multiple NOS tenets. The case is followed by a brief discussion about practical considerations for adopting this approach with other episodes from the HOS.

Sickle-Cell Anemia & Heterozygote Protection

Sickle-cell anemia is a recessive genetic disease that affects the proper function of the human red blood cell. Persons who possess two defective copies of the gene that codes for a portion of the hemoglobin molecule produce red blood cells that become sickled in shape when they are exposed to low oxygen levels, as is commonly found in the venous system. Persons who suffer from the disease experience extreme shortness of breath and pain known as sickle "crises," and the disease has both short- and long-term potential negative consequences for the normal functioning of the cardiovascular system.

The genetics of the disease are frequently used in introductory biology textbooks to illustrate the concept of heterozygote protection (e.g., Cain et al., 2000). The underlying idea is that heterozygotes (carriers) of the disease are afforded a measure of protection against malaria. There are certain areas of the world where people face near continual exposure to the mosquito that often carries the parasitic agent of malaria, Plasmodium falciparum (http://evolution.berkeley.edu/evolibrary/article/0_0_0/history_19). In the absence of treatment, children have a higher risk of mortality. Children who are carriers of the genetic disease sickle-cell anemia have a measure of protection against the invasion and proliferation of the malaria protozoan and are thus more

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likely to survive to reproductive age (Allison, 1954a). Evidence for this relationship is often illustrated in textbooks by having students consider the striking correlation between higher-than-otherwise-expected frequencies of sickle-cell anemia with areas that have high exposure to malaria.

Credit for confirming the model of heterozygote protection is usually given to the British medical researcher, Anthony C. Allison (1954a, 1954b), who performed a series of observational and experimental interventions while working as a medical researcher in Central East Africa from 1949 to 1953. In fact several scientists during this time period were interested in attempting to explain the unusually high frequencies of sickle-cell carriers. Their various lines of research led to several alternative theories.

**A Case Approach to Sickle-Cell Anemia & Nature-of-Science**

The author developed an eight-lesson unit of instruction based on the history of research on sickle-cell anemia (for detailed lesson plans and student readings, see http://www.assumption.edu/users/emhowe/Sickle.html). Though the unit was designed for an introductory college course for pre-service teachers, it is also suitable for teaching high-school students.

The unit takes the approach of a "mystery disease" that students are to solve by examining evidence taken from the history of research by past scientists who were working to understand the sickle-cell phenomenon (see Table 1). In both small-group and whole-class formats, students are challenged to consider the evidence they are given and to develop explanations to account for the various problems they encounter. Often, explanations they develop in one class are called into question in later classes as new data becomes available. In this way, students are invited to engage in reasoning that is similar to the work of past scientists. Also, throughout the unit, students are invited to explicitly and reflectively connect what they are doing with their study of the sickle-cell data to more general conceptions of the nature of science. To facilitate this, the teacher asks students to consider planned NOS-probing questions. In this case, the probing questions came directly from the curriculum development work the author did (see discussion) to tease out the important NOS morals that were a part of the sickle-cell history. The following summarizes a portion of the unit (Classes 4-6 from Table 1) and illustrates how students connect their work to several NOS tenets.

Prior to Class 4, students had worked with the genetics of the mystery disease (sickle-cell) and had proposed that because it is a relatively morbid recessive disease (reduces fitness), there should also be low incidences of the disease in the general population. In the fourth class, students are given data that was collected from the work of several scientists who studied the sickle-cell phenomenon from 1940-1949. The data (Figure 1) depicts frequencies of sickle-cell carriers in the country of Uganda (East Africa). The frequencies are striking, because they are unusually high and quite variable, and these anomalies cry out for explanation in light of the predictions students made from their prior conclusions of the genetics of the disease.

**Table 1. Class Overview of the Sickle-Cell Unit.**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>YEAR(S)</th>
<th>HISTORICAL DESCRIPTION</th>
<th>CLASS &quot;PROBLEM&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1910</td>
<td>Dr. Jim Herrick first encounters and diagnoses the mystery patient.</td>
<td>Examine histology slides and cellular models to explain symptoms of mystery patient.</td>
</tr>
<tr>
<td>2</td>
<td>1923</td>
<td>Using the Emmel test (in vitro test) to identify sicklers from non-sicklers, Drs. Taliaferro &amp; Huck propose the Dominance model of inheritance of the disease from pedigree information they have collected.</td>
<td>Examine pedigree data developed from results of Emmel test.</td>
</tr>
<tr>
<td>3</td>
<td>1949</td>
<td>Dr. Jim Neel resolves the distinction between full sicklers and heterozygotes by way of new pedigree information.</td>
<td>Examine pedigree data developed from results of in vitro and in vivo tests.</td>
</tr>
<tr>
<td>4</td>
<td>Late 1940s to Mid 1950s</td>
<td>Hematology work in East Africa uncovers high frequencies of carriers for the sickle-cell disease. Several initial theories are developed.</td>
<td>Examine Plasmodium falciparum lifecycle and propose mechanism of inhibiting its growth and development.</td>
</tr>
<tr>
<td>5</td>
<td>Mid 1940s to Mid 1950s</td>
<td>Parasitology work in East Africa also examines the distribution of the disease malaria.</td>
<td>Consider how malarial data affects students' earlier explanations for heterozygote frequencies in Uganda.</td>
</tr>
<tr>
<td>6</td>
<td>1952-1954</td>
<td>Dr. Anthony C. Allison proposes theory of heterozygote protection of sickle-cell carriers to the malarial parasite.</td>
<td>Examine DNA fragments for hemoglobin proteins from electrophoresis.</td>
</tr>
<tr>
<td>7</td>
<td>1949, 1957</td>
<td>Linus Pauling elucidates difference between normal and abnormal hemoglobin forms through electrophoresis. Dr. Vernon Ingram sequences the peptides of hemoglobin and determines the molecular difference between normal and mutated forms.</td>
<td>Review</td>
</tr>
</tbody>
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Table 2. Uganda Language Groups.

<table>
<thead>
<tr>
<th>Language Group</th>
<th>Allele Frequency</th>
<th>Europoid Features*</th>
<th>Between-Group Contact**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bantu: Eastern</td>
<td>High</td>
<td>+</td>
<td>With Nilotic</td>
</tr>
<tr>
<td>Bantu: Western</td>
<td>Moderate</td>
<td>++</td>
<td>Little to none</td>
</tr>
<tr>
<td>Hamitic</td>
<td>Low</td>
<td>+++</td>
<td>Little to none</td>
</tr>
<tr>
<td>Nilotic</td>
<td>High</td>
<td>+</td>
<td>With Eastern Bantu</td>
</tr>
<tr>
<td>Pygmoid</td>
<td>Very High</td>
<td>0</td>
<td>Little to none</td>
</tr>
</tbody>
</table>

* Europoid Features = the degree to which researchers believed that the tribal people within a language group exhibited Caucasian-like characteristic (height, head shape, skin color, etc.)

** Contact means the amount of immigration, emigration, and intermarriage

Scientists were also interested in explaining the sickle-cell anomaly (that there were unusually high frequencies of the known-to-be-deleterious gene), and their interest emerged as a result of years of various scientists collecting and characterizing blood samples from indigenous peoples across much of the continent of Africa and of lower Asia. The unusual frequency distributions for the gene encouraged scientists such as Anthony Allison to collect additional data on both sickle-cell anemia frequencies and the incidences of *falciparum* malaria through both observational inquiry and the use of controlled experimental interventions.

During this class, students are given additional data, including a table that summarizes some of the major indigenous tribal groups (Table 2) and certain environmental information (topography, weather, land and water use). They are challenged to explain the anomaly using the information available to them, including their prior conclusions about the genetics of the disease. As they deliberate in small groups (or during the subsequent whole-class discussion about their findings), the teacher periodically asks students to consider such nature-of-science probes as:

- How did you arrive at your explanation? What role did the evidence play in framing your explanation?
- Did you all come to the same explanation (there is inevitable variation)?
- Why might your explanations be different?
- How was your general understanding (or prediction) of the genetics of the disease affected?

The provisional explanations that students propose often mirror those held by the past scientists (e.g., possible environmental mutagens that raise the mutation rate, "blackness" being causally linked to having the disease, a possible pathogen causing a "spread" of the disease).

In the fifth class of the unit, students learn about malaria, which shares similar symptoms to sickle-cell anemia. They examine how parasitic diseases differ from genetic diseases and explore how the blood parasite *Plasmodium falciparum* interacts with the human red blood cell during a portion of its lifecycle.

In Class 6, students are again provided supplemental data taken from the history of research from the 1940s and 1950s. Student groups are given data that depicts the incidences of malaria in the region (Figure 2). They are encouraged to compare the new data with that given to them in Classes 4 and 5 to see if and how it potentially affects their explanations of the frequency anomalies they uncovered during Class 4. At some point during their deliberation, students are given additional data for their consideration of the results of blood work collected by Anthony Allison on Ugandan children (Table 3).

From this work, students often discover that heterozygotes of the disease appear to have some protection against the ravages of malaria, however, it is also common to find that students propose and defend alternative explanations. Similar to past scientists, some students propose that gene flow and environment (mutation) play important roles in at least partially explaining the unusually high and varying frequencies of the disease.

For those students who propose the explanation of heterozygote protection, the teacher can challenge them to think of an experimental design to test their hypothesis. Often students will suggest (with some reservation) the possibility of infecting both normal and heterozygote persons with malaria in order to follow the progressive course of the disease. This mirrors the experimental work done by Allison and raises interesting questions for discussion about the necessity of experiments to confirm theories or the potential problems with ethics in human testing.

Throughout this class, the teacher asks students (either in small-group or whole-class format) to link their work with the data to larger NOS tenets. For example:

- Does your explanation(s) replace or supplant any existing ones that you had?
- Does your group (or the class) have alternative theories to account for the available data?
- Are any explanations (or methods used to derive them) found to be in error?
- If there are alternative theories, what differences in your backgrounds may help us to understand why you proposed different explanations? Did you have access to the same (or similar) data?
- Why might we prefer one explanation to another?


<table>
<thead>
<tr>
<th>Genetic Disposition</th>
<th>Total Children Examined</th>
<th>% w/ falciparum Malaria in blood</th>
<th>Parasite Density Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (+/+ or −/+)</td>
<td>247</td>
<td>46%</td>
<td>5.9</td>
</tr>
<tr>
<td>Carrier (+/−)</td>
<td>43</td>
<td>28%</td>
<td>4.0</td>
</tr>
</tbody>
</table>
Do you think that controlled experiments are necessary to validate scientific explanations?

At some point during each of the classes in the entire unit, the teacher shares with students how past scientists struggled with similar problems to account for the sickle-cell disease. These sessions allow students greater consideration of the NOS tenets by seeing the similarities between the work and conclusions of their own groups to those performed by scientists of the past. Specific examples of this with the sickle-cell research include one of the core tenets: “Knowledge production in science shares common methods.”

Knowledge Production in Science Shares Common Methods

Allison’s formative training as a student of evolutionary genetics and parasitology provided him an important grounding in various fundamental theories that he brought to bear when initially presented with the anomalous sickle-cell data. In this regard, Allison relied upon deductive reasoning to draw from the theoretical mechanisms put forth by E.B. Ford (1940) to explain the existence of stable polymorphisms like the sickle-cell alleles. In this case, Allison reasoned that it might have been possible, under Ford’s general discussion of heterozygote advantage, for carriers of the sickle-cell gene to have a selective advantage to something such that the otherwise deleterious gene would remain high in certain locations. From this, it was entirely reasonable for him to hypothesize that such an advantage might be linked to a parasitic disease that shared a common element to the affected red blood cell.

Allison then collected data to test the validity of his prediction. His first set of data included a correlative analysis of the frequencies of sickle-cell anemia carriers in Africa and lower Asia with known distributions of falciparum malaria. This demonstrated a positive correlation, suggesting a close connection between sickle-cell anemia and endemic malaria. He then collected data from children in the area of Uganda by sampling their blood and analyzing it for the presence or absence of both the sickle-cell gene and malaria. This revealed that children who were carriers for sickle-cell anemia had lower infections of the malarial parasite. The final line of evidence came in the form of an experiment in which he gave both normal and sickle-cell carriers falciparum malaria and analyzed the progression of their health for two weeks. The results demonstrated that the sickle-cell carriers were less susceptible to the virulence of the disease malaria.

Allison’s work is in many ways representative of the idea that there are common “methods” in science that characterize the way in which knowledge is created, tested, and validated. It shows how scientists often (but not necessarily) begin by using deductive processes to consider possible ways of applying known generalizations and then making hypotheses to provisionally explain the circumstances of interest to them. Then scientists engage empirically in the selective collection of data to test their predictions, with the hope of learning whether or not their explanations hold. Further, the episode exemplifies that scientists use differing methods for collection of data (e.g., a distinction between observation and experiment). Allison initially collected blood samples in order to quantify the sickle-cell/malaria proportions (essentially an observational undertaking) and then later developed a controlled experiment to test the validity of his hypothesis.

Scientific Knowledge Is Tentative, Durable & Self Correcting

Initially there were several alternative theories to account for the anomalous frequencies of the sickle-cell gene, similar to the differing explanations that students propose during their own work. Though Allison’s theory that heterozygote protection explained the sickle-cell anomaly was generally well received by the scientific community, there were several attempts by other scientists at the time to find weaknesses in his conclusions or in the methods that he used. For example, some drew attention to the fact that Allison neglected to consider the mitigating effect of acquired immunity in his experimental trials with normal and sickle-cell carriers. This legitimate concern cast the validity of his findings in question.

The important point to consider here is that scientific explanations, whether provisional or long-standing, are always subject to potential refutation—be it the explanations themselves or the methods used to construct them. That the heterozygote protection explanation was generally received by the scientific community and has been so for over 50 years is evidence of its durability. However, scientists also found fault with some of the methods that Allison used to collect his data, but not enough to warrant the rejection of his main thesis.

Science Has a Subjective Component (Theory-Laden Character)

During the period from approximately 1949 to 1953, there were several scientists who worked to provide an explanation for the anomalous sickle-cell frequency distributions. The theory of heterozygote protection put forth by Allison was only one of several theories proposed to explain the data. Researchers Lehmann and Raper (1949) investigated the relationship between anthropologic data and the incidences of sickle-cell anemia. Their work suggested that sickle-cell anemia was more prevalent in “blacker,” more indigenous African peoples in the areas where high frequencies of the disease were present. They claimed that the disease became increasingly infrequent as tribal members engaged in intermarriage with non-affected neighboring peoples or through dilution of the gene via mating with non-black races. Neel (1952),
from the University of Michigan, supported the notion that high sickle-cell gene frequencies might be due to unusually high rates of mutation in certain areas, significantly high to offset the continual removal of the deleterious allele through selection. Foy and Kondi (1951, 1954) proposed that the high frequencies were due to the possibility of either selective reproduction of heterozygotes or to the idea that heterozygote females were bearing significantly more children (reproductive overcompensation).

With respect to the nature of science, it is important to point out that for the most part each of the scientists had access to very similar data. Yet given this, it is interesting to note that some fundamentally different explanations were proposed (and defended) to account for the sickle-cell anomaly. This is because the way in which the scientists interpreted the data and the way in which they conceptualized their respective explanations were most certainly shaped by their prior educational training, their prior theoretical commitments, and so on. For example, Allison was a parasitologist and was influenced by certain well-known evolutionary biologists (e.g., E.B. Ford) who developed the conceptual mechanism for heterozygote protection. Conversely, J.V. Neel’s prior research examined the effects of environment on mutations, and as such he brought that framework to bear on looking for potential mutagenic effects.

**There Are Historical, Cultural & Social Influences on the Practice of Science**

There are two sides to this particular NOS tenet. On the one hand, it is true that the practice of science is influenced by the historical, cultural, and social influences in which it is practiced. On the other hand, the methods and conclusions of science itself influence such things as sociological and political understandings.

The underlying mechanism involved in heterozygote protection in sickle-cell anemia has important ramifications for the sociology (or anthropology) of human disease. It is a somewhat common misconception among individuals that sickle-cell anemia is a “black” disease, often misinterpreted to mean that the disease is racially predetermined (Wailoo, 1997). What the mechanism of heterozygote demonstrates is that “blackness” per se is only correlated to the frequency of the disease, in contrast to race being causally linked. The frequency of sickle-cell anemia is most strongly correlated to areas in which indigenous peoples face endemic exposure to malaria. This holds true irrespective of race, which is why students are often surprised when they learn about heterozygote protection and sickle-cell anemia to find that the frequencies of sickle-cell are also high in certain parts of Greece and Asia.

**Science & Its Methods Cannot Answer All Questions**

Ethical dilemmas are certainly a part of the scientific endeavor. Students are often surprised to learn about Allison’s experimental intervention to test his hypothesis of heterozygote protection. They are surprised because the episode strikes to the heart of having them consider if values are an integral part of science itself or are something distinct.

Allison wanted to test the findings from his observational conclusions that sickle-cell carrier children were less likely to contract *falciparum* malaria (and also suffered less virulently from the disease if they did contract it). So he conducted an experiment in which he established two populations of volunteer adults, one half who was sickle-cell carriers and one half who was “normal.” He inoculated the members of both groups with *falciparum* malaria and then examined the health of each individual (identifying malaria and its severity) for approximately two weeks afterward. At the conclusion, each member was treated with anti-malarial medications. The findings confirmed that sickle-cell carriers were either less likely to contract malaria or, if they did, experienced a lower parasite density in their red blood cells.

Relevant to NOS is that while values are certainly a part of science from the perspective of the human connection (interpretation), the actual practice of science, the methods and conclusions that result, cannot in and of themselves in the absence of the human connection determine the “rightness” or “wrongness” of certain courses of action.

**Discussion**

What the sickle-cell anemia case illustrates is that episodes from the HOS can (and should) be used to help students interpret multiple aspects of the NOS. The approach is particularly effective because it invites students to develop their understanding of NOS tenets at the same time that they are building their own conceptual understanding of the biology content. In this way, both NOS and (biology) concepts are viewed in the constructivist model as something that the student must negotiate to understand. The context of an eight-class unit provides students with multiple opportunities to critically examine the content and NOS conceptual material that they and their peers are attempting to learn.

In developing this case, the author used the NOS core tenet list as a starting point for creating general questions to tease out the important NOS issues contained in the history of research. Table 4 summarizes many of the questions that were used and is a useful tool for any teacher who wishes to interpret an episode from the HOS in a NOS framework.
Table 4. Guiding Questions To Connect HOS to NOS.

<table>
<thead>
<tr>
<th>NOS TENET</th>
<th>GUIDING QUESTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Science demands/reliess on empirical evidence.</td>
<td>• In what ways did the past scientist(s) engage in the collection of data?</td>
</tr>
<tr>
<td>• Knowledge production in science shares similar methods.</td>
<td>• How did the scientists draw from larger generalizations (laws and/or theories) to inform their empirical work?</td>
</tr>
<tr>
<td>• Scientific knowledge is tentative, durable and self-correcting.</td>
<td>• How did the scientists draw from larger generalizations (laws and/or theories) to inform their empirical work?</td>
</tr>
<tr>
<td>• Science has a subjective element (theory-laden character).</td>
<td>• Did the scientist’s explanation(s) replace or supplant any existing ones? Were there alternative theories to account for the available data?</td>
</tr>
<tr>
<td>• Science has a creative element.</td>
<td>• What were there differences in their educational or philosophical training/grounding?</td>
</tr>
<tr>
<td>• There are historical, cultural, and social influences on the practice of science.</td>
<td>• Was how was the scientist work influenced by the culture in which he/she operated?</td>
</tr>
<tr>
<td>• Science and technology impact each other, but they are not the same.</td>
<td>• What ramifications may his/her conclusions have on sociological or political policy?</td>
</tr>
</tbody>
</table>

When teachers ask these sorts of questions of any particular HOS episode potentially worthy of using in their classroom, they essentially explicitly reconsider that episode in line with the tenets raised within the NOS core list. Using questions to tease out the NOS aspects raised by the historical episode in this way is also useful during instruction in the classroom to have students explicitly and reflectively develop their NOS conceptions (Howe & Rudge, 2005). In fact, some researchers (e.g., Clough, 2005) argue that NOS curriculum planning and implementation would be enhanced if teachers focus their planning (and their students’ learning) on guiding NOS “core questions” rather than “core” tenets. In this regard, they would be better served by using the NOS core tenet list as a guide to investigate any HOS episode that may be relevant for the conceptual material they plan to cover in class. This approach may help to make NOS instruction more frequently (and substantively) integrated into the curriculum where HOS is used.

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