

STUDY GUIDE

LORENZO'S OIL

Overview

Lorenzo's Oil is the story of the Odone's race against time for the survival of their little boy. Lorenzo at age 6 develops a classic childhood case of Adrenoleukodystrophy. Augusto and Michaela Odone work tirelessly with little assistance from the medical community and the parent support group to find a therapy to stop the progression of this devastating disease.

In 2001 Elizabeth Spike, a high school biology teacher in Rochester, New York, chose to show a film to her students to help engage their interest in biology. Like many teachers, she had used many good documentary films in class, and to good effect. But she wanted something that had more drama, more entertainment value, to help draw the interest of less motivated students. After reviewing a number of fictional films, she watched *Lorenzo's Oil*, and decided it had a number of qualities that no other film she found shared. While it was a Hollywood production, with the full entertainment values that includes, it was based on a true story. That alone puts it in small company. But also the Odone's, the real family described in the story, had a lot of input into the script and film shooting. This added to the authenticity of the story, making its gut-wrenching emotions much more legitimate than a story created just for that effect. A similar fictional story might leave the audience feeling merely entertained at best or manipulated at worst.

More importantly, there was more scientific content in this movie than any other Hollywood type film Elizabeth found, in part because of the Odone's involvement in the entire project. Furthermore, the director of the film, George Miller, had received an M.D. before deciding to become a filmmaker, a rather unusual background in the world of film. He and the Odone's clearly worked hard to include a sense of the drama involved in the medical and scientific quest portrayed in the movie. (Miller had previously made the Mad Max films, so no one could accuse him of not appreciating the importance of a little action to narrative.) Of course a good deal of the aesthetic credit must also go to the excellent acting by Susan Sarandon and Nick Nolte as Lorenzo's parents Michaela and Augusto Odone, and Peter Ustinov as Dr. Nicolaitis.

The video was a more successful educational tool than Elizabeth had hoped, stimulating the interest of her inner-city students to find out what has happened to Lorenzo since the movie was made in 1992 (almost ten years before she showed it to her class). Some students did an online web based search, and discovered the Myelin Project, mentioned at the end of the film, is still active. They inspired Elizabeth to write to the Myelin Project, which resulted in this guidebook.

Augusto Odone and his Assistant at The Myelin Project, Jacqueline, invited Elizabeth and her husband to lunch at the Odone's home to discuss how to educate highschoolers about the nature and severity of the disease, often referred to as an 'orphan' disease due to the small number of people afflicted by it each year (1 in 30,000, about 300 cases per year). As a result, their story is available for use in your classroom as a way to engage students in the science as well as the ethical dilemmas presented in the film.

Elizabeth has written a set of questions to guide discussion of the scientific issues raised by *Lorenzo's Oil*, and her husband Jeffrey Spike (a bioethicist) has contributed discussion questions on the ethical issues. Why include the ethical questions? One of the points that the luncheon group agreed on was that it was the ethical issues as well as the scientific issues that provide the drama to the film. Another point of agreement was that science education would benefit from greater integration of ethical, legal, and social issues into the science content. We believe that bringing these issues up concurrently with the scientific issues helps students see the relevance of science to their lives.

One of the best ways to avoid complaints that biology is just memorization is to include some controversial questions for discussion about the topics they learn. Indeed, for these reasons, ethical implications of science have been part of the mandate in the recently revised New York State Regents requirements for science education. Furthermore, the skills needed for web based research, such as careful reading of difficult articles and careful writing of essays, are as useful in science as they are in the

humanities. (Testing for the new Regents curriculum requirements, as a result, include essay writing with the exam as well as multiple choice questions.)

Suggested Use in the Classroom

The Lorenzo's Oil kit contains the following items:

- the film, *Lorenzo's Oil*
- one set of basic science questions
- one set of ethics questions
- one set of slides about how Lorenzo's Oil works
- two classroom activities (Competitive Inhibition: How Lorenzo's Oil Works and Demyelination Activity)

Time Schedule

The film is approximately 2 hours and 16 minutes long. We strongly counsel showing the entire film to the class. Trying to edit a few short segments, say of 10 or 20 minutes, will yield a much less engaging experience for the students. It would defeat the value of this as a full length movie narrative, a dramatic story with a beginning, a middle, and an end, and the development of understanding and sympathy for the major characters involved in the actions and events. It would, in short, result in an experience more like another educational documentary. (We do advocate the use of those sources in the classroom as well, but see this type of film as an opportunity to add something more.)

If your classes run on a traditional 40 minute schedule, we suggest you use the double period for lab time to start showing the film and two more 40 minute classes (a total of four 40 minute class periods). If your classes run on a block schedule then you could show the film in two days. However, in the spirit of teachable moments you may wish to stop the film about 10 or so minutes before the end of class in order to highlight important points or clarify misconceptions. Both sets of questions follow the film from beginning to end.

Ethics Questions

We strongly urge you to use some of the ethical questions in conjunction with the science questions during your class discussion of the film. Here's an example of how to implement the ethics. Each day before you show the film write one of the many ethics questions on the chalkboard and ask students to think about the meaning of the question and to develop an answer as they watch the film. If you leave 10 minutes at the end of class then you could use it to clarify misconceptions, reinforce models and concepts as well as address the ethical question originally written on the board. It is not our expectation that all the ethical questions be addressed but you may enjoy reading about them and become informed in case a student asks a difficult question about ethics, policy, medicine, etc.

Classroom Activities

The classroom activities have been designed to model two basic ideas about ALD: how very long chains of saturated fatty acids demyelinate axons and how Lorenzo's Oil works to reduce the production of very long chains of saturated fatty acids. One way of integrating the activities would be to do the Demyelination activity before the film, cementing the idea of how neurons fail to transmit impulses along the axons due to demyelination. The Competitive Inhibition activity could be done after the film to clarify and reinforce the chemical mechanism that makes Lorenzo's Oil halt the demyelination process.

Suggested Answers to Post lab Analyses

Demyelination Activity

1. What process did you and your classmates demonstrate in the activity?
Students demonstrated the process of demyelination.
2. What happened to the Impulse Transmission after 'Myelin' person #3 and #9 sat down?
Answers may vary but should say something like the Impulse became harder to transmit due to the loss of 'Myelin' people along the axon.
3. How does this activity model demyelination?
With each successive trial there is a loss of myelin. The loss of myelin makes the transmission of impulses more difficult. Consequently, there are less tennis balls with body functions in the 'Body' bucket.
4. Based on what you learned from the activity, how does demyelination cause a person to become impaired, eventually leading to death?
Demyelination causes a person to become impaired, eventually leading to death because the loss of myelin impedes the transmission of impulses or the sending of messages to the body.

Competitive Inhibition: How Lorenzo's Oil Works

1. What do the paper clips represent? Why are there two different shaped or colored paper clips?
The paper clips represent two carbon atoms. There are two different shaped or colored paper clips to represent the two different kinds of carbon atoms that will eventually comprise the carbon backbone of saturated and monounsaturated fatty acids.
2. What role does the enzyme play? In other words, what is its function?
The enzyme's role is to elongate the fatty acids. In other words, the enzyme links the carbon atoms together to make long chains of fatty acids.
3. How many carbon atoms long was the fatty acid chain produced by the enzyme?
Answers may vary.
4. Were there more carbon atoms from the saturated or monounsaturated fatty acids?
There should be more carbon atoms from the monounsaturated fatty acids (i.e. Lorenzo's Oil).
5. Which kind of fatty acids destroy myelin?
Very long chains of saturated fatty acids
6. Explain how Lorenzo's Oil prevents the destruction of myelin in sufferers of ALD.
Answers will vary. Competitive Inhibition will occur when sufferers of ALD consume Lorenzo's Oil. Lorenzo's Oil is made of very long chains of monounsaturated fatty acids. Saturated fatty acids will also be present in the body; however, due to competitive inhibition monounsaturated fatty acids will be produced exclusively by the enzyme complex (not both types of fatty acids). The result will be normal levels for VLCSSFA and a reduction in demyelination along the axons.

What is ALD?

Adrenoleukodystrophy is an inherited disease through the mother (X linked or sex-linked). ALD is a genetic disorder in which the impaired gene contains incorrect instructions for the enzyme responsible for the metabolism of very long chains of saturated fatty acids. In general, humans consume and naturally synthesize (Biosynthesis) VLCSCFA; however, in ALD patients VLCSCFA cannot be metabolized by the enzyme complex. As a result, the very long chains of saturated fatty acids (VLCSCFA) accumulate in the nervous system as well as the adrenal glands. The accumulation of VLCSCFA causes the myelin sheath to dissolve and strip away from the axon, causing demyelination, by a yet unknown mechanism. With the loss of myelin, impulses can no longer be transmitted along the axons and the body becomes deprived of important functions, such as hearing, seeing, moving, swallowing, breathing, etc.

Lorenzo's Oil in conjunction with a diet low in VLCSCFA slows the demyelination process and ALD symptoms. Removing VLCSCFA from the diet eliminates any external contribution to the total VLCSCFA blood level. Lorenzo's Oil, made of monounsaturated fatty acids (good fatty acids), causes Competitive Inhibition to occur. The same enzyme complex that elongates fatty acid chains becomes occupied with the production of monounsaturated fatty acids. The enzyme complex cannot produce both types of fatty acids simultaneously. Therefore the two kinds of fatty acids compete for same enzyme complex; however, monounsaturated fatty acids are formed in greater concentration than VLCSCFA. The reduction in the elongation of VLCSCFA and a diet low in VLCSCFA will slow the demyelination process.

Does Lorenzo's Oil Work?

For many sufferers of ALD, the obvious answer may be yes; however, the scientific community has not shared the same enthusiastic response for many years. Until recently, Lorenzo's Oil has been not been accepted to work scientifically. Dr. Hugo Moser (played by Peter Ustinov in the film) revealed the results of the 10-year study he conducted with his European colleagues on the effects of Lorenzo's Oil in boys with ALD. 105 boys with ALD participated in the international study. Boys who took Lorenzo's Oil consistently were less likely to go on to develop ALD than boys who received Lorenzo's Oil on an irregular basis.

Where to go from here?

The following is a collection of extension ideas meant to enrich your students' science experiences after viewing the film:

- Ask your students to consider the fact that ALD is about as prevalent in society as Phenylketonuria, or PKU, which is another demyelinating disease. However, in many states universal newborn screening is available for PKU, which is currently not the case for ALD. Lorenzo's Oil success may be due in part by the strict administration of the oil before symptoms manifest themselves. However, if one does not know if he has the ALD gene then he won't know about the possibility of a therapy to prevent the onset of the disease. In other words, if you had no reason to suspect ALD runs in your family then you might not catch the window of opportunity before it closes. Newborn screening for ALD could be a lifesaver for hundreds of boys each year.
- Ask your students to do web-based research into the recent scientific support confirming Lorenzo's Oil works. Then ask your students to look into their state's newborn screening policy to see which tests are available. Use <http://www.google.com> to locate the web site or sites that will link them to email addresses or mailing addresses to contact state health agencies and inquire into a possible newborn screen for ALD.

Try these websites for recent support for Lorenzo's Oil:

- <http://www.newscientist.com/news/news.jsp?id=ns99992851>
- http://www.usatoday.com/news/health/2002-10-21-lorenzo-oil-cover_x.htm

- Ask students to do a web search on the brain and how it works. Visit sites like
 - <http://www.dana.org>
 - <http://www.vh.org/adult/provider/anatomy/BrainAnatomy/BrainAnatomy.html>
 - <http://www.med.harvard.edu/AANLIB/home.html>
 - <http://apu.sfn.org/>
- Ask your students to make a poster about ALD and Lorenzo's Oil. Place the posters in your school's display case, on the hallway walls, or at least inside your classroom. Ask your students to teach other students about ALD.
- Visit the Myelin Project at <http://www.myelin.org> to learn more about the project's mission to remyelinate axons in sufferers of demyelinating diseases.
- Visit the Myelin Project to learn about other demyelinating diseases. Find out using <http://www.google.com> what the occurrence of each of those diseases is per year in the United States and in your state specifically. Ask students to find out what kind of therapies currently exist for those diseases.
- Ask students to calculate how much Lorenzo's oil costs per month. Visit the Myelin Project to find out how much one bottle costs. Then ask them to calculate one month's and one year's supply of Lorenzo's Oil.
- If you are inspired to do more, contact the Myelin Project and ask what you and your students can do to help the remyelination project!

If you would like to contact the authors of the Lorenzo's Oil Kit please write to the mailing address below:

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Lorenzo's Oil

Teacher version (with answers)

1. As you watch the movie, list symptoms of ALD:
 - *Symptoms include the loss of hearing, seeing, balance, speech, gait or coordinated walking, movement of arms, swallowing, and breathing.*
 - *Neurons are the main actors of the nervous system, sending and receiving messages to and from other parts of the body. They typically consist of a cell body containing the nucleus and several short radiating processes as well as one long process, the axon, extending for several centimeters. Our nerves are formed by a collection of interwoven axons.*
 - *Much as electric wires are coated by insulating material, axons are ensheathed by a white substance, called myelin, made of lipids and proteins. When myelin is destroyed, as in diseases such as ALD and MS, axons can no longer conduct messages, causing loss of functions.*

2. Using your science textbook, draw a normal neuron in the space below. After several months of ALD draw what the axons of Lorenzo's neurons most probably look like.
 - *The axons should have little or no myelin sheath.*

3. What are fatty acids? Why are some fats called saturated and others are called unsaturated? What kind of fatty acids is Lorenzo's body unable to metabolize?
 - *Fatty acids are fats found naturally in living things. Some fats are called saturated because they are saturated or full of hydrogen atoms bound to the carbon chain backbone. Unsaturated fats have at least one c=c bond, which means fewer hydrogen atoms bound to the carbon backbone.*
 - *Lorenzo's body is unable to metabolize very long chain saturated fatty acids. The VLCSCFA accumulating in Lorenzo strip the myelin coat off his nerves (a process called demyelination). This demyelination causes the ALD symptoms c.f. above #1.*

4. ALD is an X chromosome-linked (sex-linked) recessive disease. What is Michaela's, Augusto's, Aunt Dee's and Lorenzo's genotypes and phenotypes?

X^F =Normal Fatty acid metabolism

X^f =Abnormal Fatty acid metabolism or ALD

Genotypes

Michaela= $X^F X^f$

Augusto= $X^F Y$

Aunt Dee= $X^F X^f$

Lorenzo= $X^f Y$

Phenotypes

Carrier

Normal

Carrier

ALD

- *ALD is a sex-linked recessive disease. People have 23 pairs of chromosomes. The 23rd pair is referred to as sex chromosomes.*
 - *In girls the members of this pair are identical (XX) and are both functional. In boys they are not. Only one member of the pair (X) is functional. Due to its incomplete structure the other member (Y) has limited activity.*
 - *A girl who receives a defective X chromosome is a carrier but usually remains asymptomatic for most of her life. This is because one healthy X can somewhat compensate for the other defective X. On the other hand a boy who receives a defective X has no chance of escaping ALD.*
5. Redraw Augusto's sink model and explain how it represents what is happening in Lorenzo's body.
 - *Augusto's sink model represents fatty acids consumed (one faucet) through Lorenzo's diet and the fatty acids made naturally through the process of biosynthesis (second*

faucet). Avoiding dietary fatty acids should cause a decrease in the level of fatty acids in Lorenzo's blood. However, as with the water in the sink, his fatty acid levels remain the same.

- *Fatty acids are chains of carbon atoms with hydrogen atoms attached. The chain length is variable, ranging from two carbon atoms to 28 or more carbon atoms. Very long chain fatty acids are fatty acids with more than 18 carbon atoms. Like most other fatty acids, they fall into three major categories: saturated, monounsaturated and polyunsaturated.*
6. Describe the meaning of the paper clips Augusto used in the library.
 - *Augusto used two types of paper clips to represent the saturated "bad" fatty acids that ALD boys cannot metabolize and the harmless "good" monounsaturated fatty acids. He linked the paper clips together to represent the hydrocarbon chains in varying lengths.*
 - *This was a graphic way to describe what he had learned from the review of several animal experiments: when animals were fed long chain monounsaturated fatty acids, the animals' levels of long chain saturated fatty acids went down.*
 7. What does Augusto's dream reveal about the paper clips?
 - *Augusto's dream reveals that there is one enzymatic complex (not two) involved in the elongation of both monounsaturated and saturated fatty acids above the 18 carbons level of the chain. This was an important revelation that explained the results of the animal experiments.*
 8. What does competitive inhibition mean?
 - *Feeding large amounts of long chain monounsaturated fatty acids (such as those contained in Lorenzo's oil) to ALD boys has the effect of monopolizing the enzymatic complex referred to above, keeping it busy making the harmless monounsaturated fatty acids while distracting it from elongating the bad fatty acids. In other words, both the bad guys and the good guys compete for the attention of the same enzymatic complex. This is clearly a case of competitive inhibition.*
 - *It is like an intelligent machine that can produce corks and bottles, but not both of them at the same time. The machine is intelligent and produces corks or bottles in quantities proportional to the inputs it receives. Forcing large amount of cork into the machine leads to increased production of corks (the good guys) and, conversely to a decreased production of bottles (the bad guys)*
 9. Why did the Odone's ask Aunt Dee to put the combination oleic-erucic oils on her salad before giving it to Lorenzo?
 - *The Odone's needed a healthy adult family member to test whether the oil was effective in normalizing the VLCsFA and whether it had any side effect. (Aunt Dee is an ALD carrier; as such she has higher than normal fatty acid blood levels but not high enough to cause her to develop ALD symptoms.*
 10. What happens to both Aunt Dee's and Lorenzo's fatty acid blood levels after consuming oleic-erucic oils for a few days?
 - *Both Aunt Dee's and Lorenzo's fatty acid blood levels drop within the normal range. This is how Lorenzo's Oil was born.*

Lorenzo's Oil
Student Version

- 1) As you watch the movie, list symptoms of ALD.
- 2) Using your science textbook, draw a normal neuron in the space below. After several months of ALD draw what the axon of Lorenzo's neuron most probably looks like.
- 3) What are fatty acids? Why are some fats called saturated and others are called unsaturated? What kind of fatty acids is Lorenzo's body unable to metabolize?
- 4) ALD is an X chromosome-linked (sex-linked) recessive disease. What is Michaela's, Augusto's, Aunt Dee's and Lorenzo's genotypes and phenotypes?

X^F =Normal Fatty acid metabolism

X^f =Abnormal Fatty acid metabolism or ALD

Genotypes

Phenotypes

- 5) Redraw Augusto's sink model and explain how it represents what is happening in Lorenzo's body.
- 6) Describe the meaning of the paper clips Augusto used in the library.
- 7) What does Augusto's dream reveal about the paper clips?
- 8) What does competitive inhibition mean?
- 9) Why does Aunt Dee put the combination oleic-erucic oils on her salad at the same time Lorenzo is fed the same oils?
- 10) What happens to both Aunt Dee's and Lorenzo's fatty acid blood levels after consuming oleic-erucic oils for a month?

Ethics Questions

Introduction to the Ethics Questions and Answers

All of these issues fall under the heading of bioethics, a field that is only 30 years old. Some of it is what is called "clinical ethics," having to do with doctor-patient interactions, such as informed consent to a proven effective therapy. But most of it is what is called "research ethics," because it has to do with the relationship of scientists to the subjects of scientific research.

In fact the dramatic tensions of the movie come from two sources. First is the tension that exists between clinical ethics and research ethics. While the former has the primary goal of helping current patients, for the latter that is at best a secondary goal. It really is "other people's kids" that researchers hope to be able to help, because they know how hard it is to come up with any important new advances. That the Odonos were able to achieve that through their research is a remarkable, and unusual, event.

The other source of dramatic tension is, of course, the love of Augusto and Michaela for Lorenzo, which motivates their dedicated search for a 'cure.' A movie about a researcher, no matter how dedicated and hard working, would never engage us the way this movie does. Love is the most underrated force in ethics. It makes philosophers in the field of ethics uncomfortable since the most common theories of ethics emphasize the importance of universal rules applied equally to everybody, and these are promoted as part of a rational and dispassionate approach to life. Recently however there has been a renewal of interest in the importance of personal relationships, families, and "an ethics of care" in bioethics. Some of this falls under the rubric of feminist bioethics, although it has roots in two eighteenth century Scottish Enlightenment thinkers, David Hume (the greatest philosopher of the century) and John Gregory (a physician who wrote on medical ethics, and a close friend of Hume's).

Biology students can find these topics very interesting, and they allow them to use some skills that otherwise may be relatively neglected in science classes. One philosopher once said that medicine saved the life of ethics, that is, made an otherwise dull academic subject come back to life by providing interesting material for discussion. Analogously, including ethics issues in your science class might save the life of biology, giving students subjects to debate, and helping to dispel the impression that biology is nothing but "memorization."

Ethics Questions and Answers

- 1. Dr. Nicolaitis, the third doctor the Odonos go to see, is a specialist doing research on Lorenzo's disease, ALD. He hopes to slow down the progress of the disease by dietary restrictions. Should a researcher offer any hope of improvement or slowing down the destruction of an irreversible illness, when trying to get a patient to enroll in a study?**

In general doctors are advised not to promise any therapeutic response to the patient when enrolling subjects into a research study, because it really isn't known yet if the experiment will work. (Otherwise, there would be no need for the experiment or clinical trial.) But no doubt doctors are also believers that they are on the right path, and find it hard not to share their opinion with patients and families. While not unethical, researchers should be careful, because they can easily engender false hope in people who are so desperate for any hope. And even though researchers may fear that no one will enroll in a study without some hope of a response, they must remember how vulnerable people are who have a terminal illness. (Fortunately most research trials do not involve patients with a terminal diagnosis, so these concerns are not common.)

- 2. Dr. Nicolaitis' restricted diet study does not lower Lorenzo's blood levels, in fact they get worse. When the results of a study trial aren't promising, should the researcher tell the patient? At what point?**

This is an ethically difficult and statistically difficult point. The researcher can be so hopeful that his theory is correct that he fails to see when all indications are otherwise. On the other hand, it does take solid statistical evidence before any conclusions can be drawn. One failure does not suffice, because there may be some unique circumstance in that case causing the failure. For these reasons, good studies now usually involve a Data and Safety Monitoring Board (DSMB) made up of independent scientists with no involvement in the research, who are given the results as they come in, and have the power to halt the research if it looks unsuccessful or worse, dangerous.

- 3. Lorenzo's parents then enroll him in the Boston immunosuppression study. When should we allow a study that has potentially severe side effects, seriously altering the patient's quality of life?**

A study like this should not be approved easily. In general it should only be approved if there's already good evidence (from either animal research or similar treatment regimens for related diseases) that it is likely to help, or there is good reason to think the patient will be at risk of great harm even if not enrolled in the study. Another example of an unsuccessful treatment with severe side effects recently was bone marrow transplant for women with advanced and aggressive breast cancer. That too proved ineffective, and caused many women with only a short time left to live to suffer more.

- 4. Should any of the above questions have a different answer because the patient is a child, and so he can't decide for himself? Should parents be allowed to make these decisions for their kids?**

Parents are expected to make all decisions based on the best interests of their kids. When there is reason to suspect otherwise, doctors may refuse to do what the parents request. Common examples come from parents refusing treatment based on the parents religious beliefs, such as Jehovah's Witnesses refusing blood. The definitive court opinion, by Justice Benjamin Cardoza, states: "Parents can make martyrs of themselves, but not of their children."

- 5. Augusto says: "The immunosuppression was brutal, useless. We should not have consigned him blindly into their hands. He should not suffer from our ignorance."**

Here the parents are trying to save their child's life, and cannot be faulted. But it can sometimes turn out that parents' love leads to unrealistic requests and excessive treatment. This is sometimes described as prolonging dying, in contrast to extending living (on the grounds that the child no longer "has a life," even though he's still alive). See question 11 for more on this.

6. How much should kids be told, and should they have any say in these decisions?

Unspoken in this movie, but shown in many places, is how Lorenzo is aware of what is going on, but not being told much. At his age, this is not unusual. But research with children has changed its attitude on this issue considerably in the past ten years, and now children as young as seven years old are supposed to be told as much as they are capable of understanding. Furthermore, while the parents are still expected to sign the consent form, the child is expected to give his “assent,” and be a willing participant. Also, once a child is a teenager, they may be able to give their consent; this is called the “mature minor doctrine.”

7. At the ALD Foundation meeting for parents, the Muscatines assert that the Odone’s observations that Lorenzo’s blood levels have risen are only anecdotal, while what’s needed are valid statistical samples and control groups. Is good science sometimes contrary to compassion? (Michaela: “Our children are in the service of medical science. How very foolish of me. I always thought medical science is in the service of the sufferers.”)

Michaela’s statement is too harsh, but she is on to something. It would be more accurate to say that science needs consenting and voluntary subjects of research in order to make progress, and vice versa. The two need each other, but medical research is different from medical therapy, whose goal is to help the patient. Many studies use a control group for comparison, to see if an intervention is effective, and the control group often gets NO therapy (just a placebo). If the intervention being tested works, then the control group will be unhappy that they didn’t get it. (Of course they can get it later, if it’s not too late). On the other hand, if the intervention doesn’t work, or is harmful, a research subject would be happy to have been in the control group!

What makes all of these situations ethically justified is the ethical Principle of Autonomy and its correlate, informed consent. The patient or subject should be told all of this information, and the physician should be confident he or she has understood the information and agrees to participate.

8. Michaela finds the article about Polish rats and fatty acid manipulation. But she’s disturbed that scientists don’t search the literature as carefully as she does: “all these experts working in isolation, each working on his own piece of the jigsaw puzzle.” Does science work this way, and is it unethical?

Science often works this way, and historically biology has worked this way more than other sciences, for two reasons. One, it was more of a cottage industry, needing only curiosity and simple tools, compared to physics and chemistry which needed expensive equipment and big labs. Second, it was often done by doctors, who wanted to help one particular patient, and so they used trial and error. Over the past decades all of this has changed, and advances in biochemistry and biophysics and cell biology, as well as the Human Genome Project, have made biomedical research more of a ‘big project’ field.

See also question 18 below and its answer, which is a follow-up to this one.

9. Dr. Nicolaitis says research on very rare (or “orphan”) diseases doesn’t get much funding, especially with the cutbacks under Reaganomics. Opposition to taxes and government spending is a common theme in all political conservatism. Could this be unethical? What are the obligations of government to try to financially support research and cure illness?

Teachers will have to decide how to handle political issues in their classroom discussion. But it is fair to point out that tax dollars support many valuable, even essential, social purposes. Foremost among them is education, as well as research (and biology teachers might also give a plug to such things as national parks, conservation programs, clean water and clean air). It is not coincidence that states with higher taxes often also have better public schools, better research hospitals, and lower crime (police are also paid for through taxes).

That said as a starting point, it is an interesting question just how much the government should spend for health care and medical research. It is worth pointing out, since you’re already on your high-horse, that the U.S. is the only industrialized nation that does not provide health insurance for all of its citizens. While most Americans don’t realize it, most other countries do indeed think we are uncaring and unethical in that regard. Perhaps as a result, the average lifespan is longer in at least twenty other countries than it is here (including all of Scandinavia, Western Europe, Japan, and Canada, New Zealand, and Australia).

- 10. If government does have some obligation to support research, should it focus on more common illnesses, in order to help more people, or on rare diseases, in order to help the people least likely to get help from private companies?**

A utilitarian ethical theory states that one should always do “the greatest good for the greatest number” of people. To put it colloquially, we should get the ‘biggest bang for the buck.’ But in a Capitalist society, it is also true that private companies will spend quite a bit of money on research if it is likely to lead to big profits, and will have no motive to do research to help people with rare diseases. Thus even a utilitarian could argue that government should try to balance spending in order to make the outcome more proportionate to the suffering different diseases cause. Very rare but very lethal diseases could then justify substantial research dollars from governmental sources. For this reason both the NIH and the FDA do set aside some special funding to research orphan diseases.

Also, basic science inspired by one disease can often prove fruitful in the treatment of other diseases as well. Thus steering dollars too carefully towards certain diseases for whatever reason may not be the wisest allocation system. Perhaps government should give disproportionate support to basic science with the most potential to be applied to many different diseases, or even to the most creative scientists, whatever their field of interest.

- 11. After the first international symposium, there are good results to announce. The Odone’s ask the Muscatines to announce it to the parents at the next meeting of the Foundation. Again they are rebuffed. Augusto: “Sometimes the interests of the scientists are not the same as the parents...and you serve the families by informing them... They should have a choice. If they feel the way we do, they can pressure the doctors, because as parents we should challenge them...or how else will there be progress?” Mr. Muscatine defends the doctors, saying their medical board will tell us when to announce important information in their own good time. Augusto says his “acquiescence” is “disgusting.” Should patients pressure doctors, or should they wait for enough data to make sound conclusions? Who should decide when it’s time to announce the results?**

While many scientists may still have the reaction of Mr. Muscatine, there has been increasing recognition of a role for advocacy groups in research, and that they should have some say on Foundations’ medical boards. This change in attitude is probably the result of accepting the inherent ethical issues in all scientific research, and especially medical research (that is, one cannot separate the search for ‘the good’ from the search for ‘the truth’). Until the 1950’s it was common to hold that science was only concerned with truth, that there is a clear difference between ‘facts’ and ‘values,’ and that good science was value-free. But this belief may have contributed to the scientific arrogance that led to much unethical research, such as at Tuskegee and Willowbrook. (These could make good research projects for a student.)

Note this is meant to support only having values inform clinical decisions, not determine them: premature release of results can be harmful. One must be confident that the good results are not a statistical fluke before making them public, or else you risk misleading people.

- 12. Mr. Muscatine also says “If you didn’t have all this denial, you wouldn’t do a thing to prolong your boys suffering one minute longer.” He goes on to say that it was better when his first boy died quickly, compared to the way his second boy has lingered for three years. Is there a point where it is no longer worth living?**

Many people, probably even most people, would agree that there are medical conditions worse than death. This is why the timing of most deaths are now decided in part by family members: when a patient is in the hospital, and in a condition not worth prolonging, the family often chooses to withdraw a medical intervention that is keeping their loved one alive. So long as this decision reflects the values of the patient, this is considered ethical.

- 13. Soon after, Lorenzo's blood chemistry levels off, that is, stops improving. The nurse suggests placing Lorenzo in a facility, which Michaela takes to mean hospice, and Michaela fires her. Then Michaela's sister says maybe this fight is no longer worth the effort, and is also asked to leave. What is hospice?**

Hospice, also known as "Comfort Care," is a treatment plan for patients who have accepted that their death is inevitable. The goal of all medical treatment then is to improve the patient's quality of life, including pain control, mental and spiritual health, and practical things like going home to die (with good nursing care) rather than remaining in the impersonal environment of the hospital.

- 14. Augusto returns to the library, and has a dream that leads up to the request to add erucic acid to the oleic acid. Dr. Nicolaitis worries about the potential effects on the heart. Michaela replies: "The life of one boy is not enough reward for you to risk the reputation of the institution and the esteem of your peers. We are only asking for a little courage." How should a researcher decide when to try a (possibly risky) new therapy?**

Researchers are expected to consider the risks to patients before proposing any new research protocol. They then have to write their proposal and submit it to an IRB: Institutional Review Board. This is a committee made up of scientists and nonscientists, whose job is to make sure the research has promise, and does not have undue risks associated with it. IRBs are meant to protect research subjects from overly aggressive researchers.

How can a researcher know how dangerous a proposed intervention is, if he hasn't yet started his research? There are two steps that must be taken before human subjects are involved in research. First, there must be research on animals, and it must give some reason to think the idea will work. Second, the human subjects must first be exposed to very low doses or minimal risk interventions, to test for safety, before increasing the dose/intervention to a potentially therapeutic level.

All of this takes time, which is why it is common to assume that it will take ten years for any new treatment to be available for human use. Of course, this often means many patients will die before the treatment is available.

- 15. Michaela's sister Deirdre returns at Augusto's request, and offers to be the "rat" that gets experimented on. She eats the erucic acid, with no ill effect. Who should scientists ask to be the first to try something they think could be dangerous?**

Despite the protections mentioned in the previous answer, there will always be someone who goes first. And there have been some cases where a doctor decided to try something on himself first. A book entitled "Who Goes First" (by New York Times reporter Lawrence Altman, M.D.) chronicles some of these cases, and is relatively fun to read.

- 16. The new oil combination lowers Lorenzo's blood chemistries to normal, and the Odone's make a surprise announcement at the next ALD Foundation meeting. The Muscatines are incensed and Dr. Nicolaitis protests that insurance won't pay for it unless it is FDA approved, and the FDA won't approve it unless it has been tested and proven to work. The audience points out that AIDS patients' protests succeeded in speeding up FDA approval of drugs to fight HIV, because "patients were dying." Should the FDA be subject to political pressure from advocates and activists? Should the lethal nature of a disease make a difference in the scientific process of approval?**

Advocacy groups have become much more common since this movie was made. AIDS may have started it (with 'Act-Up'), but now MADD, breast cancer survivors, and many others lobby Congress for more research money. There is a danger here that some groups will suffer as a result, since there is only a limited amount of money available for research, so if the money is doubled for breast cancer, then it must be cut somewhere else.

More to the point here, it is justifiable to pressure for quick action when people are dying. And it makes "good press." This is all part of a democracy. It is not a perfect system and experts often find themselves having to defend themselves from the charge of elitism, but in the long run it seems to work better than more authoritarian systems. In this view, then, it is every citizen's duty to fight for what he or she thinks is right, and put their best case forward. The best term to understand how researchers have one legitimate goal and patients another might be dialectic: each should engage the other in discussion, be willing to listen and compromise, and trust that progress will result.

Since it is true that insurance won't pay for something until it has been FDA approved, very much is at stake with these issues. Of course, there is always the other side: insurance companies are right to not pay for unproven therapies, as it may not work and will drive up the cost of insurance (which will ultimately mean fewer people are insured because it gets too expensive).

- 17. Another year passes, and Lorenzo is still unable to communicate. Augusto worries that he is still 'in there' but that it's like being "trapped down in a dark cave... and he can't find his way out." Is it possible that some medical conditions are worse than death? Then he asks Michaela, "Do you ever think that maybe all of this struggle may have been for somebody else's kid?" If the answer should turn out to be "Yes," does that mean it was not worth it, or they should not have put Lorenzo through all of his suffering?**

Being conscious but totally unable to move is one of those conditions that many people would say is worse than death. It is called "locked-in syndrome." It can be caused by a number of things, but usually does not last long: either the patient improves or dies within a few weeks.

It certainly will be the case for many research subjects that their volunteering will benefit someone else, but will not benefit themselves. If people enroll in a study because they think it will benefit them, this is called the "therapeutic misconception." Researchers should not encourage that hope. Rather, one hopes subjects to be happy to have participated in something that will benefit someone else. This is called altruism, and is a more common human motivation than many people appreciate.

These questions are all the more difficult when the patient is not the one who consented to the research, as with parents and their kids. Unless Lorenzo can speak for himself one day, we will never know if he would say this was worth it to him. And we cannot be sure what he would say if he does speak for himself some day: he might still say it was not worth it. (The famous case of Dax is an example of this scenario, which a student might research.) Still, given his age when all of this happened, and the incredible dedication his parents have shown, it seems highly likely that he would be grateful for having a chance to interact again with the people he loves.

- 18. Dr. Duncan at Wisconsin is working on remyelination, but he says the research will take years, because "We scientists are a very competitive lot. ...Collaboration is a lovely idea, but sadly, that is not how science works." Augusto proposes a second international conference, modeled on the Apollo Project, to achieve a set goal as quickly as possible. Are scientists' motives, such as getting a job, making money, being promoted, and becoming famous egocentric and unethical? Or just human nature? Should we expect more of them?**

This is a follow-up to question eight. Science probably benefits overall from scientists being competitive and having egos and careers on the line. Not to mention that this is true for everyone else, and it is unrealistic to expect scientists to be any different. Augusto's suggestion of a conference is the right one precisely because it appeals to their egos and competitive nature.

There has been much written about the ethics of sharing research data, and whether public funding should require sharing of research data. As things now stand, alas, this is not the case. There is also discussion of whether some journal policies impede clinical research by placing blackouts on information from the date the article is accepted until it appears in print. There are also concerns that private sources of funding and private companies doing research try to prevent the publication of negative results, which can make important contributions to progress by preventing unnecessary redundancy and waste of time.

Concluding Comment and Recommended Reading and Research

Any of the 18 above questions could give a bright student a research project that could lead to a paper or class presentation, which could be for extra credit or could be a course requirement (especially for an AP class). A web search would turn up many references to any of the key words mentioned. A few book titles which might also be of interest:

1. *The Worth of a Child*, by Tom Murray.
2. *The Patient in the Family*. by James Lindeman Nelson and Hilde Lindeman Nelson.
3. *The Ethical Dimensions of the Biological and Health Sciences*, 2e, by Ruth Ellen Bulger, Elizabeth Heitman, and Stanley Joel Reiser.
4. *Protecting Study Volunteers in Research*. Cynthia McGuire Dunn and Gary Chadwick.

DEMYELINATION ACTIVITY

Demyelination is the loss of myelin around the axons of neurons. Myelin is a fatty substance which speeds up the transmission of impulses along axons. Symptoms of certain diseases like Multiple Sclerosis, Phenylketonuria, and Adrenoleukodystrophy are caused by demyelination. The sufferer develops devastating symptoms, such as loss of hearing, vision, gait or coordinated walking, feeding oneself, movement of arms, swallowing and breathing, eventually leading to death.

In order to understand the vital role of myelin, this activity will engage students to participate as 'myelin' along an axon. Their job as an axon is to pass along as many impulses as possible in a very short amount of time from the 'brain' to the 'body'. Impulses are represented by tennis balls with examples of body functions written on masking tape taped to them.

Initially, students will behave like a normal neuron and pass along many impulses. After a few rounds of normal neuron function, one or two students will be asked to sit down, representing the loss of myelin. The impulse transmission will resume but will be difficult due to the loss of 'myelin'.

MATERIALS

80 or so tennis balls = impulses

one roll of masking tape to write examples of body functions

one marker or pen

two buckets, one called 'Brain' and a second called 'Body'

one stop watch or the second hand of a clock

PROCEDURES

1. Ask 12 students to line up about 3 feet apart from each other (to help space students apart, ask students to make a 'T' with their arms and body).
2. Place the 'Brain' bucket in front of 'Myelin' person #1 and the 'Body' bucket behind 'Myelin' person #12.
3. Students will be given 10 seconds to pass 'Impulses' from the 'Brain' to the 'Body' bucket. 'Myelin' person #1 will pick up a tennis ball from the 'Brain' bucket with two hands and pass it to 'Myelin' person #2, who will collect and pass the ball along using two hands to 'Myelin' person #3. Do this until 'Myelin' person #12 receives the tennis ball. 'Myelin' people may not chase any tennis balls they may drop.
4. At this point, using two hands 'Myelin' person #12 will drop the 'Impulse' into the 'Body' bucket. Any tennis balls that fell out of 'Myelin' people hands will not be counted towards the 'Body' bucket.
5. As soon as 'Myelin' person #2 has passed the 'Impulse' to 'Myelin' person #3, then 'Myelin' person #1 can pick up another tennis ball and start another impulse transmission. Repeat this process until 10 seconds are over.
6. After 10 seconds, ask 'Myelin' person #12 to count (and name a few examples of body functions) the number of tennis balls in the 'Body' bucket.
7. Start a new Trial and ask that 'Myelin' persons #3 and #9 sit down. Make sure the other 'Myelin' people do not slide close to each other to fill the gap.
8. Reminder! The remaining 'Myelin' people must pass the tennis balls from one person to the next in the same manner as in first trial. Tossing, throwing and bouncing are not allowed. This means that 'Myelin' people may have to drop the tennis ball and hope that it rolls into the direction of the next 'Myelin' person.
9. After 10 seconds, count the number of tennis ball impulses in the 'Body' bucket. If you can, name a few examples of body functions from the tennis balls.
10. Try a third trial, ask two more students to sit down, and use the same technique described above.

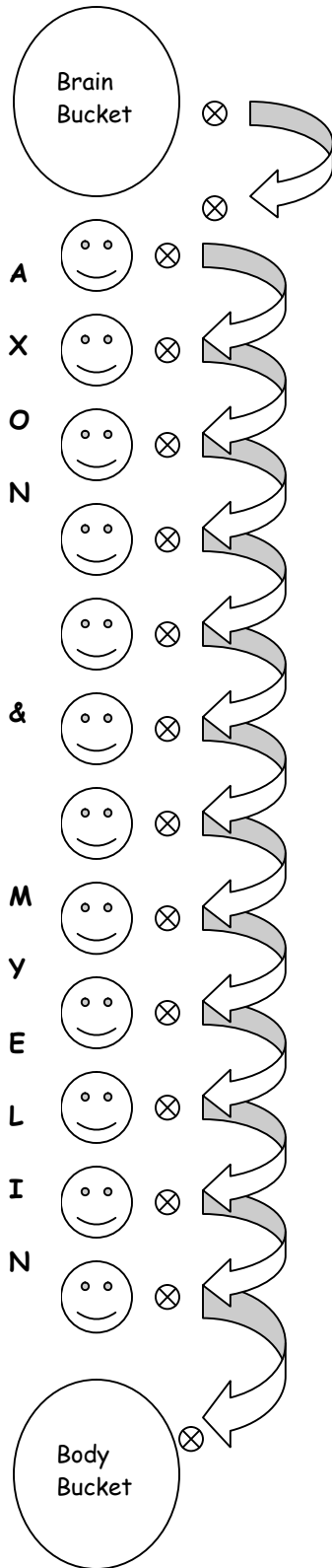
Post lab Analysis

1. What did the tennis balls represent?
2. What process did you and your classmates demonstrate in the activity?
3. What happened to the Impulse Transmission after 'Myelin' person #3 and #9 sat down?
4. How does this activity model demyelination?
5. Based on what you learned from the activity, how does demyelination cause a person to become impaired, eventually leading to death?

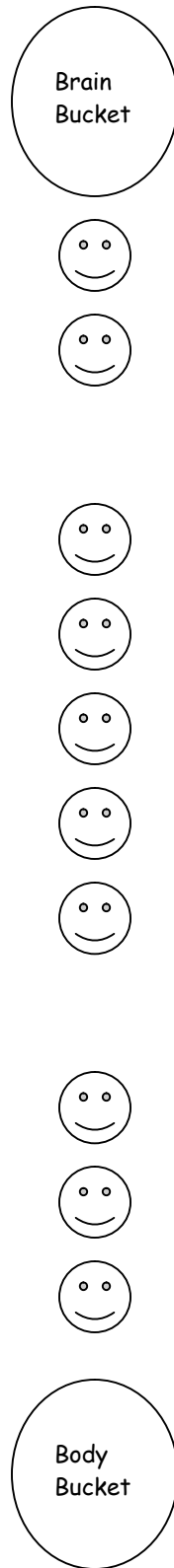
Demyelination Activity Setup

(not drawn to scale)

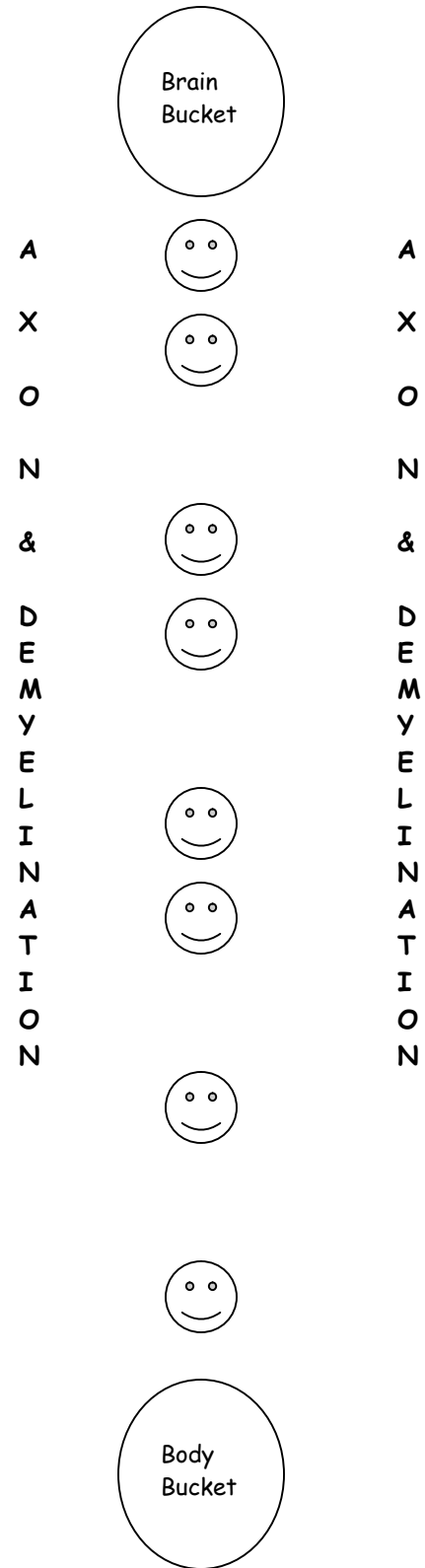
Trial One



Trial Two



Trial Three



COMPETITIVE INHIBITION: HOW LORENZO'S OIL WORKS

In the movie, *Lorenzo's Oil*, the defective enzyme complex (ALD) metabolizes short chains of fatty acids to make long chains of fatty acids for later use in the body. The defective enzyme complex metabolizes both kinds of fatty acids (saturated=bad and monounsaturated=good). The enzyme complex builds or elongates chains of fatty acids by linking two carbon atoms to each other; however, the enzyme complex does not distinguish between the carbon atoms from good and bad fatty acids. The result is the production of long chains of saturated fatty acids. This build-up of saturated fatty acids dissolves the myelin surrounding axons in the nervous system, causing demyelination to occur.

Competitive inhibition is a process by which an enzyme's active site can be occupied by more than one substrate. The result is one substrate is metabolized while the other substrate is not, or at least not to a great extent. *Lorenzo's Oil* is made up of very long chains of monounsaturated fatty acids which bind more tightly at the enzyme's active site. The very long chains of saturated fatty acids are not metabolized. The enzyme complex synthesizes long chains of fatty acids using more carbons from good monounsaturated fatty acids than carbon atoms from bad saturated fatty acids. The result is a production of very long chains of monounsaturated fatty acids and a reduction in the bad saturated fatty acids in the body. Less saturated fatty acids means less demyelination for ALD sufferers. The following classroom activity can be used to model how *Lorenzo's Oil* works at reducing saturated fatty acids in the body.

Materials

- Four students: one 'enzyme', one 'good unsaturated fatty acid', one 'bad saturated fatty acid', and one 'body'.
- Paper clips: two different shapes or colors to represent carbon atoms for each type of fatty acid: unsaturated=good and saturated=bad.

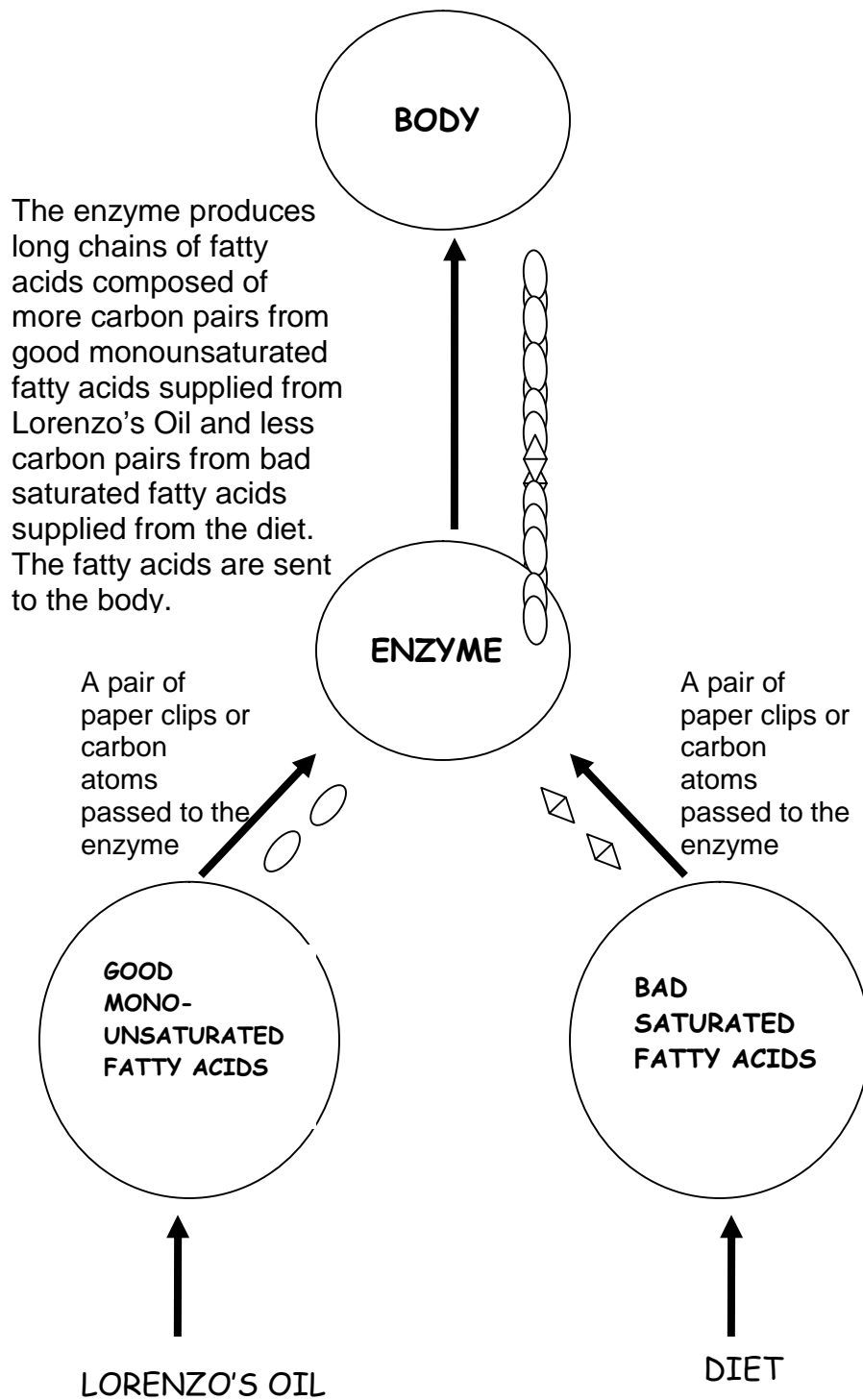
Procedures

1. The good unsaturated fatty acid passes two paper clips or carbon atoms to the enzyme.
2. The enzyme links the carbon atoms together to form a 2 carbon chain.
3. The good unsaturated fatty acid continues to pass two paper clips or carbon atoms to the enzyme.
4. After six pairs (or one dozen) paper clips or carbon atoms have been passed to the enzyme for linking in a 12 carbon chain, the bad saturated fatty acid passes two clips or carbon atoms to the enzyme and the enzyme links the bad saturated fatty acids on to the growing carbon chain.
5. The good unsaturated fatty acid passes more pairs of unsaturated fatty acids to the enzyme and the enzyme continues to link them on to the growing chain of fatty acids.
6. The enzyme stops the process and passes the fatty acid chain (with more unsaturated carbon atoms than saturated carbon acids) to the person representing the body.

Post Analysis Questions

1. What do the paper clips represent? Why are there two different shaped or colored paper clips?
2. What role does the enzyme play? In other words, what is its function?
3. How many carbon atoms long was the fatty acid chain produced by the enzyme?
4. Were there more carbon atoms from the saturated or monounsaturated fatty acids?
5. Which kind of fatty acids destroy myelin?
6. Explain how *Lorenzo's Oil* prevents the destruction of myelin in sufferers of ALD.

COMPETITIVE INHIBITION MODEL SETUP



Evaluation and Feedback for Lorenzo's Oil Kit

Please take a moment and reflect on the use of the Lorenzo's Oil kit. It would be very helpful for the Myelin Project to hear your evaluation, comments, concerns, and questions. Thank you very much!

Please use the scale to rate your responses

0	1	2	3	4	5
I don't know	Very Dissatisfied	Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied

1. How satisfied were you with the **film**?
If you rated a 1 or 2, please tell us why.
2. How satisfied were you with the **science questions**?
If you rated a 1 or 2, please tell us why.
3. How satisfied were you with the **ethical questions**?
If you rated a 1 or 2, please tell us why.
4. How satisfied were you with the **Demyelination Activity**?
If you rated a 1 or 2, please tell us why.
5. How satisfied were you with the **Competitive Inhibition Activity**?
If you rated a 1 or 2, please tell us why.
6. How satisfied were you with the **master diagrams for transparencies**?
If you rated a 1 or 2, please tell us why.
7. Would you use the kit again with other classes?
8. Would you recommend the kit to other teachers?
A. If so, please tell us what subject and grade level your fellow teachers teach.
B. If not, please tell us why.
9. Please describe the strengths of the kit.
10. Please describe the weaknesses of the kit.
11. Do you feel the kit accomplished your reasons for using it to teach science?
12. Please identify any comments, concerns, or questions you may have about the kit, the Myelin Project, etc.

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