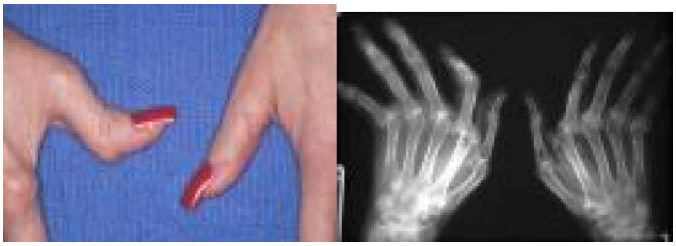
Name: _____ Date: _____
A Case Study in Pharmaceutical Research Class Work: Part I

Aim: How do Biologists *Select* their Projects?

What is Rheumatoid Arthritis?

Rheumatoid arthritis (rue-ma-TOYD arth-write-tis) is a chronic disease, mainly characterized by inflammation of the lining of the joints. It can lead to long-term joint damage, resulting in chronic pain, loss of function and disability.

Rheumatoid arthritis (RA) progresses in three stages. The first stage is the swelling of the synovial lining, causing pain, warmth, stiffness, redness and swelling around the joint. Second is the rapid division and growth of cells, which causes the synovium (the joint lining) to thicken. In the third stage, the inflamed cells release ***enzymes*** *that may digest bone and cartilage*, often causing the involved joint to lose its shape and alignment, more pain, and loss of movement.



Because it is a chronic (long-term) disease, RA continues indefinitely and may not go away. Frequent flares in disease activity can occur. RA is a systemic disease, which means it can affect other organs in the body. Early diagnosis and treatment of RA is critical if you want to continue living a productive lifestyle. Studies have shown that early aggressive treatment of RA can limit joint damage, which in turn limits loss of movement, decreased ability to work, higher medical costs and potential surgery.

RA affects 1 percent of the U.S. population or 2.1 million Americans. While there is no cure, patients are hopeful to control RA through the use of new drugs, exercise, joint protection techniques and self-management techniques.

Ref: Arthritis Foundation, Disease Center- RA, http://www.arthritis.org/conditions/DiseaseCenter/RA/ra_overview.asp (accessed on 9/12/05)

Questions for you to answer (in complete sentences):

1. In your own words, define the difference between scientific opinion and scientific fact.

2. State one opinion in this segment:

3. Describe one possible scenario that you feel could have led scientists to form this opinion.

4. State one scientific fact in this segment:

5. Describe one possible scenario that could have led scientists to state this fact.

Think like a physician:

6. Why would doctors and researchers want to study a group of people who have Rheumatoid Arthritis (RA)?

7. If you were the scientist in charge of a study, what information (data) would you want to have about the patients you were interested in studying?

8. What observations or types of tests can you think of that would give you this information (based on your answer to #7)?

Celebra is born!

Anti-inflammatory drugs such as aspirin (like Bayer) and ibuprofen (like Advil) have been used to treat arthritis for many years.

Pain, redness, heat, and swelling, which are the main symptoms of inflammation, happen when prostaglandins are released. Prostaglandins are hormones that carry local messages in the body. Aspirin and similar drugs, {all grouped together as *non-steroidal* anti-inflammatory (NSAIDS)] reduce the release of these prostaglandins by blocking an enzyme which helps to produce them, called cyclooxygenase *[referred to as "cyclo" from now on in this passage to make reading aloud easier for volunteers].*

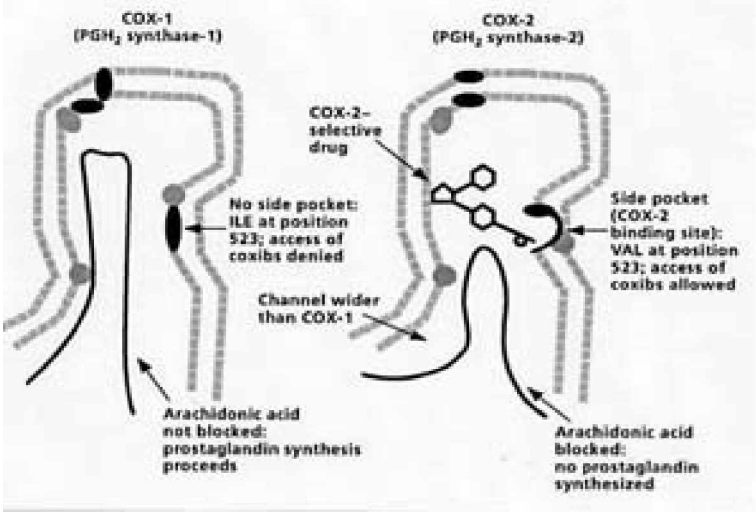
9. Use different shapes (and colors if preferable) to represent each of the molecules you just read about to draw a diagram that explains this paragraph. Be sure to include a key in the box below to help explain your sketch.

Key:

A model of the cyclooxygenase enzyme

Aspirin and similar non-steroidal anti-inflammatory drugs (NSAIDS) are among the most heavily used drugs in the world, even though they have been disappointing in their benefits and led to uncomfortable side effects, such as stomach pain, heartburn, nausea and/or vomiting. Last year, *seventy-seven million prescriptions* for NSAIDS were written in the United States! In the United States alone, NSAIDS account for sales of as much *as eight billion dollars a year!* They have been hugely popular because they were considered the best alternative to higher risk immunosuppressant therapies used to treat disabling forms of arthritis (treatments that lower the patient's ability to fight off other diseases). Yet most people who use NSAIDS have eagerly awaited something better which would promise more relief and which would abate the unwanted side effects.

Scientists made a breakthrough with a whole new class of arthritis drugs. In 1998, one new medicine, promoted as a "Super Aspirin", turned everyone's head and renewed hope among both arthritis sufferers and researchers. It earned the name Celebra in 1995, but before it ever made its way to trials on people, the head researcher, Dr. Phillip Needleman, hypothesized back in 1990 that there were two kinds of "cyclo" enzyme. One "cyclo" enzyme provided regular levels of prostaglandin that kept the stomach, platelets, kidneys, and other tissues in working order. The second "cyclo" enzyme was produced only in the event of inflammation or trauma and generated the high levels of prostaglandins that then cause inflammation in the area.



"cyclo"-1 vs. "cyclo"-2

(Note: remember how different enzymes have different shapes!)

10. Enzymes are biochemicals; to understand them we often make diagrams like the one above.
a) Based on the diagram, describe one difference you see between "cyclo"-1 and "cyclo"-2 :

b) Based on your observation and those of your group-mates, predict what you believe to be the most important difference between these two molecules with respect to the way they act with prostaglandins:

In 1991, other scientists supported his hypothesis and isolated the second enzyme. Dr. Needleman then directed his efforts to find a drug that could distinguish between the two "cyclo" enzymes. Eventually, Dr. Needleman created a chemical compound called celecoxib which blocked "cyclo"-2 yet didn't harm the important "cyclo"-1.

Questions for you to answer (in complete sentences):

11. Why would a patient with RA want to take aspirin?

12. a) What was Dr. Needleman's original hypothesis?

b) What information allowed him to later create the chemical celecoxib?

c) Why do you think it took eight years to finally give patients access to this drug?

SIDE NOTES for today… on Scientific Careers

A. Major drug companies generally do not give a researcher a great deal of funding based on his/her own hypothesis, data, and conclusions alone. Why is that in the companies' best interest?

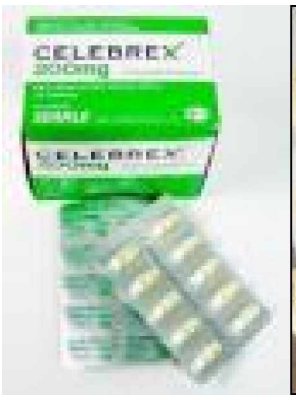
B. In your opinion, is science and individual or team effort? Be sure to explain/ defend your answer.

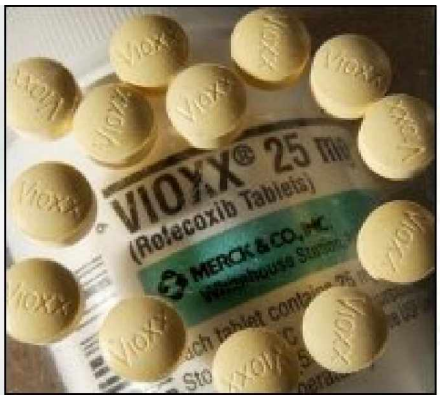
Name: _____ Date: _____
A Case Study in Pharmaceutical Research Part II

Aim: How do Biologists *Design* their Projects?

Celebra, on trial in laboratories and hospitals!

Studies of celecoxib advanced from test tube to animals to man. In March 1995, five years after Needleman presented his theories at the international conference, the first patient was treated with this new drug that the Monsanto Company (who funded his research) has named Celebra. Pfizer, one of the leading pharmaceutical companies in the world, bought the rights to the product and marketed it as "Celebrex". Merck, one of Pfizer's greatest competitors, has also produced a "cyclo"-2 inhibitor. The Merck version is known as Vioxx.





Questions for you to answer (in complete sentences):

13. Can a hypothesis ever be proven to be true? Why or why not?

14. State a testable hypothesis for this clinical trial:

Define: null hypothesis = _____

_____

15. If needed, re-state your hypothesis here:

16. Based on what you know and understand about scientific thinking so far, use the space below to outline an experiment that can be used to test this hypothesis.

You have the following materials available (circle the items you have selected to Use; you can also request one other item if needed):

- n Digital timer
- n Stethescope
- n Thermometer
- n Scale
- n Metric ruler
- n Tool for measuring angles
- n Tennis ball
- n Pen and paper
- n Other: _____

Be sure to describe the specific set of conditions for the experiment. Need help? Ponder the following questions with your group for guidance:

a) One test group or two groups? Why?
b) What are we testing in these trials? How do we use our 2 groups (experimental and control) to test the medicine?
c) If we want to focus strictly on the medicine, what should be the same between these groups?
d) What will we look for to show us if the medicine is or is not causing a change?

Compare Designs:

Carefully read and highlight the key points in the following description:

Pfizer's lead researcher considers the hypothesis that the drug Celebrex does not help relieve rheumatoid arthritis. (S)he predicts that patients suffering from rheumatoid arthritis who take Celebrex and patients who take a placebo (a starch/ sugar pill instead of the drug) do not differ in severity of rheumatoid arthritis.

1000 patients between the ages of 50 and 70 will be randomly assigned to one of two groups of 500 people. The experimental group will take Celebrex four times a day and the control group will take a starch placebo four times a day. The patients will not know whether their tablets are Celebrex or the placebo. Patients will take the tablets for two months. At the end of two months, medical exams will be administered to determine if flexibility of the arms and fingers has changed.

The experiment produced the following results: 350 of the 500 people who took Celebrex reported diminished symptoms of arthritis at the end of the trial period. 65 of the 500 people who took the placebo reported improvement. The data appear to show that there was a significant effect of Celebra. Therefore, the prediction that Celebra will have no effect must be rejected, and since the prediction is wrong, the hypothesis it was based on is rejected.

17.

a) In your opinion, is this a fair test? Why or why not?

b) Based on the results, state a conclusion for this experiment:

18. Have you proven an alternative hypothesis to be true? Why or why not?

Identifying components of an experiment:

19. Using the “elegant” (ie. controlled) experiment you just read about, fill in each of the missing components:

Part of an Experiment	***Purpose***	***Example***
1. Hypothesis:		
2. Prediction:		
3. Experimental Group:		
4. Control Group:		
5. *Independent Variable:		
6. *Dependent Variable:		
7. *Controlled Variables:		
8. Results:		
9. Conclusion		

Name: _____ Date: _____
A Case Study in Pharmaceutical Research Class Work: Part III

Aim: How do Biologists *Revise* their Projects?

The Missing Step… Reporting your Findings

Scientists publish their findings n journals and books, in talks at national and international meetings and in seminars at colleges and universities. This is an important part of their methodology.

22. Why is it important for scientists to disclose their findings to others? Why might is be a difficult decision for some groups of researchers?

23. If Pfizer and Merck were "racing deadlines", how might this have influenced this important final step of "elegant" experimentation?

24. How might the battle between 2 major drug companies alter the clinical trials?

25. Why is it important to allow other groups of scientists and agencies verify your claims to effectiveness and safety?

Vioxx [and Celebrex too] on trial again, but this time in a courtroom…

It was believed throughout the 1990s that Celebra had sparked a whole new category of drugs inciting a whole new wave of optimism and hope. However, much if this great optimism has been lost.

In September, 2001 the American Heart Association, the National Stroke Association and the Arthritis Foundation asked Celebrex' manufacturer (Pharmacia Corp.) to test whether Celebrex increases the risk of heart attack and stroke.

The US Food and Drug Administration sent Celebrex' manufacturer (Pharmacia Corp.) a "Warning Letter" on February 1, 2001. The warning letter required Pharmacia Corp. to cease certain promotional activities for Celebrex.

On Dec-17-04 Pfizer revealed that one of two clinical trials showed an increased cardiovascular risk for patients taking the arthritis medication Celebrex. Pfizer is taking steps to discover why there is a discrepancy between the two trials, but is not removing Celebrex from the marketplace. Doctors, however are becoming worried about possible heart attack and stroke for patients using “cyclo”-2 inhibitor drugs, and are advising patients with heart disease not to use drugs such as Celebrex.

Vioxx, another “cyclo”-2 inhibitor, was withdrawn from the marketplace in September 2004 when a link to serious heart problems was found in Vioxx users. Unfortunately, three-year data from a placebo-controlled clinical trial showed increased relative risk for cardiovascular events, such as heart attack and stroke. Symptoms were present beginning after 18 months of continuous treatment in the patients taking Vioxx compared to those taking placebo. Merck's decision was to voluntarily recall Vioxx and to reimburse anyone with unused medication.

Merck expects about 16,000 people to file legitimate Vioxx law suits against the company. Wall Street analysts project that the number of successful law suits will be significantly higher.

Ref: US Food and Drug Administration, “COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)” http://www.fda.gov/cder/drug/infopage/COX2/default.htm (accessed on 9/12/05).

Ref: National Claims Center, “Vioxx Claims Center” http://www.vioxx-center.com/ (accessed on 9/12/05).

26. Why do you think this problem occurred?

27. How do you think this situation could be avoided in the future?

SIDE NOTES for today… on <u>Science's Role in Society</u>

C. What role did non-profit organizations play in preventing future deaths?

D. What types of settlement do you think the families of the deceased deserve?