The Biological Sleuth Project

I. Introduction

The scientific method involves a few key elements. The most important is that it is a process in which ideas and models (hypotheses) are continually tested through experimentation. Hypotheses that cannot be supported by reproducible experimental results must be and are discarded. A second key element is the reporting of these experimental results in peer-reviewed journals so that they can be reproduced and extended by others. The scientific literature has become a critical element in the dissemination of new information as our knowledge grows.

Often there are numerous hypotheses or models related to a single scientific question. As Biological Sleuths, you will examine a specific question on which different hypotheses have been presented. Though you will not be expected to carry out further experiments, the scientific literature will provide you with an answer that is now accepted. To accomplish this goal, you will need (1) to carry out a search of the literature on a specific question, (2) find appropriate references that report scientific results and (3) assess the relevance of these results to the hypotheses being considered.

The aims of this project are: (1) to introduce you to the scientific literature (2) to provide you with the skills for searching this literature and (3) to use your analytical skills to evaluate the results you have found in relation to the specific question that you are considering.

Although this is not exactly what the master sleuth, Sherlock Holmes, has done in the past, your ability to search and evaluate the literature to find answers to specific questions is essential to learning to function in our scientific world.

II. Project RoadMap

1. Each Discussion Section will be assigned a single research topic. The assigned projects are listed as Part III of this presentation. Do not select a project from the complete list, but do complete the project assigned to your section.

2. Each student is required to attend a one-hour Library Orientation session that will be held during the first or second week of the semester. This session, which will be led to Bioscience Library staff, will introduce students to the periodical database and methods for searches of the literature and is essential for the successful completion of this project. Students will sign up for one specific orientation time period. Attendance will be taken, and **students will receive 5 pts toward their grade for attendance.**

3. Students will be expected to use the library resources to carry out a directed search of the primary literature on the assigned topic. Key Authors and appropriate dates are given for each topic and these serve as convenient starting points for literature searches, but these searches need not be limited to the Key Authors. Using the Key Authors and indicated dates should limit the number of references that you obtain for any specific problem. Students are encouraged to work in small groups to

identify the critical references related to their topic although every student is expected to hand in their individual written report.

4. One week after the Library Orientation (the second and third week of the semester, depending on the date of the Library Orientation) each student will submit electronically through the Digital Drop Box (under Tools) of the Biology 1A Blackboard site a list of 8 references, including one review that they will use to identify the final 2-3 references that will be analyzed for the specific research topic. The final paper must be completed using some, but not all, of these references. **5 points will be given for submission of this reference list.**

5. After the identification of key references on the specific topic, students will be expected to look up these specific papers and identify the key points that relate to the assigned topic. It is not necessary to read all of the papers that you have identified, and you should be able to obtain the information you need from the Abstract of the papers.

6. No more than three key references from the original list of 8 should provide the basic information to deal with the specific hypothesis.

7. A short written report (no more than 2 pages) should then be prepared that summarizes the key points identified in these references, and the results from the papers should be succinctly reported in relation to support or denial of the proposed hypothesis or question. Guidelines for the paper are as follows:

a. State the problem being considered
b. Cite the articles that were chosen to consider the problem
c. Briefly summarize the major points of the individual articles
d. What are the conclusions that you draw from the selected articles in relation to the problem being considered

Reports must be typed and can be single-spaced using a #12 font. Identify the section number and your GSI on the report. **All reports are to be submitted electronically via the Digital Drop Box for Biology 1A no later than 6 PM on October 3, 2003.** Late submissions will not be accepted.

8. Grading: Reports will be graded on three scales, as outlined below:

20 points—an overall excellent report. Contains clear and concise scientific analysis of references. Report is well written with no grammatical or spelling errors.

10 points—an average report. Not clearly presented or not concise. Displays average writing skills.

3 points—a below average report. Unclear scientific thinking and/or unsatisfactory identification of key references. Below average written presentation because of lack of clarity or contains poor English and poor grammar.

Summary of Grading for the Sleuth Project
-Maximum number of points = 30

Breakdown of points for the project:

-Attendance at Library Orientation (1st and 2nd weeks)—5 pts.
-Reference List (due one week after Library Orientation)—5 pts.
-Final project paper (due Oct. 3, 2003 by 6 PM)—maximum of 20 pts.

III. Sleuth Projects—assigned by Section. You must do the project that is assigned to your Discussion Section.

Sections 101 and 110

In the early 1960s, two alternative hypotheses were proposed to explain how chlorophyll is bound in plants. According to one model, chlorophyll is localized in the inner membrane of the chloroplast in association with lipids, while in the second model, chlorophyll has been proposed to be associated with specific proteins in the inner membrane of the chloroplast. You will carry out a literature search starting with Key Authors (J. P. Thornber, J. M. Anderson, W. Kuhlbrandt) that will provide an answer to the question of how chlorophyll is bound in photosynthetic organisms. You will then write a short report (no more than two pages) that will summarize your findings, citing no more than three specific references, stating what the relevance of these references is to the hypotheses proposed.

Sections 102 and 111

Ferredoxins are low molecular weight electron transfer proteins that function in both respiration and photosynthesis. These proteins contain equivalent amounts of non-heme iron and an unusual form of sulfur that is released as hydrogen sulfide after acidification. Soon after their initial discovery in 1962, it was proposed that the source of hydrogen sulfide were the cysteine amino acids in the ferredoxins. You will carry out a literature search, starting in 1962, using Key Authors (E. Bayer, J. C. Rabinowitz, L. Jensen) that will provide an answer to the question of what is the source of the sulfide found in the ferredoxins. You will then write a short report (no more than two pages) that will summarize your findings, citing no more than three specific references, stating what the relevance of these references is to the proposal discussed above.

Sections 103 and 112

Warburg and Luttgens discovered in 1944 that chloride was essential for plant growth. Subsequently, it was proposed that chloride was required for a specific enzyme involved in carbon dioxide fixation in the chloroplast. You will carry out a literature search, starting in 1969, using Key Authors (S. Izawa, G. Hind, C. Critchley) that will seek to answer the question of the function of chloride in photosynthesis. You will then write a short report (no more than two pages) that will summarize your findings, citing no more than three specific references, stating what the relevance of these references is to the proposal discussed above.

Sections 104 and 113

Copper has been proposed to be an essential element for the growth of oxygen-evolving photosynthetic organisms, such as plants, algae and cyanobacteria. Yet, there are reports from some research groups that some algae and cyanobacteria can grow in the absence of copper. You will carry out a literature search, starting in 1960 using Key Authors (S. Katoh, P. Wood, S. Merchant) that will answer the question of what is the function of copper in oxygen-evolving photosynthetic organisms and if it is essential for the growth of these organisms. You will then write a short report (no more than two pages) that will summarize your findings,

citing no more than three specific references, stating what the relevance of these references is to the proposal discussed above.

Sections 105 and 114

Glycogen phosphorylase is a key enzyme in the metabolism of glycogen in animal cells. It has been proposed that this enzyme can exist in two forms, a and b, one of which is active while the second form is inactive, and that these forms are interconverted by phosphorylation. You will carry out a literature survey starting in 1955 using Key Authors (E. Krebs, E. H. Fischer, E. Sutherland) that will answer the question of the existence of two forms of phosphorylase. You will then write a short report (no more than two pages) that will summarize your findings, citing no more than three specific references, stating what the relevance of these references is to the proposal discussed above.

Sections 115 and 117

While it was originally proposed that water molecules did not require a channel or carrier to cross a biological membrane, a more recent proposal has been put forward: protein molecules that form water channels (aquaporins) have been proposed to be involved in water movement across membranes of various organelles and cells. You will carry out a literature search, starting in 1990, using Key Authors (C. Maurel, M. J. Chrispeels) that will seek to answer the question of whether water channels exist and function in biological membranes. You will then write a short report (no more than two pages) that will summarize your findings, citing no more than three specific references, stating what the relevance of these references is to the question discussed above.

Sections 107 and 116

While early work indicated that protein folding is governed solely by the protein itself, researchers have recently proposed that some proteins, known as chaperones, help in the process of the folding of other proteins. You will carry out a literature search, starting in 1995, using Key Authors (R. J. Ellis, F. U. Hartl, J. Frydman) that considers the question of whether protein folding is assisted by additional proteins. You will then write a short report (no more than two pages) that will summarize your findings, citing no more than three specific references, stating what the relevance of these references is to the question discussed above.

Sections 106, 108 and 119

The 1970s saw the development of X-ray crystallography as a powerful tool for the elucidation of the structure of proteins, but this technique was limited to the application of soluble proteins, such as hemoglobin and myoglobin. It was believed that the hydrophobic nature of membrane proteins precluded their crystallization and subsequent analysis by crystallographic methods. You will carry out a literature search, starting in 1980, using Key Authors (H. Michel, J. Deisenhofer, W. Kuhlbrandt) that considers the question of whether membrane proteins can be crystallized and their complete structures determined. You will then write a short report (no more than two pages) that will summarize your findings, citing no more than three specific references, stating what the relevance of these references is to the question discussed above.

Sections 109, 118 and 120

A central dogma of modern biochemistry was the belief that all biological catalysts were proteins, known as enzymes. You will carry out a literature, starting in 1984, search using Key Authors (T. Cech, S. Altman) that considers the question of whether biological catalysts are only proteins. You will then write a short report (no more than two pages) that will summarize your findings, citing no more than three specific references, stating what the relevance of these references is to the question discussed above.

IV. Model Sleuth Paper

In 1949, Linus Pauling, one of the greatest chemists of the 20th century, called sickle cell anemia a "molecular disease," implying that an abnormal molecule was responsible for the systems. The hypothesis put forward by Pauling is the basis of the proposed research project. Students will be asked to carry out a literature survey, starting in 1949 that will identify primary research that provides either a positive or negative answer to Pauling's view of sickle cell anemia and then they will write a short report (no more than two pages), briefly summarizing the results that bear on this question, citing specific references and what their relevance to the question is.

I. Problem

Linus Pauling proposed in 1949 that sickle cell anemia was a molecular disease and more recent scientific research has led to results that support his view of this disease.

II. Key References

1. Ingram, V. M. Abnormal Human Haemoglobins. I. The comparison of normal human and sickle-cell haemoglobins by "fingerprinting"
Biochim. Biophys. Acta 28 (1958) 539-545
2. Ingram, V. M. Abnormal Human Haemoglobins. III. The chemical difference between normal and sickle cell haemoglobins
Biochim Biophys Acta 36 (1959) 402-411
3. Finch, J. T., Perutz, m. F., Bertles, J. F. and Dobler, J. Structure of sickled erythrocytes and of sickle-cell hemoglobin fibers. Proc. Nat. Acad. USA 70 (1973) 718-722

III. Review of Key References

Paper #1 by Ingram compares the properties of tryptic digestion products prepared from hemoglobin A (normal) and hemoglobin S (sickle-cell). Twenty-six different peptides are present after trypsin treatment and all but one of these, identified as peptide #4, are identical in the two proteins. Peptide #4 is uncharged in hemoglobin A but positively charged in hemoglobin S. This change is the only one observed between the two proteins and suggests there is a change in the amino acid composition of this peptide between hemoglobin A and S.

Paper #2 by Ingram compares the amino acid sequences of peptide #4 from hemoglobin A and hemoglobin S. The sole alteration that is found is the replacement of a single glutamic acid residue in hemoglobin A by valine in sickle cell hemoglobin.

Paper #3 by Finch and do-workers discusses the structure of hemoglobin S, which forms aggregates that are not present with normal hemoglobin. The structure of the aggregates is considered and shown to exist as long straight fibers, with points of contact probably involving the valine residue that is present in hemoglobin S but absent from other forms of hemoglobin. The fibers actually precipitate in sickle cell erythrocytes, resulting in the deformed shape that is present in the sickled erythrocyte.

IV. Conclusions

The work of Ingram used new methods of protein biochemistry to study the amino acid structure of hemoglobin A and S. Ingram found that a single amino acid in normal hemoglobin, an acidic glutamate residue, is replaced by a valine residue in hemoglobin S, supporting Pauling's original hypothesis that there was an alteration in a molecule that caused sickle cell anemia. The third paper, by Finch and co-workers, does not directly relate to the Pauling hypothesis, but deals with the changes in structure that occur in hemoglobin S as a result of this single amino acid replacement. This paper shows that the sickling phenomenon is related to a fiber structure that forms from interaction of individual hemoglobin S molecules, producing a change in shape of the sickle cell anemia erythrocyte and a concomitant loss in oxygen binding capacity.