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A Course in Critical Thinking for PhD Students in Biomolecular Sciences and Biotechnology: Classical Experiments in Biochemistry

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Abstract: This essay presents and discusses an eight-session seminar course designed to develop critical thinking skills in doctoral biochemistry students by exposing them to classical experiments in biochemistry. During each 2.5 session, different key topics of the discovery and development of biochemical concepts are discussed. Before each session, students are required to read the one or two classical papers. The size of the seminar course and the seating of the students are critical to make this a highly interactive environment for all students to participate in the critique and re-designing of key experiments, including control experiments, which helped formulate these classical concepts. Final student evaluation of the course's goals has two equal components: Course participation and a final take home exam due two weeks after the course is completed. Together with the take home exam students are also required to write an evaluation of the course, preferably no longer than half a page. Students' comments of the course have been uniformly positive. The author notes the sooner students are exposed to this manner of thinking, the better they will be equipped to choose an appropriate mentor and contribute creatively to attempt to solve the scientific problem of their PhD thesis.

Keywords: Doctoral students, biomolecular sciences, biochemistry, classical experiments, course outline, critical thinking, scientific thinking, reasoning skills

Why Such a Course?

The most important lesson for a PhD student is to develop her/his manner of scientific thinking. One starting point in acquiring such skill, as I tell the students at the beginning of the first session, is to critically review the papers which led to key discoveries which eventually resulted in many of the authors being awarded the Nobel prize.

The aim of the course is very simple: If the students learn how to think about science as these scientists did, then the students would have learned the essential lessons to become outstanding scientists! Proof that this course resulted in significant progress towards this goal was obtained after evaluating the take home final exam. This consisted of answering an important follow up question of any of the papers and topics discussed in the course using modern approaches and methods (see later section).

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Background

Approximately 10 years ago the *Journal of Biological Chemistry* (JBC) celebrated its centennial with weekly publication of classical papers in The Journal which had reported key discoveries and concepts in Biochemistry during the 20th century. At the same time, I was given the opportunity to develop and present a seminar course for beginning PhD students in Biomolecular and Life Sciences at the Universidad Andres Bello in Santiago, Chile. I decided to name the seminar course “Critical Thinking: Classical Experiments in Biochemistry”. As seen below, the course consists of eight, two and one half hour sessions during which different key topics of the discovery and development of biochemical concepts are discussed. The topics are very diverse, yet all are fundamental in the discovery of key biochemical finding. Thus, the choice is arbitrary and one can easily choose dozens of other topics that would fit the same fundamental and classical criterion.

Practical Aspects and Prerequisite

For students to understand these papers it is an absolute requirement to have completed a rigorous course in Biochemistry. The course in critical thinking has an optimum of no more than 15 students seated around a large table together with the instructor. A projection screen is provided to make it easier for all to see figures and tables from the papers. Before each session, students are required to read the one or two classical papers to be discussed in that session. The size of the seminar course and the seating of the students are critical to make this a highly interactive environment for all students to participate in the critique and re-designing of key experiments, including control experiments, which helped formulate these classical concepts.

Lessons to Be Learned

The crucial aspect of this course is for students to develop the ability to think critically. The instructor will select from these papers those experiments which he or she feels are fundamental in developing the new concepts to be studied. The corresponding figures and tables are projected on the screen. Using the Socratic method, students are asked to comment on why the given projected table or figure represents an important experiment, the strengths and weaknesses of such experiment and why it is being presented at a particular place of the paper (not earlier and/or not later). Students must take a stand when asked a particular question by the instructor by either agreeing or not with statements which the instructor makes. Sometimes students may not agree or disagree with the instructor’s statement but if they chose to be neutral, they must give a reason. An example which occurs early on during the first session is the question of which control in the proof that the enzymatic synthesis of DNA requires a template DNA is better: no DNA template or DNA pretreated with DNase? Usually students favor one or the other control and a lively discussion between them follows. My question to them is whether the controls in this case are easy or difficult to execute? After they all agree they are easy, my take home message for the students is to do both, as this will usually satisfy reviewers of papers with different preferences. This lesson can be applied to different sessions.

The following is an outline of each session with the caveat mentioned previously that the selection of each of these topics is complete arbitrary and can be replaced by many other subjects that are equally appropriate. However, as can be seen below, the subjects are deliberately very diverse. This is done intentionally so that students become aware that the specific manner of scientific thinking transcends the specific topic and can be applied to any regardless of the subject manner.

Outline of Each Session	
Session	Reading Materials
First Session: Arthur Kornberg's Discovery of DNA Polymerase I	<ul style="list-style-type: none"> Enzymatic synthesis of deoxyribonucleic acid. I. Preparation of substrates and partial purification of an enzyme from <i>Escherichia coli</i> [Lehman, I. R., Bessman, M. J., Simms, E. S., & Kornberg, A. (1958). <i>J. Biol. Chem.</i>, 233(1), 163-170] Enzymatic synthesis of deoxyribonucleic acid. II. General properties of the reaction [Bessman, M. J., Lehman, I. R., Simms, E. S., and Kornberg, A. (1958) <i>J. Biol. Chem.</i>, 233(1), 171-177]
Second Session: The Discovery of Feedback Inhibition by Arthur B. Pardee	<ul style="list-style-type: none"> Control of pyrimidine biosynthesis in <i>Escherichia coli</i> by a feedback mechanism [Yates, R. A., & Pardee, A. B. (1956). <i>J. Biol. Chem.</i>, 221(2), 757-770] The enzymology of control by feedback inhibition [Gerhart, J. C., & Pardee, A. B. (1962). <i>J. Biol. Chem.</i>, 237(3), 891-896]
Third Session: The Kennedy Pathway for Phospholipid Synthesis: The Work of Eugene Kennedy	<ul style="list-style-type: none"> Oxidation of fatty acids and tricarboxylic acid cycle intermediates by isolated rat liver mitochondria [Kennedy, E. P., & Lehninger, A. L. (1949). <i>J. Biol. Chem.</i> 179(2), 957-972] The function of cytidine coenzymes in the biosynthesis of phospholipides [Kennedy, E. P., & Weiss, S. B. (1956). <i>J. Biol. Chem.</i>, 222(1), 193-214]
Fourth Session: Earl W. Sutherland's Discovery of Cyclic Adenine Monophosphate and the Second Messenger System	<ul style="list-style-type: none"> The relationship of epinephrine and glucagon to liver phosphorylase: IV Effect of epinephrine and glucagon on the reactivation of phosphorylase in liver homogenates. [Berthet, J., Rall, T. W., & Sutherland, E. W. (1957). <i>J. Biol. Chem.</i>, 224(1), 463-475] Formation of a cyclic adenine ribonucleotide by tissue particles. [Rall, T. W., & Sutherland, E. A. (1958). <i>J. Biol. Chem.</i>, 232(2), 1065-1076]
Fifth Session; Precocious Newborn Mice and Epidermal Growth Factor: The Work of Stanley Cohen	<ul style="list-style-type: none"> Purification and Metabolic Effects of a Nerve Growth-promoting Protein from Snake Venom [Cohen, S. (1959). <i>J. Biol. Chem.</i>, 234(5), 1129-1137] Isolation of a mouse submaxillary gland protein accelerating incisor eruption and eyelid opening in the new-born animal [Cohen S. (1962). <i>J. Biol. Chem.</i>, 237, 1555-1562] The primary structure of epidermal growth factor [Savage, C. R., Inagami, T., & Cohen, S. (1972). <i>J. Biol. Chem.</i>, 247(23), 7612-7621]
Sixth Session: The Discovery of tRNA by Paul C. Zamecnik	<ul style="list-style-type: none"> A soluble ribonucleic acid intermediate in protein synthesis [Hoagland, M. B., Stephenson, M. L., Scott, J. F., Hecht, L. I., & Zamecnik, P. C. (1958). <i>J. Biol. Chem.</i>, 231(1), 241-257]

Seventh Session: Four Decades of Research on the Biosynthesis of Urea: The Work of Sarah Ratner

- The enzymatic mechanism of Arginine formation from citrulline [Ratner, S. (1947). *J. Biol. Chem.*, 170, 761-762]
- Biosynthesis of urea I. Enzymatic mechanism of arginine synthesis from citrulline (Ratner, S. and Pappas, A. (1949). *J. Biol. Chem.* 179(3),1183-1198]
- Biosynthesis of Urea VI. Enzymatic cleavage of arginosuccinic acid to arginine and fumaric acid. [Ratner, S., P. Anslow, & Petrack, B. (1953). *J. Biol. Chem.* 204(1),115-125]
- Biosynthesis of urea: Molecular and regulatory properties of crystalline arginosuccinate synthetase Rochovansky, O., Kodowaki, H., and Ratner, s. (1977). *J.Biol. Chem.* 252(15), 5287-5294]

Eight Session: Perspective on 35 Years of Research Experience and NIH Funding; The Role of Protein Glycosylation in Development and Pathogenesis of Eukaryotes. Carlos B. Hirschberg

- Transporters of nucleotide sugars, ATP and nucleotide sulfate in the endoplasmic reticulum and golgi apparatus [Hirschberg, C. B., Robbins, P. W., & Abeijon, C. (1998). *Annu. Rev. Biochem.*, 67, 49-69]
- Golgi apparatus nucleotide sugar transport and leukocyte adhesion deficiency II [Hirschberg, C. B. (2001). *J. Clin. Invest.*, 108(1), 3, 2001]
- Nucleotide sugar transporters of the golgi apparatus: From basic science to diseases [Caffaro, C. E., & Hirschberg, C. B. (2006). *Acc. Chem. Res.*, 39(11), 805-812]
- The role of nucleotide sugar transporters in development and disease [Liu, L., Xu, Y.-X., & Hirschberg, C. B. (2010). *Semin. Cell. Dev. Biol.*, 21(6), 600-608]

Acceptance of novel concepts. An important lesson for the students in discussing these classical papers is the reluctance of many in the scientific community to initially accept these new concepts: a good example are the caustic comments of the JBC reviewers of the paper by Kornberg on DNA polymerase where words like “banalities” were used, among others, to initially decline the paper for publication. It is important that students be aware that new concepts in science, until today, are often initially ridiculed: this happened with “prions”, and with “quasi crystals” the latter when Linus Pauling commented in a large meeting that there are no quasi crystals but only “quasi scientists”. Pauling did not live long enough to see Dan Schechtman, the “quasi scientist” receive the 2011 Nobel Prize in chemistry.

A short, concise summary. A more recent addition to the course, which has proven to be highly successful, is the requirement that a student at random, must summarize in three short sentences, at the end of each session the key concepts that were developed during that session. My advice to them is that they should imagine they meet a fellow student when they leave the class who asked them what they discussed in the particular session. They might imagine that they are riding in an elevator and have only a few minutes to explain the content of the discussion meaningfully. At the beginning this is not easy for students and I often tell them that they have used already two short sentences and the student who asked the question hasn’t learned anything yet. Surprisingly, after one or two more sessions the students become much better in summarizing the key issues of each session. We also repeat this at the beginning of the next session when one student is asked to do this with the previous session.

Language of the course. Until two years ago the course was taught in Spanish as I am fluent in Spanish and English. Last year, at the suggestion of the program director of the Biomolecular Sciences PhD program, half of the course was in English. Beginning in 2016 all of it will be in English towards the goal of having the entire didactic portion of the PhD program being taught in English.

Evaluation of Students and How Do We Know if Students Made Progress Towards the Course's Goal?

Final student evaluation of the course's goals has two equal components: Course participation and a final take home exam due two weeks after the course is completed. Students are asked to answer an important scientific follow-up question related to any of the sessions' topics. To answer such question students are asked to use modern approaches and methods.

Examples students have chosen include determining whether cells have a cAMP receptor, whether there is a single tRNA or multiple tRNAs for different amino acids, whether phospholipid and urea biosynthetic pathways previously demonstrated to occur in vitro also occur in vivo and whether site directed mutagenesis and crosslinking can identify the regulatory and catalytic sites of aspartyltranscarbamylase.

Course Evaluation by Students

Together with the take home exam students are also required to write an evaluation of the course, preferably no longer than half a page. Students' comments of the course have been uniformly positive. A few examples of these are:

"... the course is very important for PhD students as it allows to open one's mind, to see beyond what we are used to, to realize the limitations of each scientific approach and to ask follow up questions using different approaches". (Student A)

"This course is completely different to others I have had in the PhD program. In this course we learned to think which were the next follow up steps of each experiment and how to answer these questions and the limitations of the approaches. I also learned that sometimes the simpler questions and methods to answer them are the best". (Student B)

"I believe this course allowed us to think, opine and to question what we were studying in an open manner". (Student C)

"This course teaches one to think, solve problems in a simple manner, to say the most with the least words...and also to think in an independent manner, to say openly what one thinks and to dare challenge established hypotheses". (Student D)

"I also learned that the simpler the question the easier it is to try to find an answer". (Student E)

"the sessions in English were a bit intimidating at first but I think it is a good strategy to get used to". (Student F)

"The summary of each sessions allows us to improve our ability to synthesize in a few sentences the importance of each subject discussed". (Student G)

Future Perspectives

Both the students and I have learned several lessons from this course. To teach and learn a manner of critical scientific thinking takes a willingness by the instructor and the students to be open minded. While nothing can substitute for the role of a PhD thesis mentor who constantly should reinforce critical concepts of this course, the sooner students are exposed to this manner of thinking the better they will be equipped to choose an appropriate mentor and contribute creatively to attempt to solve the scientific problem of their PhD thesis.

While I have also repeatedly mentioned that the selection of topics is completely arbitrary it goes without saying that this type of course can also be applied to other scientific disciplines and is not restricted only to the biological sciences. The thought process of eminent physicists, mathematicians, chemists and other scientists who are not afraid of challenging current “dogmas” is the only manner by which new concepts arise. Never the less, students must also become aware, that the more novel the concept, the more initial “push back” by fellow scientists may occur, sometimes, as shown above, even in hurtful manners! However, the wonderfulness about science is that sooner or later the experimental proof will prevail and vindicate those creative thinkers who were willing and had the courage to lay out their novel ideas.

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