

Original Paper

Classic Experiments in Education Technology

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Abstract

Classic experiments in Biomedicine are presented that inspire students to enthusiastically continue in this field, written by a U.S. Presidential Award winning, American Association for the Advancement of Science Fellow. Four experiments are selected: the structure of DNA, the structure of the cell membrane, sugars in cell adhesion, and unconventional dealing with a deadly cancer problem. Papers, written mostly by students, from the author's lab are also included that support the concept that students will enter a science research field if they are introduced to it by easy to read, enjoyable, papers. Some of the author's papers strongly support one of the Classics presented, the role of sugars in cell adhesion. Using these Classics to teach students at all levels is presented, as the author has used them for decades, helping him win a US Presidential Award for Mentoring and supporting his election as Fellow, American Association for the Advancement of Science (AAAS) (Note 1). This approach helps students to understand the personalities involved in great discoveries, making them unforgettable.

1. Introduction

The author has decades of experience in the 4 selected classics and is therefore qualified to show how they are used and can be used by many folks to excite and inspire students in today's classrooms, pre-college and college.

2. The Structure of DNA

“What Mad Pursuit” is the title of a short book (Note 2, Note 3) written by the late Francis Crick, co-discoverer of the molecular structure of DNA, that won a Nobel Prize in 1962, and has been cited as the greatest advance in life science of the 20th Century.

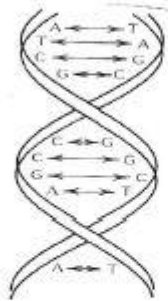
Francis Crick was honorary chair of a program led by me, Steve Oppenheimer, at California State University, Northridge. He visited the university for about 10 years, working with students, colleagues

and staff. He signed autographs and spent hours taking photos with the hundreds of individuals in attendance. What an inspiration!

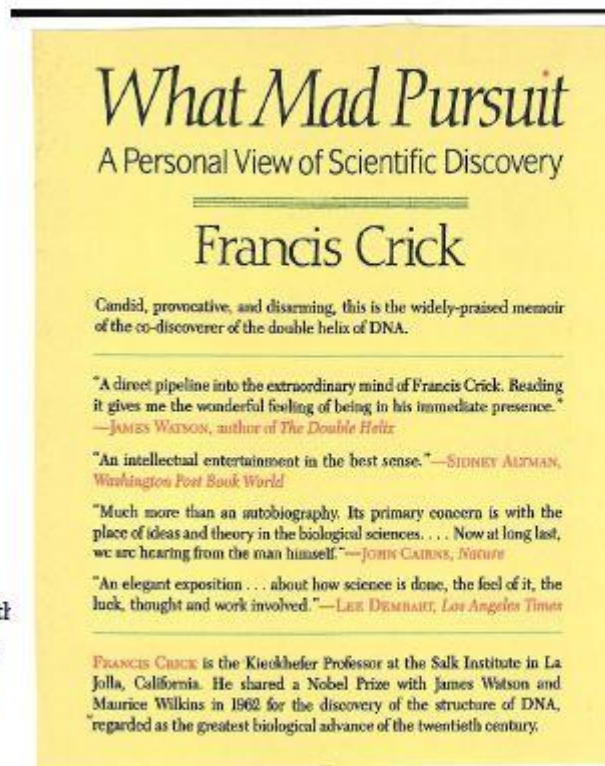
In one of his visits Francis Crick showed the movie *Race for the Double Helix* (Note 2) before presenting his personal insights into this great discovery. I suggest that everyone see this film. It is the most inspiring movie that I've seen in 50 years. It can be shown in two 50 min parts. It was developed for BBC. It was released initially by Studio Hamburg Enterprises and stars, among others, Jeff Goldblum. What is so important about this movie is that gives us a glimpse of the personalities of the scientists involved. It shows that the structure of DNA was developed by Crick and Watson with the help of others such as Rosalind Franklin. The interplay of Watson and Franklin, for example, is fantastic and unforgettable. There is little doubt that Franklin would have shared the Nobel Prize if she did not pass away before it was awarded. Her x-ray crystallography pattern of DNA was key evidence that led to the concept of DNA as a double helix, an idea developed by Crick before Franklin's x-ray crystallography provided solid evidence.

As for the base pairing, a key clue was provided by Edwin Chargaff, when he told Watson and Crick, that his studies indicated that there was a rough equivalence of the bases A and T and also C and G in cells. This suggested to Watson and Crick that A and T might pair and C and G might pair. The chemical structures of A, T, C and G were drawn and modeled leading to the discovery of how the bases actually paired. The video is a masterpiece but reading Crick's memoir, *What Mad Pursuit*, only 182 pages long, gives even more detail, *What Mad Pursuit* was originally published by Basic Books, a Division of Harper Collins Publishers and the Alfred P. Sloan Foundation (ISBN 0-465-09137-7, cloth, ISBN 0-465-09138, paper, sells for \$10) (Note 3)

By seeing the film and/or reading the book, students will never forget how the DNA double helix model was developed. Without the film or book, the flavor of the discovery will be hard to understand. Drawings of the double helix DNA model showing base pairing will help. But, of course great teachers can make the DNA story come alive. A purpose of this section is to entice educators to try to get a hold of the movie/and or book. I've used the video in my classes for decades.



DNA double helix showing
base pairing A with T and C with
G. From Nobel Prize discovery
by Crick, Watson and Wilkins.
From Oppenheimer, S.,
Introduction to Embryonic
Development, Allyn and Bacon
1980, Boston, p. 296.

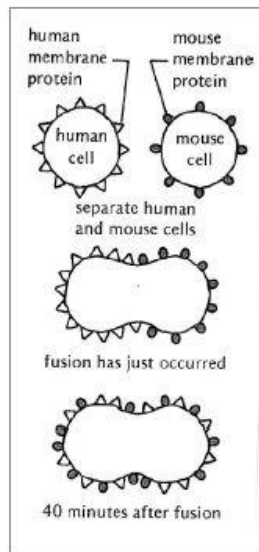


3. The Structure of the Cell Membrane

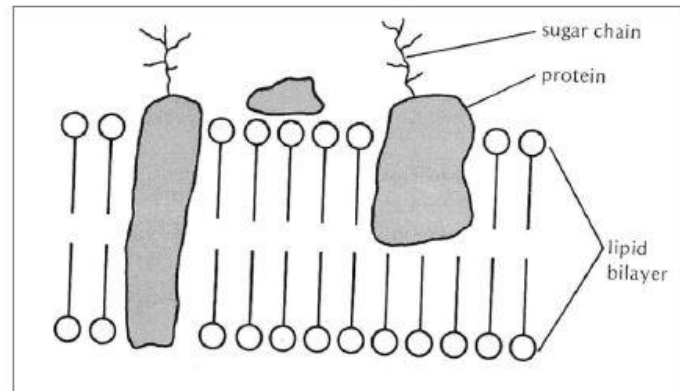
The cell membrane was thought to consist of a lipid bilayer with a protein coating on its outside and inside. The exciting story of the discovery of the modern version of cell membrane structure is another exciting Classic. The story begins with experiments by Larry Frye and Mike Edidin at Johns Hopkins that started around 1970. This was Larry's Ph.D. thesis project. They used mouse cells and human cells and antibodies that bound to membrane proteins in each cell type. Then they used green and red fluorescent dyes to visualize the proteins that were embedded in the cell membranes of each cell type. They then fused the mouse and human cells with Sendai virus (or no virus in some experiments). Right after applying the antibodies and fluorescent stains, the mouse cells were of one color and the human cells fused with the mouse cells were of the other color. But by 40 minutes after fusion the protein antigens of both cell types intermixed (Note 4).

S.J. Singer's and Garth Nicolson's analysis of this intermixing indicated that intermixing of the proteins in the cell surfaces was consistent with lateral diffusion of the proteins in a sea of lipid. They presented this analysis in their paper appearing in *Science* titled the Fluid Mosaic Model of the Structure of the Cell Membrane (Note 5).

These sets of simple experiments are Classics. This is easy to teach. Have the students draw the fluid-mosaic model of the cell membrane and the Frye and Edidin fusion experiment as shown below.



Frye and Edidin
Experiment (4) From
Oppenheimer, Introduction to Embryonic
Development, Allyn
and Bacon, 1980, p.
257



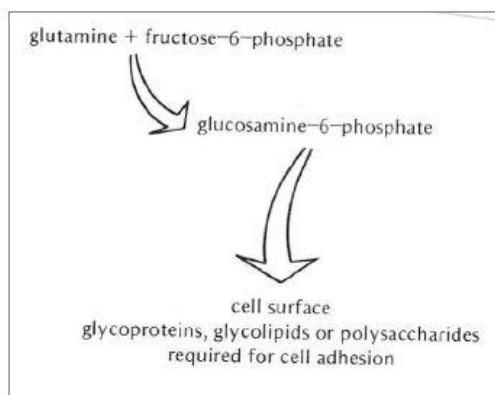
Fluid Mosaic Model of Cell Membrane. Based
on Singer and Nicolson(5). From
Oppenheimer, Introduction to Embryonic
Development, Allyn and Bacon, 1980, p. 38.

4. Sugars in Cell Adhesion

When Larry Frye was doing the human/mouse fusion experiments at Johns Hopkins, Steve Oppenheimer, also at Johns Hopkins, was doing his Ph.D. thesis project with Saul Roseman, Mike Edidin and Charlie Orr that became arguably the first solid evidence for a role of sugars in cell adhesion. This was also a set of Classic experiments of importance in many areas such as cancer spread. Steve found that a group of cells (mouse ascites teratoma cells) adhered to each other when L-glutamine was added to the culture medium, while no other medium component including other amino acids, sugars, vitamins and co-factors caused the cells to adhere (Note 6). Other cell types also responded by adhering with L-glutamine (Note 7). As glutamine is an amino acid, did glutamine act in the formation of adhesive proteins? No. A complex series of experiments showed that L-glutamine donated its amino group to fructose-6-phosphate, forming glucoasamine-6-phosphate. Glucosamine-6-phosphate was the key intermediate in the formation of cell surface sugars in polysaccharides, glycolipids and glycoproteins. This work was published in the Proceedings of the National Academy of Sciences (PNAS) (Note 6). This Classic finding provides an important target in cancer cells, that often possess altered cell adhesion. Experiments from the author's lab are very simple

and will excite students' interest in research science (Notes 1-91). And many experiments from the author's lab support the role of sugars in cell adhesion and cell surface behavioral properties (Notes 5, 6, 7,8, 9,10,11,12,13,14,15,16 16,18 19, 20, 21, 22, 23,24,25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37 38, 40,41, 42, 43, 44,47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 67, 69, 71, 73, 74, 75, 77, 79, 81, 83, 85, 86, 87, 88, 89).

See the PNAS paper for details of the biochemistry involved in the glutamine reaction (Note 6). Teaching this Classic can be at different levels from simply showing that L-glutamine causes cells to adhere, to the complex biochemistry, using specific inhibitors, that show how glutamine is acting.



Pathway of L-glutamine's role in cell adhesion.
Based on Oppenheimer et al.(6). From
Oppenheimer, Introduction to Embryonic
Development, Allyn and Bacon, 1980, p.367

5. Classic Approach to a Cancer Problem

I've used the Nova video, The Cancer Detectives of Lin Xian, October 7, 1980 (Note 90) for decades in my classes. It, like the Race for the Double Helix, described in part 1 of this paper, is a true Classic but almost nobody knows about the cancer detectives video. This video showcases what was done in China to deal with a cancer that affected the people in Lin Xian in epidemic proportions. The Chinese approached esophageal cancer in a way so different than done in Western nations. This video can inspire new generations of students to tackle big problems, not only by spending billions of dollars on molecular biology, but by a focus on prevention that worked well.

First, the health workers carefully examined the food and drink of the people. They found high levels of nitrite, nitrate, nitrosamines and mold, as well as too low levels of vitamin C in the food that the people ate. They improved food storage and increased vitamin C in food and broadcast the new information to the people. They checked the temperature of the drink and found it was no hotter than what was consumed by people in neighboring regions without high rates of esophageal cancer. The chickens owned by people with high rates of esophageal cancer also had tumors in their gullets. It was believed that the table scraps fed to the chickens might be a cause of the cancer. It will take years to see if any of these dietary improvements lower the rate of esophageal cancer, so the health workers and scientists did not stop at the dietary improvements.

They developed an abrasive balloon that was swallowed by the people and pulled up gently scraping the esophagus. They wiped the balloon on slides that were examined by technicians to see if the scrapings contained cells that were pre-cancerous or cancerous. Medicines were given to people who had pre-cancerous cells to reduce the advance of the cancer. Such people were examined regularly. Those with advanced cancer were offered standard operations with standard anesthesia. In such operations, the cancer in the esophagus was removed and the ends of the esophagus were sewn together. Today, in the West, smoking and heavy alcohol consumption have been added as causes of this cancer. But in the West, little attention is given to early detection strategies, unlike what is done for breast cancer, where frequent checks are made.

China has been doing relatively well in dealing with esophageal cancer. One hospital in China reports an 82.4% decrease in mortality from this cancer from the 1970s to 2018, Five year survival is reported at 92.7%. This report was published by Science/AAAS Custom Publishing Office and presented on page 1 in the December 10, 2021 issue of Science (374, 6573) (Note 91).

This Nova program is as relevant today as it was decades ago. It is a Classic teaching tool. While smoking and heavy alcohol consumption, particularly smoking, have been reduced in the West, nothing like the Chinese multi-factor approach that focuses on prevention has been implemented for esophageal cancer in Western societies. Very few people have seen the Nova video, which is a model for cancer prevention. While billions of dollars spent by the West on molecular biology of cancer, has improved the cancer picture, more effort should be focused on cancer prevention strategies. The Cancer Detectives of Lin Xian is a Classic that should be viewed by all.

6. Conclusions

This paper gives students a depth of understanding of fundamental biology experiments that can not be obtained from standard textbooks or from the usual classroom presentations.

The 4 Classic sets of experiments presented have been used in my classes for up to 50 years and have helped me win a U.S. Presidential Award for Mentoring and election as Fellow of the American Association for the Advancement of Science (AAAS). The election as Fellow of the AAAS recognized my contributions to the Sugars in Cell Adhesion Classic that began with the PNAS paper (Note 6). The video Race for the Double Helix (Note 2) and the book What Mad Pursuit (Note 3) present the personal insights into the Nobel Prize winning discovery of the double helix/base pairing structure of DNA. Students will find that these personal insights give life to the monumental discovery. They will learn that this great discovery included the work of others in addition to Crick and Watson and that the contributions of the scientists involved were instrumental in this major breakthrough. With this approach using Classics students will never forget what went into this major discovery. The discovery of the fluid-mosaic model of the cell membrane was also a collaboration of more than one group and illustrates how a great new model was developed. The Nova program, the Cancer Detectives of Lin Xian (Note 90) is a seminal journey into unconventional approaches to a deadly cancer. Finally, the

scores of mostly student co-authored papers cited here, from the author's lab, make for readings that could inspire new generations of students to enter science research fields. This paper provides new thoughts about areas of study that can be inspirational to students in science and technology. Many of the cited papers deal with the Classic finding of a role of sugars in cell interactions, an area that has not been thought of as a Classic in the past. I believe that election as Fellow AAAS supports the notion that this indeed is a Classic. Hundreds of students took part in the experiments cited here and this contributed to the U.S. Presidential Award for mentoring received by Steve in addition to the AAAS Fellow designation.

Acknowledgements

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