Issue 119
June 2015

Natural Selections

A NEWSLETTER OF THE ROCKEFELLER UNIVERSITY COMMUNITY

Twenty-four visits to Stockholm: a concise history of the Rockefeller Nobel Prizes

Part IX: F. Peyton Rous, 1966 Prize in Physiology or Medicine

Joseph Luna

"Whatever you do, don't commit yourself to the cancer problem." These were ominous words for a young pathologist named Peyton Rous to hear from his famed mentor William Welch. In the early 1900s, it seemed accurate. Cancer, then as now, is a terrifying constellation of diseases. This was all the more true in 1909, when few tools to study its deadly forms were available beyond the pathological descriptions afforded by the microscope. Added to this frustrating mix were scientific debates on the origins of cancer: some cancers were clearly inherited from one generation to the next, suggesting a genetic cause. And yet other cancers defied an inheritance rule and were instead closely associated with certain chemically-laden occupations, such as "soot wart" carcinoma among chimney sweepers. What if chemical exposures were the real culprit? In an era when chemical regulation was effectively non-existent for industrial workers, one can only imagine what Gilded Age employers would've thought of this theory. As a result, "cancer" was seen as a thorny and complex issue, only likely to become thornier. There seemed little a scientist could do to definitively address causes, let alone suggest treatment for cancer. Welch's words were not far off the mark.

Portrait of Peyton Rous, then in Welch Hall. August 2010. Photograph by the author.

Yet, others were not as pessimistic. Simon Flexner, the Rockefeller Institute's first director and also a student of Welch's, offered Rous a position to take up the cancer problem, and Rous, despite some reluctance, went against his mentor's advice and accepted the offer. Rous was hired ostensibly to take up studies of an epithelial tumor in rats known as the Flexner-Jobling tumor, notable in that it could be transplanted with some success between animals. The position, however, afforded the 31-year old pathologist considerable freedom to explore other potential models of cancer.

Soon after Rous got to work, at a time when live chickens were not an uncommon sight in Manhattan, one inquisitive poultry breeder brought to the institute a Plymouth Rock hen bearing a large tumor. We neither know what her precise motivations were to approach the new institute for medical research on Avenue A with a diseased chicken, nor do we know what Rous initially made of such a strange curiosity. But it was a chance and a fortuitous encounter. Rous took the chicken and attempted to do what many a would-be cancer researcher had tried but failed. After determining the type of cancer under the microscope, he attempted to transmit the tumor to a healthy bird. To his surprise, it worked. The once healthy bird developed tumors that looked almost exactly like the original. This work, published in 1910, established that a "sarcoma of the common fowl" could be transmitted. Such a model for cancer was an important first step in figuring out what caused it.

Rous next dove head-first into this causation problem. In an extraordinary hypothetical leap, Rous repeated his tumor transmission experiment with a twist. Instead of directly injecting bits of tumor into a bird, Rous first passed the tumor cells through a bacteria-tight filter and then injected a bird with the now cell-free filtrate. Scientific consensus of the day held that cancer, as a distinctly cellular phenomenon of "somatic mutations," shouldn't arise with injections of cell-free material. Yet within a few weeks, some of the injected birds developed tumors, though nothing was conclusive for Rous until he plied his trade at the microscope. Coming into focus, the methylene-blue and eosin stained tumor cells of bird number 177 almost shouted their answer: cancer. The spindle-cell sarcoma Rous observed in the new bird was indistinguishable from the tumor in the original hen. Rous had discovered that a filterable agent, in modern parlance a virus, could transmit cancer.

Published in 1911, the discovery of the first virus transmitted tumor caused quite a stir among cancer researchers, in that it demonstrated a viral origin in addition to suspected chemical and genetic causes of cancer. Without a unified theory of cancer, each of these three hypotheses was compelling individually, but appeared mutually incompatible with the others. Not surprisingly, few were convinced by the viral hypothesis in Rous's day. The scientific establishment cried "contamination!" almost in unison upon reading his findings. Many doubted that Rous's filtrates were completely devoid of living cells. When Rous and James B. Murphy freeze-dried the filtrate to ensure that all cells (if any) were killed and found that the filtrate was still tumorigenic, prominent researchers demonstrated that some cells could survive the freeze-drying treatment. No matter the suggestive

Figure 1 from the 1910 paper describing a transmissible sarcoma of the common fowl.

evidence, there was always an alternate, if increasingly far-fetched, explanation. And for those few that believed Rous's results, there was still the real concern of generality. Perhaps viral cancer transmission was a strange quirk of avian biology, and not applicable to more sophisticated mammalian tumors, which had eluded cell-free transmission. Rous's own experience almost bore this out; he tried in vain for a few years to isolate a mammalian tumor virus. By the outbreak of World War I, he had moved on to other studies and shelved the project.

Shelved perhaps, but not forgotten. In 1933, more than two decades after the initial observation of a cancer-causing virus, Richard E. Shope from the Department of Animal Pathology at Princeton and a close friend of Rous, isolated a virus that caused wart-like growths in cottontail rabbits. While some might be hesitant to re-visit past work, Rous enthusiastically dove into the study of Shope's papilloma virus, and within a year, reported from his Smith Hall laboratory that the warts were indeed true tumors. Over the ensuing decade until his retirement, Rous studied the Shope virus in great depth, proving its tumorigenic potential, its relations to other carcinogens, and characterizing its induced disease in no shortage of contexts. By the time Rous officially retired in 1945, it was clear that while not all cancers were viral in origin, a notable few certainly were.

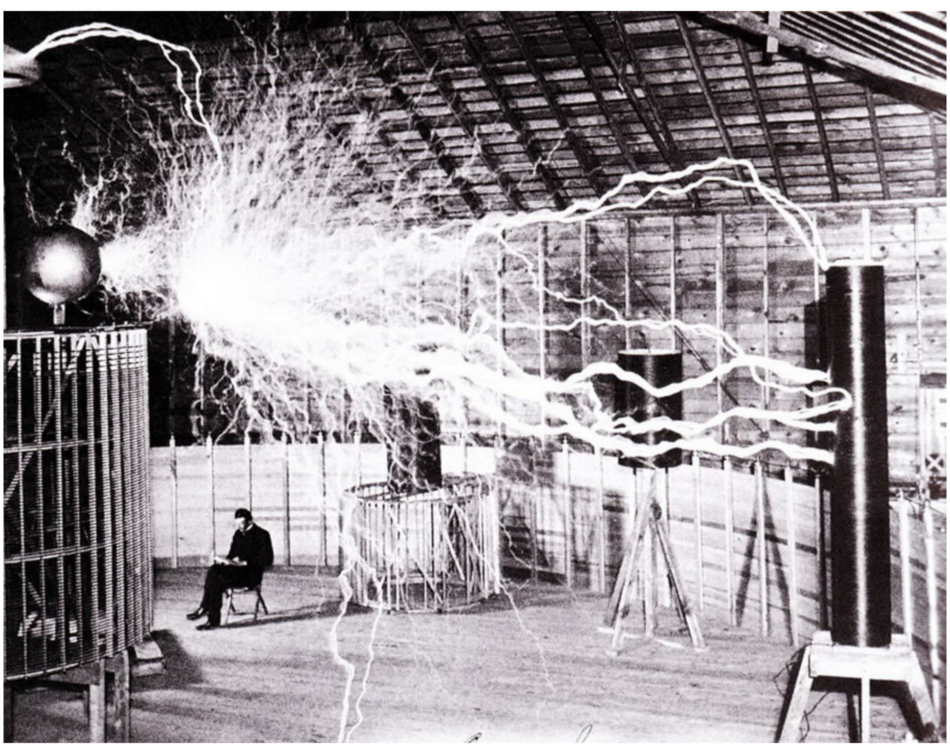
Ultimate vindication wouldn't arrive for yet another two decades, when in 1966, at the age of 87, Rous was finally awarded the Nobel Prize in Physiology or Medicine. It remains the longest "incubation period," from discovery to prize, on record. ⊙

Nikola Tesla

Aileen Marshall

Who was Nikola Tesla? Does this name ring a bell somewhere in your brain but you can't quite place him? Wasn't he some sort of scientist? The showing of the movie "Tower to the People: Tesla's Dream at Wardenclyffe" by the Rockefeller Science Communications and Media Group inspired me to find out. It turns out Tesla was quiet a visionary scientist who worked on many aspects of electricity and physics.

Tesla was born on July 10, 1856 to Serbian parents in what is now Croatia. When he was 19 he started at Austrian Polytechnic and did remarkably well there at first. During his third year he developed a gambling problem and did not take his final exams. He did not receive grades for his final semester and never graduated. He worked as a draftsman until 1880 when his family sent him to Charles Ferdinand University in Prague. He arrived too late to enroll but audited courses there for a year.



Nikola Tesla in his Colorado lab, 1899

The next year he moved to Budapest and worked to improve equipment for the Budapest Telephone Exchange. He moved to New York City in 1882 and was hired by Thomas Edison. He worked on redesigning the Edison Company's direct current generators. When he came up with a more efficient design, he was offered a mere $10 raise over his $18 a week salary. Tesla felt that was an insult and quit.

In 1886 he found investors to finance a company to make lighting systems and electric motors. However they didn't agree with his idea to develop a new electric system infrastructure and forced him out and he lost his patents. Then he found other backers who built a lab for him at 89 Liberty Street. It is here that Tesla developed his alternating current motor. Alternating current (AC) is now used to send electricity over long distances over power lines. Direct current (DC) is what we have in our households. Tesla gave a demonstration of his AC system at the American Institute of Electrical Engineers (now The Institute of Electrical and Electronics Engineers) in 1888. He later served as the organization's vice president. His presentation was reported to George Westinghouse. His AC motor was licensed to Westinghouse Electric & Manufacturing Company and he was hired to work in their labs in Pittsburgh, developing AC system to power the city's streetcars. This was the beginning of the "War of Currents" between Edison's DC system and Westinghouse's AC system. By 1892 Edison's company was purchased by General Electric.

In 1891 Tesla founded a lab on South Fifth Avenue (now LaGuardia Place) and then 46 East Houston Street where he invented his Tesla coil. A Tesla coil is a high-voltage, high-frequency transformer producing AC wireless electricity. Tesla was always an advocate of wireless energy. He held a demonstration of wireless energy at Columbia University. He had two zinc sheets suspended on each end of the room, and when he passed between the two sheets, a light bulb in his hand was turned on. He would often give demonstrations to friends, one of whom was Mark Twain.

Besides electricity and motors, Tesla worked over the years on x-rays, radio waves and developed a remote-controlled boat that was eventually sold to the US Army. In March of 1895, a fire destroyed his Fifth Avenue lab and all his notebooks were lost. Tesla was devastated.

After a few years, Tesla got interested in investigating the resonant frequency of the earth's crust as a means to transmit power. But that was impossible to do in Manhattan with its infrastructure. So in May of 1899, he moved to Colorado Springs. He had contacts there who would give him electricity for free. He observed natural lightening and produced his own. The thunder from his lightening could be heard 15 miles away. The electricity in the air would cause butterflies to fly in circles and glow with St. Elmo's fire, a phenomenon where an aura around an object appears due to ions in the air during a lightening storm. Over the front door of the lab Tesla had the quote from Dante's Inferno "abandon all hope all ye who enter here." It was in Colorado that he observed signals from his receiver in the pattern of "1, 2, 3…." He was convinced it must be from intelligent life of another planet. While he was greatly mocked in the press, it was later reported that Marconi observed the same phenomenon. It is now known that these are signals from stars.

Having established the possibility of wireless energy, he returned to New York. He met with financer J.P. Morgan for funding to build a wireless transmitter. He wanted to send radio signals from New York to Greenwich, England. He even proposed a handheld device that would receive stock prices in real time, so that brokers would not have to stay on the Stock Exchange floor all day. Morgan promised him $150,000 and Tesla bought land in Shoreham, Long Island from a man named Warden. He called his facility Wardenclyffe in his honor. His friend, the famous architect Stanford White designed the plant and tower. Besides a lab and plant building on the property, he also built many small houses for workers he called "Radio City" and a 186 foot tower to send radio signals to England. The tower had a 300-foot shaft into the ground and tunnels connecting it to the buildings.

Tesla's dream of providing free wireless energy to the world ended in 1901 when Marconi successfully transmitted a radio signal to Newfoundland, Canada. After that Morgan lost interest. Tesla proposed to build an even bigger tower to transmit electricity and started construction. While Morgan still owed him the balance of the original $150,000, he never answered any of Tesla's letters. Tesla sent Morgan 50 letters over the next five years and got further into debt. Morgan finally answered in 1904, saying it would be impossible for him to do anything more. After World War I, Tesla lost the money from his European patents. He finally sold the land in 1917 and it fell into disrepair. It was eventually bought by a company making chemicals for film developing, but they later abandoned it.

After Tesla moved back to New York, he published an article on a proposed system to detect submarine locations using an "electric ray" with the signals viewed on a fluorescent screen. He later developed plans for a vertical-lift airplane. He and Edison were nominated for the Nobel Prize several times over the next twenty years, but in their animosity, each belittled the achievements of the other. Neither one ever won the prize.

On January 5 in 1943, he left his room to feed the pigeons in Bryant Park as was his habit. He was hit by a cab, and was taken back to his room but refused to see a doctor. He died a few days later of his injuries.

The movie "Tower to the People: Tesla's Dream at Wardenclyffe" details the history of the Wardenclyffe facility and the efforts of a community group to buy the property and restore it as a historical monument. The producer, Joseph Sikorski, also made the movie "Fragments from Olympus" about Nikola Tesla. Information about both movies can be found at http://www.fragmentsfromolympus.com/ ⊙

Cancer immunotherapy: how to shoot a target moving faster than a bullet?

Jun Tang

One out of every two men and one in three women will be affected by cancer in their lifetimes. Cancer devastates the people it afflicts, traumatizes their family and friends, and puzzles scientists and physicians who dedicate their lives to understanding and fighting the disease. When President Richard Nixon signed the National Cancer Act of 1971 and declared an all-out "War on Cancer," many naively believed that cancer would soon be defeated, just as we celebrated our victories against smallpox and tuberculosis. Half a century later, we are still far from winning the war. As the Pulitzer-winning author Siddhartha Mukherjee dubbed it, and as we have gradually learned from endless battles with the disease, cancer is *The Emperor of All Maladies*.

Recent news from the front lines of cancer research suggests that we are gaining ground in the war on cancer. The FDA approved the first antibody immunotherapy targeting CTLA-4 (marketed as Yervoy by Bristol-Myers Squibb) in 2011 and the second, more effective antibody neutralizing PD-1 (marketed as Keytruda by Merck) in 2014, both for late-stage melanoma. In 2013, the journal *Science* named cancer immunotherapy "Breakthrough of the year." Since then, cancer immunotherapy has dominated the discussion in the field of oncology and is gradually catching public attention. So what is cancer immunotherapy, and why is it inspiring so much optimism? Simply put, cancer immunotherapy aims to use our own immune system to fight cancer. Before expanding on cancer immunotherapy and its distinction from previous cancer therapies, let's first understand how cancer acts.

Imagine our bodies as a city, where cell types with specialized functions—melanocytes, neurons, epithelial cells, and many others—work seamlessly together to keep the city functional and thriving. One day, a regular cell decided to join a cult called "cancer," which mandates its members to trespass every law, regulation, and social order to achieve one single mission—conquer the entire city. Gradually, the cancer cells occupy a block, then a borough, and finally invade all parts of the city. When cancer cells enter a new place, they evict existing cells from their buildings, steal their food, tear down their homes, and decimate their communities. Gradually, cancer cells hijack all major resources while contributing nothing to the city. Starved and dismantled, the city has no defense to keep normal cells safe, no nutrients to feed the hungry, no caretakers to nurture the young, and no energy to keep everyone warm. The city is dying.

To save the city, and indeed the body, we need to fight the cancer cells. Typically, we first identify the weaknesses of cancer cells and use the most effective weapons to attack them. If cancer cells have a base camp in a block, we demolish every building in the neighborhood or even throw in a small-scale nuclear bomb (similar to surgery and radiotherapy for treating local tumors). If cancer cells have spread across the city, we target the cancer cells' weak spots, killing most cancer cells while inevitably paralyzing many normal ones (similar to chemotherapy for treating metastatic cancer). We might poison or deplete cancer cells' unique source of nutrients or sabotage their distinct mechanism of growing, eradicating cancer cells at a minimal casualty on normal cells (similar to targeted therapies such as Gleevec that are very effective with negligible side effects). In most cases, these coarse offenses work well initially but slowly become ineffective as cancer cells mutate to fix their weakness and learn to look like normal cells, making them "invisible" in our body. At this point, any weapons would do as much harm to normal cells as to cancer cells, and we are doomed to defeat.

Cancer is a persistent and elusive foe. Its unprecedented survival capability originates from the fruit of billions of years' evolution—genetic mutations. Cancer mutates at a frenetic speed in response to our anti-cancer offenses, creating tremendous opportunities to outmaneuver. This is a small-scale, accelerated "natural selection" at work inside the body, where cancer cells are driven to become "the fittest" under the selection imposed by traditional cancer treatments like radiotherapy, chemotherapy, and even some targeted-therapy. Eventually, cancer cells develop many effective but distinct tactics to dodge cancer treatments, which means not one but many different cancers are attacking the body at the same time. At this stage, any single treatment that may kill some cancer cells would spare or even help other cancer cells with different mutations.

Can we also tap into the power of genetic mutations to create counter-strikes to fight ever-changing cancer cells? After all, cancer does not monopolize genetic mutations. In fact, our own immune system has also evolved to harness the power of genetic mutations to fight constant invasion of unknown foreign pathogens. In the immune system, B cells tirelessly generate antibodies (small proteins that specifically bind to invading antigens), which can call in macrophages—the defensive agents of our body—to terminate the antibody-bound invaders; dendritic cells can spot the plain-clothed, radicalized cells that are plotting a massacre in the body; cytotoxic T cells can hunt down viruses hidden in cells that reside in the most inaccessible alcove in the body. Through well-controlled genetic mutations, B cells can generate a reservoir of antibodies that target almost any invaders, and cytotoxic T cells can distinguish the hair-width difference between virus-infected cells and normal ones, marking the former for the kill. However, against cancer cells that look almost identical to normal cells, these immune cells are hesitant to train their weapons on seemingly innocent, healthy cells. By taking advantage of immune cells' conservation, cancer cells continue their rampant sabotage of the body.

The main strategy of cancer immunotherapy is to educate the defense and investigative agents in our immune system to specifically attack cancer cells. The first attempt dates back to 1891, when William B. Coley injected bacterial toxins—Coley's toxin—into patients with bone cancer. After a century of trial and error, we have finally learned a few tricks that can persuade immune cells to battle with cancer cells. We now can develop antibodies that specifically bind to cancer cells, which then can be "seen" and executed by immune cells such as macrophages. We can feed intelligence about cancer cells to dendritic cells that will subsequently urge all immune cells to watch out for cancer cells. Armed with the intelligence from dendritic cells, cytotoxic T cells can direct their unparalleled weapons to terminate cancer cells. Once immune cells see cancer cells as invaders in the body, they will comb all corners and terminate any confirmed cancer cells. This extensive and thorough strategy is a much more effective counter-strike to the guerilla tactics of cancer.

Although today's cancer immunotherapies only unleash a small fraction of power residing in our immune system, they have already transformed the landscape of a few cancers. Melanoma, the deadliest skin cancer, has been successfully treated by immunotherapies in a number of patients by anti-PD1 antibody immunotherapy. In the case of acute lymphoblastic leukemia (ALL), T cells from an ALL patient can be extracted and engineered in a petri dish to recognize unique antigens on the surface of leukemia cells. Once the "educated" T cells are infused back to the patient, they can kill the cancer cells bearing the antigens, no matter where they reside, leading to long-term remission lasting for years in the patient.

Immunotherapies have produced several medical advances in the past few years and many more seem to be on their way. But none of these achievements would have been possible without decades of basic research by dedicated scientists. It was three decades of painstaking research on CTLA-4 and PD-1 (two molecules that prevent T cells from attacking cancer cells) that built the basis for Yervoy and Keytruda, the two drugs that cure melanoma in some patients. It was the discovery of dendritic cells led by Ralph Steinman, the 2011 Nobel Laureate from Rockefeller University, in the 1970s and the invention of chimeric antigen receptors (CARs) in T cells pioneered by Zelig Eshhar that opened the door to dendritic cell-based cancer vaccines and cancer-killing T cells that have saved many lives from hopeless late stage cancers.

"If you know both yourself and your enemy, you can win numerous battles without jeopardy," said the legendary Chinese general Sun Tzu more than 2,500 years ago. In our fight against "The Emperor of All Maladies," we need to better understand our foe to predict its next tactic of attack, and we need to comprehend basic biology of our own immune system to respond with an effective counter-strike. The key battles are likely to be fought not just by the bedside, but also in a petri dish, because that is the place where we observe, most clearly, both our enemy and ourselves. ⊙

Culture Corner

The Elegant Movie – Thoughts on the films The Theory of Everything *and* The Imitation Game

BERNIE LANGS

[Note: Professor John Nash, featured in this set of reviews, passed away tragically in an auto accident as this article was going to press.] The physicist Brian Greene named his widely successful book, which served as an introduction for many in the general public to the mysteries and wonder of string theory, "The Elegant Universe." This title gave that sub-specialty of the study of physics a kind of mysterious and glamorous dressing up of sorts. I enjoyed that book immensely, although I did struggle at times with his sometimes less than laymen's explanations. But I was definitely enamored by the excitement he generated about the study of physics and came away feeling that it was physics itself that was elegant, since the universe and the Biblically-termed "heavens and earth" are more what we make of them ourselves from a "blank canvas" rather than having any inherent, purposeful order or Divine scheme and blueprint. God's abhorrence of the roll of the dice being, of course, duly noted, Professor Einstein.

The genres of mathematics and physics are difficult to master, with many students peaking in high school or early college in the ability to understand them. To bastardize an amusing observation on the nether world spelled out on the television show "The Sopranos": Math is hard—that's never been disputed. Perhaps this is because at some point in its study, the student cannot just throw back extrapolations of dictated, memorized facts as done for other academic courses using cookie-cutter solutions. At some point the mathematicians and physicists have to enter a realm of intuition in tandem with a talent to locate obscure paths on the road to solutions through a maze of often maneuvering electron-like unfixed data. I don't even know if that is true, but that's my own hunch on why I was an "A" math student until hitting the harsh roadblock of calculus, the wall on which I came to a dead stop with such studies.

The general consensus that math and science at the highest levels is "really, really hard" has led to several movies in recent years romanticizing the notion of the lone genius mathematician and physicist, and I for one enjoy these kinds of films. The general plot lines of such movies show the trials, tribulations and struggles of the men and women who are at the top of these fields, where the mind can be subject to terrific loneliness amid troubled social situations that are a result of seeing and knowing what most people can't begin to fathom.

The first movie that I saw that explored the fictional tale of the genius mathematician was *Good Will Hunting* starring a then very young Matt Damon as a math prodigy from a working-class background in South Boston. Damon's character, Will Hunting, having grown up as a beaten foster child, is in and out of trouble with the law as he runs around with an amusing group of loose characters (including the actors Ben and Casey Affleck). Hunting is unearthed and discovered by a Fields Medalist professor at MIT (Stellan Skarsgård) where Damon, as a janitor, fairly easily solves near impossible math problems left on a chalkboard in a hallway for the brilliant students of the university to try their hands at solving. The story evolves to include emotional scenes with Damon's appointed psychiatrist, played beautifully by the late Robin Williams, as Williams tries to free the scarred youth from his stunted emotional growth so he can ease into maturation and grow into the man he is destined to be. There' a wonderful scene where Will's girlfriend, a Harvard premedical student played by Minnie Driver, asks with wide-eyed wonder, "*How do you do it*?" Damon explains with confidence that just as Mozart could simply look at a piano keyboard and solve the puzzle of making music, he can use his intuitions to see mathematical solutions as they open up before him.

Next up in the genre was *A Beautiful Mind* starring Russell Crowe as the deeply disturbed mathematician John Nash, who went on to overcome his mind's demons and win the Nobel Prize for his theoretical work in game theory. Crowe's depiction of the descent into madness that leads to a horrific hospitalization is heart wrenching. The life of Nash is shown in the film from his student days at Princeton to the start of his twilight years after his return to that university, and it is a marvelous and intellectually stimulating journey to behold. There are scenes where Crowe is filmed as Nash working out his complex formulas with an erasable marker on the latticed windows of the library at Princeton. Although most of us who watch the film can't come close to translating these numbers and brackets and symbols into any sense at all, we understand that it is a poetic language that is on display and we can intuit it as graceful and beautiful as any actual work of poetry or music.

Time rolled on after *A Beautiful Mind* and we currently have been treated to two

Biophysics as studied at The Rockefeller University (photo courtesy of Mario Morgado – see morgadophotography.com for more of Mario's work).

films in this area of professorial biography, *The Imitation Game* about the British wartime math code breaker, Alan Turing, and *The Theory of Everything*, a biopic of Stephen Hawking.

I enjoyed both of these films and I am appreciative that in the sea of madness that is Hollywood's idea of "entertainment" that they were both able to find their way to the big screen and worldwide distribution. "The Theory of Everything" boasts the Oscar-winning performance of Eddie Redmayne as Hawking. Redmayne, in incredible fashion, transforms himself from a promising and brilliant physics student at Cambridge to an absolute genius of an astrophysicist, writing on subjects such as theoretical time and black holes as he is nearly completely crippled by a motor neuron disease. The movie business, given what it has to be in terms of catering to popular tastes to insure box office appeal, focuses less on the mind and science, and more on the personal relationship between the physicist and his wife, Jane Hawking (sweetly played by Felicity Jones). I did enjoy the emotional family story, but there is no doubt that it consumes the film and so many of Hawking's accomplishments are quickly glossed over. Nothing can take away from Redmayne's admirable, awe-inspiring performance and the way in which he captures our familiar idea of the heroic Hawking. One could even say it's a role for the ages, not too surprising given that Redmayne was so interesting, complex, and intriguing in a supporting role in the Robert De Niro-directed feature film "The Good Shepherd" and yet oddly miscast, while still displaying talent, in *Les Miserables*, where he shares the operatic stage with the unlikely singing Russell Crowe (are you not entertained!). Nash meets Hawking. Interesting. An actor, the actual man, is, one could postulate, the sum of his roles.

That leads us to *The Imitation Game*. Alan Turing, played by Benedict Cumberbatch, is enlisted as part of an elite group of top-notch, mathematical Brits during World War II, to figure out the impossibly complex "Enigma" secret code used by the Germans to relay their strategic moves across the various parts of their war machine. And it is a machine that Turing builds to solve the mystery. Cumberbatch, an amazing actor to say the least, seems to be making a living out of playing socially awkward, blindingly brilliant loners, since he is also the star of the excellent television series from the BBC, "Sherlock" (as in Holmes). The actress Kiera Knightly is the lone woman amongst the not-so-merry band of mathematicians on the quest to solve the near-impossible riddle, and it's great to see this talented actress do her work and magic on the eccentric Turing, making him put his ego aside and join in conjunction with the others for the higher purpose of a wartime nation.

Turing was horribly and famously chemically castrated in the UK after the war as punishment for the crime of being homosexual. Soon after his "cure," he took his own life. Cumberbatch, who lost the Academy Award nod to Redmayne, almost deserved a tie for the statue, such is his complex performance. There aren't many Hollywood films featuring a protagonist often reduced to whimpering sobs while maintain a strong, compelling dignity. Britain, showing its great solid upper lip, recently retracted its ignorant, murderous damning of Turing in a fabulous gesture of a posthumous reprieve and award. I am reminded of the scene in *Monty Python and the Holy Grail* where the Medieval knight played by John Cleese, believing he is slaying the captors of a kidnapped princess (Terry Jones in the tower!), lays murderous waste to a wedding in progress in a castle. Realizing his error, Cleese stands on a grand stairway to the sounds of the groaning injured and weeping women and with a broad smile, cries out, "Sorry! So sorry! My mistake!" to which a man yells back "You killed the groom!" For the groom and for Turing, it's a case of "far too little and much too late."

In all four movies I've mentioned, the science and math take back seat to the emotional and personal relationship stories. However, the moments that they do dig into the mind's matter, it is fascinating. Matt Damon and Stellan Skarsgård finish a proof in the MIT professor's office by crossing out equivalents on either side of a blackboard equation to an almost giddy happiness. The "eureka" moments of both Nash and Turing occur amid bar and party scenes with their drinking friends, but the excitement generated is wonderful and palpable. The professor (David Thewlis), however, who presides over Stephen Hawking's Ph.D. studies does a far more convincing job in his role as a professor at Hogwarts in the Harry Potter films than as a physicist at Cambridge. Yet his kind spirit, I must say, is contagious.

To reach my own office in the Development Department at Rockefeller University, I have to pass by the offices of the university's physicists. I do so quietly and with respect, because there is a tactile (in the art historian Bernard Berenson's theoretical use of the term) energy in the air and the excitement of slow and steady discovery that keeps one on the verge of awe at what the human mind is capable of at its very best. Just the books and bound journals on the shelves alone are enough to entrance, as are the wonderful black and white group photos of physicists of days long past. Immediately after The Beatles broke up, John Lennon gave an interview saying that if he'd had to do over again he'd just as well have been "a [expletive deleted] fisherman." In my own memoir, I wrote that I would have been "a [same Lennon expletive] physicist" given another opportunity. Alas, Mr. Lennon had the talent to fish and I had no talent with math, so as for myself, as the late great Oliver Reed says in the film "Gladiator" to the actor who would soon play John Nash, I say: "Me? I'm just an entertainer." ⊙

Quotable Quote

"The legendary cellist Pablo Casals was asked why he continued to practice at age 90. 'Because I think I'm making progress,' he replied."

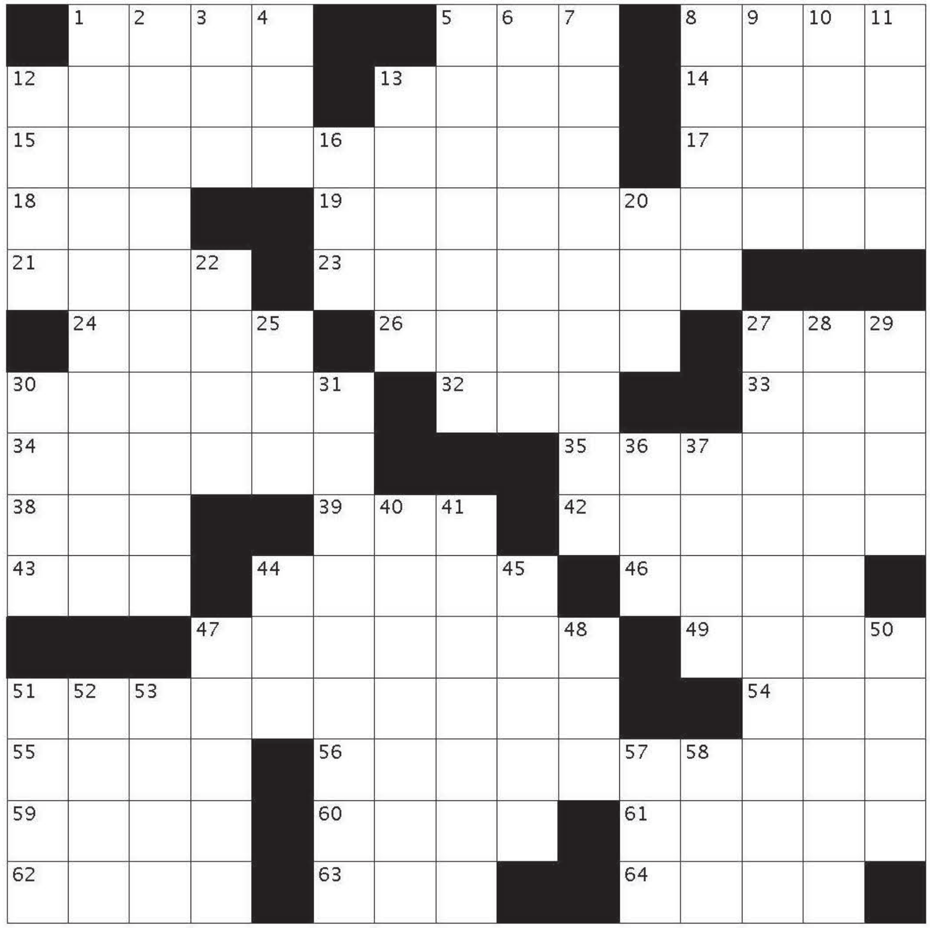
From *The Little Red Book of New York Wisdom*. Copyright 2011 by Gregg Stebben and Jason Katzman, Skyhorse Publishing, with an introduction by Former Mayor Ed Koch.

Send in interesting quotes to be included in future issues to nseditors@rockefeller.edu. Quotes can be philosophical, funny, clever, anecdotal - but NOT too salacious or outright unpublishable - and short enough not to need copyright permission.

Technophilia

ARTHUR ROTHSTEIN AND GEORGE BARANY

George Barany is a Rockefeller alum (1977) currently on the faculty of the University of Minnesota–Twin Cities. Arthur Rothstein is a software pathologist and plumber in San Francisco. Some 45 years ago, they were teammates on the Stuyvesant High School Math Team. For more about this specific puzzle, including links to the answer and a "midrash," visit http://tinyurl.com/technoNSpuz. More Barany and Friends crosswords are at http://tinyurl.com/gbpuzzle.



Across
1. One in Bonn
5. Mil. status after 20 and out
8. Tesla wannabe
12. Baseball writer Buster
13. With 14-Across, HP HQ
14. See 13-Across
15. YouTube sensation
17. Ratio phrase
18. DDE's wartime command
19. Internet felony
21. Flying Cloud and Speed Wagon, e.g.
23. Consoled
24. "Hurry up!"
26. Accounted for the container weight
27. Govt. contracting agency
30. Played ten frames
32. Letters from the morgue
33. Wine: Prefix
34. "You'd better believe it"
35. Snappy answer
38. Whistle blower?
39. Monogram of Beat novelist and adding machine heir
42. "Wild Thing" group
43. Soft & ___ (former Gillette product)
44. Henry VIII's second and fourth, and 28-Down's first
46. Companion of Baker and Charlie
47. Flockhart of *Ally McBeal*
49. Pop style of France Gall and Françoise Hardy
51. Cable type
54. 42 gal., to OPEC
55. Love god
56. Pleasure palace for gadgeteers
59. Purely academic
60. Groupon offer
61. Stand-up
62. Paul who composed Johnny's theme song
63. Cardinal letters
64. Library ID

Down
1. Celebrity at Facebook or Twitter
2. Hotel amenity
3. Humanities benefactor: Abbr.
4. Word div.
5. Spot that's never seen
6. Foe of Spider-Man
7. Cheered up
8. Nixon's defense secretary
9. Boris's "bride" of 1935
10. Aleutian island
11. Vittles
12. Finished
13. Early Palm device
16. Startup investors
20. Yellen's realm
22. Convinced
25. Early 8-bit game console
27. Search-rank deceiver
28. Larry Page's co-founder
29. Echidna lunch
30. Angry character in popular game
31. iTunes deliveries
36. Babe Ruth's league-leading stat in 1916
37. Circus boy Tyler
40. Brief excerpt
41. Bill Gates to Paul Allen, once
44. Alpine flower
45. Bathtub beverage maker
47. Jai alai basket
48. Rickenbacker, e.g.
50. Computer juice: Abbr.
51. Govt. crisis responder
52. Big ___, colloquial term for mainframe computers
53. 20th century reading device
57. Bio. or chem.
58. How-___ (guides)

Life on a Roll

Elodie Pauwels

Spring has arrived early in France this year. I was lucky to spend a few days outdoors with my camera to (re)discover three parks in the suburbs of Paris. While the Parc de Saint-Cloud allows the walker to enjoy a stunning view of Paris, quiet or crowded plots alternate in the Bois de Vincennes. Port-aux-Cerises is a huge recreational area where I however spotted some old photogenic rowing boats. ⊙

Photos: Elodie Pauwels
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