DUJS | Dartmouth Undergraduate Journal of Science

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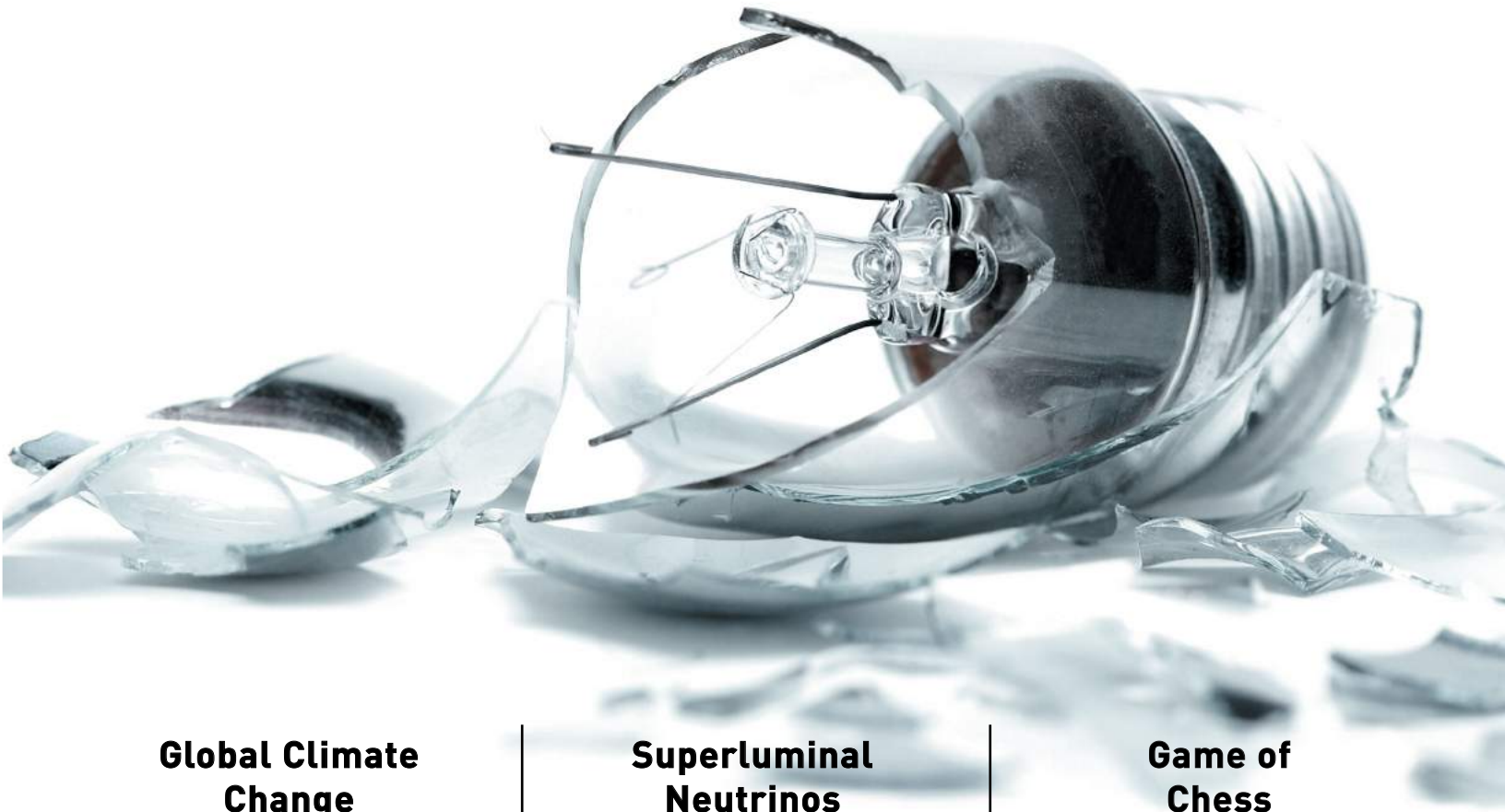
BREAKDOWN

When our efforts fail and our systems collapse



Global Climate Change

Featuring Erich Osterberg, Ph.D.

p. 3

Superluminal Neutrinos

Mistakes from the 21st Century

p. 9

Game of Chess

The Revenge of Deep Blue

p. 43

Note from the Editorial Board

Dear Reader,

We have always celebrated humanity's accomplishments. And, indeed, there is much to praise; within just the past century, we have uncovered the secrets of relativity, designed vaccinations that protect us from innumerable diseases, and created a global system of computer networks that connects the entire human race. We celebrated these achievements in earnest and elevated the innovators behind these discoveries and inventions to the statuses of champions. But in glorifying these moments of triumph, we often obscure the mountain of failures that served as stepping stones toward each success and misrepresent the road to success as one that is simple and smooth in its progression. In reality, the road to success is winding, difficult—often with no clear end in sight and very little sense of progress. But if humanity's past successes are any indication, it is that we must not lose heart—that if we grapple long enough in the dark, we are bound to find something. Nothing exemplifies this more than Thomas Edison, who famously said, "I have not failed. I've just found 10,000 ways that won't work."

As a reminder of the rocky nature of scientific progress, our articles in this issue of the *DUJS* look past the often lauded successes and explore what happens instead when our efforts and systems breakdown. Kartikeya Menon details the flaws behind the experiments that sought to prove the existence of faster-than-light neutrinos. Ali Siddiqui describes the history behind Einstein's cosmological constant, what Einstein mistakenly proclaimed to be his "biggest blunder." Merritt Losert analyzes the factors that led to the 2011 meltdown of the Fukushima Nuclear Power Plant. Matthew Jin recounts the dark history of lobotomy. Yvette Zou reports on how a single point mutation can lead to the devastating cystic fibrosis. Stephanie Alden explores the effects of autoimmunity, and Joshua Wan takes us back to the recent government shutdown and its impact on science. This issue's faculty interview features Erich Osterberg, PhD, a climatologist and assistant professor of Earth Sciences at Dartmouth College. Dr. Osterberg explains the present scientific research behind global climate change and the importance of scientific communication.

This issue of the *DUJS* also features three external, original research submissions. Raymond Maung, Rian Chandra, and Jake Hecla present findings that shed new light on the behavior of Farnsworth-type reactors. Quang Nguyen reviews the pharmaceutical potential of patulin, highlighting the intricate relationship between poison and remedy. And finally, Dartmouth student James Brofos presents the riveting history behind artificial intelligence and the computer science of chess engines.

This issue of the *DUJS* would not be possible without the diligence and dedication of the writers, editors, staff members, and faculty advisors. We would like to thank all of those involved in maintaining the *DUJS*'s continued success as an outstanding undergraduate scientific journal.

Thank you for reading the *DUJS*, and we hope you enjoy this issue.

Sincerely,
The DUJS Editorial Board

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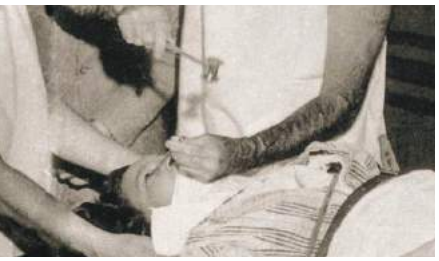
Table of Contents

Faculty Spotlight: Erich Osterberg **3**
Scott Gladstone '15

Superluminal Neutrinos:
A Scientific Anomaly and Costly Mistake **9**
Kartikeya Menon '16

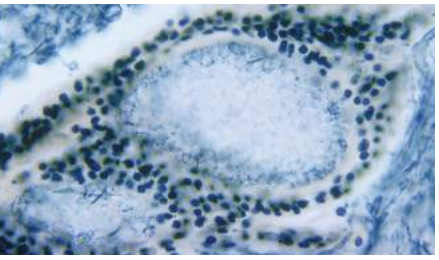
Einstein's Greatest Mistake
or Universe's Greatest Mystery? **13**
Ali Siddiqui '17

Failure at Fukushima: What Went Wrong? **18**
Merritt Losert '17



The Rise and Fall of Lobotomy **22**
Matthew Jin '17

Cystic Fibrosis:
From Point Mutation to Systems Failure **26**
Yvette Zou '16



When the Immune System Fails: Autoimmunity **30**
Stephanie Alden '16

Government Shutdown: What Happens to Science? **34**
Joshua Wan '16

SUBMISSIONS

Patulin: A Mycotoxin or an Anti-Cancer Chemical? **37**
Quang Nguyen, Duke University

Investigation of Neutron Emission from a
Farnsworth IEC Fusion Reactor **39**
Raymond A. Maung, Rian N. Chandra, Jake J. Hecla

Man vs. Machine: The Rivalry in Chess **43**
James Brofos '15

Photo courtesy of Erich Osterberg

Erich Osterberg: Understanding Global Climate Change

BY SCOTT GLADSTONE

Introduction

Dr. Erich Osterberg is an assistant professor of Earth Sciences at Dartmouth College, an ice core climatologist and glaciologist, and a member of several national scientific advisory boards. Working with both the U.S. Ice Core Working Group and his research team based in Hanover, NH, Osterberg focuses on exploring the signatures and causes of past climate change and training the next generation of polar ice researchers.

Osterberg places a strong emphasis on examining regional—as opposed to global—climate change. His efforts are currently directed toward understanding the dynamics and mechanisms influencing meteorological conditions and glacial melting in Greenland and Alaska, where his team investigates precipitation variability, atmospheric pollution, and chemical markers of climate change. At Dartmouth, Osterberg teaches a variety of courses, ranging from introductory-level classes such as Evolution of Earth and Life, Elementary Oceanography, and Meteorology to upper-level geology and paleoclimatology courses such as Marine Geology and Climate Dynamics. He is also a thesis advisor to graduate and undergraduate students, and a public outreach coordinator of scientific awareness in New Hampshire's Upper River Valley.

Prior to taking on these roles, Osterberg was a graduate student researcher at the Climate Change Institute at the University of Maine in Orono and a J. William Fulbright Graduate Fellow at the University of Otago in Dunedin, New Zealand. He received his Ph.D. in Geology from the University of Maine in 2007. In an interview with the *Dartmouth Undergraduate Journal of Science*, Osterberg describes his climatology research and shares some of his thoughts on global climate change, the breakdown between scientific information and environmental policies, and teaching Earth Science at Dartmouth College.

Global Climate Change

One of the driving themes of many of the classes you teach at Dartmouth is the importance of acknowledging humankind's impact in causing global climate change. What are the trends in global climate change right now?

We can think of global climate change as the combination of humans changing the atmosphere and the climate responding to that change. We, as humans, are constantly changing the atmosphere through increasing carbon dioxide emissions. There is a very steady rise in atmospheric CO_2 that we observe as a result of fossil fuel burning, approximately an increase of two parts-per-million per year. The evidence that the rise is caused by human fossil fuel burning is also quite clear: the rates of fossil fuel consumption match the rise in atmospheric CO_2 concentration, and the CO_2 chemical signature indicates a fossil fuel-based origin. The interesting question from that trend is then: how is the climate responding?

One of the things that has garnered a lot of attention in the media in the last couple years is the supposed "hiatus" in global warming since 1998. The idea of the "hiatus" is that temperatures haven't really continued to increase since 1998

Osterberg and student researchers at the edge of the Greenland Ice Sheet. (Left to right: Matt Bigl, M.S. '13; Erich Osterberg; John Thompson '13; Ellen Roy '13)

Photo courtesy of Erich Osterberg

and that we've been sitting at a sort of temperature plateau. It's clear that the temperature rise that picked up dramatically in the 80's and 90's, globally speaking, did begin to slow down in the 2000's. However, the data suggest that it is due to another global trend: rising ocean temperatures. It is interesting because we are always worried about what "the land" is doing, but the majority of the Earth is covered with water, and water is much better at retaining heat than land. So there has been a new focus in research recently trying to understand how exactly the oceans have been warming. If you look at the oceans, the rise in temperature has been very steady through the 2000's, despite this land-based "hiatus."

Scientists know that there are many other things that control climate besides CO_2, such as the intensity of the sun and weather patterns, like El Niño, that can last for several years. The global climate is a complex picture, but we have very high confidence that continually rising CO_2 concentrations in the atmosphere will lead to global warming, on average. In specific locations at the regional level, the trend is more difficult to predict.

What do you predict will occur in terms of global climate and meteorological conditions in the next 10-, 50-, and 100-years?

There is a lot of ongoing research investigating the relationship between global warming and hurricanes, and between global warming and storms in general. The data are a little tricky with things like extreme weather, but it looks like hurricanes will get less frequent in the future, but the ones that form will be stronger. So we'll see more Category 4 and 5 storms, but fewer storms altogether. And more hurricanes will be making it farther North to places like Long Island because the average ocean temperatures will be higher and able to support the storms longer before they weaken.

In terms of events such as droughts, we expect dry areas to get drier; in terms of flooding, we expect wet areas to get wetter. Of course, we'd like to see dry areas get wetter and wet areas get drier, but that's not how the climate system works. You'll see a very interesting dichotomy of more droughts and more floods in different areas of the world. In the Northeast United States, the predictions are that we'll see more precipitation—more rain, specifically—and that rain will be concentrated into more intense periods. We expect more "downpours:" two-inches-of-rain-in-one-day kind of storms. Naturally, those events have effects on farming, road conditions, and other infrastructure.

In terms of temperature changes, you're looking somewhere on the order of a four to ten degree Fahrenheit increase. But again, those numbers will change based on where you are because those numbers are a global average. We expect to see more warming toward the poles and less so toward the equator. The weather patterns will likely change a lot, and subsequently dictate how the temperature will change in places like here in New England. A lot of the temperature change will be more acute in the winter, but we also expect to see more heat waves in the summer.

So the next logical question is: what does that mean for people?

That, I think, is where research is increasingly focusing right now. Not just by climate scientists, but by sociologists, economists, and a variety of researchers. What does a 5.0 degree Fahrenheit temperature rise mean in terms of increased costs and day-to-day things that people will notice? My research group is beginning to look at this question in New England. I tend to think that what people will notice will be the extremes: the heat waves being more frequent and the cold of winter being less snow-covered because we'll have more rain and warmth in general. It will be the dead of winter and the dead of summer when we'll really notice all of the changes, in addition to events such as high intensity rainstorms and large hurricanes coming up the coasts.

Has this knowledge affected how we, as humans, contribute to global climate change?

I think we are definitely becoming more "climate conscious," but in terms of the actual rates of CO_2 emissions and fossil fuel consumption, the trends haven't really changed in recent years. The United States has actually decreased our CO_2 emissions recently, but that is mostly because the economy has been hurting for the last four years. As the economy picks back up, we'll likely see CO_2 emissions pick up as well.

What is an interesting trend though is the transition from the predominant use of one fossil fuel to another. In America, about 50% of our electricity has historically come from coal. But because of new fracking initiatives and the recovery of natural gas from new places like the Northeast United States, we can start transitioning our power plants from coal to natural gas. You can say that it's still fossil fuel-to-fossil fuel, but in terms of energy output, natural gas puts out half as much CO_2 per unit of energy as coal. Any movement in that direction would make a real difference. However, it will be primarily market forces that motivate any fossil fuel transition. With so much natural gas around, it will become cheaper than coal and people will convert to it.

All of the changes in CO_2 emissions we have seen in this country up to this point have been purely market based. I'm talking about market forces such as the downturn of the economy or falling energy prices due to new natural gas availability. We have yet to see any significant change in people's behavior based on policy, with the possible exception of higher fuel efficiency standards for vehicles. But that's a relatively small effect in terms of our overall CO_2 output. The bottom line is that we haven't started to get serious yet about reducing CO_2 emissions, and there is no political motivation or will to do so right now. In the near future, unless something happens that drastically changes people's perceptions of climate change, I don't see there being any major steps forward in policy aimed at reducing CO_2 emissions.

So must we wait for some sort of major catastrophe to generate sufficient demand to solve the global climate change problem?

Both in the United States and in Europe, the things that move us to act are high profile things that, in our modern language, "go viral." The environmental movement in this country, for example, was to a significant degree sparked by media coverage of a river in Ohio catching fire, and that story went viral. At the time, it just happened that there was a national news crew there who captured the whole thing, and it ended up all over the news and in the papers. Now, that river would catch fire all the time, but nobody was there before on a national level to photograph and make a big deal out of it. When that happened, there was a national outpouring of concern and disgust. That pollution had gotten to a point where water could catch on fire was unacceptable, and people decided to do something about the cleanliness of our air and water. Then, and only then, did we pass the Clean Air Act. There was a nascent environmental movement before that time, but this event galvanized the movement around an iconic image. There are definitely tipping point events like that.

Do you see any "tipping point" events currently making their way onto the global stage?

Hurricane Katrina was almost one of them. Ironically, it would have been for all of the wrong reasons, because Katrina probably had nothing to do with global climate change. But people perceived that it did, and Al Gore put a hurricane on the cover of his *An Inconvenient Truth* movie and people made that connection. Hurricane Sandy received similar treatment as well. There was a lot of press about whether Sandy happened because of global warming, and the answer is almost certainly no. It looks like it was a once-in-800-year event that happened because of a complex array of weather factors that, according to recent research, are actually less likely to occur with global warming.

At the end of the day, it's all about people's perceptions. Perception is reality. Unless there is some major climate change event—my guess is that it would be a drought similar to the one in California and the Southwest U.S. right now. If it got to a point where the major urban areas in the Southwest—San Diego, Los Angeles, Phoenix—were all of a sudden really struggling for water, then change could happen. The governor of California announced a national water emergency this past January. So far, there are no imposed limitations of water use, but simply a request that people decrease their water use by about 20%. If it gets to the point where the government is stepping in and forcing people to stop using so much water, that is the kind of event that could trigger action. These types of events are consistent with what we predict will occur: dry areas will become drier and wet areas will become wetter. If there is something that occurs where day-to-day lives of people are affected—for example, people can't take showers or wash their cars or keep their lawns green—that's when action will start happening.

Public Perception versus Scientific Reality

Has there been a media failure in spreading awareness about global climate change?

There are so many factors at play in the way that the media presents these issues. One factor is simply that sensationalism sells. The vast majority of these media outlets are companies that are selling advertisements. Even if the material that is presented isn't substantiated by facts, it still sells. The media tends to seek out scientists who are alarmist in their language, and the danger of being alarmist is that it's not based in reality.

Another part of the issue is that there is this stress to always show both sides of the story. So, for every 95 scientists who believe in the basic scientific facts as we understand them regarding global warming, the media will still find one from the 5 who strongly disagree and pit them one-to-one against each other instead of 95-to-5. As opposed to expressing the balance in terms of what the actual proportion of scientists think, the media presents the issue as if it is completely even and up to debate. Fifty-fifty: believe this person or the other one, it's your choice. And that is not the reality of where the

"The media tends to seek out scientists who are alarmist in their language, and the danger of being alarmist is that it's not based in reality."

science is.

The reality is that the truth of what we face is not as alarmist and sensational as a lot of the claims and images circulating in the media. Climate change is going to be something that people notice, something that costs a lot of money, and something that will cause people to suffer in countries that don't have sufficient resources to pay their way out of the biggest impacts. It's not going to be "the end of this" or "the end of that" as we know it. It's not going to be like the movie *The Day After Tomorrow*, where people are running away from the next ice age and the polar vortex as it freezes behind them. But this is what sells and this is what people are getting into their heads.

So is there a better way to spread awareness and curb the rate of human-driven global warming?

The other major part of this problem with the media is that there is a reluctance of the vast majority of scientists to go and talk to the press. Partly because many scientists are not good communicators, but also partly because the press will generally have a story that they want to tell in mind. So your words then end up in print—and are attributed to you—but perhaps not in the way that you intended them to be expressed.

More than that, there is also this notion in academia and in science that researchers shouldn't be muddling in the policy and media arenas. Many scientists believe that we should be doing our science and putting our information out there, and it is up to the policy makers and the media to look at our results and decide for themselves what to do with them. But I personally feel that there is a role for scientists to be contributing more to the dialogue than we currently are, and it comes down to better communication, training for how to speak to reporters and the public, and publishing as much as we can in mainstream media, not just scientific journals. Getting our message out to the public in a way that we believe is accurate, even if it isn't in as much technical detail as we normally talk about, is key.

I agree that it is a very slippery slope anytime you start transitioning from scientist to advocate. There is a strong stigma against that in science—and rightfully so! We have to be impartial, and if we can't be impartial, then our results and motivations will be called into question. But I feel strongly that we can communicate our science more effectively without slipping into advocacy.

Ice Core Research

Turning toward your personal work, you've been on various expeditions to glaciers around the world for your climatology and glaciology research. Where are some of the places that you've been, and what are the goals of your research?

My research is really focused on zooming in on regional climate changes. We have a pretty good understanding of what's happening globally or across hemispheres, but what about conditions in Alaska, or in Greenland, or New England? I look to hone in on those areas. I do that by looking into the glacial record to understand how climate changed in the past and what factors controlled those changes. Then I look at climate conditions today, determine if today's trends are in the natural range for those regions, and, if not, ask why not? To what can we attribute the change?

I'm also very interested in how glaciers respond to climate change because of how ice affects sea level rise. As we melt glaciers, global sea level continues to rise. A major question that I am investigating is how will the Greenland Ice Sheet melt in the future? There is about 20 feet of sea level stored in the ice sheet on Greenland, so how quickly that 20 feet gets introduced to the oceans is critical to our understanding of how sea level will rise in the future. My research in Greenland is focused on that question.

In Alaska, we have a research project in Denali where we are focused on precipitation. A lot of work has been dedicated to examining temperatures and how those trends are changing over time, but very little attention has been paid to precipitation. So we are looking at the questions: how much did it rain and snow in the past, what caused those changes in rain and snowfall patterns in the past in Alaska, how do changes in the snow affect the glaciers, and what sorts of trends have we seen recently and why?

With my work, we are really trying to focus in on regional areas that are particularly important to our climate system. There are a lot of glaciers up North that are melting very quickly, but Alaska is a unique place right now to study climate because it is one of the fastest warming areas in the world. To do this research, we collect ice cores. Ice cores can tell us how climate changed in the past, and we can apply these data to climate models that can then project climate into the future.

What does an ice core research expedition usually consist of in terms of planning, funding, hiking, collection and analysis?

These expeditions require a lot of intense planning. We usually have large groups of people—on the order of 10 researchers, including students—who are collecting ice cores from Denali, for example. First, we spent a lot of time traveling all around Denali National Park looking for the best place to collect an ice core. It is very expensive to collect ice cores, so we spent five years traveling to Denali every season to find the place with the deepest ice, because the deepest ice is usually the oldest ice. We also look for places where the ice doesn't melt very much over the summer, and places where the ice doesn't flow too fast, so that the climate record is kept intact.

After we found our collection spot, a 14,000 foot high mountain next to Denali, it took us a couple of years to secure funding from the National Science Foundation (NSF). Then, this past summer in 2013, we had our team of ten who went to Denali to collect the ice cores. The team flew in to base camp, which was on a glacier, via a ski plane. In order to work at 14,000 feet for six weeks, you have to become acclimatized by climbing Mt. McKinley over a period of about two weeks. For those couple of weeks, you're living full time on a glacier, climbing every day, and employing a bunch of mountaineering techniques such as roping up to protect yourself from falling into crevices. In that time, the team makes its way up to 14,000 feet on McKinley and stays there for a couple days to make sure that our bodies have adjusted to the altitude. Then we hike back down to base camp to start our work.

So how do you go about extracting and analyzing the ice cores?

We would take a helicopter from base camp straight up to the drill site, which was on the mountain next to base camp. We had about 12,000 pounds of equipment between food, tents, and drilling and scientific equipment that we were constantly moving. Once camp was set up at the drill site, the ice core drilling began. Basically, we collect a cylinder of ice that is about 4.0 inches in diameter, and we can collect it about 3.0 feet at a time. For each core, we drill, collect the ice, place it into a specially cleaned plastic bag, and then put the drill back down the same hole to collect the next 3.0 feet. We repeat this process until we get through the whole thickness of the glacier; for reference, the glacier at Denali was 700 feet thick. To collect each core, it took us about two weeks of drilling. At Denali, we actually collected two cores right next to each other, with the idea being that if we analyze both of them, we'll be able to look for climate signals common to both and avoid interpreting noise due to wind or melting.

For the Denali expedition, transporting the ice cores off the mountain was a major operation that took us about 20 helicopter trips. We then had eight ski planes that were filled with all of our equipment and the cores, and the planes brought the cores to a town nearby where two tractor-trailer freezer trucks were waiting to take our samples to the National Ice Core Lab in Denver, Colorado.

Analyzing Ice Cores: BY THE NUMBERS

12,000 pounds of equipment

Each core is **4.0** inch wide, **3** feet long, collected for the entire thickness of the glacier

Denali glacier was **700** feet thick

2 weeks of drilling

20 helicopter trips for transport

8 filled ski planes

2 tractor-trailer freezer trucks

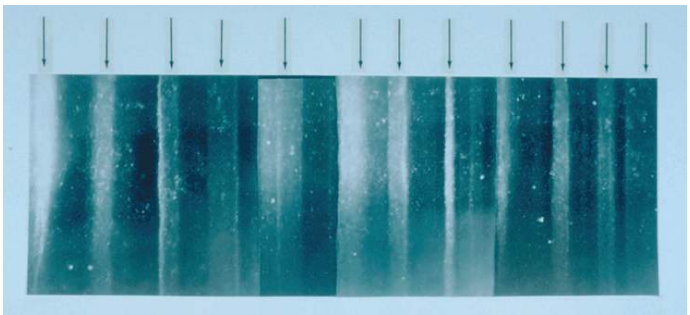


Image courtesy of Wiki Commons. Available at http://en.wikipedia.org/wiki/File:GISP2_1855m_ice_core_layers.png

Figure 1: An example of an ice core. Ice cores can provide data about the environment during certain time periods in their layers.

In September, we went to Denver to cut up the ice cores into pieces that we could bring back to our lab here at Dartmouth. My research specialty is in examining ice chemistry and using chemical markers to learn about how climate changed in the past at the drill site. For example, anything that falls on to the glacier is trapped in the ice and becomes part of the ice core. Dust, ocean sea salt, or volcanic eruption ash can all get deposited onto the glacier, and we can look at the chemistry of the ice and determine how strong the storms were in the past or examine the specific H_2O molecules in the ice to determine the temperature of the region at that time with pretty high accuracy. Overall, it will take us about two years to do all of our analyses here in the lab, so we have a large group of undergraduates, graduate students, post-doctoral researchers, and full-time faculty members involved in this research.

Teaching Science at Dartmouth

You are a Professor in the Dartmouth Earth Sciences Department, a member of various national scientific organizations, and a leader of glaciological and climatological field research. How do you balance research, public service, and undergraduate teaching?

You don't sleep a lot! Balancing everything is perhaps the largest challenge with this work, especially for younger faculty like myself. How do you go from being a student or being a post-doc where you can dedicate most, if not all, of your time to your research, to introducing a whole variety of tasks such as being on review boards, writing papers, conducting fieldwork, and teaching? What I have found is that making sure that you surround yourself with amazing students and a strong support staff is paramount. I have amazing students who, after they get started, take their research in really interesting directions on their own. Those students are able to keep my productivity at a high level.

While it may seem like a lot, the wild diversity is what makes this job fun! One day I'm teaching, another I'm in Washington, D.C. on a scientific panel, the next I'm writing my own research paper, and a month later I'm on a glacier in Greenland. That's a really cool spectrum of activities in your job description that keeps things really interesting.

The Dartmouth Class of 2013 chose you as one of Dartmouth's "Top 10 Professors." What are your perspectives on undergraduate teaching and are there any methods that you find particularly successful in connecting to students in the classroom?

I approach teaching in a couple of different ways. One is that I try to understand the research behind how students learn best. We often hear it said that "teaching is an art," and while there is certainly some "art" and intangible qualities to it, there is a ton of science behind teaching as well. I work hard to understand the science behind what makes a good class, a strong lesson, and what helps students to learn the best.

In one of my introductory classes, for example, we use a new technology called LectureTools. I decided that I wanted to make these larger introductory classes much more interactive. I wanted to get a smaller classroom experience out of a large lecture. So I approached Dartmouth's Classroom Technology Services office and told them that I was interested in clicker

technology, and they said that they have something even better and let me do a test run of it. And that was LectureTools. Some part of succeeding in teaching is being willing to try new things, but an even bigger part is to trying things based on the data.

Then there is the more intangible side to teaching, which is asking yourself how you can keep students interested and engaged in the topic that you are teaching. For me, it really comes down to continuing to learn the material myself. If I'm going to teach a lecture, I try not to just teach the same lecture that I did a year ago if it's the same class. Instead, I'll check Science and Nature and find out what the latest work is that's come out on the topic. If I find something interesting and then go teach it, it is clear to the students that I find it interesting, and they are inherently more interested because they know that I am engaged. So I think the number one way to get students engaged in the classroom is to be engaged yourself in the material that you are teaching.

So are introductory classes a particular challenge in that regard?

I love the things that I get to teach. I love the opportunity to teach non-majors in my introductory classes. In many cases, I am teaching them one of the only science classes that they will have for the rest of their lives. And what a great opportunity that is! That idea keeps me engaged in my lessons and happy to teach the material to those who are learning it for the first time. Figuring out the things in what I teach that I find interesting and highlighting those things in lectures makes the lectures more exciting for me and keeps the students engaged in the material. But it takes work and it takes time, and it comes back to the idea of balancing the many things here that we, as faculty, have to do here and deciding the ways that we want to make things work.

What do you think the role of science is at Dartmouth?

What we are emphasizing here at Dartmouth is a liberal arts education. The students that choose to go to scientific institutions are choosing that route because that is what their interests are. Our students come here because they want the breadth of a liberal arts education. I believe that we do a good job here of balancing the requirement of students to take some science while allowing them to pursue their areas of interest to great depth. We work hard to expose students to a scientific way of thinking regardless of their fields of interest. Science brings to the table a unique way of thinking logically through problems, challenging students to observe the world quantitatively and remove bias and preconceived notions from any situation.

One of the things that I love about the way that we can approach science here is that, in one of my introductory classes, for example, I am talking about the evolution of all life and all geology on this planet in just nine weeks. So we all, myself included, have to look at the big picture. That is what I think is so much fun: putting on that "big picture" lens and scanning through the weeds to find the common elements in all of the minutiae that researchers are investigating. What are the take-home points that students can internalize and have with them for life? If students walk away from an introductory class with the notion that life and geology on this planet are inevitably intertwined, and have the experience of seeing the world through that lens—even if they don't remember all of the details—then I am happy.

Osterberg samples snow for chemistry in a clean suit in Greenland on the North Ice Cap.

Photo courtesy of Erich Osterberg

Superluminal Neutrinos: A Scientific Anomaly and Costly Mistake

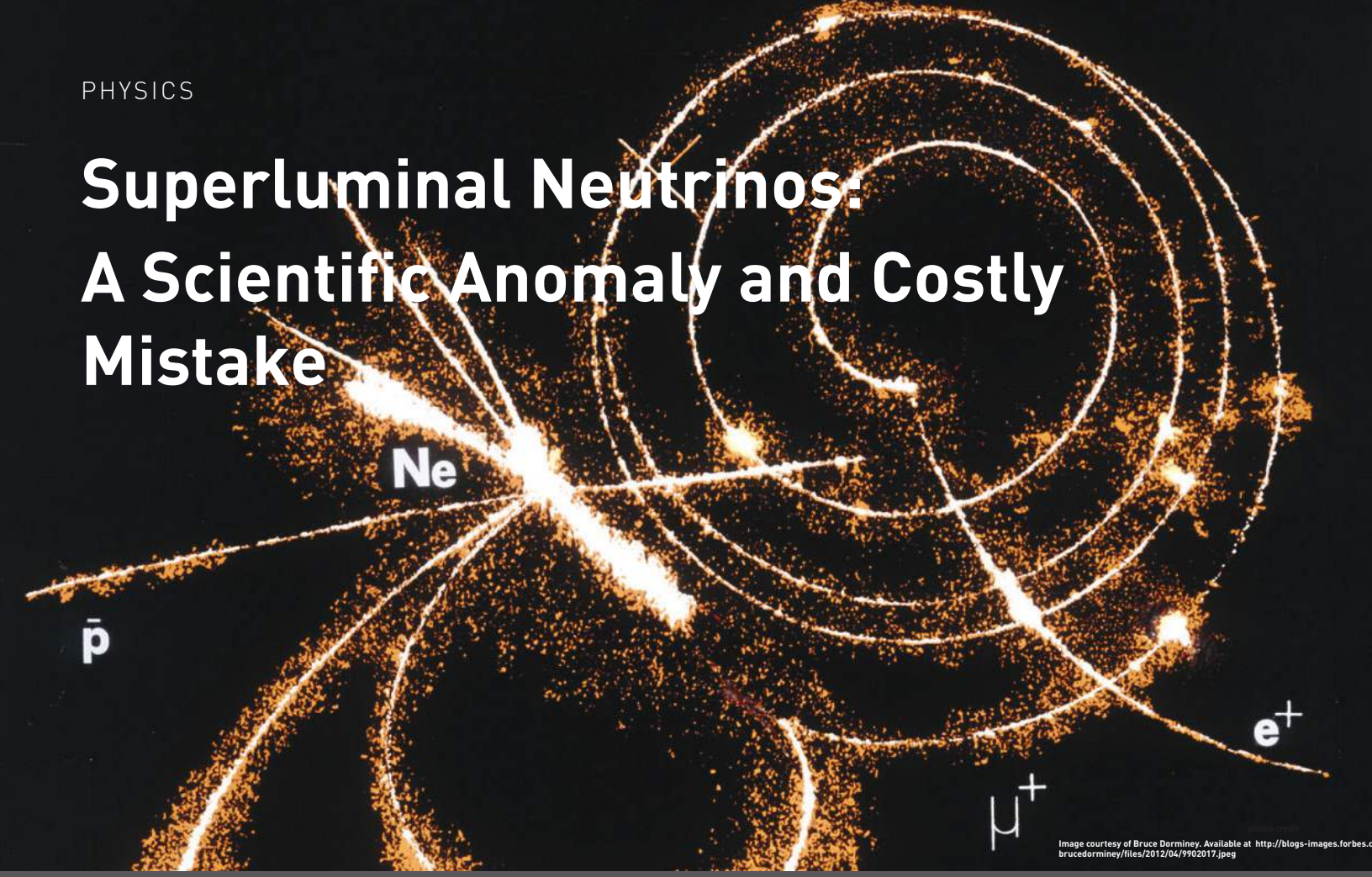


Image courtesy of Bruce Dorminey. Available at http://blogs-images.forbes.c
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BY KARTIKEYA MENON

On September 22, 2011, the Oscillation Project with Emulsion-Tracking Apparatus (OPERA) collaboration at the CERN particle physics laboratory in Geneva published that it had observed neutrinos traveling faster than the speed of light (1). Using a detector situated under the Gran Sasso Mountain in Italy, OPERA observed the properties of electrically neutral fundamental particles—called neutrinos—that rarely interact with other matter and have vanishingly small mass. In the famous experiment, OPERA sent a beam of neutrinos produced at CERN through 730km of the earth's crust, and observed that the neutrinos arrived at the detector approximately 60 nanoseconds sooner than if they had been traveling at the speed of light (2, 3).

During the months it took to eventually confirm the inaccuracy of the result, the possible existence of superluminal subatomic particles sparked debate within the scientific community. Should the results prove true, they would defy Einstein's special theory of relativity and upend our understanding of modern physics (4). One of special relativity's primary postulates is that the speed of light is equal for all observers, meaning that no matter how fast one is moving or where one is going, the speed of light is a universal, unsurpassable constant. The theory's predictions have been experimentally tested over the course of a century with no discrepancies since its publication in 1905 (5). If something were to travel faster than the speed of light, "basically, all of special relativity would be wrong" says Drexel University physics professor Dave Goldberg. According to Stephen Parke, a theoretical particle physicist at Fermilab in Illinois, the existence of superluminal particles implies the possibility of backwards time travel.

OPERA's spokesperson at the time, Antonio Ereditato, responded to many who questioned the results with confidence, stating that he believed strongly enough in the results to make them public. "We have checked and rechecked for anything that could have distorted our measurements but we found nothing. We now want colleagues to check them independently," Ereditato said (6).

OPERA researchers claim to have measured the 730-kilometer trip the neutrinos take between CERN and the detector to within 20 centimeters, and the time of the trip to within 10 nanoseconds (making the 60 nanosecond early arrival measurement statistically significant). OPERA's belief in the results was also supported by some previously recorded instances of the superluminal effect, or the observation of faster-

Figure 1: Colliding muons decay into electrons, positrons and neutrinos.

than-lightspeed travel. As such, OPERA believed that the result had a confidence level of six-sigma, meaning that the results were almost certainly accurate (3). Additionally, in another experiment performed several years earlier by the Main Injector Neutrino Oscillation Search (MINOS) in Minnesota, scientists observed a similar effect, though with a much lower confidence level. The MINOS experiment also observed neutrinos from the physics facility Fermilab arriving ahead of schedule to the detector, but the result was downplayed due to the high uncertainty in the measurement (3).

"There are many distortions in physics. You have to have a very high standard to see if something is truly correct."
—George Smoot III, Nobel Laureate in Physics

Despite OPERA's confidence in the experiment, many voices of skepticism remained both inside and outside the OPERA collaboration (2). Physics Nobel laureates George Smoot III and Carlos Rubbia expressed doubts that Einstein's theory could be so easily overthrown: "There are many distortions in physics. You have to have a very high standard to see if something is truly correct," said George Smoot III (6). Fermilab's Stephen Parke countered by saying it was possible to explain the findings without tossing out special relativity. It was speculated that the neutrinos might have traveled through different dimensions, taking shortcuts from Geneva to Gran Sasso, leading to their arrival 60 nanoseconds early (4).

More skepticism about the result came from a separate analysis of a neutrino pulse from a nearby supernova called 1987a (7). If the superluminal neutrino speeds seen by OPERA were achievable by all neutrinos, then the neutrino pulse from the exploding star would have shown up years before the flash of light—instead, they arrived within hours of one other (7). Among the 160 members of the OPERA collaboration, some believed that further checks on the data were required before a paper reporting the results could be submitted, especially given the potentially paradigm-altering nature of the results. (2)

Choosing to be cautious, OPERA decided to perform a new set of measurements to confirm the result before paper submission (2). The new measurements did away with the statistical analysis method that was used previously to determine the time-of-flight since critics noted that this analysis might not be reliable (2). The statistical analysis involved comparing the temporal distribution of protons generated at CERN with that of the neutrinos detected at Gran Sasso. In other words, this method involved modeling the signatures of the neutrino pulses (called waveforms) at CERN and comparing the waveforms of the emitted neutrinos with the arrival events at the OPERA detector (8).

The new tests split each neutrino pulse into bunches one or two nanoseconds long (considerably shorter than in the original experiment), allowing each neutrino detected at Gran Sasso to be tied to a particular bunch produced at CERN (1). Instead of firing lots of neutrinos and piecing together what arrived and when (as in the previously used statistical analysis method), OPERA slowed the measurements down and detected each neutrino from start to end individually (1). In their second round of experiments, OPERA observed only 20 superluminal neutrinos, a significant reduction from the original experiment's 16,000. However,

Figure 2: The inner machinery of the OPERA project.

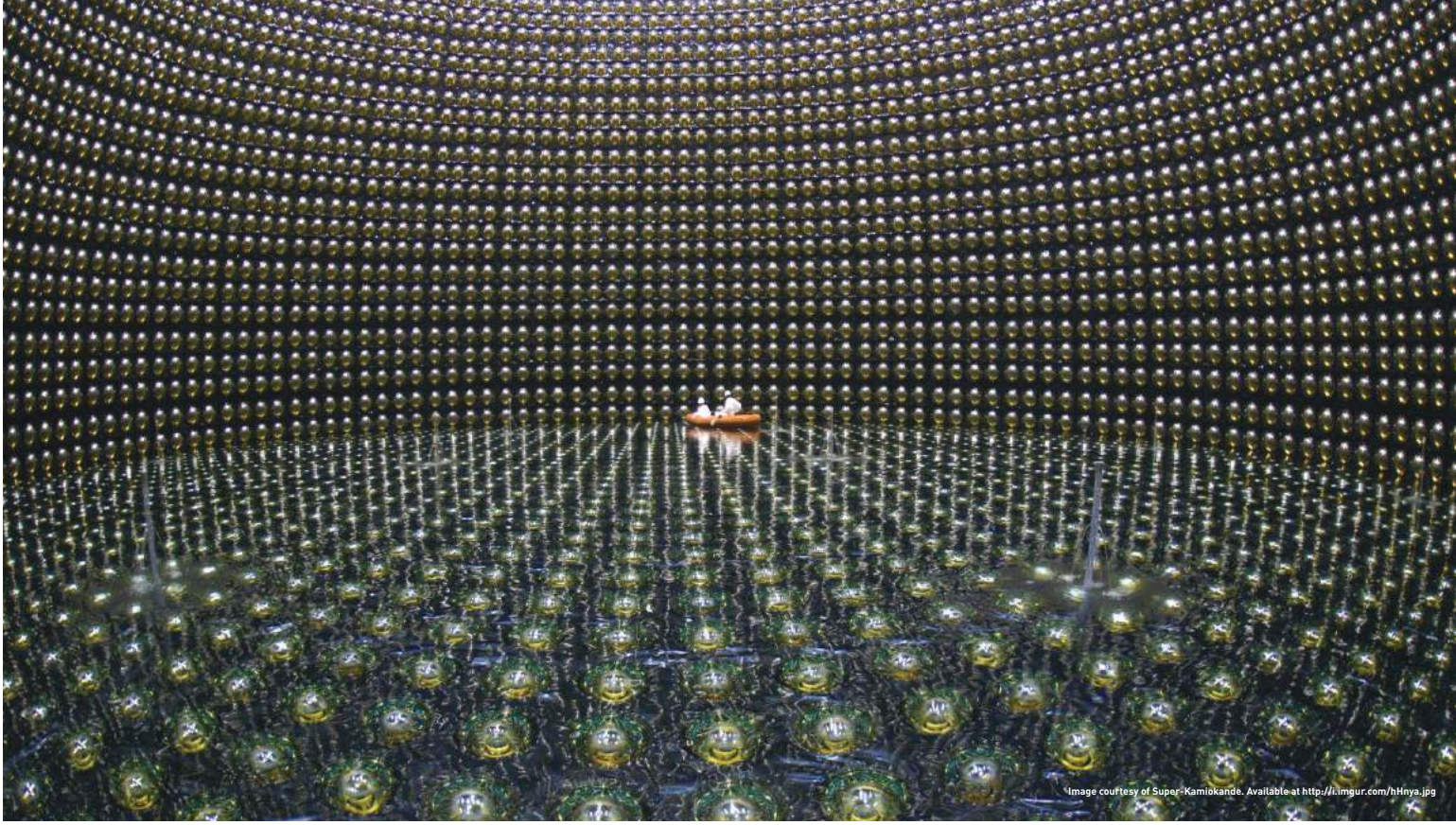

Figure 3: The chamber in which neutrino beams are detected.

Luca Stanco of the National Institute of Nuclear Physics in Padua, Italy, working with the OPERA project, claimed that the tighter particle bunches made those 20 hits easier to track and time, "so they are very powerful, these 20 events." The OPERA collaboration reconfirmed their error measurements to ensure that the uncertainty on the timing was indeed 10 nanoseconds and subsequently published their observations of the superluminal neutrinos (9).

After the new higher precision tests were completed on November 6, 2011, the OPERA collaboration confirmed its claim that neutrinos moved faster than the speed of light. But many of the collaborating physicists were still uneasy. "I'm not so happy. From a theoretical point of view, it is not so appealing. I still feel that another experiment should make the measurement before I will say that I believe this result," Stanco said (9). Others also wanted the result to be confirmed by an outside experiment: "Although our measurements have low systematic uncertainty and high statistical accuracy, and we place great confidence in our results, we're looking forward to comparing them with those from other experiments," said Dario Autiero, another OPERA physicist (10). Despite the unease, the OPERA collaboration planned to submit the results to a European physics journal.

Imaging Cosmic And Rare Underground Signals (ICARUS), another project that studies neutrino initiated by Carlos Rubbia, performed a similar experiment in which they observed that neutrinos travelled at roughly the speed of light, and no faster (11, 12, 13). Rubbia, the spokesperson for ICARUS, noted that their results "are in agreement with what Einstein would like to have." Neutrinos measured by ICARUS arrived within just four nanoseconds of the time that light travelling through a vacuum would take to cover the distance, well within the experimental margin of error (11).

Soon after ICARUS announced its rival results, physicists began looking for errors in OPERA's analysis. Sure enough, on February 23, 2012, researchers within OPERA announced that they had discovered possible timing issues with their original measurements that could have caused the 60-nanosecond discrepancy (11). Specifically, the team encountered a faulty connection at the point at which the light from a fiber-optic cable brings a synchronizing GPS signal to the master clock; the loose cable could have delayed the GPS signal, causing the master clock to run fast and make the neutrinos' travel time appear shorter (14). Another issue OPERA discovered was that the oscillator within the master clock was running fast; that would also interfere with accurate timing of the neutrino's travel (14).

Two other independent checks of the measurement are still being considered, as "it's never a bad idea to have multiple measurements," says MINOS spokesperson Rob Plunkett. One of the studies is Japan's Tokai to Kamioka (T2K) neutrino experiment, and the other will be at MINOS. The MINOS experiment will proceed at a cost of approximately $500,000 (14).

Jorge Páramos, a physicist at the Higher Technical Institute in Lisbon, says that the

announcements by OPERA point to an honest mistake, though one that should have been avoided. "The putative origin of the systematic error reflects the innards of the experiment —something that should have been checked exhaustively before any public announcement," he said (14).

Scientific mistakes are relatively common. Errors in calculations and analyses often lead to mistaken results, some of which end up being published (15). OPERA's misfortune was that their results challenged one of the fundamental tenets of modern physics. In the case of OPERA, which operates on a scale comparatively larger than most other laboratories, its mistakes are also more costly. According to the CERN estimate, OPERA's operating cost is approximately 48 million Swiss Francs, which is roughly 53 million US dollars (17). After the dust had settled, Antonio Ereditato, the spokesperson for OPERA, resigned on 30 March 2012 for his involvement in the proliferation of the results (16).

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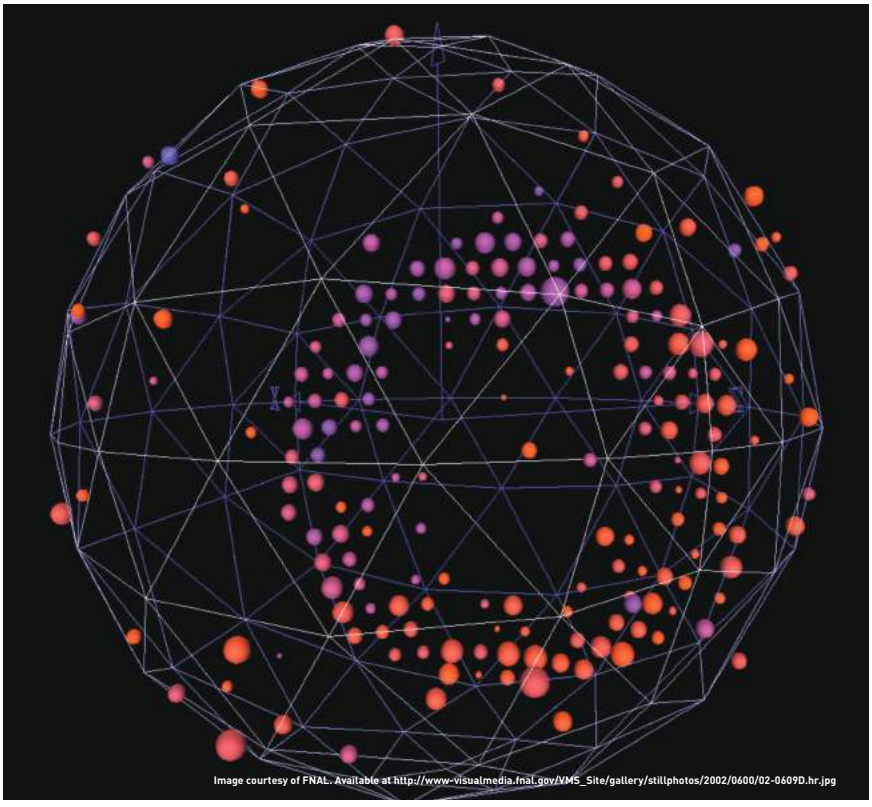

Figure 4: An observed neutrino signal.

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The Cosmological Constant: Einstein's Greatest Mistake or Universe's Greatest Mystery?

BY ALI SIDDIQUI

Introduction

Albert Einstein revolutionized the world of physics with his theory of general relativity, but even he was not completely satisfied with its implications. In order to explain how the universe kept from contracting due to the effects of gravity, he introduced a fudge factor that he called the "cosmological constant" (1). After the discoveries of Hubble and other scientists, however, Einstein retracted this constant since the universe was evidently expanding. The "cosmological constant" was later called his "biggest blunder" (2). More recent findings, however, call for a cosmological constant to explain the presence of dark energy (1). Perhaps Einstein's fudge factor was not that great of a mistake, but rather a prelude to one of the most enduring puzzles of our universe.

Einstein's Blunder

In 1917, Einstein wanted to derive a cosmological model of the universe using his theory of general relativity. Wanting his model to reflect the beliefs held by him and the majority of the scientific community at the time, Einstein assumed that the universe was homogenous, that the universe was closed, having a set volume, and that the universe remained static, meaning that its inherent properties did not change over time (3).

Taking all these assumptions into consideration, Einstein determined that the universe was either expanding or contracting (4), a conclusion that did not seem intuitive to him. To keep the universe static, he added an extra term to the equations of general relativity. This term was called the cosmological constant. This constant represented the vacuum energy density of space (5), which can be attributed to the presence of particles and antiparticles that are constantly made and destroyed through collisions, thereby giving energy to empty space (6). The cosmological constant exerts a negative pressure, if one considers the pressure of typical matter and gravitational attraction to be positive. In and of itself, the constant could take a negative, positive, or zero value (7). Each value has a different implication: a positive value would add a repulsive force to the gravitational forces already present in the universe, a negative value would add another attractive force alongside gravity, and a value of zero would have no effect on the original

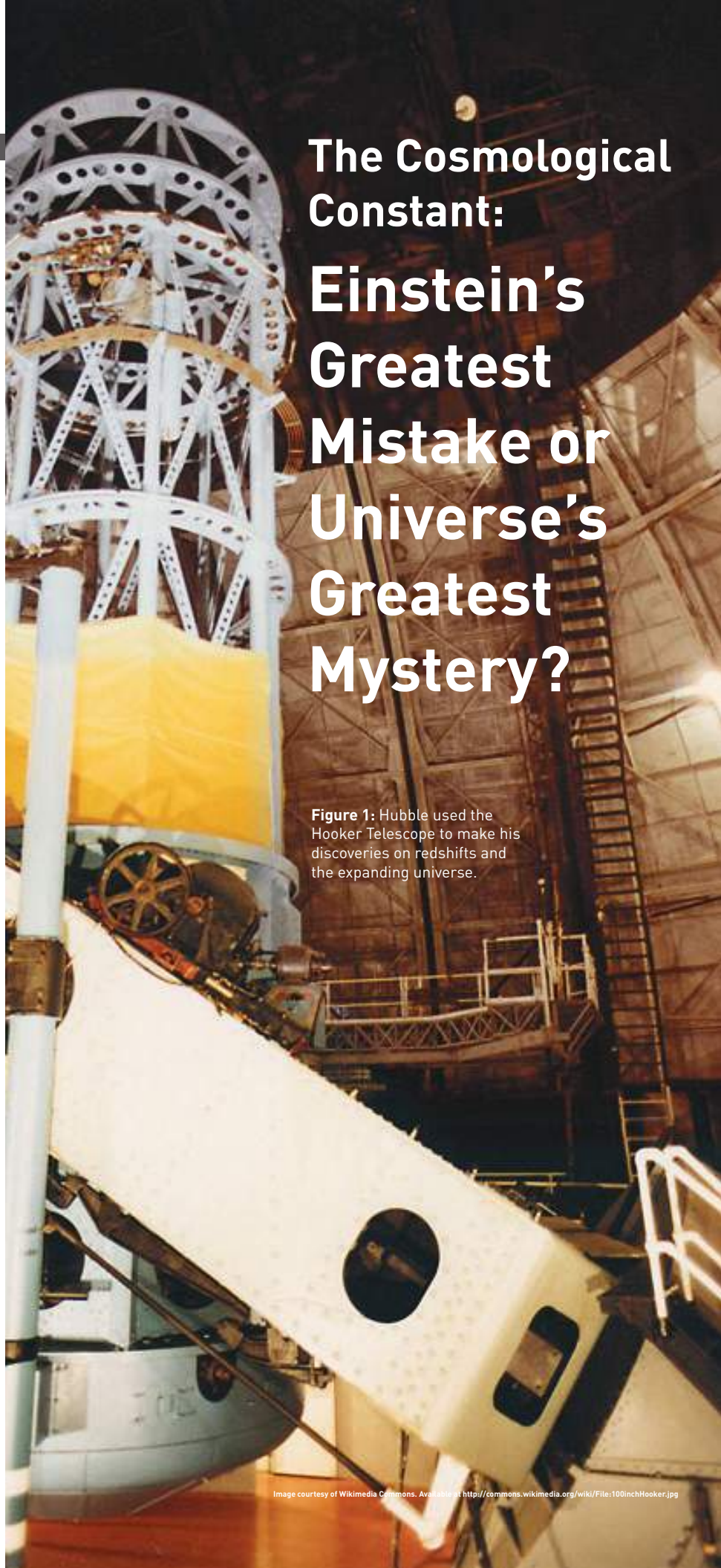
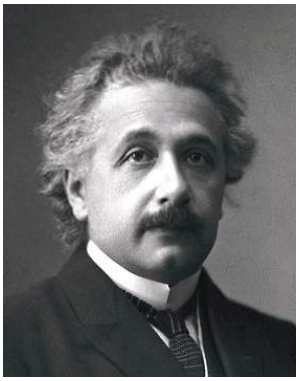


Figure 1: Hubble used the Hooker Telescope to make his discoveries on redshifts and the expanding universe.

Image courtesy of Wikimedia Commons. Available at http://commons.wikimedia.org/wiki/File:100inchHooker.jpg

Figure 2: Einstein's desk



Albert Einstein

equations. Einstein was inclined to believe that the constant had a positive value, allowing the constant to counteract the gravitational forces in the universe and keep the universe static.

The Einstein model of the universe, while conforming to the views held by many physicists, did not go unchallenged. In 1930, Arthur Eddington found that Einstein's model was unstable (8). Eddington noted that, in Einstein's model, potential disturbances in the universe could decrease the density of a region of space. As the vacuum energy density, or the cosmological constant, would remain constant, the only other density, that of matter, would have to decrease across that region of space. This would result in negative gravitational acceleration (9), causing the radius of that region of space to increase. That increase in radius would further decrease the matter density of space in the expanded region, thereby causing further increases in the radius of the disrupted area. There would be no force to stop this lowering of density and increasing of disruption. Furthermore, suppose a disturbance were to increase the density of a region of space. To maintain Einstein's model, the radius of that disrupted space must decrease, thereby increasing the matter density in that contracted space. This leads to additional gravitational attraction, thereby inducing a cycle of unlimited contraction. Since there is an uneven distribution of matter in the universe itself, as shown by the presence of stars and clusters, such disturbances would certainly occur (10). Since there was no evidence for a continual contraction or expansion in the observable universe at the time, Einstein's solution did not make sense.

In addition to problems with his static universe solution, Einstein himself had to grapple with other theories and data that suggested the possibility of non-static universes. Physicist Willem de Sitter was able to find a solution to Einstein's equations for a universe without matter while maintaining a cosmological constant (11). De Sitter's universe would be dominated by the constant, thereby expanding infinitely (12). In 1922 and 1924, Alexander Friedmann published papers that suggested an expanding universe composed of baryonic, or everyday matter; Friedmann's universe did not depend on the cosmological constant (13). In 1927, Georges Lemaître independently found similar results to Friedmann's. In Lemaître's paper, however, the cosmological constant remained the same over time while the density of baryonic matter decreased continuously. At some point, the cosmological constant would become the dominant effect, leading to an ever-expanding universe, like that of de Sitter (13). When Einstein read Lemaître's work, he reportedly said, "Your math is correct, but your physics is abominable" (7). Even though the results demonstrated theoretically expanding universes, Einstein, as well as most of the cosmology community, would only accept a static universe.

Around the same time, Edwin Hubble made some groundbreaking discoveries about how the universe was actually behaving. At the time, knowledge of the known universe was quite limited. As of 1917, the universe was conceived to be the Milky Way, with the sun near the center. In 1918, Harlow Shapley found that the sun was really at the edge of the Milky Way and that there was a separate bulge of stars at the center of the system (13). Until Hubble, what were really spiral galaxies were considered spiral "nebulae", and their distances from the Milky Way were not known. Between 1923 and 1924, using the Hooker Telescope, the largest telescope of his time, Hubble found that the distance between the Andromeda "nebula" and the Milky Way was almost a million light years, a distance too large to be within the Milky Way itself (14). He also found stars within the Andromeda "nebula" quite similar to those in the Milky Way, thereby establishing that the Andromeda "nebula" was really the Andromeda Galaxy (14). His results showed a universe much larger and more complex than what was commonly conceived at the time.

Later on, Hubble gathered data on the distances between the Milky Way and other galaxies as well. He looked at the spectral lines of the stars in various galaxies. A spectral line is a single wavelength of light emitted from excited gases (7). Different gases emit different lines, so one can determine the composition of a star based on the star's spectral lines. More

importantly, the spectral lines can deviate from what is expected of a certain gaseous element. If the frequency of light of a spectral line is lower than expected, then the source of that light has a redshift, moving away from the observer. If it is higher than expected, than the source has a blueshift, moving towards the observer. Hubble found that most galaxies had redshifts, so most were moving away from the Milky Way. He found that the farther away a galaxy was, the more of a redshift it had, implying that farther galaxies were moving away from our galaxy faster than closer galaxies. This concept was called Hubble's Law, and the implication of this law was that the universe was not static. Hubble reached this conclusion in 1929 (15).

Lemaître had an explanation for Hubble's Law. He believed that the redshifts were due to the Doppler Effect, and that the results could be explained by an explosion, later called the Big Bang. Those galaxies that were faster to begin with had reached farther distances from our galaxy than the slower ones (7). This explanation strengthened the argument for an expanding universe. Einstein did not hesitate to retract his cosmological constant because he could have concluded the possibility of an expanding universe based on the equations of general relativity without the constant (15). Without the support of Einstein, many physicists stopped exploring the cosmological constant. By creating the cosmological constant, Einstein had, as physicist George Gamow reported, made "the biggest blunder of his life" (2).

Dark Energy

With the expanding universe and the Big Bang theory in mind, scientists began research on the origins of the universe.

The universe, without a cosmological constant, would be composed of two distinct sets of particles, each exerting its own level of pressure. The first set includes matter that moves at relativistic speeds, such as photons and neutrinos. The second set includes particles that do not move nearly as fast, such as baryonic matter and dark matter. Both of these categories have their own mass density. The sum of the mass densities of the different components would equal the total density parameter for the universe (16). Assuming that the mass density of both baryonic matter and dark matter is greater than the mass density of relativistic particles, one would find a universe dominated by attractive gravity, leading to a contracting universe.

Considering the age of the universe, which is approximately 13.7 billion years old (17), one would expect that the effects of contraction would now be apparent without a force to counteract

"Considering the age of the universe, which is approximately 13.7 billion years old (17), one would expect that the effects of contraction would now be apparent without a force to counteract the contraction."

it. However, we find that the universe is actually quite flat and the temperature measured from the cosmic microwave background radiation to be isotropic, or uniform. The Far Infrared Absolute Spectrophotometer aboard the COBE satellite (18) in the early 1990s determined that the temperatures differed within 0.1% of the average temperature (19), giving a measurement of 2.725 ± 0.002 K. This is an odd result, for the universe is so vast that there is no mechanism for the temperatures to reach an equilibrium of any sort. We also find that the remote parts of the universe are 28 billion light years apart, far greater than the age of the universe. Any irregularity in the universe should be quite pronounced by now, yet there is very little evidence of any irregularity.

In the 1980's, Alan Guth addressed both the "flatness problem" and the "horizon problem", suggesting that near the beginning of the universe's development, the universe underwent a period of inflation, or rapid expansion. This phenomenon would account for the universe's current size as well as the universe's few observable irregularities. Assuming that the early universe before inflation was uniform, the rapid rate of expansion would have maintained the uniformity (19). Before inflation, electromagnetism, the weak force, and the strong force were unified. Inflation occurred as a result of the strong force separating from the other two forces (20,21). This separation occurred when the energy dropped below 80 GeV, allowing the two forces to become distinguishable. Guth's theory was corroborated by the temperature distribution found later by COBE. However, Guth himself was reluctant to say that the early history of the universe was devoid of any contribution from a cosmological constant. In order for the universe to expand, according to Guth, the vacuum energy density due to the cosmological constant had to be greater than the thermal energy density present before the breakdown of the Grand Unified Theory, in which electromagnetism, the weak force, the strong force, and gravity were all combined. Guth called the present, almost negligible value for the cosmological constant "one of the deep mysteries of physics" (23).

While discussions of inflation and the Big

Georges Lemaître


Edwin Hubble


Alan Guth

Bang theory continued, the fate of the universe was still under debate. It has been found that the universe's flat nature can be attributed to its expansion rate, implying that the universe is close to its critical density. At any higher density, the expansion of the universe would slow down and eventually collapse upon itself in what has been called the "Big Crunch" (22).

To see if the universe would cross this threshold, we would have to look for changes in the rate of expansion. In the 1990s, scientists studied Type Ia supernovae. These supernovae occur when a white dwarf takes matter from a binary star, either an ordinary star or another white dwarf, causing the star to reach a mass of 1.44 solar masses, also known as the Chandrasekhar threshold (24). The star will then undergo the Type Ia supernovae, which may obtain a maximum luminosity of 10 billion suns. Scientists can then obtain useful data from this supernovae at distances greater than 10 megaparsecs. With similar masses in their original stars, these explosions exhibit similar luminosities. Therefore, astronomers know the absolute magnitude of these explosions. Using the inverse square law, in which brightness decreases with the square of the distance, and the fact that these supernovae should have the same brightness, astronomers can compute how bright the explosion should have been at a certain distance (25). There are slight issues with variation in maximum luminosities, but the data can still be used because dimmer supernovae dimmed out faster than brighter ones after achieving maximum luminosity (12). Using data from various Type Ia supernovae at differing lengths away from Earth, Adam Riess and Brian Schmidt in 1998 (26) and Saul Perlmutter in 1999 (27) determined that the universe must be under the influence of some cosmological constant. They found that if the universe was more dominated by matter than dark energy, or if the mass density of dark and baryonic matter were dominant, then the supernovae with larger redshifts, or those that were farther away, should have been about 25% brighter (28). The data corroborates a universe with accelerated expansion. This discovery earned Riess, Schmidt and Perlmutter the Nobel Prize in physics in 2011.

These results establish that matter cannot be the dominant density in our universe. It still remains to be seen what this cosmological constant, or dark energy, truly represents though. In the 2000s, the Wilkinson Microwave Anisotropy Probe found that the universe was composed of 4% baryonic matter, 23% dark matter, 73% dark energy, and 0.00824% radiation (16,17). These percentages are based on the mass density. Currently, dark energy has the dominant mass density, leading to accelerated expansion in the universe. In the past, during the very beginnings of the universe, radiation and matter were the dominant densities. However, as the universe expanded, the densities of radiation and matter decreased as both radiation and matter were spread across a larger volume. Their mass

Figure 3: Perlmutter, Riess, and Schmidt receive the Shaw Prize for Astronomy, five years before receiving the Nobel Prize in Physics.

Image courtesy of Wikimedia Commons. Available at http://commons.wikimedia.org/wiki/File:Shaw2006astro_lightened.jpg

densities will continue to decrease in the future. As implied by its original name, dark energy has and will remain largely constant. Therefore, it is likely that dark energy will possess the dominant mass density in the foreseeable future of our universe (15).

Despite knowing about the role of the cosmological constant, we still have little idea where the constant originates or why it has such a small value. Dark energy has been seen to have the energy density of a vacuum, caused by the interactions of electromagnetic fields and matter-antimatter fields in empty space (23). The energy of this quantum vacuum is 120 powers of 10 greater than the observable upper limit of 10^{-9} erg/cm^3 (10,23). Somehow, this term would have to be exactly canceled out to conform to what we observe today. Unfortunately, no such large term comes to mind. For inflation to be driven by dark energy, the vacuum energy density had to be constant throughout inflation, yet have a larger value than that observed today. The remaining mystery is why the value is so small now.

Dark energy also plays a role in the future of the universe. As opposed to the "Big Crunch" phenomenon, an accelerated expansion may face a Big Chill, where the galaxies and stars spread out and the universe becomes a cold, vast void. With even greater acceleration, there may be a Great Rip, in which the galaxy clusters come apart, followed by the galaxies themselves, and then the stars, and even the atoms. Until scientists can determine whether dark energy is truly a constant, the fate of the universe will remain a mystery (29).

Conclusion

Einstein was, in a sense, wrong to completely reject his own mistake. The universe is clearly not static as Einstein had hoped. General relativity, inflationary theory, and the supernovae data reveal the presence of dark energy but do very little to explain its nature. From the Big Bang to the uncertain future of the universe, the miniscule cosmological constant remains a big mystery, not a big mistake.

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"Einstein was, in a sense, **wrong** to completely reject his own mistake. The universe is clearly not static as Einstein had hoped."

Failure at Fukushima: What Went Wrong?

BY MERRITT LOSERT

Figure 1: Devastation in Minamisōma, Fukushima after the tsunami struck the Japanese coastline.

Introduction

On March 11, 2011, a magnitude 9.0 earthquake struck the Pacific Ocean floor by the Tohoku coast of Japan (1). The massive upheaval in the earth's crust created a tsunami 14 meters high, landing on the Japanese coastline about an hour after the quake. As well as costing Japan over 20,000 lives and up to $300 billion in damages, the tsunami crashed into the Fukushima-Daiichi nuclear power plant, unleashing the worst nuclear plant disaster since the Chernobyl meltdown in 1986 (2). But what exactly went wrong at Fukushima? Could this type of disaster be prevented in the future? Or was the failure at Fukushima inevitable given the nature of nuclear energy and the magnitude of the quake and tsunami? Moreover, is nuclear energy unavoidably dangerous? An in-depth look at the events at Fukushima can reveal much about nuclear energy and its application throughout the world.

How Nuclear Energy Works

Before examining the failure of the Fukushima-Daiichi plant, one should first understand the fundamentals of nuclear energy. On one level, nuclear power plants are no different than traditional coal-burning plants: a source of heat warms water and produces steam which is forced past a turbine, thereby generating electricity. In nuclear plants, the fission of radioactive material generates this necessary heat (3).

Fission is a process in which a large atom, like uranium, splits, forming two smaller atoms. In the case of uranium fission, a split atom also releases several free neutrons, which can hit other uranium atoms, causing them to also undergo fission. A fraction of the mass of each nucleus is transformed into heat energy when the atom splits; if enough fissile material is present in the reactor, a nuclear plant can harness an enormous amount of energy from a small amount of uranium (3).

Uranium is most often mined as uranium oxide, or yellowcake. A converter plant transforms yellowcake to uranium hexafluoride, which is loaded into cylinders as a gas and then condensed to a solid. This uranium compound is then enriched. Most uranium has an atomic mass of 238 atomic mass units (amu)—meaning there are 238 protons and neutrons in the nucleus of the atom. On earth, about one percent of natural uranium has an atomic mass of 235, which is much more likely to undergo fission. To produce fuel suitable for a reactor, natural uranium must be enriched so that uranium-235 makes up three to five percent of the total uranium (3).

After enrichment, the uranium compound is converted to uranium dioxide, which is pressed into pellets and loaded into noncorrosive zirconium alloy tubes. A bundle of these tubes, together with control rods or blades—also called control elements— make up the reactor core of a nuclear plant (3). The fuel rods enable the heat-producing reaction. The control elements, made of neutron-absorbent material like boron, hafnium, or cadmium, can be lowered into the collection of fuel rods, called the fuel assembly, halting the fission reaction during a shutdown (4).

A cooling system is vital to a nuclear power plant. After water is boiled to produce turbine-driving steam, it must be re-condensed so it can be reused in the plant. Moreover, without cool water reentering the reactor core, the fuel assembly can overheat, even after the control elements have been

lowered into the fuel assembly: the byproducts of fission are radioactive and can generate energy through radioactive decay (4).

If the cooling system fails, the fuel rods can overheat and melt to collect at the bottom of the reactor vessel. This situation is known as a meltdown. In a worst-case scenario, this molten fuel can pool through the reactor core's protective casing and expose the outside world to harmful radiation (4).

What Happened at Fukushima?

Immediately after the earthquake on March 11, the three reactors operating that day shut down. Authorities detected a tsunami but could not determine its magnitude or direction. A seawall protected the plant from the first wave but could not stop the second wave that followed eight minutes later (5).

The wave quickly knocked out the main power supply behind the cooling pumps. Soon, it drowned the emergency diesel engines, stored in the basement, which provided the plant's backup supply. Workers tried to power the pumps with car batteries, but their efforts could not prevent the reactor core from overheating, and fire trucks and emergency power vehicles were blocked by tsunami debris (5). As the remaining water boiled away, the Tokyo Electric Power Company, or TEPCO, operator of the Fukushima Daiichi plant, added boric acid, a neutron absorber, hoping to slow the reaction (6). All the while, the combination of steam and boric acid caused a buildup of hydrogen. The pressure inside the reactors reached dangerous levels, especially in Reactor Building No. 1, where melted fuel had begun to pool at the bottom of the containment vessel. Workers attempted to relieve this pressure by venting the excess gas, but damages to the plant prevented them from operating the gas release valve (5).

Due to the hydrogen buildup, the first hydrogen explosion occurred on March 12, a day after the earthquake, in Reactor Building No. 1, and then in buildings 3 and 4. On March 15, a blast near Reactor Building No. 2 drained a suppression chamber that absorbed steam from the core, and a fire raged around a spent-fuel pool in Reactor Building No. 4 (5). A Japanese Defense Force helicopter had been used to drop seawater on the reactors, keeping them cool, but the radiation spewing upward prevented it from dousing the most damaged buildings (6). Military fire engines arrived that evening, spraying water over the plant's remains. Several days later, a more elaborate system of fire trucks was set up to bring sea water to the reactors to cool them, steam-cooling the reactors for months in an effort known as "feed and bleed" (5).

Despite their efforts, workers at Fukushima could not prevent the fuel from reaching complete meltdown. Increases in the radioactive isotopes in the atmosphere above California, although harmless at their present concentrations, have provided more evidence for the catastrophic scale of the meltdown (7).

In fact, the Fukushima accident still releases radiation, much of it as radioactive coolant water that finds its way into the pacific; it was estimated that up to 80 percent of the radioisotopes released by the plant have flowed into the ocean (8).

What Went Wrong?

While the tsunami was the direct cause of the accident, it only revealed much larger, more fundamental problems. Since the plant's construction, Japanese scientists overlooked evidence that suggested the Tohoku coast is susceptible to larger earthquakes and tsunamis than previously thought (1). Thus, the plant was built to withstand tsunamis of only about 19 feet—less than half the height of the wave that struck March 11 (5).

TEPCO failed in other respects to ensure the safety of its nuclear plant. In 2002, TEPCO and other companies issued a report claiming that there was no need to take precautions against hydrogen explosions. TEPCO has also admitted to falsifying repair records and concealing emergencies at Fukushima and other plants (5).

Much of this disregard for safety can be traced to the power of Japan's nuclear industry. Nuclear energy had been heralded as the energy source of the future in Japan since World War II. After the country's destruction during World War II, nuclear energy seemed to be Japan's ticket to economic regrowth. A massive public relations campaign ensued for many years. The Japanese

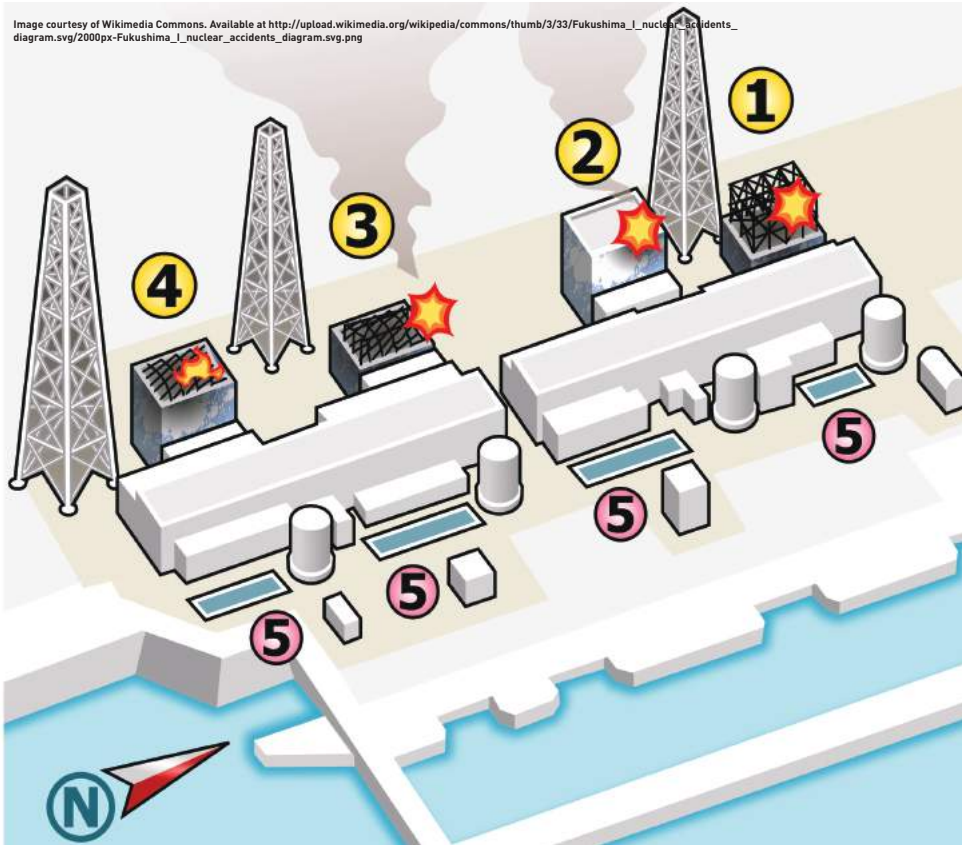

Image courtesy of Wikimedia Commons. Available at http://upload.wikimedia.org/wikipedia/commons/thumb/3/33/Fukushima_I_nuclear_accidents_diagram.svg/2000px-Fukushima_I_nuclear_accidents_diagram.svg.png

Figure 2: This image illustrates the locations of explosions and the relative states of the Fukushima reactors after the tsunami.

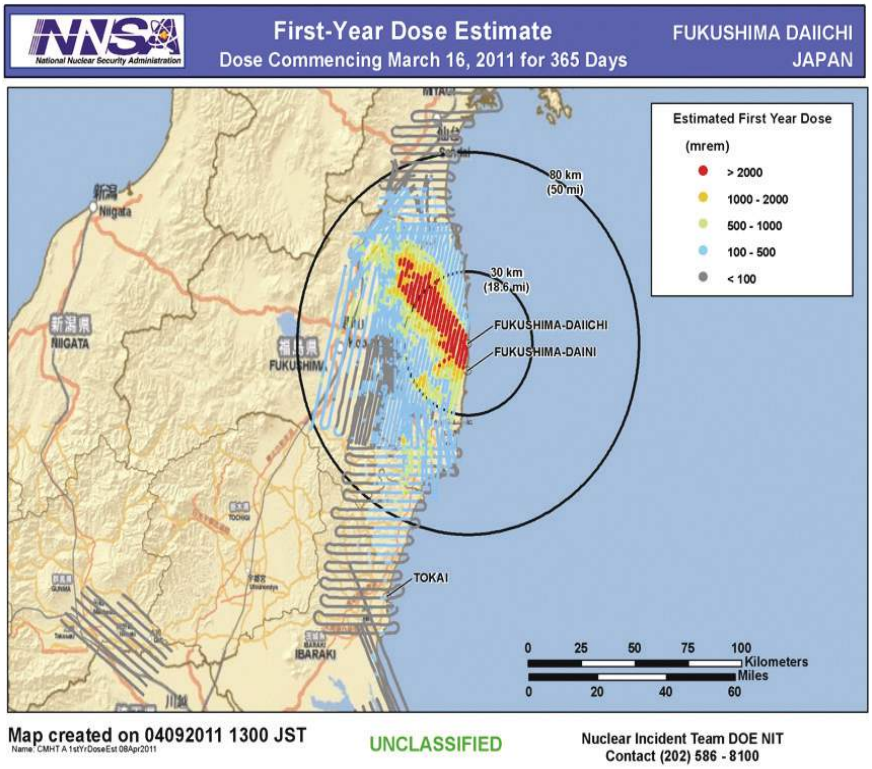

Image courtesy of Wikimedia Commons. Available at http://commons.wikimedia.org/wiki/File:NNSA_DOE_Dose_Map_Fukushima.png

Figure 3: A map illustrating first-year radiation dose estimates in the region surrounding the Fukushima plant.

government poured huge amounts of money into nuclear energy, and the plants built museums and other attractions to encourage family visits and imbue familiarity with the technology. During this process, nuclear regulators took advantage of boundless job opportunities, and energy executives became influential political donors. As nuclear energy expanded, Japan lost sight of the potential dangers associated with nuclear energy (5).

Even recently, TEPCO has faced embarrassment regarding their handling of the accident. On August 29 of 2013, TEPCO admitted that contaminated cooling water leaks are 18 times worse than previously thought. Some of this water was found to give off 1,800 millisieverts (mSv) per hour, enough to kill a person in four hours. A water leak even went unnoticed for days by the company (8).

Environmental, Health, and Economic Impact

The Fukushima meltdown has had many economic, environmental, and social impacts on Japan. The disaster left the economies of surrounding areas in ruin. People were forced to evacuate and leave their jobs, and many have since had difficulty securing new ones (9). Other industries have been affected; commercial fishing, for instance, has been banned in the area (8).

The damaged plant spewed radiation into the air and the surrounding environment, undoubtedly affecting local ecosystems. In 2011, for example, a Japanese team studied the bird population in Fukushima, uncovering a shocking result: as compared with predictions based on normal biodiversity, the bird population, a natural indicator of general biodiversity, was down 30 percent (10). The abundance of other animals, such as butterflies and cicadas, had also decreased as the radiation leaks continued (11).

While the radiation undoubtedly has harmed the local environment, it is not clear how it has impacted human physical health. First responders and emergency personnel at the plant during the accident received high doses of radiation. Many local firefighters, for example, who received no instructions on how to deal with radiation, walked among shards of radioactive fuel and developed acute radiation sickness. 28 died within months (5). But a rapid evacuation effort by the Japanese government likely protected most of the Fukushima residents from much of the radiation. Estimates suggest that the maximum radiation dose incurred by evacuees was 25 mSv, and only doses over 100 mSv have been linked to an increased cancer risk (12). Based on a linear extrapolation model used to estimate cancer risks with low radiation exposure, a there could be a maximum 0.2 percent increase in an individual's risk of cancer, a risk which is nearly negligible when compared with the 42 percent likelihood of an individual contracting cancer under normal conditions (2). This increase, moreover, will not be visible for two to three decades in health data.

While the accident's physical health impacts are not clear, the meltdown has caused a negative impact in mental health. Evacuees were forced to leave their homes and their livelihoods in search of safety. Unstable living conditions, combined with a fear of the invisible radiation, has created enormous anxiety for the evacuees. In 2012, a survey sent out to all evacuees suggested 15 percent of adults displayed signs of extreme stress (12). Many also suffer from post-traumatic stress disorder. Studies after the Chernobyl accident have suggested that extreme stresses caused by nuclear meltdowns can cause lasting psychological harm (12).

On a broader level, the meltdown has created a general mistrust of the Japanese government and especially of nuclear energy. Government actions in the days after the accident caused this mistrust. Radiation readings issued soon after, for example, were often wrong or inconsistent (9). Moreover, in order to legally allow workers to remain on the plant, the government had to raise the legal radiation limit for workers from 100 to 250 mSv (the maximum legal exposure for American workers is 50 mSv). To some, this sudden change in safety standards garnered mistrust in the Japanese government. Also, in order to open schools in Fukushima, the government had to raise the legal school radiation limit, another move which angered the Japanese public (5).

The accident prompted evaluations of nuclear

plants in the United States in the hopes of preventing another similar disaster. Unfortunately, many of the problems with the Fukushima-Daiichi plant exist in American plants as well. About a third of American plants have been found to contain emergency equipment vulnerable to extreme circumstances like earthquakes or tsunamis (5).

After the accident, many Japanese nuclear plants closed for maintenance and have not reopened. For a while, environmentalists and politicians spoke out against nuclear energy, along with other protestors affected by the accident. Even other nations, like Germany, vowed to phase out nuclear power (5). However, it does not seem like much change will occur in Japan's dependence on nuclear power. A relatively small island, it is difficult for Japan to utilize other green energy sources like wind and solar power. Nuclear fuel, on the other hand, provides a carbon-free energy solution that, while not renewable, generates far less waste, is far less environmentally harmful, and is far less uncertain than fossil fuels. Some environmental activists have since come to the view that nuclear energy is a necessity to prevent catastrophic effects of climate change (5). A Japanese government panel recently suggested that Japan should embrace nuclear power. It seems that nuclear energy will not go away (13).

Solutions

Much can be done to improve the safety and security of nuclear plants like Fukushima-Daiichi. Physical changes can be made to the plants. For example, diesel backup generators, fuel, and switch gear can be housed in elevated, waterproof rooms, guaranteeing their functionality in the case of floods and tsunamis. This design feature has already been implemented in some nuclear plants. Furthermore, improved backup power to vents or passive vents could be used to ensure that hydrogen does not build up inside reactors, and passive cooling systems for spent-fuel pools and reactors that prevent overheating in the first place could be explored. Lastly, leaving greater distance between reactors at a plant would ensure that incidents at one reactor do not affect the performance of others (2).

Improvements in the handling of disaster situations could also be made. Governments could ensure the availability of excess staff to keep control of the plant and portable backup generators to provide power in the case of an outage. Overly-conservative evacuations should be avoided to prevent excessive stress on the region, and qualitative, intuitive units of radiation, like units of average background radiation, should be used when presenting information to the public to prevent confusion. Lastly, the public should be clearly informed about how much radiation is dangerous (2).

Conclusion

The world relies on science and technology to provide people with the quality of life they expect. Sometimes, though, these technologies fail, as nuclear technology did in the case of Fukushima. A technology's failure, though, does not generally ensure its demise. Rather, improvements are made to the system to prevent such a failure in the future. Nuclear energy will not go away. In a world with increasingly high energy demands, diminishing resources, and impending environmental problems caused by the burning of fossil fuels, nuclear energy is a necessity. 15 percent of the world's electricity and 20 percent of America's comes from nuclear plants (4). But, as Fukushima reminded the world, nuclear power has its inherent dangers. The events at Fukushima will hopefully serve as a lesson to nuclear operators and regulators the world over, a firm reminder that natural disasters can occur unexpectedly and that safety and redundancy should never be compromised—losing attention to these details can result in catastrophe.

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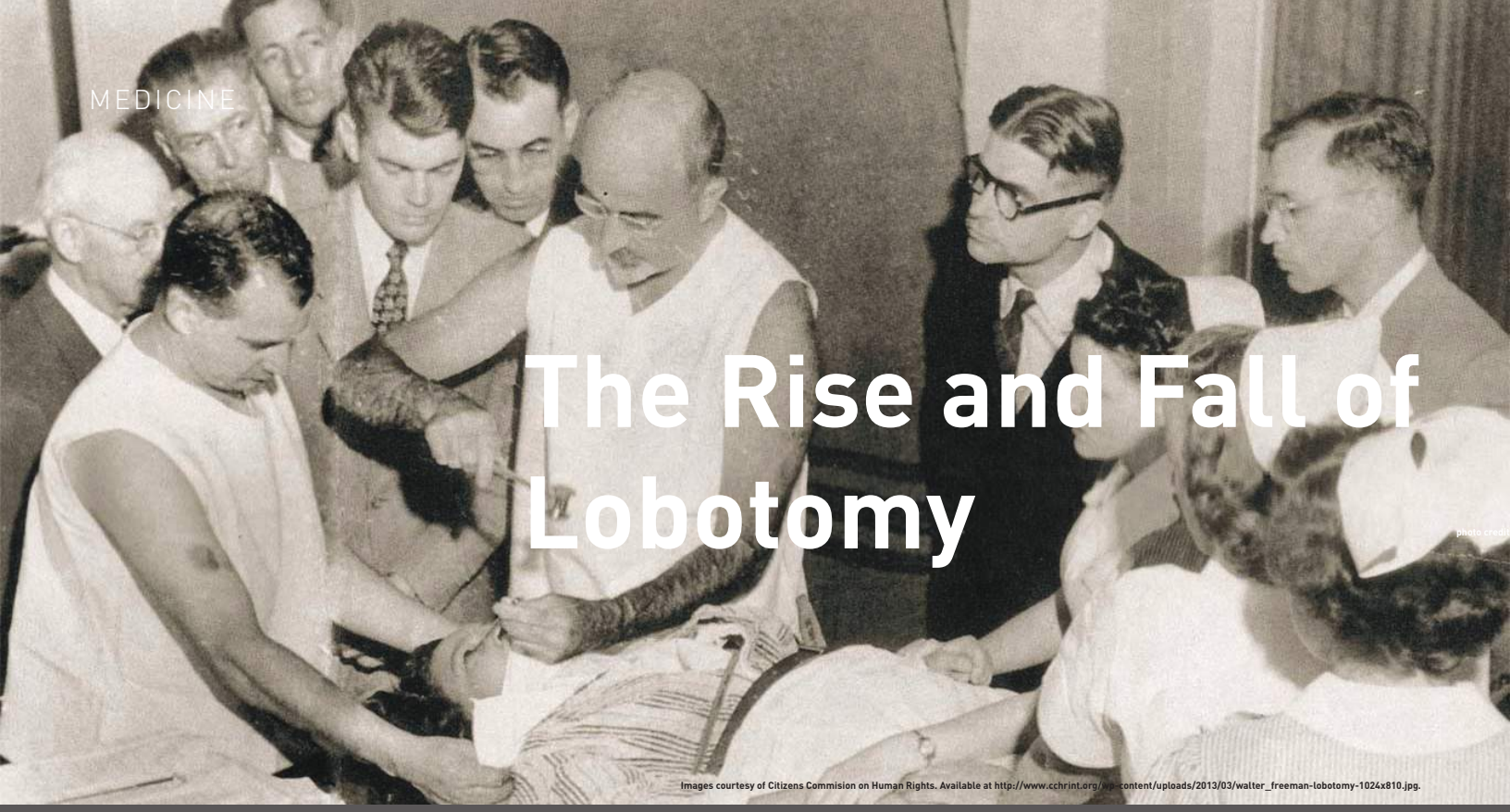
"**Nuclear energy will not go away.** In a world with increasingly high energy demands, diminishing resources, and impending environmental problems caused by the burning of fossil fuels, nuclear energy is a necessity. **15** percent of the world's electricity and **20** percent of America's comes from nuclear plants."



The Rise and Fall of Lobotomy

Images courtesy of Citizens Commision on Human Rights. Available at http://www.cchrint.org/wp-content/uploads/2013/03/walter_freeman-lobotomy-1024x810.jpg.

BY MATTHEW JIN

Figure 1: Physician Walter Freeman often performed lobotomies before audiences with neither gloves nor a mask

During the 1930s and 1940s, costs associated with American asylums rose, while conditions within them worsened. Mental illness was rampant—statistics during that time found that 55% of all hospital beds were occupied by patients with psychiatric problems. Of 15 million men examined for armed service, 1,846,000 were rejected for psychiatric reasons, and 632,000 were discharged from service for psychiatric reasons (1). Asylums were overcrowded, understaffed, and underfunded. Because most mental illnesses were chronic in nature, superintendents often focused on running the asylum smoothly rather than rehabilitating the patients. Given these factors, as well as information then regarding the frontal lobe's role in disruptive behavior, the scene was set for America's acceptance of lobotomy, a drastic and invasive new neurosurgery that promised to alleviate the psychotic attributes of the mentally ill.

Initial inspiration for lobotomy derived from the observations of Carlyle Jacobsen and John Fulton, who performed learning experiments on two chimpanzees. One chimpanzee in particular displayed extreme frustration if she was not rewarded for a poor performance. However, after undergoing removal of her frontal lobes, her frustration disappeared. These results, presented at the Second World Congress of Neurology in London by Jacobsen and Fulton in 1935, led Portuguese neurologist Antonio Egas Moniz to investigate whether a similar operation might relieve intense anxiety in humans (1,2).

The field of psychosurgery, the treatment of mental disorders using neurosurgery, arguably began on November 12, 1935, when Moniz directed a neurosurgeon, Almeida Lima, to perform a prefontal leucotomy (an operation on the patient's white matter in the region of his or her prefrontal cortex) on a female asylum inmate who suffered from paranoia, depression and acute anxiety. After drilling holes into the sides of her skull, he injected ethanol into the area below her brain's prefrontal cortex in order to destroy the white matter connections to and from her prefrontal cortex. He sought to destroy these fibers because he knew that the frontal lobe is responsible for the high-level thinking that is often compromised in mentally ill patients, and suspected that these fibers stabilized the fixed brain circuits responsible for their obsessive thoughts. Moniz declared the operation a success, stating that the patient's depression had been alleviated. However, the patient never left the mental hospital (1).

Moniz and Lima operated on seven more patients in the same manner, and often injected patients several times in order to produce favorable results. For the ninth patient, they used a leukotome, a new implement that they had developed for the procedure. It was a cannula through which a wire was inserted and used to cut the white matter of the brain; with this tool, they made more precise 1-cm diameter lesions in the brain (1,3).

The initial group of patients would arrive at Moniz's clinic from the nearby Bombarda asylum, undergo operation typically on the same day they arrived, and often return to the hospital within ten days of surgery. There was little observation of the patient post-surgery, and Moniz did not make any follow-ups on the long-term effects of the operation. Furthermore, although the director of the Bombarda asylum, José de Matos Sobral Cid, initially agreed to let Moniz operate on his patients, he later grew opposed to the operation and refused permission. Nonetheless, Moniz determined the first group of his 20 patients to be a success, stating that one-third of patients greatly improved, one third slightly improved, and the remaining third remained unchanged. He also described three of the 18 patients in his second group as almost cured and two as significantly improved, and concluded, "Prefrontal leukotomy is a simple operation, always safe, which may prove to be an effective surgical treatment in certain cases of mental disorder" (1,4,5,6).

Despite not having made any detailed or long-term observations of his patients, Moniz was quick to publish his results. Less than four months after his initial leucotomy, on March 3, 1936, he presented the results of his first 20 patients to the Academy of Science in Paris, and those results were afterwards published in Le Bulletin de l'Acadamie de Medicine (1,6).

Later, when Moniz's results for a second group of 21 patients were presented to the Société Médico-Psychologique in Paris, Cid harshly criticized the procedure, saying that the patients whom Moniz had operated on suffered a degradation of personality post-surgery and behaved as though under shock (4).

Although Moniz's data was neither objective nor did it contain information on the long-term effects of the operation, his work garnered the attention of the medical community across the world. The treatment became popular internationally, and in 1949 Moniz was awarded the Nobel Prize in Medicine (1).

Moniz's work in particular garnered the attention of renowned physician Walter Freeman. On September 14, 1936, using Moniz's technique, Freeman directed neurosurgeon James Watts to perform the first leukotomy in the United States on a 63-year-old woman named Alice Hood Hammatt, who suffered from symptoms of anxiety, depression, and insomnia (1).

As Freeman and Watts performed the procedure more and more, they soon began modifying Moniz's procedure. They developed three modes for the operation: minimal, standard, and radical. For patients with neurosis, a minimal amount of brain tissue was severed, whereas for patients with schizophrenia a large amounts of brain tissue was severed. Furthermore, Freeman and Watts gradually realized the connection between specific brain fibers connecting the frontal lobes and the thalamus, and their roles in human thought and emotion. They concluded that they should attempt to limit incisions to those fibers which would cause degeneration in the areas of the thalamus responsible for the moods and emotions of the patient (1).

Of their first 200 lobotomy cases, Freeman

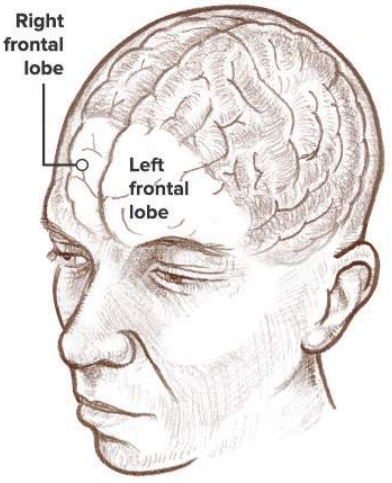


Figure 2: This picture illustrates the locations of the left and right frontal lobes that had been removed in the chimpanzees.

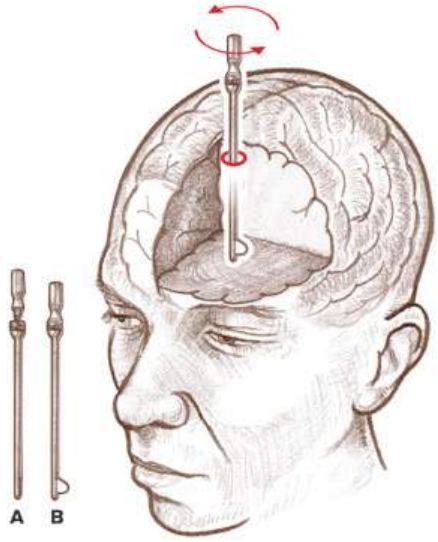
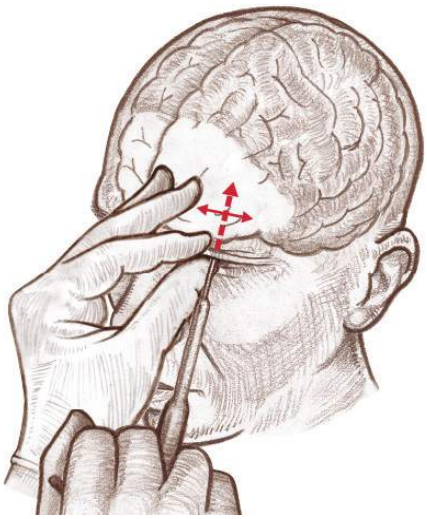


Figure 3: Moniz and Lima would create a hole in the skull, insert a leukotome through the hole, expose the cutting wire, and then rotate it to sever neural connections.



Images courtesy of Wall Street Journal. Available at http://projects.wsj.com/lobotomyfiles/?ch=two

Figure 4: Moniz and Lima would create a hole in the skull, insert a leukotome through the hole, expose the cutting wire, and then rotate it to sever neural connections.

BY THE NUMBERS

For their first 200 cases, Freeman and Watts reported that:

63% improved

23% unchanged

14% worsened or died

and Watts reported that, post-surgery, 63 percent of the patients improved, 23 percent remained unchanged, and 14 percent worsened or died. Despite the relative success of the surgery, patients often developed seizures and became apathetic or unable to act in a socially appropriate way (1).

Wanting to minimize complications and make lobotomy a more widely used procedure, Freeman developed the transorbital lobotomy. Freeman based his new method off of the work of Italian doctor Amarro Fiamberti who operated on the brain through the patient's eye sockets. After rendering the patient unconscious using electroshock therapy, Freeman placed an implement much like an ice-pick just behind the eye-socket and used a mallet to drive it in roughly 7 cm into the frontal lobe of the patient. Then, he swept it back and forth approximately fifteen degrees in order to sever the connections to the prefrontal cortex (1).

Unlike the previous techniques, this procedure could be performed in as few as ten minutes. Furthermore, it did not require the expertise of a neurosurgeon or an anesthesiologist. These factors, along with the increasingly pressing issue of asylum management, catalyzed the procedure's spread throughout America. Mental asylums, which seldom had surgeons on hand and therefore could not easily perform lobotomies, now found the operation very feasible. Meanwhile, Freeman zealously promoted his technique by traveling to hospitals and mental asylums throughout the country to perform lobotomies. As a showman, he shocked audiences by hammering the ice-pick instrument into both eyes at once, and in a single day lobotomized 25 women. He also exploited the media so that popular magazines frequently published articles praising the effectiveness of lobotomy usually without any form of objective scientific support (1,7).

With his promotion of the transorbital lobotomy, he created a divide between himself and many of his scientific colleagues, including Watts who left their practice. Some neurosurgeons, such as Watts, were outraged that the surgery was reduced to a mere office procedure. Others condemned the operation itself. Nolan Lewis, professor of psychiatry at Columbia University and Director of the New York State Psychiatric Institute stated, "Is the quieting of the patient a cure? Perhaps all it accomplishes is to make things more convenient for the people who have to nurse them… I think it should be stopped before we dement too large a section of the population" (1).

Outside of concerns about the effectiveness and the crude performance of the surgery itself, complications were frequent. Some arose due to the frequent disregard to sterility—Freeman himself often operated without either gloves or a mask and even experienced instrument breakage. Indeed, Freeman himself wrote after one such instrument breakage during an operation, "…when I thought I had a stronger instrument, the shaft broke at the 6 centimeter mark and lacerated the eyeball of the patient so that not only was she not benefited by [the] operation but she lost the sight of her eye and had to be operated upon for removal of the steel fragment." Patients who underwent the transorbital lobotomy also risked brain hemorrhage, which was often fatal (1,8).

Despite numerous concerns with the safety of the operation and its effectiveness, Walter Freeman championed lobotomy as the general solution to a variety of mental disorders. One patient, Anna Ruth Channels, who suffered from severe headaches, was prescribed a lobotomy by Freeman. Post-operation, according to her daughter Carol Noelle, she was cured of her headaches yet was left with the mind of a child. Freeman's liberal use of lobotomy garnered the criticism of Dr. Florence Powdermaker, chief of the U.S. Department of Veteran Affairs' psychiatric-education section, who noted, "Has Dr. Freeman shown any disposition to modify his idea that lobotomy is useful for practically everything from delinquency to a pain in the neck?" (1,7,8).

In spite of criticism from the scientific community, the transorbital lobotomy quickly grew in popularity. Excited by sensationalist reports that lobotomy could calm a patient that might otherwise need to be restrained, mentally ill patients and their families requested the

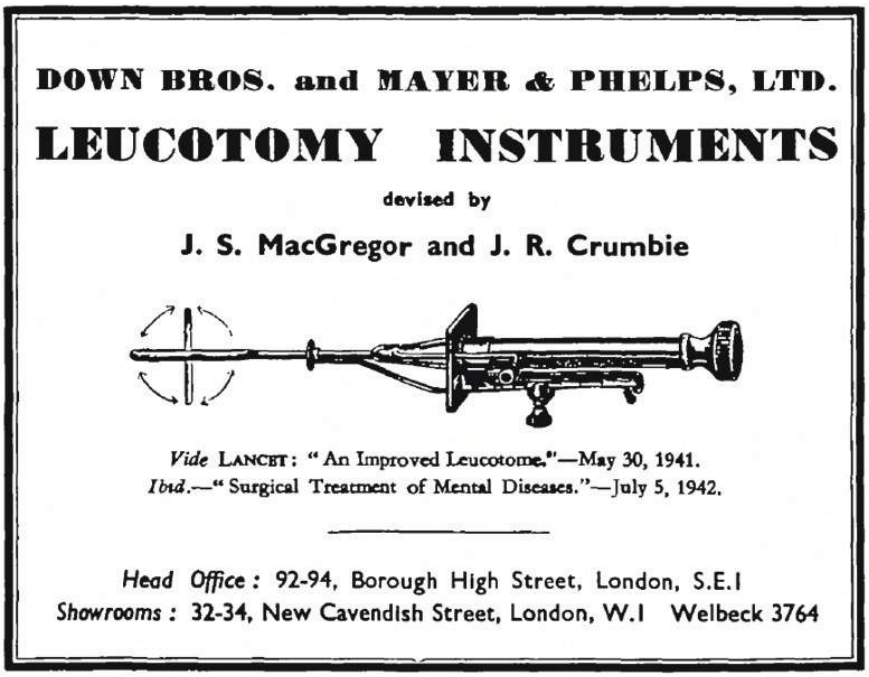


Figure 5: Moniz often used a leukotome when performing leukotomy.

Image courtesy of Wikimedia Commons. Available at http://commons.wikimedia.org/wiki/File:Leucotome.gif

procedure. Physicians, without any choice of alternative treatment for mental illness, also encouraged lobotomy. Hundreds of lobotomies were performed by physicians not licensed to do surgery. Freeman alone performed 3,439 lobotomies during his lifetime, with a 14% fatality rate. Even famous figures, such as Rosemary Kennedy, the sister of President John F. Kennedy, and Rose Williams, the sister of author Tennessee Williams, underwent the operation. In both cases, the patients showed post-procedure signs of possessing excessive lesions in their brain tissue and were left incapacitated for the rest of their lives with acute frontal lobe syndrome (1,9).

Economic considerations and pure convenience undeniably played a significant role in the prominence of lobotomy. Hospital and asylum directors employed it as a means to ease the overcrowding and understaffing of their institutions. Notable American neurophysiologist John Fulton remarked that through the use of psychosurgery, up to $1 million of taxpayer money could be saved per day. According to some reports, patients who were criminally insane were offered the chance of undergoing the operation in exchange for their freedom, and in the haste to perform the operation, the issue of the patient's informed consent was often neglected (1).

As the number of patients who underwent lobotomy grew, scientists around the world began to gather objective and quantified data on the surgery outcomes. G.C. Tooth and M.P. Newton reviewed the outcomes of over 10,000 prefrontal lobotomies performed between 1943 and 1954 to show that patients improved 70 percent of the time, suffered seizures post-operation one percent of the time, suffered from frontal lobe syndrome 1.5 percent of the time, and died six percent of the time. However, due to the widespread performance of lobotomy, reliable data on post-operational mortality are difficult to obtain, and successes tended to be highly publicized, while failures were left unreported (1).

Despite the growing criticism against lobotomy, it would have remained a widely used procedure given its relative success, its economic benefit, and above all, the lack of a viable alternative treatment, had the drug chlorpromazine (Thormazine) not been approved by the FDA in 1954. Chlorpromazine provided a safer, more effective, and cheaper alternative to lobotomy. By the end of that same year, it had been administered to an estimated 2 million patients in the United States alone. Medicines for psychosis and depression were approved shortly after, and the use of lobotomy quickly waned. Indeed, in 1967 Freeman performed his final lobotomy on Helen Mortensen. During the operation, he ruptured a blood vessel in her brain, causing her to die of a brain hemorrhage three days later. As a result, the hospital revoked his surgical privileges (1).

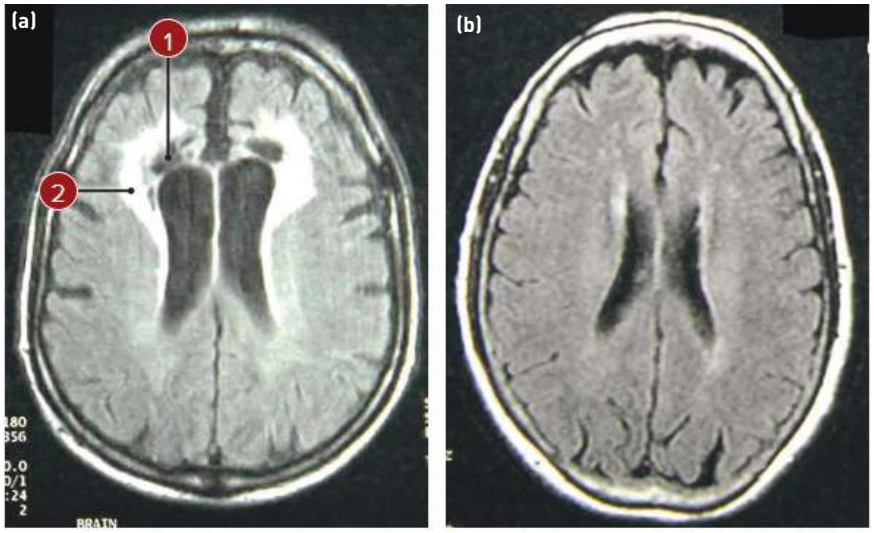


Image courtesy of David Sultzer. Available at

Figure 6:

(a): Overhead brain scan, made in 1998, of a lobotomized 71-year-old World War II fighter pilot. Area 1 shows the cavity within the brain (dark area) resulting from lobotomy. Area 2 shows the scarring, that appears as a white halo.

(b): Brain scan of a healthy, 72-year-old woman.

American lobotomy was performed to suit economic convenience at the price of conjectured medicinal benefit. Because a procedure unsupported by scientific data was embraced so quickly and widely, many patients ran the risk of death notwithstanding being rendered permanently or severely incapacitated. The story archetype warns of the danger in heeding media sensationalism without regard to proper scientific analysis.

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Cystic Fibrosis: From Point Mutation to Systems Failure

BY YVETTE ZOU

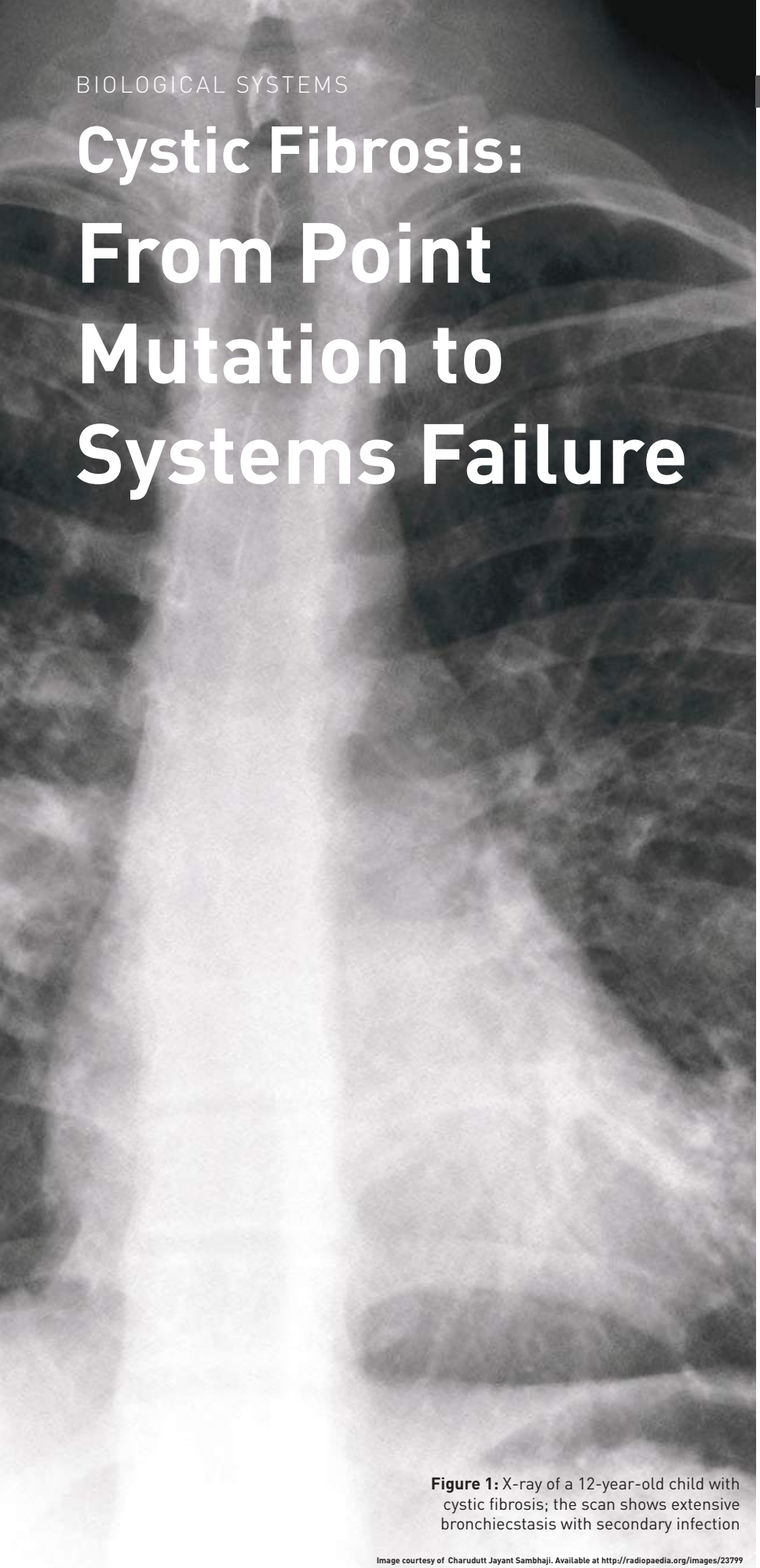

Figure 1: X-ray of a 12-year-old child with cystic fibrosis; the scan shows extensive bronchiecstasis with secondary infection

Image courtesy of Charudutt Jayant Sambhaji. Available at http://radiopaedia.org/images/23799

Introduction:

Cystic fibrosis (CF) is an autosomal recessive genetic disorder in which the gene responsible for the production of an important membrane protein is mutated, resulting in the malfunction of physiological systems throughout the entire body. This essential membrane protein is the ion channel CFTR (cystic fibrosis transmembrane conductance regulator), which transports anions across epithelial cell membranes (1). CFTR are normally found in epithelial cells throughout the body. Epithelial tissue forms the lining of all internal and external body surfaces as well as organs and glands, so any defect in the function of CFTR will have widespread consequences (2). When CFTR is defective, electrolyte transport across epithelia is disrupted, and mucus secretions of various glands and organs become very thick and viscous. This increase in viscosity causes the most injury in the lungs, but can also do significant damage in other parts of the body, including the intestines and pancreas (3).

CF is most common in people of European descent, with one in every 2,500 to 3,500 newborns inheriting two copies of the mutated CFTR gene (4).

Clinical Manifestations

Cystic fibrosis primarily affects the lungs. The thick sputum resulting from poor electrolyte transport builds up in the airways and traps bacteria and inhaled particles, causing infection and inflammation. Symptoms can include persistent, sputum-producing coughs, shortness of breath, and recurring chest infections such as pneumonia. More severe respiratory conditions include sinusitis, pneumothorax, and bronchiectasis, which is the scarring and widening of the airways due to frequent damage. Lung disease is the primary cause of death in CF patients (3).

In addition, the digestive system is also affected by mucus buildup. Thick mucus can block ducts in the pancreas and prevent enzymes from reaching the intestines, inhibiting the intestines from fully absorbing fats and proteins. One of the characteristic symptoms of CF in children is poor weight gain and growth; these children must be put on a high-calorie and high-fat diet to stay healthy. (3)

In newborns, a very common problem resulting from CF is meconium ileus, a condition due to the blockage of the intestines by abnormally thick feces. An additional problem present in almost all males with CF is the congenital bilateral absence of the vas deferens (CBAVD) and, consequently, infertility. Fertility is also affected

in females because the mucus lining the cervix is abnormally thick. Other complications resulting from CF include diabetes, which results from pancreas damage, and osteoporosis, which results from the insufficient absorption of Vitamin D (5).

Ion Channel Structure and Function

CFTR Structure

The ion channel CFTR is the 1480 amino acid protein product of the CFTR gene, and is composed of several domains. Two membrane-spanning domains form the pore of the ion channel. Two nucleotide-binding domains bind and hydrolyze ATP, which regulate channel gating by providing energy for the transition between closed and open states. A regulatory domain, when phosphorylated by protein kinase A, also regulates the opening and closing of the channel (1). CFTR is a non-selective ion channel that allows chloride and a range of anions to pass through. These include other halides such as F^-, Br^-, and I^- as well as bicarbonate ($HCO3^-$) and thiocyanate (SCN^-). However, Cl^- is still the primary ion CFTR transports due to the ion's ability to pass through the channel more easily than larger anions and the ion's tendency to bind less tightly to the pore (6).

CFTR Functions

CFTR serves two crucial functions. First, CFTR conducts chloride ions across epithelial cell membranes, which helps keep glandular and mucus secretions relatively thin. Second, CFTR is an integral part of an airway defense mechanism, which produces a bactericidal compound that prevents lung infection.

Chloride Conductance

CFTR channels are found in epithelial cells throughout the body. Epithelial cells are polar, meaning they consist of distinct apical and basolateral sides. The apical side of the cell faces the lumen of the organ or gland, while the basolateral side is in contact with the extracellular fluid (7). CFTR channels are located on the apical side of the epithelial cell, and they transport chloride ions from inside the cell into the lumen across the apical membrane. These chloride ions then draw water out of the cell and into the mucus layer lining the lumen (8), which keeps the layer moist and allows the cilia of the epithelial cells to sweep away the harmful bacteria and particles trapped inside the mucus. Lack of chloride conductance resulting from dysfunctional CFTR causes thickening of the mucus, which in turn prevents the cilia from clearing away the debris caught inside the mucus, leading to infections and inflammation (8).

Airway Defense Mechanism

In addition to chloride, CFTR also transports bicarbonate ($HCO3^-$) and thiocyanate (SCN^-) ions across the apical epithelial membrane. These ions are essential components of an airway defense mechanism that normally protects the lung against infection. However, these ions are ineffectively transported in people with cystic fibrosis (9).

In a normally functioning defense mechanism, CFTR secretes bicarbonate ions into the airway surface liquid (ASL), a thin layer of fluid that lines the luminal surface of the airway epithelia (10). The bicarbonate causes the ASL to become alkaline, and in order to re-acidify the ASL, protons are transported into the ASL by the proton channel HVCN1. These protons are then combined with the superoxide (O2-) in the ASL to form hydrogen peroxide (H2O2), which combines with thiocyanate (SCN-) to form the bactericidal compound hypothiocyanate ($OSCN^-$) (9). In individuals with cystic fibrosis, CFTR cannot secrete bicarbonate into the ASL, and consequently, this entire mechanism is disrupted, resulting in no bactericidal compound being formed. Frequent and often life-threatening lung infections may then occur (9).

Genetic Mutation

CF can arise from over 1,000 different mutations of the CFTR gene, which is located on the long arm of chromosome 7. There are six main classes of gene mutations that lead to CF (1).

Class I mutations result from nonsense mutations that lead to a premature stop codon, which causes the mRNA synthesis to be terminated too soon. As a result of this defective

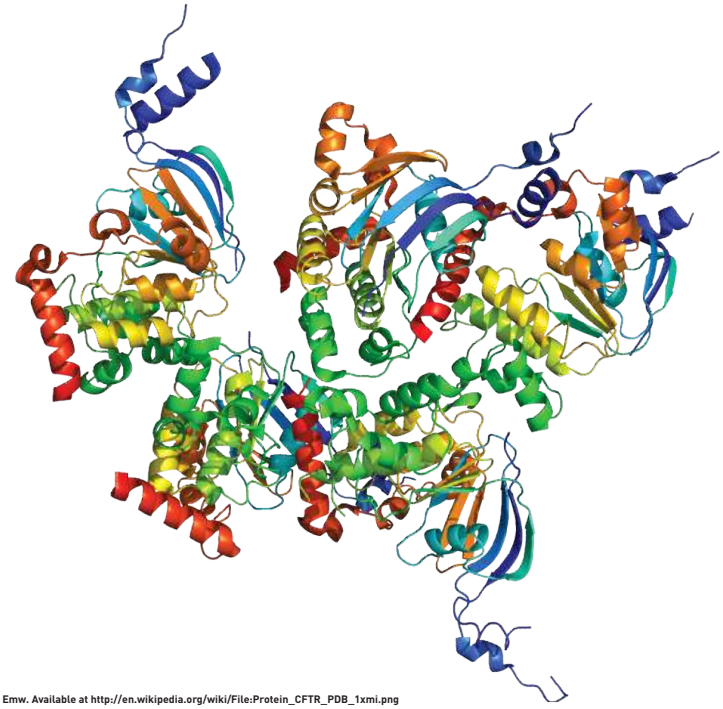

Image courtesy of Emw. Available at http://en.wikipedia.org/wiki/File:Protein_CFTR_PDB_1xmi.png

Figure 2: Three-dimensional structure of CFTR (cystic fibrosis transmembrane conductance regulator) protein

mRNA, the protein product is either incomplete or completely absent.

Class II mutations are caused by the deletion of individual amino acid residues. With this type of mutation, CFTR is still produced but is defective and therefore not properly glycosylated. Consequently, it is degraded in the endoplasmic reticulum before it can reach the cell membrane. The delta-F508 mutation, a class II mutation, is by far the most common mutation, accounting for 88.5% of all CF mutations (11). The nomenclature of the delta-F508 mutation indicates that the amino acid phenylalanine (F) is missing (delta) at position 508 in the CFTR gene.

Mutations in classes III through V all result in CFTR proteins that are able to reach the cell membrane, but cannot function properly once they are there. The last category of mutations, class VI, is the least understood. It involves frameshift mutations that cause a truncation of the CFTR protein, impairing the protein's ability to regulate other types of ion channels (1).

"Patients with CF often undergo lung transplants when their own lungs become too damaged. However, this procedure only 'buys time' for the patient..."

Current Treatments, Future Research & Development

Lung Transplants

Patients with CF often undergo lung transplants when their own lungs become too damaged. However, this procedure only "buys time" for the patient and does not address the root of the problem, since faulty CFTR channels still exist in the pancreas, intestines, sinuses, and reproductive tract (11). In addition, many complications may arise from this procedure. In order to prevent the immune system from rejecting the lungs, immunosuppressive drugs must be taken every day for the rest of the patient's life. These drugs have been known to cause side effects, including diabetes, kidney problems, and cancer-like tumors. Furthermore, only about 50% of patients receiving a lung transplant survive after 5 years (11).

Targeted Drugs

Rather than treating the symptoms as they arise, another course of treatment involves drugs that target the mutated CFTR channels themselves. Currently, the most promising drugs being researched are Kalydeco (VX-770) and Lumacaftor (VX-809), both developed by Vertex Pharmaceuticals (11).

VX-809, which is currently undergoing clinical trials, was developed specifically for patients with the homozygous delta-F508 mutation, which results in defective trafficking of CFTR to the apical cell membrane. VX-809 is a corrector, a category of drugs that increase the amount of mutant CFTR transported to the cell membrane by interfering with the protein degradation pathway that targets the misfolded CFTR proteins. Although this drug does not correct the mutation in the CFTR channels, the drug increases the presence of CFTR at the cell membrane, which still significantly increases ion transport (11).

Kalydeco (or VX-770) is a potentiator, another class of drugs which, instead of targeting the transportation of the protein to the membrane, improves the activity of mutant CFTR already at the cell membrane. This drug was developed for class IV mutations, in which the CFTR can still reach the cell membrane, but the gating of the channel is faulty, resulting in insufficient amounts of ions flowing through the channel. It is thought that a combination of correctors and potentiators would be the most effective in treating CF. A corrector could bring more of the mutated CFTR to the cell membrane, and then a potentiator could increase its activity (11).

Pharmacogenomics Approach

Aminoglycosides, a group of antibiotics, have been used to repair stop codon mutations (class I mutations). These drugs bind to a specific site in ribosomal RNA and disrupt codon-anticodon recognition at the aminoacyl-tRNA site (1). In cultured cells, this method has been shown to restore CFTR synthesis up to 10-20% of normal levels.

Genistein, a flavonoid compound, can be used to increase the channel open time of any wild type CFTR that remain in patients with CF, and consequently restore (to some degree) chloride transport. (1)

RNA Editing

A recent study published in April 2013 by Montiel-Gonzalez, Vallecillo, and Ydowski describes a new technique that uses site-directed RNA editing to correct the genetic mutation of the CFTR gene. Adenosine deaminase is a type of enzyme that acts on RNA by catalyzing the natural process of site-directed mutations. These enzymes convert adenosine to the nucleoside inosine, which is read as guanosine during translation. As a result, during mRNA editing, codons can be "recoded," changing the function of the resulting proteins (12).

In this study, Montiel-Gonzales et al. were able to engineer recombinant enzymes that could be directed to edit anywhere along the entire RNA registry. They accomplished this by replacing endogenous targeting domains from human adenosine deaminase with a different complementary strand of RNA. The resulting enzyme is capable of selectively editing a single adenosine.

The W496X mutation of the CFTR gene, which is caused by a premature stop codon, was chosen in this study for targeting by adenosine deaminase. By developing a "guiding" strand of RNA that

would specifically target this adenosine, in vitro correction of the premature termination codon could be corrected while minimizing unwanted mutations at other adenosines in the RNA (12).

Testing in frog oocytes revealed that after applying this technique, an average of 20% of the RNA was corrected with no noticeable off-target editing. In addition, properly glycosylated CFTR proteins were detected, and CFTR-mediated currents were partially restored to about half the current levels of wild type CFTR (12).

The ability to correct genetic mutations by editing mRNA is appealing for many reasons. First, mRNA is far more accessible than DNA. Genomic DNA is located in the nucleus and often tightly bound by histones, whereas mature mRNA is located in the cytoplasm. Moreover, RNA cannot integrate itself into the genome and is relatively unstable. This makes off-target edits less concerning than they would be in techniques that target DNA. Another advantage of site-directed RNA editing is that this procedure does not affect the level of mRNA expression. This is important because for many proteins, both under-expression and over-expression can lead to disorders. Lastly, there are numerous tools available for the manipulation of RNA because several enzymes are already known to be able to modify RNA in a base-specific manner. The ability to target and edit specific nucleosides has the potential to affect a myriad of genetic disorders beyond CF (12).

Future of Cystic Fibrosis

In the 1950s, life expectancy for people with CF was approximately ten years. Now, the average life span is around 37 years due to extraordinary advances in medicine (CFF). Further research is currently being done on a variety of potential treatments. Earlier this year, Vertex Pharmaceuticals began to conduct Phase 3 clinical trials of the drugs Kalydeco and Lumacaftor. Another recent line of research seeks to apply stem cell therapy to CF, which is a "model disease" for this kind of research because the recurring lung inflammations cause frequent damage and remodeling, which could facilitate the engraftment of stem cells (13). Recently, researchers were able to induce stem cells isolated from umbilical cord blood to express phenotypic characteristics of lung epithelial cells in vitro, including expression of the CFTR protein. Although significant progress has been made in this endeavor, many challenges still remain. For instance, there is a wide range of phenotypes exhibited by various types of lung cells, so it may not be enough to get the cells to exhibit one specific phenotype (14). In addition, lung cells resulting from the differentiation of stem cells may not be chromosomally stable and could cause tumors (14). While clinical trials for stem cell therapy may not occur for a long time due to the exploratory nature of this research (14), considering how far the field of cystic fibrosis research has progressed in just the past few decades, the future of this field seems very promising.

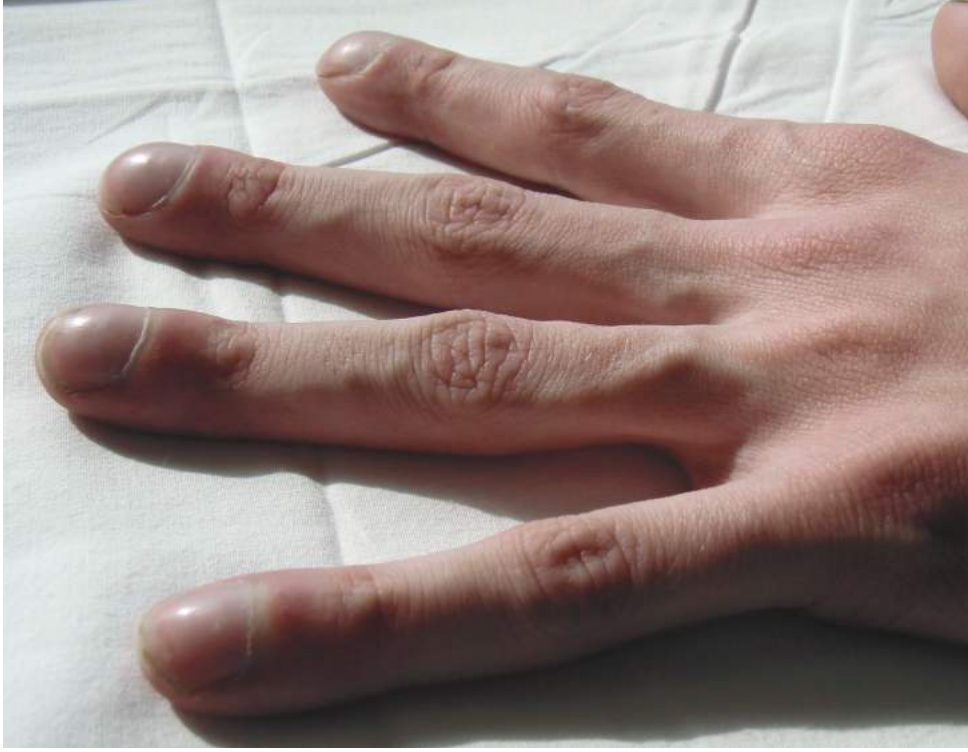

Image courtesy of Wikimedia Commons. Available at http://upload.wikimedia.org/wikipedia/commons/4/4e/ClubbingCF.JPG

Figure 3: A common symptom of cystic fibrosis is digital clubbing, which involves noticeable bulging of the fingertip.

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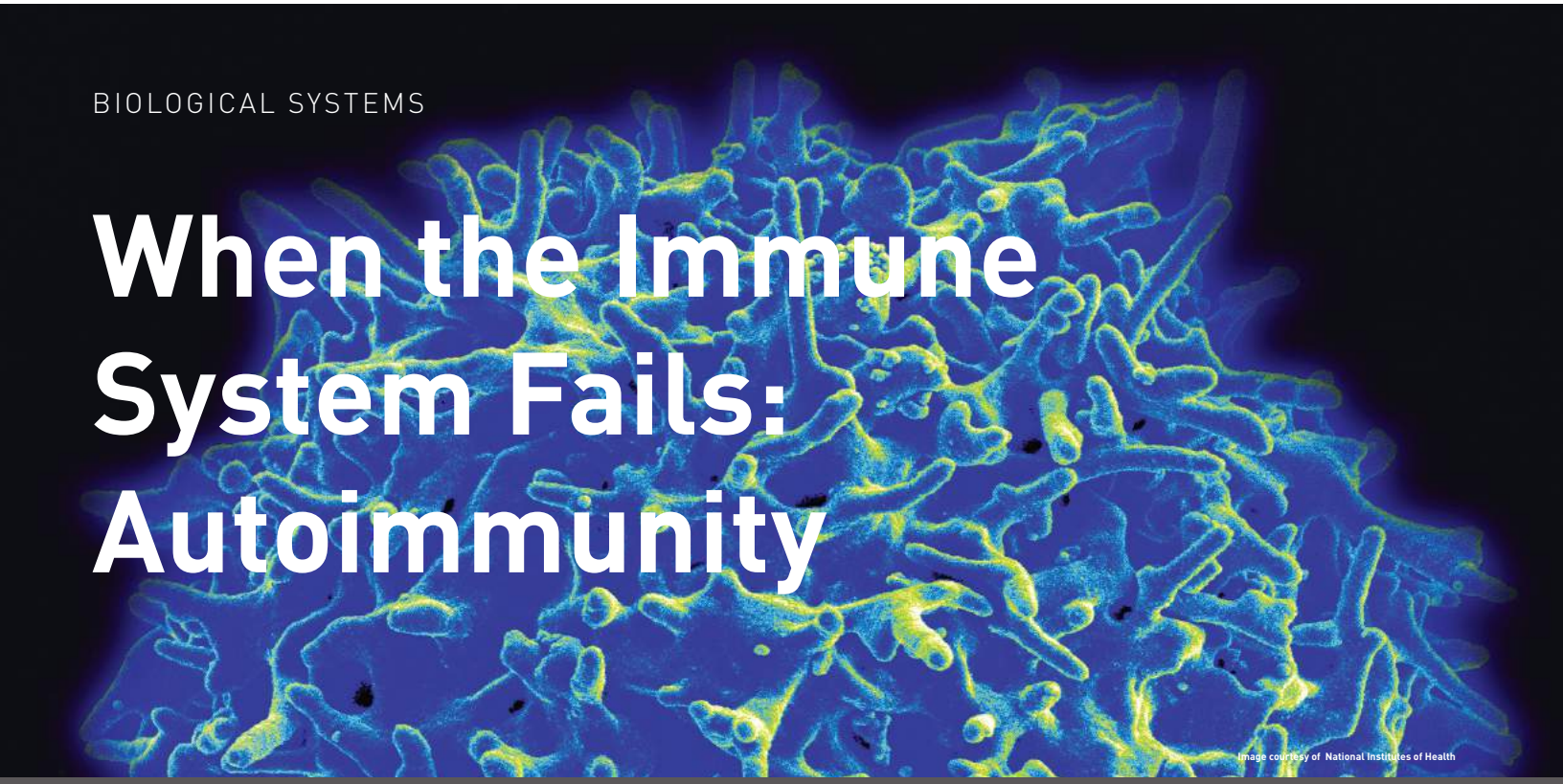
When the Immune System Fails: Autoimmunity



BY STEPHANIE ALDEN

Figure 1: Healthy human T-cell; T-cells control the cell-mediated immune response

Introduction

The body's immune system normally can recognize and attack foreign molecules, effectively protecting the host (1). In patients with autoimmune diseases (ADs), however, the immune system loses its ability to distinguish between self (host) and non-self (foreign) proteins, causing the immune system to turn on the host and attack the body's healthy cells and organs (1).

There are more than 80 recognized ADs, ranging from organ specific to systemic (2). Over 23.5 million people in the United States currently have an AD, which results in $100 billion in direct health care costs every year related to patient treatment (2). As the frequency of AD diagnoses increases, questions in the field of immunology are of increasing significance (3).

Tolerance and the Immune System

The adaptive immune system, which both creates an immunologic memory and prepares the body for future attacks, consists mainly of two types of lymphocytes: B-cells, which orchestrate the humoral immune response, and T-cells, which control the cell-mediated immune response (1). Contrary to intuition, it is natural for the human body to produce autoantibodies, which are created by B-cells, as well as self-reactive T-cells, both of which are sensitive to self-antigens (1).

The complications associated with ADs arise when the body does not properly regulate these self-reactive T-cells and autoantibodies. It therefore does not build a tolerance, or unresponsiveness, to its own cells (1). Central tolerance is the first and strongest mechanism employed by the body to protect against self-reactive immune cells (4). In this process, self-reactive T-cells and B-cells are deleted by apoptosis, or cell death, before they can mature and interact with other molecules in the circulatory system (4). In addition to completely deletion, some B-cells undergo receptor editing. Certain genes that recognize self-antigen are altered through gene rearrangement, so they no longer recognize and attack cells in the body (1).

While central tolerance is normally very effective, some self-reactive cells can survive this process and enter the bloodstream. When this occurs, peripheral tolerance acts to prevent these cells from harming the host (4). In one mechanism of peripheral tolerance, self-reactive cells in the periphery are improperly activated, which can result from improper cell signaling or inadequate costimulation. As a result, the cells either die or enter an unresponsive state called anergy in which they do not attack host cells (1, 4). The final process used in peripheral tolerance occurs through regulatory T-cells, or T-cells that control the actions of other immune cells (1). These regulatory cells prevent activation of immune cells and attempt to block the functions of nearby self-reactive cells (4).

Autoimmunity Causes

Although scientists do not yet fully understand the underlying complications that cause many ADs, most researchers point towards a dynamic interaction between the host's environment and genetic makeup. Together, these factors produce

deficiencies in the tolerance building processes discussed above.

Genetics

Substantial evidence, ranging from familial histories to increased affected percentages in entire races, supports arguments behind genetic origins of ADs (4). Using genome wide association studies (GWAS), a collection of data that enables matching of genetic variants with traits and diseases, scientists have identified genes associated with ADs, most of which are involved in induction of cell apoptosis, clearance of cellular debris, inflammation, and other immune functions (5).

For example, researchers linked NOD2, a gene that creates a protein necessary for recognition of bacteria and stimulation of the immune system, to increased susceptibility to four different ADs: lupus, psoriasis, Crohn's disease, and type 1 diabetes (4).

In another experiment, researchers investigated a knock-out mutation in mice for the "death receptor" on B-cells and T-cells; this receptor induces activation-induced cell death and plays a key role in the central tolerance process. The mutation resulted in AD development and impairment of cell death pathways (1). Both of these studies demonstrate a direct causal relationship between genetics and the onset of ADs.

Environment and External Factors

While genetic factors play a significant role in an AD's development, they often only serve to increase the likelihood of developing an AD. In many cases, environmental factors must combine with certain susceptibility genes to promote the onset of an AD (5).

There are many viruses and bacteria that may induce AD through a mechanism known as molecular mimicry. In this process, a pathogen presents an epitope, a site specific to a molecule recognized by B-cells and T-cells in the immune response, that closely resembles a self-antigen (1). This similarity causes T-cells and B-cells to mistake self-antigens for the original pathogen, leading to autoimmunity (1).

Recently, researchers found that infection with Epstein-Barr virus (EBV), a herpes virus, is connected to an increased risk of developing multiple sclerosis (MS), an AD where the immune system attacks the myelin sheath that covers the body's nerves (5). Higher anti-EBV antibody levels linked with certain genetic variants lead to an even greater risk of developing MS (5). There is still much debate, however, as to whether EBV prompts an immune response involving cells that mistake nerve coverings for the virus to directly cause MS, or whether MS causes irregular immune responses (6).

In addition to infectious agents, chemical hazards can increase the risk of AD development (4). Crystalline silica, also known as quartz, can increase "proinflammatory cytokine production and immune cell activation," boosting the overall immune response and leading to autoimmunity in many cases (4). In many occupations, such as mining, construction work, and granite work, silica exposure is very common, and many workers develop rheumatoid arthritis, lupus, scleroderma, and vasculitis as a result (5).

Case Studies

With such a large number of ADs, there are many different types with different characteristics and symptoms. Some ADs are systemic, meaning that self-reactive T-cells and autoantibodies damage several different organs and tissues, while other ADs are organ- or tissue-specific. In the latter case, the target antigen, and thus the damage resulting from the immune response, is contained to one area (1). These diseases also vary in terms of their severity, with diseases such as MS causing irreparable nerve damage and others like psoriasis causing rashes and skin irritation (1, 4).

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) can attack any part of the body, from the kidneys to the heart, making the disease very difficult to diagnose and treat (7). Antinuclear antibodies that target the host's DNA, histones, and nucleoproteins are produced and promote the formation of antibody-antigen immune complexes that form deposits on internal organs (1).

These deposits stimulate an additional immune response, causing more inflammation and organ damage (7). Many researchers believe that these autoantibodies develop to compensate for deficiencies in clearance of apoptotic cellular

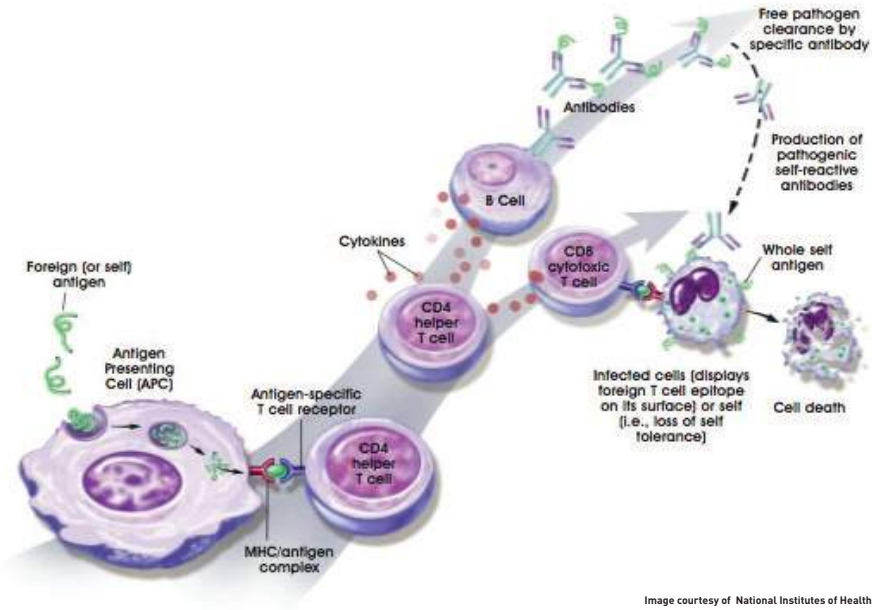


Image courtesy of National Institutes of Health

Figure 2: The immune response is very complicated, with several important steps occurring after antigen recognition.

debris; B-cells begin to recognize and attack host cells with antigens expressed by this cellular debris, leading to autoimmunity (7).

Depending on the specificity of the autoantibodies produced, SLE can cause anemia, heart inflammation, arrhythmias, seizures, strokes, and kidney failure, among other complications (7). Because scientists do not yet fully understand the fundamental causes of SLE, treatment options are limited and there is no cure (8).

To address systemic inflammation and other symptoms, many doctors use nonsteroidal anti-inflammatory drugs (NSAIDs), while some use corticosteroids to treat patients with more serious inflammation of internal organs (9). Both of these treatments can have serious side effects, with prolonged corticosteroids having more severe effects, such as tissue death, bone thinning, and diabetes, among other issues (9). Immunosuppressants are another alternative for severe SLE, but these medications may compromise patients' immune systems and make them vulnerable to opportunistic infections (8).

Recently, scientists turned to drugs that specifically target B-cells to prevent production of autoantibodies (9). One treatment employs an antibody known as rituximab, which decreases the number of B-cells in circulation by recognizing a protein expressed exclusively by B-cells and eliminating these cells. Another medication contains belimumab, an antibody that blocks B-cell stimulation and causes autoantibody death (10).

In addition to these treatments, researchers discovered that antimalarial medications target receptors that recognize self-proteins, self-DNA and self-RNA (10). These medications prevent the receptors from sending signals that promote inflammation and tissue damage (10). Future research will focus on treatments that block complement and inflammatory pathways (10). Furthermore, some researchers are trying to promote the clearance of cellular debris that may cause SLE to prevent SLE onset (10).

Narcolepsy

While diseases such as SLE have been characterized as ADs for decades, researchers at Stanford found evidence indicating that narcolepsy is an AD within the last five years (11). Patients with narcolepsy experience temporary loss of muscle control and function, abnormal REM sleep, and moments of irresistible daytime sleepiness due to low levels of an excitatory hormone called hypocretin, which promotes wakefulness (12). In the early 2000s, researchers discovered that these undetectable hypocretin levels resulted not from mutations in hypocretin genes but from the loss of hypocretin producing neurons in the brain of narcoleptic patients, with reductions of up to 90% in affected patients (12).

Researchers also discovered that the majority of narcoleptic patients have a specific human leukocyte antigen (HLA) genetic variant, another sign of autoimmunity (11). HLA genes encode the antigens that identify molecules as self or non-self and interact with T-cells in the immune response (11). HLA associations are found in many ADs, but the mechanism behind HLA associations and increased AD susceptibility in many diseases is unknown (11).

In narcolepsy, however, researchers discovered a widely shared T-cell receptor genetic variant that is responsible for recognizing antigens produced by HLA molecules (12). Coupled with the HLA association, this information indicates that an antigen presented by hypocretin-producing neurons may be targeted by specific T-cells, resulting in neuronal damage (11).

In addition to the genetic factors discussed above, environmental factors such as upper airway infections are linked to the onset of narcolepsy (13). In China, narcoleptic diagnoses normally follow seasonal patterns, increasing after

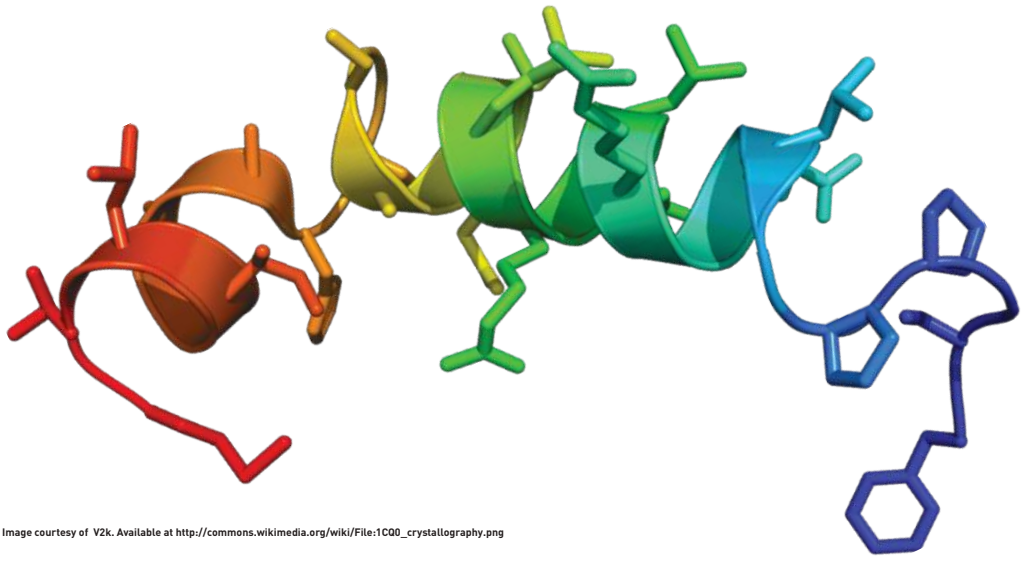


Image courtesy of V2k. Available at http://commons.wikimedia.org/wiki/File:1CQ0_crystallography.png

Figure 3: The structure of hypocretin-2, one of the excitatory neuropeptide hormones that regulates the sleep cycle and is lacking in narcoleptic patients.

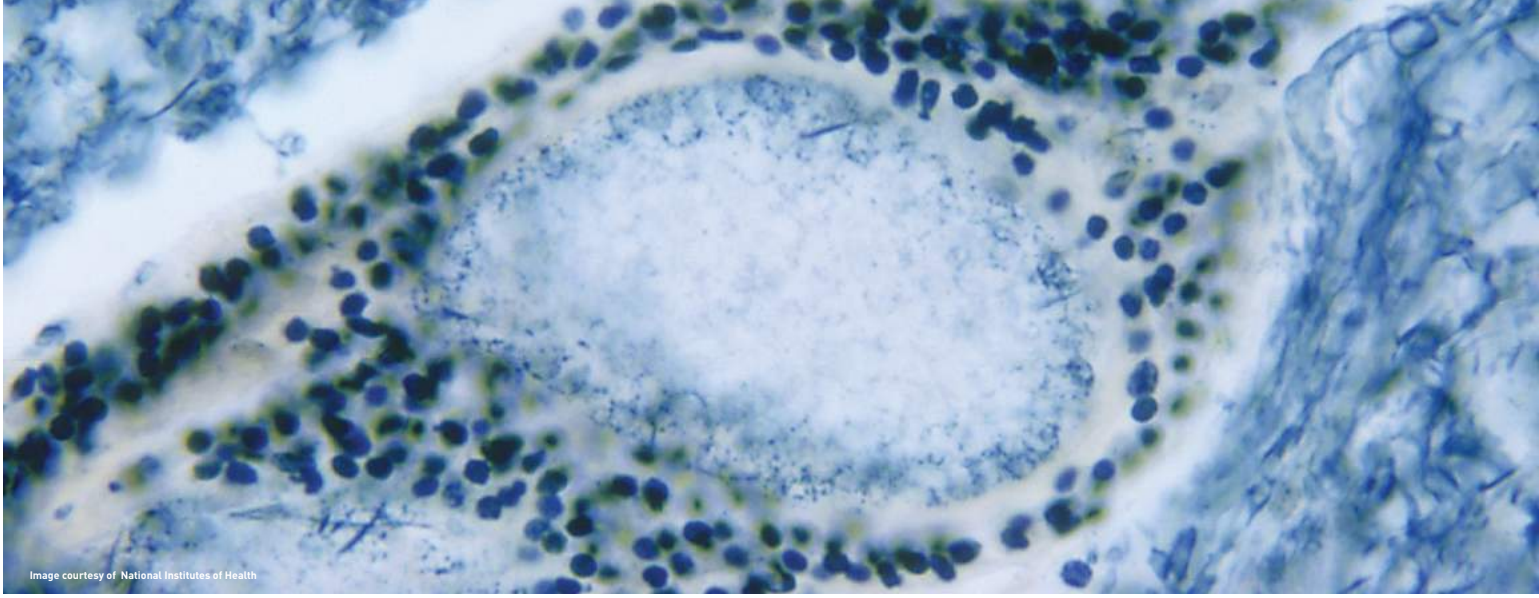


Figure 4: Multiple sclerosis attacks the myelin sheath surrounding nerves. Pictured is a human spinal cord that has been damaged as a result of demyelination.

flu season (12). Following the H1N1 pandemic in 2009, there was a drastic increase in narcoleptic diagnoses in China (12).

In Scandinavia, researchers discovered that H1N1 vaccination increased risk of narcoleptic diagnosis in children and young adults 13 fold compared to those who did not receive the vaccination (13). Researchers believe that molecular mimicry may be at work, explaining that certain H1N1 antigens may resemble hypocretin antigens (13). The infection may activate T-cells that attack both H1N1 and hypocretin-producing neurons, causing narcolepsy (12).

Researchers around the world have made extensive discoveries linking certain genetic variants to narcolepsy development, but they have not discovered any specific T-cells or autoantibodies associated with narcolepsy (11). Despite the strong evidence presented above, narcolepsy is not officially classified as an AD (11). Currently, researchers are searching for anti-hypocretin autoantibodies that may cause neuronal loss, while continuing their research of cell-mediated immune responses.

There is presently no cure for narcolepsy, but researchers hope that by finding an autoimmune foundation for the disease they will discover potential targets for treatment. As with many other ADs, current treatments only address the symptoms, not the underlying causes, of narcolepsy. These treatments consist of stimulants to promote wakefulness, anti-depressants to prevent loss of muscle control, and various medications that improve nighttime sleep (14).

Conclusion

Autoimmune disorders are extremely complex illnesses, with a variety of symptoms and underlying causes. Researchers are still identifying many of the mechanisms that cause ADs, and, therefore, many treatment methods serve to alleviate, not prevent, illness. As the molecular basis of various ADs becomes clearer, however, scientists hope to find new, more effective treatments.

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Government Shutdown: What Happens to Science?

Figure 1: NIAMS Deputy Scientific Director Vittorio Sartorelli, M.D., (right) consults with postdoctoral fellow Benedetta Zaniboni, Ph.D. The NIAMS Laboratory of Muscle Stem Cells and Gene Regulation is an institute of the NIH that focuses on the cellular and molecular mechanisms underlying specification, differentiation, and regeneration of skeletal muscle cells. During the shutdown, many experiments had to be put on hold.

Image courtesy of National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

BY JOSHUA WAN

Introduction

This past year's political failure to produce a bipartisan federal funding agreement led to a 16-day government shutdown in October 2013, the effects of which reverberated through out all aspects of US government operations. Federal agencies, budget-less without congressional approval, were forced to implement contingency plans that called for the furlough of non-essential workers and cessation of non-essential activities. Science was among the government's multitude of initiatives that experienced disruption.

Government in Science

The US federal government is highly involved in scientific development. Several government organizations including the National Institutes of Health (NIH), the Department of Health and Human Services (HHS) and the National Science Foundation (NSF) fund billions of dollars of internal and external research. Scientific organizations sometimes operate as sub-divisions of larger groups, such as the Science and Technology Directorates (S&T) of the Department of Homeland Security (DHS) and Central Intelligence Agency (CIA), the Science and Technology Branch (STB) of the Federal Bureau of Investigation (FBI), and the Office of Research and Development (ORD) of the Environmental Protection Agency (EPA). Other prominent agencies include the National Aeronautics and Space Administration (NASA), Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), National Institute of Standards and Technology

(NIST), National Oceanic and Atmospheric Administration (NOAA), Patent and Trademark Office (PTO), and the United States Geological Survey (USGS). No doubt, the list is incomplete and the impact underestimated.

Government agencies such as these involve themselves with science by collecting and providing data highly relevant to scientific research, conducting scientific research in-house, and providing support to scientists financially and in other ways.

Effects of the Shutdown

National Institutes of Health

Located in Bethesda, Maryland, near Washington, D.C., the NIH occupies a key place in medical research. Organized as 27 institutes and centers with unique focus areas, the NIH employs nearly 20,000 scientists and is active in studies researching cancer, infectious diseases, diabetes, mental health, neurological disorders, minority health, general medical science, environmental health sciences, and other related fields. One center, the NIH Clinical Center (CC), focuses on first-in-human clinical trials of treatments for rare diseases and diseases with high public health impact. In addition to its internal efforts, the NIH funds approximately $25 billion of external research each year.

When the government shut down, the NIH placed studies on hold, enrolled fewer patients in its CC, and postponed hundreds of peer-review meetings. For many projects, the 16-day hiatus meant irreparable damage to experiments. In addition, trials at the CC could not move forward as planned. While patients who were currently enrolled would not face disruption in their treatment, the NIH implemented a no-new-patient policy, with exceptions for life-threatening cases, throughout the shutdown. Patients typically will only seek treatment at the CC as a last resort; although the CC sees around 200 new patients each week, less than 20 could be enrolled during the nearly three-week long shutdown.

Outside the NIH, researchers were also affected. For scientists receiving funding already, the NIH could not provide administrative support for any grants. For scientists in the process of applying for grants, while the online portal would accept submissions, applications would not be reviewed (Kaiser). After the shutdown ended, the NIH rescheduled review sessions, and actually extended deadlines so that researchers could continue working on their submissions with full access to the NIH's grant-submission resources.

Centers for Disease Control and Prevention

Elsewhere, in another division of the Atlanta-based Health and Human Services (HHS), 13,000 members of the CDC primarily work for the nation's public health. Among its various activities, the CDC operates a Biosafety Level 4 (BSL-4) facility designed to house research on extremely dangerous pathogens, monitors diseases around the world in order to provide advance warning on outbreaks, and offers comprehensive information on health and safety topics online and on the phone. The CDC is also prepared to work closely with local, state, and federal agencies on emerging public health crises, and maintains an Emergency Operations Center.

During the shutdown, routine inspections of the BSL-4 facility were skipped, weekly reports of flu could not be generated, and information on the website could not be updated. As an agency with a national purview, the CDC's flu reports drive strategic decisions on flu vaccine programs across the country, but for the 2013 flu season, the CDC announced it would be "unable to support the annual seasonal influenza program" (Plumer). Coincidentally, and more pressing at the time, a salmonella outbreak affecting around 20 states occurred during the shutdown, and tested the monitoring capabilities of the CDC's skeleton crew (Morrison). Several strains of the salmonella outbreak were confirmed to be drug-resistant, though testing could not continue with emerging strains, as the CDC's special laboratory had been shuttered. For the duration of the shutdown, gaps like this persisted in the agency's capabilities. According to a published interview with CDC Director Thomas Frieden during the shutdown, about one million emails at CDC went unread each day the government was shutdown (McKenna).

Food and Drug Administration

The FDA is another agency within the HHS that focuses on public health, specifically in the area of ensuring the safety of food and medical products. The administration oversees mostly non-meat products, human and veterinary drugs, vaccines, and medical devices. The FDA conducts internal laboratory research, and is also largely involved with private-sector science through its prerogative to approve and regulate industries, such as the pharmaceutical, biotechnology, and medical device industries.

During the shutdown, the FDA suspended routine food safety inspections, leading to over 150 delayed inspections per week. Typically, FDA inspections are supplemented with contracted state inspections; due to the shutdown, however, the agency could not fund these outsourced activities (Satran). Furthermore, under normal

Image courtesy of Centers for Disease Control and Prevention (CDC)

Figure 2: CDC's Emergency Operations Center in Atlanta. Public health officials were among the 800,000 federal employees that were furloughed due to the shutdown.

fiscal circumstances, the agency will monitor both domestic and international food facilities. In fact, the U.S. agency has foreign offices to ensure that large food and drug exporters to the U.S. are compliant with U.S. standards. The FDA inspection system both in the U.S. and abroad were disrupted over the course of the shutdown. Additionally, the agency's role as a regulator for a variety of private sector industries was affected. While the drug regulation arm could continue operation with past funds collected through user fees, the system in place to accept new fees was shut down. Thus, though the process for reviewing applications that had already been submitted could continue moving, new submissions of several types of application forms could not be accepted. Effects of the shutdown on the FDA include hampered initiatives to promote consumer safety and facilitate private sector innovation in the sciences.

National Science Foundation

The science- and engineering-research giant of the federal government is the NSF, supporting non-medical fields outside the purview of its peer agency, the NIH. In addition to its funding of studies in mathematics, computer science, economics and the social sciences with its budget of over $7 billion, the NSF also operates facilities for the research community as a whole. Examples include its Antarctic research sites, ships and submersibles, and gravitational wave observatories. Still, the NSF's most important function is to facilitate its competitive grant program. Each year, it receives around 40,000 proposals, and funds about 10,000 of them. Dartmouth professor David Kotz of the department of computer science received a $10 million, five-year grant from the NSF over the summer of 2013; in his words, the project will address many of the basic challenges in securing information systems for use in health and wellness, as confidential information and health-related tasks are increasingly moved to mobile devices and cloud-based services.

With the NSF, the disruptive effects of the shutdown were centered on its grant review process, with meetings delayed and deadlines extended. In fact, professor Kotz said, "The government shutdown had little effect on my research. I had a meeting that was postponed with my NSF program managers, but it was not particularly time-sensitive so it worked out fine. Long term, sequestration will be a bigger challenge, because lower NSF budgets will make all NSF programs much more competitive." Sequestration refers to the automatic budget cuts passed as part of the Budget Control Act of 2011 (BCA). The ongoing nature of budget talks in Congress contributes to the uncertainty surrounding the future of science funding in America.

Figure 3: FDA Inspector Teresa Fox gives an overview of the seafood inspection process to then-HHS Secretary Mike Leavitt and then-FDA Commissioner Andrew von Eschenbach. Routine inspections of facilities keep operators alert to potential quality concerns.

Conclusion

Several months after the government shutdown, though vestiges of that 16-day stoppage of work may still remain, normalcy has basically returned to the operations of the federal government's scientific agencies like the NIH, CDC, and NSF. Research efforts and grant reviews have resumed at NIH labs, and new patients are being enrolled at the Clinical Center. The CDC is now able to perform its essential duties in monitoring the flu and tracking disease clusters around the nation. Finally, the NSF grant submission process is running smoothly again. At the same time, the causes of system failure that led to the acute disruption of work in October still remain, and disagreements over budget priorities will continue to threaten the landscape of scientific research.

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Patulin: A Mycotoxin or an Anti-Cancer Chemical?

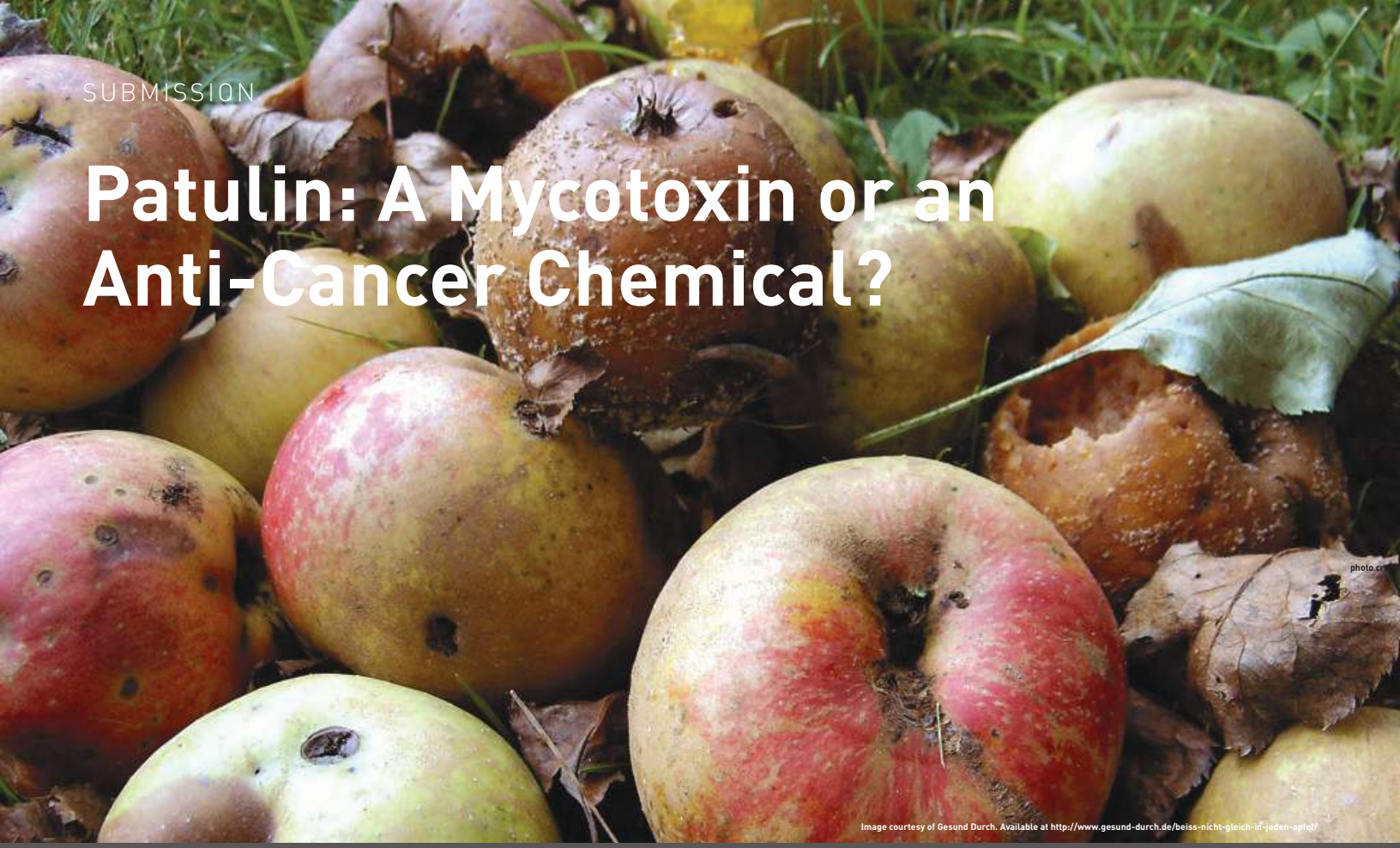

Image courtesy of Gesund Durch. Available at http://www.gesund-durch.de/beiss-nicht-gleich-in-jeden-apfel/

BY QUANG NGUYEN

Many people know the phrase, "an apple a day keeps the doctor away." Interestingly, this old wives' tale may have a scientific origin relating to patulin (PAT). PAT is a secondary metabolite produced by several postharvest fungal strains belonging to the genera Penicillium and Aspergillus (1). Currently, for the Penicillium genus, there are 13 species that produce PAT of which *P. expansum* is considered to be the main source of PAT production (2). PAT is usually found in moldy fruits and fruit/vegetable-based products, especially rotting apples, apple juice and other apple-derived food for young children (3). In 1944, it was assessed in a controlled trial conducted by the Medical Research Council (MRC) for potential antibiotic properties to fight the common cold (3,4). Despite of the study conclusion that 'no evidence was found that patulin is effective in the treatment of the common cold' (4), the famous saying is still commonly used today.

Since then, many *in vivo* animal studies, in fact, have shown that PAT is actually toxic with many serious health complications to the consumers (5). Previous animal studies, such as those conducted in rats (6), mice (7), monkey (8), and chicken (9), seem to suggest that because of its electrophilic properties, PAT covalently binds to sulfhydryl groups on proteins and amino acids, exerting its toxicity by inhibiting normal functions of many enzymes (1,3). Specifically, PAT can cause organotoxicity in adult mammals, damaging the liver, gastrointestinal tract and kidney (7,10,11), as well as causing premature death in rats (12). Repetitive doses of PAT were also shown to produce neurotoxicity in rats, indicated by tremors, convulsions, and dyspnea (3). In rodents, distention of the gastrointestinal tract was also observed, and several enzyme activities were inhibited in the intestine and the brain (3). In humans, PAT was shown to trigger local irritation and an acute intoxication (5). In addition, PAT can interrupt the cell cycle and damage DNA with subsequent apoptosis (14). Lupescu and colleagues (2013) also indicated that PAT is a powerful stimulator of a suicidal death of human erythrocytes in which cells shrink and their membrane scramble as a result of an increase in cytosolic Ca2+ concentration. This process is called eryptosis, which is also observed in other clinical disorders, such as diabetes, sickle cell disease, iron deficiency and malaria (14).

Although it is generally accepted that reactive oxygen species (ROS) generated and oxidative damage by PAT are responsible for exerting its toxicity, detailed intracellular

Figure 1: Patulin is a mycotoxin commonly found in rotting apples.

mechanism of action, specifically on cancerous cells, remains controversial. In fact, PAT's ability to trigger apoptosis in tumor cells was recognized as potential anti-cancer intervention in treating colorectal cancers in humans (11). Regardless of its beneficial potentials, because of many serious PAT contamination-related health complications in existing animal studies, the U.S. Food and Drug Administration (FDA) and the World Health Organization (WHO) have established a maximum allowable limit of 50 μM of PAT in apple juice (15). According to the FDA, small children less than two years old are at particular risk since they consume a higher amount of apple juice relative to their body weight than older age people, especially those who are 2-10 years old (15). Currently, the safety limit of PAT, which is .4 μg/kg body weight/day, is well below the provisional maximum tolerable daily intake (PMTDI) (5). Moreover, certain processes, such as alcoholic fermentation, pasteurization, irradiation treatment and powdered activated carbon application, have been considered to reduce its concentration in food products. Nevertheless, as PAT is heat stable at pH less than six and because of inadequate apple quality control during sorting, it can still remain after processing, resulting in apple juice can "occasionally be heavily contaminated" (5,16).

As apple is an essential source of antioxidant phytochemicals that help reduce the risk of some cancers, cardiovascular disease asthma and diabetes (17), future researches are warranted to develop methods to effectively eliminate possible toxins in its derived products and those from other fruits and vegetables. Furthermore, as Paracelsus (1493-1541), a founder of the field of toxicology, once said, "all substances are poisons: there is none which is not a poison. [Only the] right dose differentiates a poison and a remedy," it is important to also recognize the therapeutic potentials of these toxins. Science research is an evolving and continuing learning process in which what is proved to be harmful today may be considered as beneficial later. Nothing is invalid until it can be disproved with significance.

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Figure 2: Three-dimensional structure of patulin (PAT)

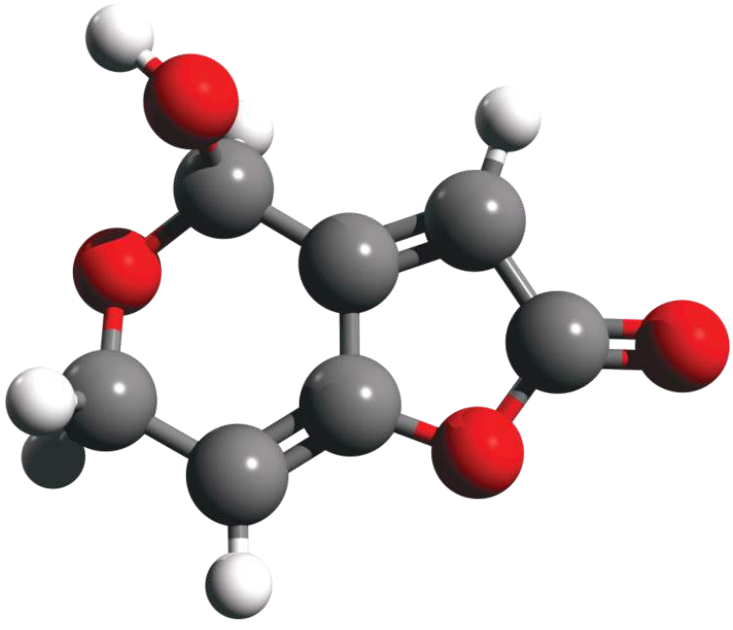

Image courtesy of Giorgiogp2. Available at http://commons.wikimedia.org/wiki/File:Patulin_3d_structure.png

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Investigation of Neutron Emission from a Farnsworth IEC Fusion Reactor

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Abstract

The Farnsworth-type IEC reactor was once considered to behave as a point source of neutrons with reference to the spherical central accelerating grid, assumed from the inherent isotropy of the D(d,n) reaction and that the majority of the fusion events happen near the deepest region of the potential well. We tested this assumption by measuring deviations from uniformity in the neutron flux using CR39 plastic, BTI bubble detectors and He-3. The CR39 slides were exposed to fast neutrons (2.45 MeV) at a fluence of 10^6 n/cm^2, and indicated apparent anisotropy (p-value of 0.0035) with higher flux at the front and rear of the machine. The BTI bubble detectors and He-3 tubes also corroborated a higher neutron density at the front and rear of the reactor. We hypothesized that beam loading on the front and rear conflats by the plasma jets emanating from the central cathode could be responsible. Measurements with paired He-3 tubes after blocking the jets with a quartz glass showed the apparent anisotropy reduced 38% on average ($p \ll .001$). This quantitative confirmation of anisotropy, and the signicant (but not sole) role that beam loading plays therein, represents an important shift in the understanding of the Farnsworth-type reactor.

1. Introduction:

Current hypotheses of the operation of the IEC fusion reactor (fusor, Fig. 1) state that the central cathode is the highest fusion-density point in the reactor. It is the point with the highest negative potential, and therefore will have the most accelerated deuterons and collision-fusion events. Because of the isotropy of the primary reactions occurring within plasma (Eqs. 1 and 2), and the spherical geometry of the inner cathode, the neutron flux should demonstrate complete isotropy with reference to the central cathode.

$$ {}^2_1D + {}^2_1D \rightarrow {}^3_1T + p^+ \qquad (1) $$

$$ {}^2_1D + {}^2_1D \rightarrow {}^3_2He + n^0 \qquad (2) $$

However, research done by the University of Wisconsin [1] and tentative results from other IEC fusion reactors have suggested that off site fusion events causing systemic anisotropy in the neutron flux may exist. Because of the possible ramifications to current fusor theory, we sought to determine the existence of off cathode fusion by investigating the isotropy, or lack thereof, of the system's neutron flux. To that end, we first created a 3D map of the neutron output using CR39 plastic dosimeters. We chose CR39 to produce a full map of the reactor's neutron flux. However, CR39 has not been used in this specific application before; therefore we used more standard detectors (BTI bubble detectors, He-3 tubes) to validate our results. The final phase of our research was to try to explain the observed anisotropy.

2. Types of Dosimetry:

2.1 CR39:

CR39 is a carbonate plastic (Allyl Diglycol Carbonate) originally created by Columbia Resins. It is chemically inert, fracture resistant, and easily manufactured. CR39 responds to particle radiation by forming microscopic pits at the impact sites of ionized particles with high linear energy transfer values. These pit regions are full of broken polymer chains and are far more reactive than the surrounding material, and are therefore vulnerable to etching in caustic solutions. The pits begin at sub-micron sizes, but rapidly inflate by 10-20 μm when etched in a basic solution [3]. NaOH or KOH is used, and etch times usually range between 3-20h at 70° C. After etching, the impact marks are usually conical in profile, and are visible under a magnification of 100-200x in a standard optical microscope.

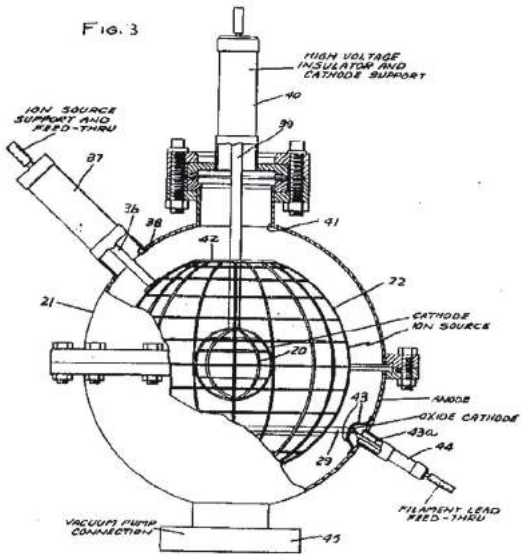

Figure 1: Schematic of a Farnsworth IEC Fusor (2)

[1] All work done at the Northwest Nuclear Consortium, Federal Way, Washington

[2] All authors contributed equally to this work.

2.2 BTI Bubble detectors:

These detectors are a form of reusable fast neutron dosimeter that uses tiny pockets of superheated fluid suspended in a polymer matrix. When a neutron causes a shower of recoil protons in the polymer, a nucleation site is formed which makes the now gaseous bubbles of fluid visible and spherical [4]. These can be reset by compressing the polymer. Non-reactive to all other forms of radiation, BTI bubble detectors are an excellent method of detecting neutrons.

2.3 He-3 Tubes:

He-3 tubes are an extremely common form of neutron detection. They are used in reactors worldwide and are standard for the detection of thermalized neutrons. The He-3 gas in the tubes has a large cross section for thermal neutrons, by which neutron capture events release 0.764 MeV in the reaction products [5] (Eq. 3). The energetic products produce a pulse of ions in the tube, which is significantly larger than any interference induced by gamma-rays. Our Reuter-Stokes tube was encased in a 3in radius x 12in length high-density polyethylene moderator during our shield-up test.

$$n + {}^3He \rightarrow {}^3H + {}^1H + .764\,MeV \qquad (3)$$

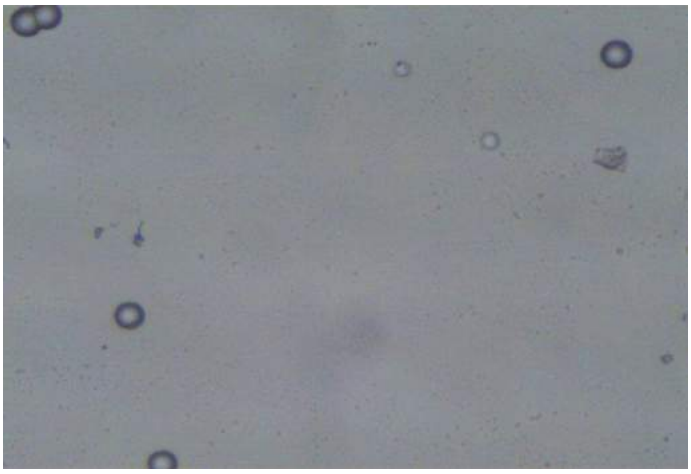

Figure 2: An unprocessed slide

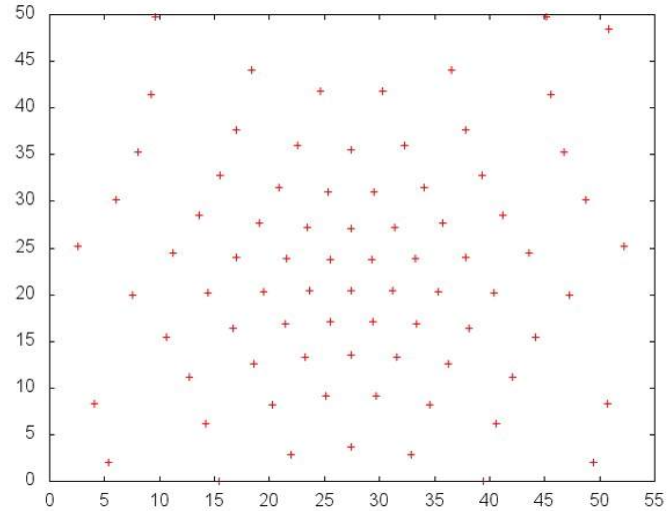

Figure 3: Slide placement map for the front side of the reactor

3. Experimental Procedure:

3.1 Radiation Map

The CR39 test for anisotropy required mapping and mounting 200, 2 cm^2 slides, chemically etching them, and then photographing the results. We used reverse gnomonic mapping to create a sphere of equidistantly spaced points around the reactor at an arbitrary radius, and then projected them out towards a set of 2D Cartesian planes. The resulting maps were used to affix the CR39 slides to boards, which were set up in a box around the reactor (we will refer to the front of the fusor as being 0° from the negative y-axis as seen from the top-down, the right as 90°, the back as 180°, and the left as 270°) (Fig. 3). The slides were irradiated at a measured neutron flux of 125,000 neutrons/sec for 100 minutes. They were then removed and etched in NaOH for ten hours, and rinsed in a cold bath for six hours [3]. A picture was taken at ten consistent locations on every slide using a 100x microscope with a USB scope-cam. The photos were converted to a Bitmap array [6] and then iterated pixel by pixel. Each pixel color value was converted from RGB color space to YUV color space (two types of color encoding), which allowed the intensity value (Y) to be pulled separately. The darker regions (smaller Y) were separated from the lighter background (larger Y) and a threshold value was set to distinguish the areas of high neutron counts from those with lower neutron counts. The darker pixels were counted and added to the other nine pictures from every slide to get an average sample for the neutron density for the entire slide. The radiation dose data points from the walls were adjusted back to a constant radius from the reactor, generating a radiation sphere, accounting for $1/r^2$ decay and allowing the data points to be compared (Fig. 4).

3.2 BTI bubble detectors

Further neutron dose data collection was done using two 45 bubbles/µrem BTI fast neutron detectors, one placed in the front and the other on one of the other conflat flanges of the fusor chamber. They were exposed for 600 sec runs at a flux of 125,000 N°/s for each test. The detectors were photographed, pulled, re-armed, their positions switched, and then the run was repeated. Repeating this method for all of the flanges allowed for comparison of the dose ratio between sides.

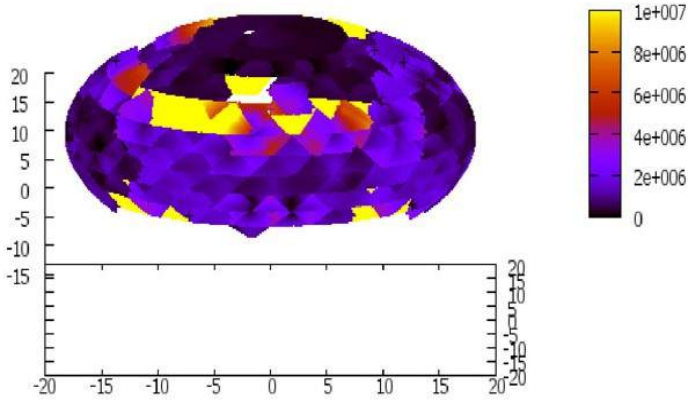

Figure 4: Back side density map: radiation dose from the reactor as seen from the top looking down. Lighter colors represent higher doses, and units are arbitrary

3.3 He-3 tubes

We did an additional corroborating test to ensure the validity of the previous two. During one continuous test, the moderated He-3 tube was placed at equidistant and coplanar points on each side i.e. front, back, right, left. For this test, the shield was raised to allow access. A secondary benefit was that raising the shield removed the possibility of moderator reflection affecting the results.

3.4 Quartz Glass

Our hypothesis was that the deuterium plasma jets were impinging on the stainless steel flanges and creating a metal hydride, and thus a deuterated target. The subsequent accelerated deuterons then would fuse with the deuterons in the flange, creating a beam-on-target system. Deuterated targets have been experimentally created by the University of Wisconsin IEC team by sputtering the inner walls of the vacuum chamber with titanium [7]; however, the spontaneous creation of such targets has not been previously observed. We tested the beam-on-target hypothesis with a quartz glass viewport placed inside the vacuum vessel in lieu of the back flange. The glass blocked the front-back plasma jet emanating from the central grid from impinging on the flanges, thus preventing fusion with a deuterated target. The test used two He-3 detectors; one on the back, and one on the right side of the fusor. The experiment was done first without the quartz glass, and then with the quartz glass. Afterward, we compared the ratios between the two detectors.

4. Results:

4.1 Radiation Map

The counts from the slides, having been adjusted to a common radius, were displayed visually as a sphere of radiation doses. The different views and statistical analysis show the front as receiving, on average, a higher dose than all other directions except toward the rear of the fusor. The left, right, and back sides received similar doses, whereas the top slides showed neutron counts statistically lower than all other sides. The Phi-degrees map, depicted in Fig.(5), in particular demonstrates these trends.

4.2 BTI bubble detectors

The dose recorded on the front shows a strong difference from that of the right, left, and top, while showing a similarity to the dose received on the back. Counts represent bubbles recorded after the run:

Location	Right	Left	Top	Front	Back
Count	28	20	22	105	91

4.3 He-3 tubes

The dose recorded on the front and back, in microrem, was double the radiation detected from the left and right:

Location	Front	Back	Left	Right
Count (μrem)	26	26	13	13

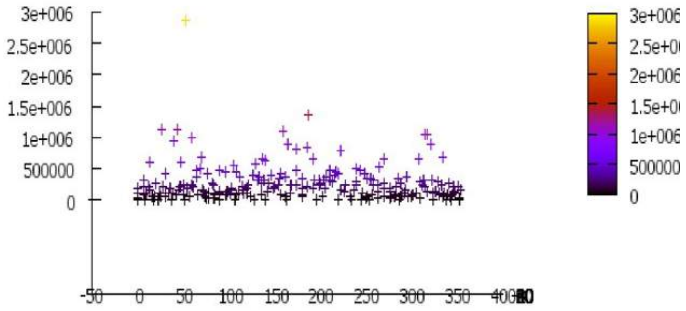

Figure 5: Density by phi: graph of the dose at various points as a function of phi, where phi refers to the position clockwise around the reactor in the x-y plane, and wraps at 0 and 360. The peak in the center represents higher counts in the back, and the two peaks at the sides represent the hotspot at the front.

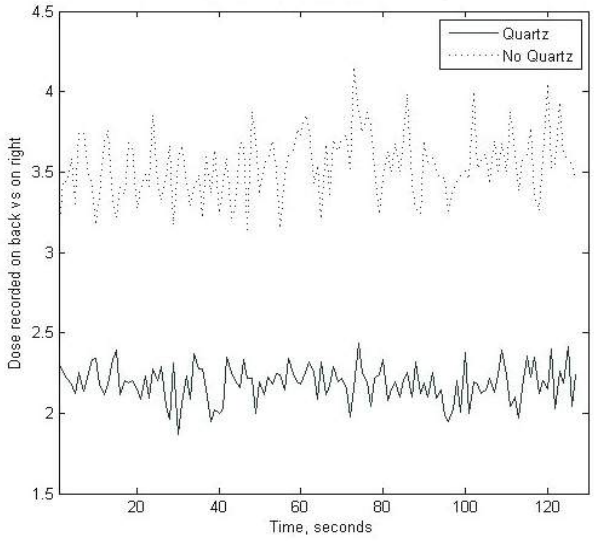

Figure 6: Dose ratio before and after quartz implementation

4.4 Quartz Glass

Figure 6 charts the change in ratio between the right and back before and after the addition of the quartz. The data shows an average 38% drop with a significance level of $p \ll .001$. The results indicate a clear decrease in anisotropy (shown by the decrease in relative dose ratio in Fig. 6) upon blocking beam-target fusion.

5. Conclusion

The data we gathered on the neutron flux from the NWNC IEC reactor shows strong deviation from point source behavior, as evidenced by the CR39 radiation map, BTI flux sampling, and He-3 tube test. All detectors corroborate that there are regions of significantly higher flux near the front and the rear of the reactor, suggesting that it may no longer be accurate to model the IEC reactor as a point neutron source. Furthermore, our observation of the decrease in anisotropy when quartz glass was implemented suggests that beam-on-target fusion was responsible for approximately 38% of this behavior. These other sites of fusion closer to the detectors could account for the observed variation, as

the detectors' distance to the conflat flanges is 4.92 cm shorter than their distance from the cathode. It should be noted that these results are highly geometry-specific; in a reactor which did not exhibit such pronounced plasma jets, or in one which was made of a material which could not sustain a deuterium target,these results could be drastically different. It should also be noted that the He-3 experiment required opening the chamber to atmosphere to insert the quartz, which changed the operating conditions. Also, the methodology in the processing of the CR-39 slides allowed for high background noise. Even so, statistical analysis can conclude deviation from point-source behavior (p-value of 0.0035 from CR39 and p-value $\ll$.001 from He-3 detectors). In the future, we recommend that investigation be done using different reactor geometries. We hope that future research can take advantage of the finding that reactor geometries may alter neutron output [8], from a three dimensional point of reference.

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Man vs Machine: The Rivalry in Chess

JAMES BROFOS

Abstract

The game of chess presents a non-trivial challenge to computer scientists to create powerful "chess engines." The history and future of these chess engines are the topic of this paper, and the problems typical of chess in general, and of computer chess in particular, are offered "for fun" to the readership.

A Brief History of (Computer) Chess

These days, nearly everyone has had exposure to the game of chess. The appeal of chess has a legacy millennia long, springing into existence first in northern regions of Afghanistan or India around 500 AD (1). In all this time there have been landmark events which have influenced the game in the highest degree. Examples of these include: in the 15th Century the emergence of modern chess in Italy (2); in 1656 the first recorded chess analyses by Gioachino Greco (3); in 1972 the Cold War confrontation between American Bobby Fischer and Soviet Boris Spassky in the Match of the Century in Reykjavik, Iceland; in 1996 the games between Garry Kasparov and the IBM supercomputer Deep Blue with a convincing three victories, two draws, and one loss in humanity's favor.

The Opening Game: Prior to Deep Blue

The Deep Blue-Kasparov match, and the subsequent rematch in 1997, represent something of a culmination in the history of computers in chess. And it is to this fragment in the history of the game that we devote our attention. The novelty of a chess-playing automaton emerged for the first time in 18th Century Hungary under the auspices of diplomat-inventor Wolfgang von Kempelen (4). Von Kempelen's machine, affectionately called "The Turk" by its contemporaries, was intended to amuse the courts of Napoleon and Maria-Theresa. Even Benjamin Franklin, a comparatively able player for his day, was extended a personal invitation to match wits against The Turk.

Yet, as shall be seen, von Kempelen's contraption must have been, from a computational perspective, something of a "let-down" for the field of automata in chess. The apparent appeal and subsequent disappointment of The Turk stem from its presentation of the illusion of mechanical thought.

In actuality, von Kempelen's machine was just an elaborate deception. Yet, for all that, The Turk had introduced, for the first time in history, the idea that a machine could engage in a distinctly human game. It constituted an instance which elevated the quiet game of chess to something of a celebrity. Benjamin Franklin himself, as asserted by his grandson, "enjoyed his game with the automaton and was pleased with it" (5). Edgar Allan Poe in 1836 wrote the essay "Maelzel's Chess-Player" in speculation of the device's *modus operandi*, declaring in the first line of his exposition, "Perhaps no exhibition of the kind has ever elicited such general attention as the Chess-Player of Malzel. Wherever seen it has been an object of intense curiosity, to all persons who think" (6).

Yet after the spectacular success of The Turk in the 18th and 19th centuries, the public's fascination with "thinking machines" in chess plunged into an abyss for more than one-hundred years. Indeed, it would require the onset of the Second World War and the advent of early computer technology to reignite interest in chess automata. Enter Claude Shannon, a computer scientist then in the employment of Bell Telephone Laboratories. In 1949, Shannon published his revolutionary "Programming a Computer for Playing Chess" (7). The work proposed the first algorithm to empower a computer with the ability to intelligently play chess, which relied on a theoretical board evaluation function f(P), where:

$$f: \{\text{board space}\} \longrightarrow R$$

and so P represents the state of the board at any given turn and the resulting real number the strength of the board. Shannon's idea is relatively intuitive and elegant: he asserted that every position that can legally arise in a game of chess may be numerically captured by attributes that are characteristic of a strong or weak position for the player, and from an evaluation of those attributes can spring all manner of strategy and foresight required for skillful play. Positions that were advantageous for the computer player would be evaluated positively with higher numbers reflecting stronger winning chances, while losing positions would be evaluated negatively. Games where the position was drawn would be evaluated as zero. On the basis of centuries-worth of human experience in determining the relative strength of a position, Shannon identified the following as being crucial to any evaluation function f(P):

1. **Piece values**: According to the three-time United States Open Champion I. A. Horowitz, every piece in chess has a strength relative to the worth of a single Pawn. Thus, if a Pawn represents a single unit of strength, then, generally speaking, the Knight is equivalent to three Pawns, the Bishop three Pawns and some slight amount more, the Rook five Pawns, and the Queen nine, while the King is infinitely valuable (since a loss of the king means a lost game) (8). The side possessing the greater material advantage according to this metric has some advantage in the position.

2. **King safety**: A King that is vulnerable to attack by the opponent reflects fragility in the position. The side whose King is well protected (e.g. by castling) when the opponent's King is relatively undefended, enjoys benefit in the position. See Figure 1.b.

(a) The opening position of chess from which all board variations must inevitably spring. Game sequences exist in finite number, yet are so multitudinous as to defy enumeration by computer.

(b) White has sacrificed a piece to obtain a dangerous attack on the Black sovereign. Thus, Black's material advantage in this position may be sorely outweighed by the relative insecurity of his King.

(c) The Black Queen-side Pawns cannot defend themselves against a White attack. Both sides have a position development, yet Black's pieces may be tied down in defense of the unstable flank.

Figure 1: Chess positions that are instructive both of the game itself and of the value of Shannon's key positional attributes. Chess diagrams adapted from those discussed first by Horowitz [8]. All chess diagrams created by the Shredder Classic 4 GUI.

(a) Magnus Carlsen vs Helgi Gretarsson, Rethymnon, 2003

Carlsen won the game with White pieces with a mate-in-two from this position. If White were to play, Prinz' program could find the winning sequence of moves.

(a) Bobby Fischer vs. Greenblatt Program, Cambridge, 1977

The final position of one of three games played between the former FIDE World Champion Bobby Fischer and Greenblatt, playing White and Black respectively.

Figure 2: Endgame positions in chess.

3. **Pawn structure:** A poor Pawn structure is characteristic of a weak position. In chess the Pawn structure is weakened by the existence of isolated Pawns (Pawns that are unprotected by supporting Pawns), doubled Pawns (Pawns that, by capturing a piece, have wound up on the same column of the board), and backward Pawns (Pawns that support other Pawns, but are incapable of advancing due to lack of protection). Lack of sound Pawn structure allows for easy infiltration of the camp by the enemy, which is an advantage to the opponent. See Figure 1.c.

4. **Piece development**: Shannon characterizes this attribute of a position by the example that strong Rooks are typically placed on the open rows or columns (i.e., no piece inhibits their range of movement along that dimension) of the board. The key idea here is that pieces should be moved out of their initial positions on the board to squares where their attacking chances are best put to use. Especially in the opening phase of chess, the side with superior development will typically have the better game.

Claude Shannon had set the stage for computer chess, and let loose on hordes of eager mathematicians a complex problem in desperate need of a solution. In the years following 1949, numerous attempts were made to create computer chess players. In 1951, for instance, the German-born Dietrich Prinz developed at the University of Manchester a program capable of solving chess' "mate-in-two" problem (9, 4). See Figure 2.a. Yet Prinz's program was weak in the sense that it was restricted to endgame play (in fact, only the *last two moves* of the endgame).

Other pioneers in computer scientists followed in Shannon's wake, including Alan Turing and Alex Bernstein of IBM. Bernstein's involvement in 1957 marked the dawn of two major events in computer chess history: first, IBM's first foray into the field of chess automata, initiating a four-decades-long journey that would culminate in the creation of Deep Blue; second, Bernstein and colleagues at MIT created the first

computer program capable of playing a full game of chess against a human opponent (10). Bernstein's chess program represented a vast improvement over Prinz' two-move solver in extent of ability, but still failed spectacularly to match the skills and intuition of a master human player. Indeed, International Master Edward Lasker delivered a crushing defeat to the IBM machine, remarking in victory that the machine had played perhaps a "passable amateur game" (11). Yet the computational impasse confronting Bernstein and others was two-fold, as computers were falling short both in terms of strategic capability and in terms of speed. Prinz's computer required approximately fifteen minutes to solve a single mate-in-two puzzle, and Bernstein's program suffered eight minutes to evaluate a single position. Even if computers could outplay humans skillfully, they would certainly lose tournament games to time constraints. Computers needed to play well, and they needed to play quickly.

Hindered by the slow execution time of 1950s-era computers which were capable of only 10,000 calculations per second, chess pioneers turned to heuristics to improve machine understanding of positional strength. The idea of the heuristic emerged with MIT's Richard Greenblatt and his chess machine *Greenblatt*. What made *Greenblatt* unique among other Shannon-inspired chess automata was that it incorporated "considerable chess knowledge[, which had] been programmed in" (12). If computers could not be made to evaluate positions *faster,* they could as compensation be made to evaluate them *better*. Richard Greenblatt captured, in code, fifty aspects of the game that he had gleaned from experience and instinct, aspects that were beyond the scope of what might be grasped by Shannon's evaluation function f(P). As a result of these improvements, *Greenblatt* was far and away the strongest chess automata of its day. But even so, the computer failed miserably to win even a single match against Bobby Fischer in a three game exhibition in 1977. See Figure 2.b.

Despite the setback, 1977 was a momentous year for computer chess if only on the grounds that the subject had emerged both as a legitimate computer science benchmark and also as something of a competitive sport. As if to capture the spirit of the times, Monty Newborn issued the following declaration at the Second Computer Chess Championship:

> *In the past Grandmasters came to our computer tournaments to laugh. Today they come to watch. Soon they will come to learn.*
> – Monty Newborn, Toronto, 1977 (13)

In the same year, Ken Thompson and Joe Condon, working at Bell Laboratories, recognized that the truly exceptional chess computers would be constructed not only on purpose-built software, but also on purpose-built hardware (4). Thompson and Condon's machine, affectionately (and perhaps chauvinistically) called Belle, was assembled to contain circuitry that allowed for exceptionally fast positional evaluations. Belle was a realization that perhaps the singular advantage the computer had over the human mind was its ability to repetitively perform simple tasks very quickly and typically without severe error—Belle would use brute force, rather than intrinsic knowledge, to examine a massive number of possible variations (160,000 positions per second) that could emerge from the game (4).

All of the advancement in computer chess, and Monty Newborn's challenging statement, did not go unnoticed by the human chess community. In a bet made in 1968, Scottish International Master David Levy had boasted that no computer would be able to defeat him in ten years' time (14).

Playing against the imaginatively-named chess automata Chess 4.7—a machine constructed by Larry Atkin and David Slate of Northwestern University—fate had it that Levy would win his bet. In a match of six games, Levy claimed victory in four and fought one to a draw. Yet the Scotsman emerged from the ordeal somewhat humbled by the experience, no longer singing praises to the invincibility of the human world champion. Indeed, Levy confessed that the computer opponent was "very, very much stronger than I had thought possible when I started the bet" and that "Now nothing would surprise me" (14). As shall be seen next, Levy's admissions were the harbingers of a kind of "fall from grace" for human chess champions.

Deep Blue vs Kasparov

In the mid-1990s, IBM's research division set out with the purpose of building "a world-class chess machine" that could play skillfully enough to defeat the most capable human opponent (15). The matter of who represented the most capable human opponent was, at the time, not as contentious as it might have been. Garry Kasparov of Russia was the reigning FIDE World Chess Champion for the last fifteen years of the 20th Century, having defeated Anatoly Karpov, the previous champion, in 1985. Further, Kasparov was widely regarded as one of the strongest chess players, if not the strongest, in the history of the game, having dominated the field of chess in the nineteen years between 1986 and 2005 as the world's highest rated player. Indeed, Kasparov also went on to achieve the highest rating in the history of the game, a record that was only recently outdone in January 2013 by Magnus Carlson of Norway. To challenge Kasparov's throne, IBM created the supercomputer Deep Blue.

Deep Blue began first in 1985 as the dissertation of Fen-hsiung Hsu, then a graduate student at Carnegie Mellon University. In its early years, Deep Blue was known by another name entirely: Chip Test (16). Hsu and his classmate Murray Campbell worked as the chief architects of Chip Test's evaluation function, and the automata itself proved capable enough to win the 1987 North American Computer Chess Championship (17, 18). The success of the university project attracted the attention of IBM's research division and the two were brought into the company with the extraordinary purpose of constructing a computer capable of defeating the World Chess Champion. Renaming the IBM project to "Deep Blue," a name inspired by an earlier incarnation of the program "Deep Thought" (itself named after Douglas Adams' famous computer character in *The Hitchhiker's Guide to the Galaxy* (19)), the IBM began the process of building its world-class machine.

Unfortunately for computer chess, Hsu's and Campbell's first forays against the world champion were met with defeat. The initial attempt to dethrone Kasparov came in 1989 with a two-game exhibition match played in New York. Kasparov, who had demonstrated his prowess against chess automata four years prior by demolishing thirty-two similar programs simultaneously in an exhibition match in Hamburg, Germany (20), was undoubtedly confident in his chances of victory. Like the machines that had come before it, IBM's chess playing contraption met with a quick end against the seemingly-insurmountable Russian King of Chess. In the face of the defeat

Hsu and Campbell reconsidered their approach to the problem and realized that, while neither of them were unfamiliar to the game, they did not have the knowledge and skill possessed by chess masters at the highest level. So entered the American Grandmaster Joel Benjamin, brought to the IBM team explicitly as Deep Blue's "official Grandmaster consultant," training "the computer to think more position ally" (17, 21).

Development of Deep Blue continued to the year 1996, having been coached and adjusted and maintained for slightly over a decade since its inception. In the judgment of Hsu and Campbell, Deep Blue was ready for its first rematch against Kasparov. In a match arranged by the Association for Computing Machinery in Philadelphia, Deep Blue and Kasparov again contended from across the board—this time for a $500,000 prize (22). The 1996 showdown did not go unnoticed by humanity, and the publicity storm around the event led to Time Magazine running the rather provocative cover story, "Can Machines Think?" (23). Indeed, the Deep Blue-Kasparov match seemed to represent something of an "identity crisis," an apparent struggle for "the meaning and dignity of human life" (23). If anyone had been anxious, then their fears were realized when the first game went to the IBM computer, marking the first time in history that a computer had unseated the reigning world champion in tournament play (24). Yet after an undoubtedly grim start for humanity, Kasparov proved a resilient opponent, drawing the third and fourth games, while outright winning the second, fifth, and sixth, finally achieving a score of four against two in Kasparov's favor. After the match, the victor remarked of Deep Blue that, "I could feel—I could smell—a new kind of intelligence across the table.. Although I think I did see some signs of intelligence, it's a weird kind, an inefficient, inflexible kind that makes me think I have a few years left" (25). Public interest would not be satisfied with letting matters stand, and another confrontation between the machine and the champion was set for 1997.

Played in New York City at the Equitable Center, IBM's revenge match in 1997 was fought out "with cameras running, press in attendance and millions watching the outcome" and called the "most spectacular chess event in history" (16, 26). Deep Blue, operating on 480 processors (versus a mere 216 a year prior) (15), had been vastly improved since its last encounter with the human world champion with Kasparov admitting that he was "afraid of the machine" (26). Six games were again played between man and machine in "a small television studio. The audience watched the match on television screens in a basement theater in the building, several floors below where the match was actually held" (16). This time, the computer emerged with two victories, Kasparov with one, and both with three drawn games. The victory represented the culmination of a three-centuries-old idea: that a computer could be made to play chess skillfully. In a legacy began with von Kempelen's The Turk and in a concept refined by Shannon and in an unrivaled implementation by Campbell and Hsu, Deep Blue had shown that computers were capable of making informed decisions in games involving strategy, forethought, and deep complexity. Today, Deep Blue sits silently in the Smithsonian Museum, continuing to inspire and awe as the machine that defeated the world champion (27). Meanwhile, computer chess programs that play as competently as Deep Blue, and in some instances even better, can be downloaded from the internet and played on a modern laptop computer.

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