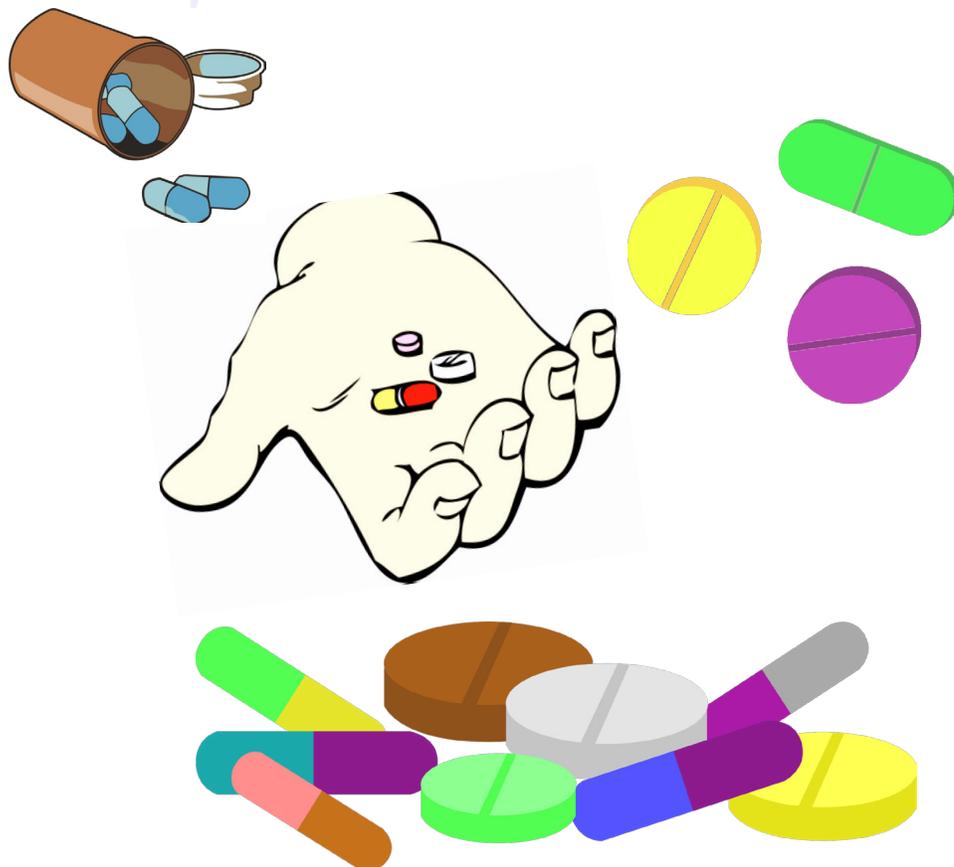




Natural Selections

A NEWSLETTER OF THE ROCKEFELLER UNIVERSITY COMMUNITY



The price of mistakes in clinical trials

GUADALUPE ASTORGA

Last January 11, a human clinical trial in phase I caused brain death in one healthy volunteer, while five others were hospitalized. Unfortunately, this is not the only case where healthy volunteers have died or been severely affected.

The molecule (BIA 10-2474) produced by the pharmaceutical company Bial, is an inhibitor of the fatty acid amide hydrolase (FAAH), an enzyme that catabolizes bioactive lipids, including the endocannabinoid anandamide. The drug was developed as a therapy for anxiety and motor disorders associated with Parkinson's disease, as well as chronic pain in people with cancer and other conditions. Other pharmaceutical companies have previously performed clinical trials to test the analgesic effect of other FAAH inhibitors with no signs of

toxicity. However, these studies ended in phase II due to lack of drug effectiveness. Remarkably, the affinity of the inhibitor tested by Pfizer was 14,000 times higher than that of BIA 10-2474. This implies that the specificity of BIA 10-2474 to inhibit the FAAH enzyme is very low. Moreover, the molecular structure of BIA 10-2474 includes a highly reactive imidazole aromatic ring that can bind to other brain enzymes, including 200 other hydrolases with similar structure and whose activity is far from being understood. The investigation, led by the French National Agency for Medicines and Health Products Safety (ANSM), has also shed light on a series of irregularities that occurred during the

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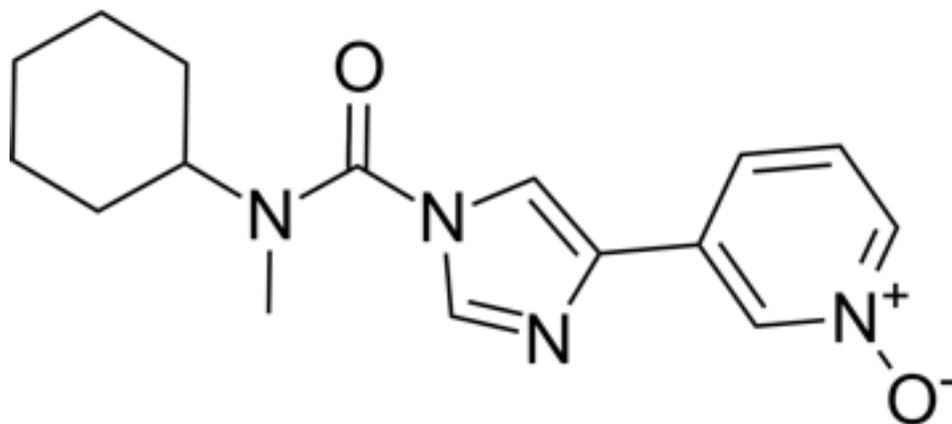
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Structure of Bial's BIA-10-2474 as described in their Clinical Study Protocol N° BIA-102474-101. Referred to as Compound A in US patent # 20130123493 A1

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preclinical trials and were kept secret by Bial, as part of trade secrets. Conceivably the most serious among these is that according to the chemical structure of BIA 10-2474, it is most likely to be an irreversible inhibitor to other hydrolases, rather than reversible as the company claims. This implies that even very small concentrations of the drug can irreversibly inhibit, not only the activity of the FAAH enzyme, but also the 200 other hydrolases present in the human brain. Considering this crucial information, it is inconceivable to understand how the trial design could comprise consecutive administrations of high doses of the inhibitor. This piece of evidence seems to be clearly related to the brain damage induced by the drug, as the severely injured volunteers were those who received only the highest doses of the drug. From sixteen groups of eight volunteers administered with increasing doses of BIA 10-2474, only five people were hospitalized after receiving repeated doses of 50 mg (almost the highest tested concentration). According to the ANSM report, this concentration is 10 to 40 times higher than that required to completely inhibit the FAAH enzyme. Indeed, extrapolation of the data taken in animals to humans, suggests that complete inhibition of FAAH is achieved with doses 20 to 80 times smaller than the maximal dose planned to be tested in humans (100mg). Furthermore, even after the first person was hospitalized, the other 5 still received

one more dose the next day. The Report of the ANSM states that the mechanism of toxicity of BIA 10-2474 is clearly beyond FAAH inhibition and evidence of this subject needs to be presented by Bial Laboratory in future months.

Another critical piece of information that was kept secret by Bial is the number of animal deaths (including dogs and primates) during the preclinical trial. How could the drug be considered safe and approved to be tested in humans, if closely related animals died? Had the volunteers known this information, would they have taken the risk to test the drug?

Trade secrets can seriously block access to critical information obtained during preclinical trials performed in animals by pharmaceutical companies. It is astonishing that even scientists and institutions involved in the evaluation and approval of these dossiers cannot have access to some of the information. As a result, it is not surprising that important details are omitted by the pharmaceutical companies in order to start a clinical trial in humans.

In 2006, six healthy volunteers almost died during the clinical trial of the TGN1412 antibody. It was developed by the German company TeGenero to activate the immune system's T cells. A few minutes after the drug infusion, all the volunteers suffered severe cytokine release syndrome leading to severe inflammation. In this case, the clinical trial went wrong because the drug tested in animals during preclinical trials showed strikingly different pharmacological properties when ad-

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ministered to humans. TeGenero omitted key differences between the amino acid sequence of the antibody receptor present in the animal model that was used during the preclinical trials (monkeys) and in the human sequence. These differences are crucial to predict how strongly TGN1412 would bind to the receptor in humans compared to the monkey cells. This was actually critical for the observed reaction in humans.

In 1993, five human volunteers died while two others required liver transplantation to survive during a clinical trial conducted by the National Institutes of Health. During the 13th week of administration of Fialuridine, a thymidine analog developed for its antiviral activity against the Hepatitis B virus, the drug induced severe hepatic toxicity and lactic acidosis. In this case, the preclinical trial performed in animals did not last long enough to assess the toxicity that was observed in humans only after the week 12th of drug administration.

Transparent and complete access to all scientific evidence and data is crucial to perform efficient evaluation of preclinical trials and further approval for drug tests in humans. Trade secrets in pharmaceutical companies have been shown to be extremely dangerous and represent a threat to human life in clinical trials. Rigorous legislation would guarantee complete data accessibility from experts evaluating the research done during all preclinical trials to protect the life of healthy volunteers in later phases of the trials. ■

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

Part XIX: Günter Blobel, 1999 Prize in Physiology or Medicine

JOSEPH LUNA

Let's start with a fantastical scene: picture a band of Neolithic humans in a hot air balloon overlooking modern New York City. What would they see and experience? Lacking a vocabulary and a mental model of twenty-first century life, our ancient friends would be awestruck at seeing minuscule specks and strangely ordered structures, lines and squares, in green and gray. Perhaps the occasional yellow rectangle from which specks would enter and exit would catch their attention. Or they might ponder a box with flashing lights, speeding its way across a grid. It's near impossible to imagine being in their shoes, but it's easy to envision the excitement as they try to describe and make sense of what they saw.

This totally novel experience wasn't far off from what early cell biologists encountered, as they used the electron microscope (EM) as a sort of hot-air balloon to discover the cities inside cells. By the mid-1960s, they had plotted the geography of all sorts of cellular worlds, had given names to energy-making blobs and recycling vesicles, and with the help of radioactive amino acid labeling, had a basic sense of where proteins were made and where they ended up. But big questions remained such as how did a protein know where it needed to go? For a discipline built on EM observations from high above, this was a challenging question to answer, but it captivated a young German post-doc enough to dream as if he landed his hot air balloon and walked among molecules, where the view was much clearer.

Günter Blobel arrived in George Palade's laboratory in 1967, shortly after completing his PhD at the University of Wisconsin at Madison. He joined a dynamic group of researchers who had stumbled upon an odd observation concerning the protein factories of the cell, its ribosomes: proteins destined to remain inside the cell were often made from a pool of freely cytoplasmic ribosomes, whereas proteins meant to be exported from the cell quickly associated with ribosomes attached to the endoplasmic reticulum (ER). How a new protein made this decision to stay in the cytoplasm or go to the ER was a mystery.

Within a few years, and overwhelmingly without much evidence, Blobel and a colleague (and Rockefeller University alum) named David Sabatini formulated what became known as "the signal hypothesis" that might explain how proteins got sorted to

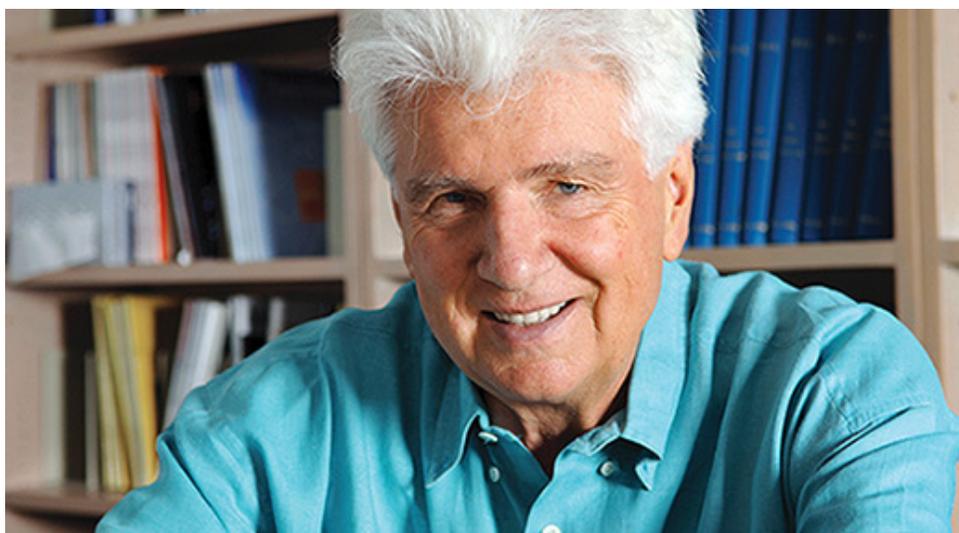


Photo courtesy of the Rockefeller University

their proper locations. It represented a truly imaginative and startlingly precise leap, as if one could envision a five digit postal code and a stamp authentication system simply by watching mail trucks from space. Blobel and Sabatini proposed that ER destined proteins contained a special stretch of amino acids that acted like a signal that became apparent the moment the protein was being made at a ribosome. This signal sequence, located at the head of a protein, would be recognized by a factor (or factors) that would, in turn guide the synthesizing ribosome to the ER, where the protein in question could finish being born as it *translocated* across the ER membrane. Once properly sorted into the ER, the signal sequence was no longer needed and could be removed by an enzyme, even while the protein was still being made. Once finished, the protein could then go and do its job.

For many, this all sounded needlessly baroque. One attractive alternative was to consider different types of ribosomes, where each type was responsible for ferrying a nascent protein to a particular location. Another idea postulated that the mRNAs encoding proteins somehow got to the correct place before undergoing translation from any nearby ribosome. The signal hypothesis was one of many possible models, and a far-fetched one at that. But it made very precise predictions that could be tested, the first of which was the existence of a transient signal sequence.

Myeloma cells provided the first toe-hold for testing the signal hypotheses, since they secreted lots of IgG antibody light chains that could be readily detected. Using cell-free translation systems, based on these cells, oth-

er laboratories had observed slightly heftier IgG molecules than those secreted from intact cells, suggesting that a larger precursor was made and pruned to a final, smaller form. Yet, worries of an *in vitro* artifact abound. Blobel first repeated this experiment, and once confirmed, tinkered with his cell free system to uncover the order of events. Using detergent, he separated ribosomes from bits of ER (called microsomes) and added a drug that blocked new IgG production. He then let the ribosomes that had already started making an IgG to finish, keeping track of what they produced and when. Early in the experiment, only the smaller form emerged, which made sense if these ribosomes had already been at the ER and were nearly finished making IgG when Blobel had isolated them. But later in the experiment, a mixture of larger and smaller forms showed up: ribosomes that had just started making IgG indeed made a larger version. But lacking sufficient ER targeting, the signal sequence wasn't pruned efficiently. Blobel had glimpsed a totally new feature in the early lives of proteins.

This was just the start. Over the ensuing years, Blobel and his team devised ways of recapitulating numerous aspects of protein targeting in the cell, from isolating the complex that ferried a signal sequence bearing protein to the ER (the aptly named "signal recognition particle") to later confirming and characterizing the protein channel at the ER (the *translocon*) that nascent proteins traversed for proper processing. In part because of Blobel's efforts, the hot air balloon view gave way to detailed explorations from the ground. A dream, as all good hypotheses are, turned out to be true. ■

The Lowline

AILEEN MARSHALL

Have you heard of the Lowline? No? Well maybe because it doesn't fully exist yet. And no, it's not under the Highline, although its name was inspired by it. It will be an underground park in an abandoned trolley terminal under Delancey Street. The park will use new solar technology to redirect sunlight underground to grow plants and light the park.

The Williamsburg Bridge Trolley Terminal opened in 1908 on Delancey Street. Trolleys went back and forth to Brooklyn across the aforementioned bridge. The station extends three blocks underground from Essex Street to Clinton Street, and has interesting architectural features, such as cobblestones and a 15-foot ceiling. It closed in 1948 and has been sitting empty ever since.

Then in 2009 architect James Ramsey, who used to work at NASA developing optics for satellites, heard about it. He discussed it with his friend Daniel Barasch, a strategist for Google. Ramsey thought he could use fiber optics to collect and redirect sunlight underground to make it into a park. They made a proposal to the city.

Two feasibility studies were started in 2011. One was by HR&A Advisors, a real estate, economic and energy consulting firm. The other was from the engineering firm Arup. Both came up with positive findings, indicating that it would be helpful to the community. Since 2012 the Lowline organization has run a program called Young Designers. They offer educational programs to local schools and other groups, using the lab for lessons in science, technology, engineering and design.

By 2012, the pair had raised \$150,000 on Kickstarter to build a laboratory exhibit of the



Photo Courtesy of Dan Barasch via Kickstarter.com

solar technology that would be used in the Lowline. As of 2015, the Lowline organization has raised \$155,000 to build the park. The exhibit lab uses what Ramsey calls "remote skylights," the technology that would be used in the park. An above-ground parabolic disk collects sunlight, then a concentrator increases the light 30-fold and filters out the hotter rays. Protective tubes send light to a central distribution point via fiber optic cables, then to an aluminum canopy in the lab. That, in turn, reflects the light into the lab. This illuminates the lab and allows the plants to grow. Since it is reflected sunlight, it contains the full spectrum of sunlight, including the wavelengths needed for photosynthesis. Optic technology allows the outdoor disk to follow the sun during the day and maximize the amount of sunlight it collects. Mirror boxes would toggle the light between electric and sunlight to allow for

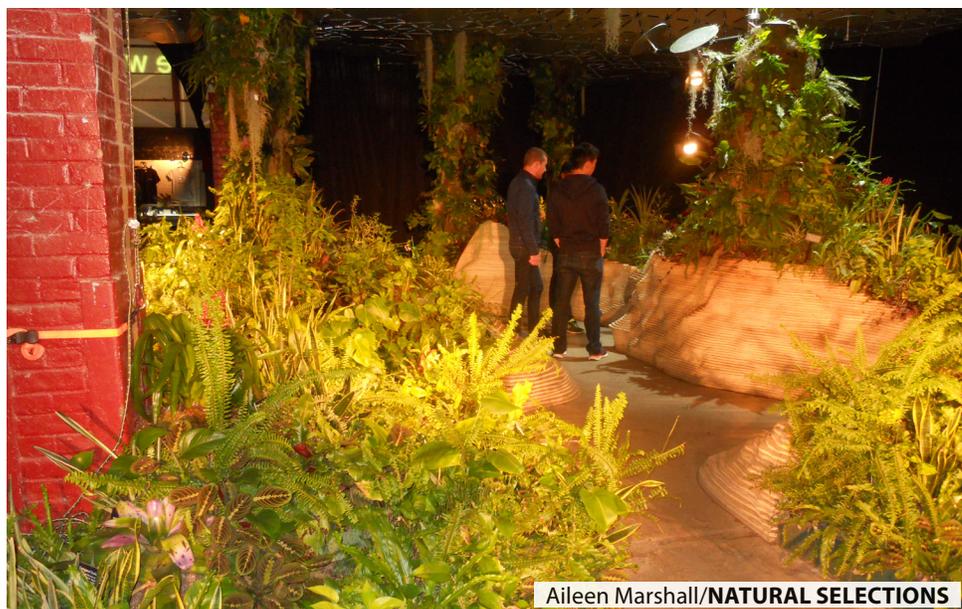
variations, such as cloudy days.

Landscape artists have planted many different species inside the exhibit, such as mosses, lavender, strawberries and hops, all of which continue to grow. Light is measured in foot candles, or fc. The light intensity in a typical office space is about 10fc. Plants need about 700 to 3000 fc to grow. Signe Nielsen, John Mini Distinctive Landscapes, and the Brooklyn Botanic Garden are using the lab to determine which plants grow best. They are looking at temperature, humidity, light, and water as factors. The plan is to grow different plants at different levels of the park based on the amount of light needed.

The Lowline Lab, at 140 Essex Street, opened last October, and will be open on weekends, from 11am to 5pm, until March 2017. It is in the space of the old Essex Street Market, which was built in 1940. The new market is one block south. Admission to the exhibit is free, although there is a suggested donation of \$10. As of this writing, it has had over 50,000 visitors. You can find more information at <http://thelowline.org/>.

When I visited the lab, I found it darker than I expected. However, the plants were very lush and did create a pleasant environment. I would imagine this park would be a nice respite during the very hot summer days.

Manhattan Community Board 3, Assembly Speaker Sheldon Silver and Senator Kristen Gillibrand have endorsed the project. While City Hall has indicated support for the park, it has not yet been officially approved. Ramsey and Barasch are in negotiations to buy the trolley terminal from the Metropolitan Transit Authority. They hope to have the park open by 2020. ■



Aileen Marshall/NATURAL SELECTIONS

Manhattan Spring and Summer Fun

SUSAN RUSSO



Consider these (mostly) FREE events in NYC Parks, many falling between June and October:

At **Bryant Park** (between Fifth and Sixth Avenues, from 40th to 42nd Streets) check out <http://bryantpark.org/> for days and times of events. For adults and kids, there are games to play, such as chess, checkers, mah jongg, and board games, plus active sports, which include petanque (much like bocce or lawn bowling), ping-pong, and a putting green. Under a tent is the outdoor "Reading Room," stocked with books and magazines for all ages. In addition, there's an "Art Cart" in June, August, and September, with free supplies to use and artworks to take home. The park has three restaurants, food stands, and crafts and souvenir shops. There are coffee, pastry and deli shops all along 40th Street. If it's too hot or it rains and the outdoor Reading Room is full, duck into the magnificent main library building, <http://www.nypl.org/locations/schwarzman> (for open hours), which has a very large but comfortable Children's Library (with books, CDs, and DVDs for kids, and seven PC terminals), as well as a beautiful Map Room, a great shop, and a small café. And the youngest ones will thrill to the many, many inviting stairs to climb.

Madison Square Park (between Madison and Fifth Avenues, from 23rd to 26th Street) <http://madisonsquarepark.org/>

In addition to a great playground and a "water wheel," there are concerts, workshops in horticulture, and outdoor art for all ages, and, for kids, story times and "Art in the Park." There is also a large outdoor plaza with tables and seating. Vendors are set up all around the park. (If it rains, I've heard good things about the **Museum of Math** at the north end of the Park (11 East 26th Street) <http://momath.org/>. Their website says it has "a special emphasis on activities for 4th through 8th graders," but it's expensive – free for toddlers, \$9 for children, students, and seniors, and \$15 for adults.)

Besides local parks in Manhattan there are "Art Parks," playgrounds for kids

with works they can climb on:

"The Tom Otterness Playground - Silver Towers" on 42nd Street between 11th and 12th Avenues;

"The Real World" in Rockefeller Park between Chambers and Warren Streets in Lower Manhattan;

"The Imagination Playground" at the South Street Seaport at Berling Slip on John Street between Front and South Streets.

For a reasonable price, at **Hudson River Park Mini Golf** <http://www.manhattanyouth.org/pier-25/mini-golf.aspx> (in Tribeca - "cross at North Moore Street" for Pier 25) you can play eighteen holes - "CASH ONLY" - \$5 for kids under 14, and \$6 for kids 14 and over and adults.

For older kids and adults, there's **Brookfield Place** <http://brookfieldplace.com/> (the old World Trade Center area) at 230 Vesey Street on the Hudson River waterfront, with special events in June and July: concerts, dance programs, an exhibit of inflatable fabric birds (that will fly, they say), games, and nighttime films.

For an evening event, though not in a park, you may want to take the crosstown bus to **Lincoln Center**, at 64th Street and Columbus Avenue, where, at the circular fountain, the Amateur Astronomers Association will have high-power telescopes every Friday and Saturday evening in June and July (weather permitting) for stargazing from 7:00 -11:00pm.

For all ages, there's **Governor's Island**, <https://govisland.com/info> for details. Take a ferry from the Battery Maritime Building (10 South Street). Round-trip ferry tickets are \$2 for adults, \$1 for teens and seniors, kids free. In 10 minutes or so, you'll be on an island that's a massive public park, with food stalls, bike trails (take your own or rent), historic houses, two 1812-era forts, live music events, outdoor and indoor art installations, lawn parties, a "teaching garden", vintage baseball, an archaeology site, and loads of open spaces for playing and relaxation - all for free (except for the ferry and food.) The island is open now through September. ■



Photo Courtesy of the National Museum of Mathematics

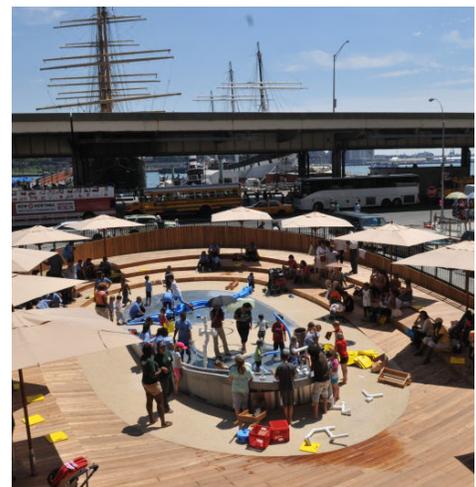


Photo Courtesy of NYC Parks



Photo Courtesy of Amateur Astronomers Association of New York



Culture Corner

Sacred and Profane Images in Venice and Padua

BERNIE LANGS

The laws and edicts are laid out in the Old Testament in exacting terms specifying the ornaments, utensils and measurements for these objects utilized in the holy temple and for the division of spaces designated as sacred from those places for mortals. The biblically assigned priestly caste was left to minister the negotiation between man and God. Only he could physically enter the area behind the curtain or veil beyond the altar separating the congregation from the Holy Spirit.

The Jewish religion prohibits graven images of God, forbidding representational sculptures or paintings of biblical stories and heroes. There are examples of Jewish burial tombs and other remains that had been decorated with the symbols for rituals and life in the ancient world that were later mutilated or chiseled away by disapproving rabbis as a reminder of these edicts. Early Christian images, after co-opting ideas from those previously of service to ancient Roman and Greek gods or from secular life, accelerated into the early medieval time with flourishes of astound-

ing profundity and beauty. Lives were lost over the iconoclast notion that to pictorially represent Christ and the Holy Spirit was a dangerous trespass on the immaculate and omniscient ideal since no picture could or should imitate or approximate the Divine.

At the culmination of the middle ages and into the early and High Renaissance there was no holding back the master illuminators, sculptors and painters in Italy and in the northern areas of Europe. Great religious art peters out by the mid-seventeenth century at which time there was no longer room for innovation and the power that such images had previously attained was lost.

Today we live in a time of hyper self-awareness. As many people abandon notions of a God who is aware of mankind's actions and is capable of direct intervention in human affairs, there remains a void to be filled for a higher purpose in life. From some perspectives, a desirable end of ritualistic and avid dogmatic doctrine might relieve a great deal of worldly

tensions since fanatics and zealots hold strong so-called inspired revelations. Equally profound and illuminating might be a more objective and scientific study of those in the past who, in the written word or through the plastic arts, drew inspiration on the notions and ideas of their times of what was holy and greater than human endeavor. Some might find interest in a religion that reluctantly winks at the thought of a Primary Mover and nothing else, yet still finds fascination in what was revealed by others who had taken a different, mystical path as they groped for understanding a higher purpose.

I was recently in the ethereal city of Venice and found time to visit Padua on a day trip. I decided that I did not need sanctioned Priest to lift the veil of bygone mystery, since such an idea is metaphoric at best. To see Titian's painting *The Assumption of the Virgin* above the altar where it has hovered for hundreds of years was but one example of sublime mo-

CONTINUED TO P.6



CONTINUED FROM P.5

ments of unreal vision. Mary rises towards the heavens and Titian's notion of what that entails is open to all interpretations. Below the earth-bound, beautifully rendered crowd of Apostles move and dance in graceful wonder.

Tintoretto's many paintings from the 1500s in the Scuola di San Rocco also left me in awe and breathless. There are dozens of massive works on the walls and two ceilings of the gallery giving the eye multiple places to look as one sways in blissful dizziness. The apex is found in a large side room with an entire wall depicting a massive scene of the Crucifixion, which I experienced as a series of planar rectangles bouncing and folding out in various impossible directions and dimensions. The elegantly painted blues and reds, and the soft palate of the master leaves one knowing that mankind is capable of the most subtle ideas of beauty and grace.

In Padua, I was treated to viewing the rare fine wine of fourteenth century frescos in the Basilica of Saint Anthony, the Oratorio di San Giorgio, and the Arena

Chapel. I stood in the large chapel of the Oratorio with just two other amazed tourists and took in the wall painting rendered by pupils of the greatest Early Renaissance master, Giotto. At the Arena Chapel frescoed by Giotto, I can hardly describe the aura of sublime artistic wonder that the master evokes, especially in his wall sized depiction of *The Last Judgment*. Giotto's achievement is the height of both technical and mystical genius. The art pops off the walls at the viewer and there is much to feast on for soulful edification. Giotto helped usher in humanism and the Renaissance spirit and his paintings gave the world a quantum leap in depicting spiritual ideas and human and so-called divine emotions. By the time Veronese, Bellini, Carpaccio, Tintoretto and Titian were painting in Venice two hundred years later, their figures displayed the most subtle of physical characteristics and in the expressions of their men, women, saints, and ancient gods, one can sense the very ideas stirring within them.

Titian is again found in the main museum of Venice, L'Accademia. In his late painting on the meditation of the dead

Christ, he is found in self-portrait as Saint Jerome who gently holds the hand of the impressionistically rendered avatar. I wondered if Titian is almost pleading for spiritual guidance as he ponders his own impending demise. One leaves the museum viewing Titian's wall-sized depiction of *The Presentation of the Virgin* where Mary rises up a stone stairway towards the Temple where an imposing bearded priest awaits.

The problem with lifting the allegorical veil to study the mindset of the mystic painters of the wild Freudian Id is that it is at times not easy to close the door again from the rush of ideas and possibilities. And I awoke in my bed in the hotel just outside Venice, half awake, half asleep, and I gently swayed as if sailing on a canal and from the corner of my eye I could see high above the spiritual cauldron of yore and of Idea, generating the cloud images offered by the imaginations of those who'd come before. As I returned to slumber, I imagined I could hear a gentle and profound word or two of encouragement and perhaps approval uttered by the Conscript Fathers or maybe even by the spirit of the Doges and his Magistrates themselves. ■

56-Downed-Up Charges

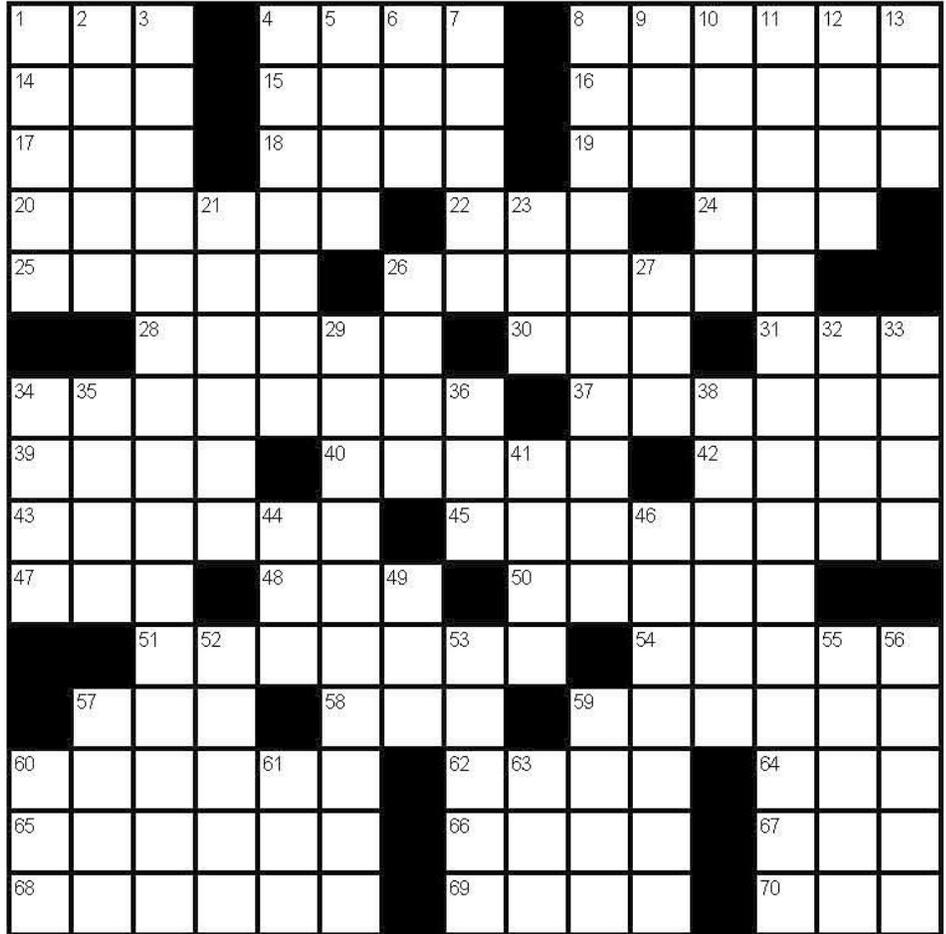
GEORGE BARANY,
CHRISTOPHER ADAMS,
MARTIN HERBACH, AND
ALEX VRATSANOS



Across

1. Jeanne d'Arc, e.g.: Abbr.
4. Number of freedoms, to FDR
8. Mexican motel (and one-time Yankee catcher Jorge)
14. Punching tool
15. Recommend emphatically, as money to fight Zika
16. Beat Murdoch at his own game?
17. My follower in 1968?
18. Genuine, in Germany
19. Homophone for homophobe "Lyn' Ted"
20. Hungarian short-haired dog
22. Narrow waterway
24. Metric weights: Abbr.
25. Live, as an interview
26. Self-important bureaucrat from "The Mikado"
28. Senator Sherrod (since 2007) or Scott (who lost to 3-Down in 2012)
30. Hide-hair connection
31. Disapproving sound
34. Goes too far
37. One-under bridge, in the Pledge of Allegiance
39. Staff member?
40. Turkish name that means "desire"
42. One-named Irish Grammy winner
43. Goddess with a spear and a national capital named for her
45. Seaweed product with a reduplicative name
47. Like FDR's Deal
48. ___-cone
50. Minuteman Davis, memorialized through an iconic French sculpture
51. Sarah Palin, e.g.
54. Apple's instant messaging software
57. Historic introduction?
58. Hit CBS procedural with three spinoffs
59. Star in Aquila
60. Mexican beer brand
62. Harmony, so to speak
64. Sch. in Monroe whose alumni include Bubby Brister, Tim McGraw, and Ben Sheets (anagram of NUL)
65. First game
66. "___ Smile Be Your Umbrella"
67. Highgate (London) or Père-Lachaise (Paris): Abbr.
68. With 56-Down, 3-Down's Twitter antagonist
69. Decorative pitcher
70. Clairvoyance, e.g.

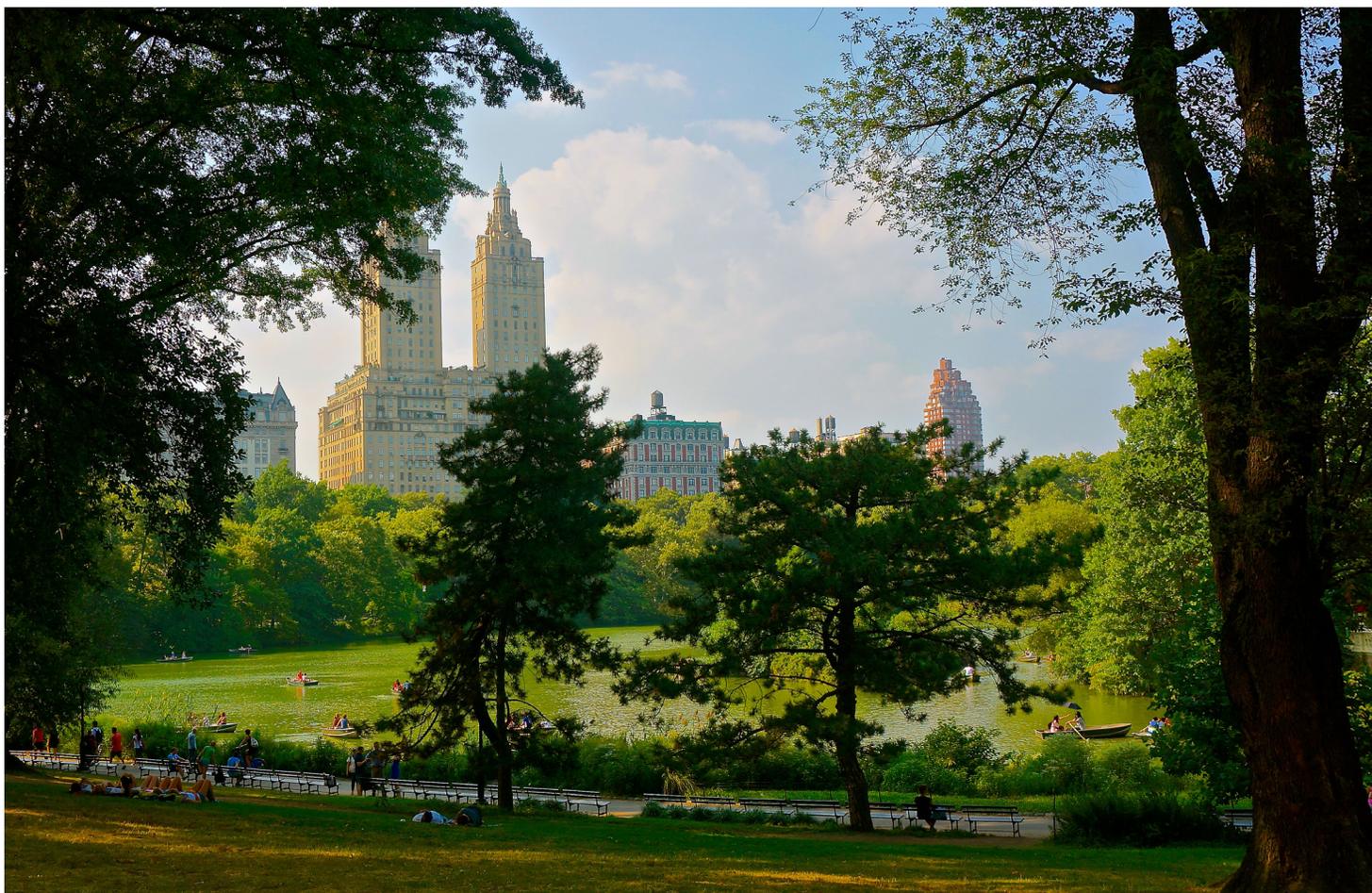
George Barany is a Rockefeller alum (1977) currently on the Chemistry faculty of the University of Minnesota-Twin Cities. Christopher Adams is a graduate student in mathematics at the University of Iowa, Martin Herbach is a retired computer scientist living in Silicon Valley, and Alex Vratsanos is studying business and psychology at Kutztown University in Pennsylvania. For more information, including a link to the answer, visit [here](#). More Barany and Friends crosswords can be found [here](#).



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Down

1. Blast, perhaps via Twitter
2. He wrote "... get your facts first, then you can distort them as much as you please"
3. Senator who admonished 68-Across/56-Down to "... fling as much mud as you want ... your words and actions disqualify you from being President & I won't stop saying it"
4. Nuclear reactor component
5. Marine killer
6. "That's disgusting!"
7. So out it's in
8. 3-Down, as per a tweet from 68-Across/56-Down
9. "Now is the winter of ___ discontent ..."
10. Luftwaffe bomber
11. "Potent mix of memoir and policy" (2014) by 3-Down
12. Sleep, to Brits
13. Green Knight's weapon, in "Sir Gawain and the Green Knight"
21. Emphatic follow-up to yes or no
23. ___ thruster (propulsion technology NASA has their eye on)
26. Produit de Michelin
27. Bosom buddy?
29. It's played by 3-Down, as per a tweet from 68-Across/56-Down
32. Bean used to make miso
33. Tree knot
34. Dorothy Parker's parrot, so named because he spilled his seed upon the ground
35. Activity slated for November 8, 2016
36. Mrs., in Madrid
38. It led to a party in Boston
41. Opposed, in Dogpatch
44. Govt. grp. that once subcontracted work to Edward Snowden
46. Train component
49. Authorizes
52. "Queen of Mean" Helmsley
53. Congressional divide
55. Megyn Kelly's boss Roger (anagram of 53-Down)
56. See 68-Across and this puzzle's title
57. Cops, slangily
59. Pay to play
60. New England seafood staple
61. "___ Blu, Dipinto di Blu"
63. Taxol source



QUOTABLE QUOTE

“It is to be a school of Political Prophets I Suppose -- a Nursery of American Statesmen...I am making of it annual, for Sending an entire new set every year, that all the principal genius’s may go to the University in Rotation -- that we may have Politicians in Plenty. Our great Complaint is the scarcity of Men fit to govern Such mighty Interests, as we are clashing in the present Contest -- a scarcity indeed! For who is Sufficient for these Things? ...You and I have too many Cares and occupations and therefore We must recommend it to Mrs Warren and her Friend Mrs Adams to teach our Sons the divine Science of the Politicks: And to be frank, I suspect that they understand it better than we.”

John Adams.
-John Adams, who had been appointed to serve as a delegate to the First Continental Congress, in a letter to James Warren, a legislator in the Massachusetts General Court, who was also to serve (June 25, 1774).

Natural Selections wants your ART!

Whether you can't stop drawing while waiting for the bus, or taking a walk around the city; if photography is your passion, or if you're more of a painter, this is your chance to share your art.

Beginning in 2016, Natural Selections will publish a picture of the art we receive every month. To take advantage of this opportunity, email us your work with a title, a brief description, and your name. We'll make sure to include it in a future issue. We hope to receive several images to create an open space for art!

We'll be delighted to receive your artwork, please email hi-res image or vector files to:

nseditors@rockefeller.edu



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Life on a Roll

Musical Fountains Show in Versailles

ELODIE PAUWELS



Imagine the magnificent Palace of Versailles under a clear blue sky. Imagine spring has just sprung. Imagine strolling in that environment, going from one statue to a pond, then turning left to discover

a mysterious alley. Suddenly, as if by magic, classic music is played, and water is turned on at each fountain in the vicinity of the Palace. Welcome to the musical fountains show, every weekend afternoon

from Spring to Fall! Here is my favorite: the Apollo fountain, representing Apollo on his chariot. More pictures are available on my photo blog:

<http://elodiephoto.wordpress.com/> ■



Photos by ELODIE PAUWELS