

# S&T

A newsletter on research, teaching, management, policy-making and leadership in **Science & Technology**

Bryn Mawr College October 2007 [www.brynmawr.edu/sandt](http://www.brynmawr.edu/sandt)

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## Biostatistics: Science by the Numbers

BY DOROTHY WRIGHT



Heidi Christ-Schmidt '91

As a reporting biostatistician to an independent data monitoring committee for a clinical trial, **Heidi Christ-Schmidt '91** was responsible for summarizing interim safety and efficacy data for the committee in written reports and answering questions during their meetings. Sponsored by the biotechnology company, Genentech, the clinical trial aimed to show that administration of its drug, Avastin (*bevacizumab*), to patients with metastatic colorectal cancer would reduce mortality. The data monitoring committee (DMC) was composed of four members — three clinicians and one biostatistician — who were independent of Genentech. As part of the U.S. Food and Drug Administration's (FDA) clinical trial process, the committee was responsible for reviewing real-time safety data, selecting the experimental arm of the trial at an interim analysis, and assessing efficacy at a second interim analysis.

"My challenge was to present the interim trial data succinctly and accurately so that the DMC could make the appropriate decisions at

each meeting," recalls Christ-Schmidt, a biostatistician with Statistics Collaborative, Inc. (SCI), Washington, D.C., a biostatistical consulting firm serving pharmaceutical and biotech companies and government clients.

At any one of their reviews, the committee could have recommended stopping the study if safety data indicated that patients were being exposed to a potentially harmful treatment. Genentech remained blind to any information by the treatment arm during the course of the clinical trial. The trial, which proceeded to its planned end, showed that the risk of death in the treatment group was about two-thirds that of the risk in the control group. The probability that the difference in mortality would have occurred by chance if the drug treatment were ineffective was less than one out of 1,000.

"On the basis of this study, the FDA approved Avastin for patients with metastatic colon cancer," Christ-Schmidt says.

The term "biometrics" (often used interchangeably with biostatistics) has been used since early in the 20th century to refer to the application of

(Continued on page 11)

Google Search

for

# “Work Life Balance”

BY THOMAS W. DURSO

**G**oogle didn't become Google overnight; its journey from small niche start-up to public online empire was incremental. From its beginnings in 1998 as a no-frills search engine with a unique twist — returning the most relevant results by analyzing the links on Web pages — the company gradually developed its own new products and services and acquired those of other companies until it became arguably the world's widest-known e-brand, with a current market capitalization of \$156 billion.

Similarly, **Angela T. Lee '89** took her time trying on different roles as she found her way to what she calls her dream job. Lee is an international product manager at Google, and has been responsible for introducing the company's most recognizable products and services in dozens of countries around the globe. Along the way there were career changes and industry changes and life changes, all of which, Lee says, were instrumental in leading her to where she is now.

“You can't take one big step to land at your ultimate vision,” she says. “You have to change yourself little by little.”

That final vision began half a world away, in Japan, where Lee was raised by her Chinese parents. She developed an affinity for mathematics and science, and came to the United States to attend Bryn Mawr as a physics major. A summer job in the microfabrication lab at the University of Pennsylvania led to a career insight that she calls “a life-changing moment.”

“I still remember the excitement I had when I saw my first transistor work,” Lee recalls. “It was an amazing thrill. I said, ‘This is it. I'm going to be an electrical engineer.’”

Lee had been accepted into the College's 3-2 Program in Engineering and Applied Science, a partnership with the California Institute of Technology. After three years at Bryn Mawr she studied for two years at CalTech, and graduated with a bachelor's in physics from the College and a bachelor's in electrical engineering from Caltech. Lee earned a master's at the University of California, Berkeley, and accepted a position at Applied Materials in Santa Clara, Calif., to engineer flat-panel displays.

## FROM MOM TO DOT-COM

When she became pregnant with her first child, Lee shifted from engineering to marketing at Applied Materials, to avoid exposure to chemicals used in the manufacturing process. When her daughter turned two, she put her career on hold for a year-and-a-half to become a stay-at-home mother.

“I found out that I loved being a mom, but not so much that I wanted to stay home all the time,” Lee says. “I have high respect for stay-at-home moms, but I personally felt I was not getting everything done that I wanted.”

Living in Silicon Valley at the start of the Internet boom, Lee decided to join a dot-com firm. She found it difficult to get a job without experience in the field until a friend who had launched an online start-up brought her on board in a marketing capacity. The company went under in six months, but now that Lee had a foot in the industry's door she soon landed at another start-up, this time doing product management. That

*Tom Durso writes about science, health care and business for a variety of publications, including the Philadelphia Business Journal and Family Business magazine.*



company's bubble also burst, and she joined another start-up, an online business-to-business venture.

Her new job had an international dimension that Lee had coveted; she was helping the company enter the British, French and Japanese markets. Once again funding dried up, but no matter — Lee had, finally, after all of those smaller steps, found the job that came closest to her ultimate career vision.

#### DREAM JOB

"It took three hops to get where I wanted to get," she says. "By then I was ready to identify the company I wanted to work for. That's how I found Google. If I had tried to knock on Google's door straight from my job at Applied Materials, there's no way Google would have talked to me."

Google hired Lee in 2001 as its first international product manager. Over the last six years she has played a pivotal role in bringing the company's ever-expanding suite of online products and services to a multitude of international audiences — in Japan as well as China, France, Brazil, and more than 40 other countries.

"International software is not just about translating words," Lee says. "It's about understanding how people in different countries think and work. They have their own workflow and business logic, and that varies from country to country. It's very important for businesses entering foreign markets to understand these variations, if they are to succeed."

Two years ago Lee, with her husband and two daughters, relocated to Japan to launch Google's product management team there. She returned to California this summer and is taking a leave of absence to recharge her batteries and decide how best to balance career and family demands. Ideally she hopes to find a way both to remain at Google and to spend more time with her children, who are approaching ages that typically feature "changes and challenging times."

"I'm going to take a step back and think about what I want to do with my life," she says, then quickly emphasizes, "And I don't limit that to my career. It's my *life*."

# MANAGEMENT

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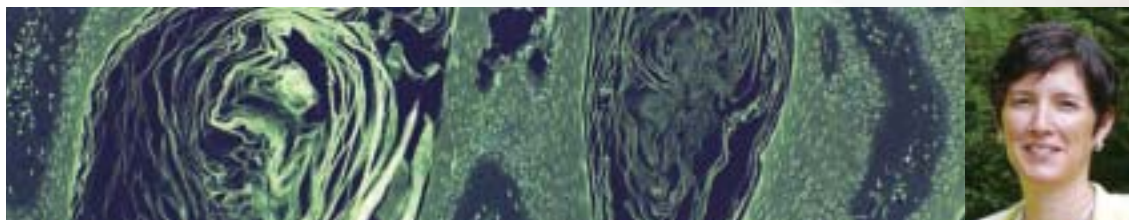


Angela T. Lee '89

## AT THE INTERSECTION OF

# Need, Science and

BY THOMAS W. DURSO



Barbara Fox '78

**T**he restlessness that marked the academic career **Barbara Fox '78** believed she was destined for was not a sign of “a short attention span,” as she originally thought. Instead, it was a growing desire to be an entrepreneur — to start up new companies rather than join established academic programs, and to pursue applied drug discovery instead of advancing basic research. That desire ultimately led Fox to leave the academy for industry.

“My father still says, ‘I can’t believe I have a daughter who reads the *Wall Street Journal*,’” she says.

### STARTING OUT

After earning her bachelor’s in chemistry from Bryn Mawr, Fox embarked upon what she assumed would be a decades-long march through academia — doctorate, post-doctoral fellowship, faculty appointment, teaching, research, publishing, tenure, more teaching, research and publishing. After working as a lab technician at Rockefeller University, Fox moved on to the Massachusetts Institute of Technology, where she earned a Ph.D. in biochemistry in 1983.

“But I decided early on that I didn’t want to dedicate my life and career to doing bio-organic chemistry,” Fox recalls. “I just didn’t have enough interest to fully appreciate the wonders of enzymes and make an impact in the field. I was looking for something with a broader application.”

To widen her horizons, Fox accepted a postdoctoral fellowship in cellular immunology at the National Institutes of Health. In her four years at NIH, she “learned a lot of biology really fast.” She joined the faculty at the University of Maryland School of Medicine in 1987 and rose to the rank of associate professor. For seven years Fox worked her way up the ladder, earning tenure and landing grants.

Yet she realized she still did not especially enjoy what she was doing.

“I didn’t take to academic science. I didn’t like the grant pressures, and I didn’t think I was doing anything particularly important,” Fox says. “When I was approached by a recruiter to consider a private-sector job in the Boston area, I jumped at it.”

### STARTING UP

That opportunity was at ImmuLogic Pharmaceutical Corp., a Massachusetts biotech firm that was exploring immunology-based drug therapies. In 1993 Fox came aboard as senior scientist, and was rapidly promoted to vice president of discovery research.

“After leaving academia, I discovered that one can do all sorts of different things and have the freedom to move in all sorts of different directions,” she says. “I had a better personality fit with industry. I like applied science — and the challenge of figuring out how to translate basic science into a useful, marketable product. I love the breadth of responsibilities you take on and the new skills you learn. You’re not tied to the preliminary data you’ve generated for 15 years. You can jump into new areas.”

Five years after Fox joined ImmuLogic, the firm’s lead programs in allergy ran into problems and the company foundered. Instead of returning to the relative security of academia, Fox made the bold choice to leverage the business knowledge she acquired at ImmuLogic to start up her own company, despite “total naiveté of how hard that that could be!” She founded Addiction Therapies in 1998 (later renamed Recovery Pharmaceuticals) and assumed the roles of president and chief scientific officer. But after five years, funding dried up, and her first venture failed.

# Market

"I like applied science — and the challenge of figuring out how to translate basic science into a useful, marketable product. I love the breadth of responsibilities you take on and the new skills you learn. You're not tied to the preliminary data you've generated for 15 years. You can jump into new areas."

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Fox then started working with Oxford BioScience Partners, a Boston firm that provides venture capital and management assistance to emerging life sciences companies, where she evaluated investment opportunities. She also was a corporate development consultant at Ensemble Discovery Corp., a Cambridge, Mass., firm that develops novel classes of therapeutics and bioassays. With a solid grounding in venture-capital funding and corporate development, Fox was better prepared to once again start up her own company.

## **STARTING OVER**

In 2005 Fox launched Avaxia Biologics, an antibody company ("I'm going back to my immunology roots," she says) still in its very early stages. Avaxia is applying for funding and building its staff, and the uncertainty surrounding its future is not something that bothers Fox in the least as chief executive officer.

"You have to be totally optimistic whether you can get it to work," she says, "but it's still up in the air whether we can pull it off — which is the state I love the most."

Fox started Avaxia with the aim of developing influenza therapeutics, but found that there was little venture-capital interest in that business model. So she has switched the firm's focus to treatments for gastrointestinal diseases — in particular celiac disease, an autoimmune disorder of the small bowel that interferes with the absorption of nutrients from food, which afflicts an estimated 1 in 130 people in the United States. She's continuing to pursue leads on flu grants, but the GI focus allows her to combine market interest, technology and science in a way that addresses a medical condition in need of treatment.

"It's not just market-driven," Fox says. "There's a need. It's not like making drugs for male-pattern baldness, which I'm sure some people consider a real need. I'm very gratified to be working on celiac disease. If you can find the intersection between where there's a need, where there's good science and where there's a market, then you have the opportunity to create something worthwhile."

# ENTREPRENEURSHIP

# How Oats, Peas, Beans + Bar

BY DOROTHY WRIGHT

**W**hereas most people strolling through a field of sweet clover in summer hear only the hum of honeybees and rustling of tender leaves in the breeze, **Valerie Oke '88** also is aware of an intimate conversation between the legume and the nitrogen-fixing bacterium, *Sinorhizobium meliloti*.

Oke, a biology professor at the University of Pittsburgh, studies the transformation of *S. meliloti* cells from vegetative bacteria into bacteroids in nodules on the roots of legumes, such as alfalfa and several species of sweet clover. Bacteroids are a distinct cell type that fixes atmospheric nitrogen into ammonia, which provides a usable form of nitrogen for plants. In this symbiotic relationship, the plant is able to survive in nitrogen-poor soil, and the plant provides nutrients to the bacteria.

Because this is a species-specific relationship, the partners must first introduce themselves. The plant exudes compounds from its roots, which identifies its species to the bacteria in the soil. When *Rhizobium* bacteria recognize those compounds, they produce “Nod factor,” which identifies them to the plant. If the plant recognizes the bacteria as the right species, it forms nodules on its roots.

“We already knew about this conversation,” Oke says, “but there are probably a lot of other molecular signals going back and forth because it is an incredibly intimate interaction.”

Once the bacteria have infected the root nodules, they differentiate into bacteroids in “a process that involves an alteration of cell fate, presumably with an underlying developmental pathway,” Oke says.

## GENE EXPRESSION

Oke’s lab uses a molecular genetic approach to identify and characterize the bacterial genes involved in the bacteria’s infection of the nodule and its subsequent differentiation into bacteroids. “We are characterizing the roles of these genes during symbiosis by studying the functions of the gene products, testing for host-specific defects, and using genetic screens to identify the regulatory circuits that control gene expression during bacteroid formation,” she says.

Oke says she knew she wanted to be a biologist from the age of 16, as an international baccalaureate student at Armand Hammer World College in Montezuma, N.M., where she wrote an extended essay about oncogenes. “I read my first few ‘real’ journal articles,” she recalls, “and I got all fired up about biology.”

At Bryn Mawr, Oke concentrated on molecular and cell biology, working with a Haverford College biologist, Kaye Edwards, on development in the worm, *Caenorhabditis elegans*. As a graduate student in cellular and developmental biology at Harvard University, she worked in a microbiology lab, where, Oke says, “I fell in love with microbiology.” In 1997 she completed a National Science Foundation postdoctoral fellowship in plant biology at Stanford University. She joined Pitt’s Department of Biological Studies in 2000.

## STRESS RESPONSE

The *Rhizobium*-legume relationship is usually described as a mutually beneficial symbiosis. “From the plant point of view, that is really obvious,” Oke says, “because it interacts with this bacterium that directly provides it with nitrogen. From the bacterial point of view, it is less clear whether or not it is definitely beneficial. After entering the root nodule, the bacteria are trapped there until the plant degrades the soil, and many of them die.”

Oke’s research points to bacterial stress responses as a key to their survival in the root nodule. “We are studying how the bacterial cells live within a plant and identifying the challenges for them,” she says. “I am fascinated by genes and regulatory circuits — which groups of genes are turning on to enable the bacteria to survive there?” Her research into *S. meliloti*’s RpoH protein-mediated stress response has implications for understanding the stress responses of bacteria in general.

# PLANT BIOLOGY

# ley Grow

However, Oke observes, “Money is tight in basic lines of research. Over the long term, that is a problem for our country because pure research can lead to a breakthrough that nobody could have predicted.”

Today, Oke says, it is particularly difficult for a junior faculty member to generate the steady stream of grants that is essential to maintaining a basic research lab. “Even senior people who have never had trouble with funding are losing grants,” she says. “People submit really good proposals, and they don’t get funded. They have to submit them again, and again. And what gets rewarded is persistence. Meanwhile, how do you maintain your lab? I don’t think anyone has come to terms with it.”

Broadly, Oke’s research is of interest to scientists who are studying ways to tweak the symbiotic relationship between crop legumes and various species of *Rhizobium* bacteria to produce more nitrogen and reduce agricultural dependence on nitrogen fertilizers, which are not only expensive, but also contribute to water pollution.

Oke recalls a traditional children’s nursery rhyme that refers to three-field crop rotation:

*Do you, do I, does anyone know,*

*How oats, peas, beans and barley grow?*

“Only peas and beans can obtain usable nitrogen from symbionts,” she says, “while the others must obtain usable nitrogen from the soil.”

And she reflects on the potential benefits of basic research into the developmental relationship between bacteria and plants for crop production. “A real pie-in-the-sky goal is to extend this sort of symbiotic interaction to non-legumes,” Oke says. “Imagine a world where rice did not need nitrogen fertilizer. That would be incredibly beneficial in terms of trying to feed the world while also protecting the environment.”

*Dorothy Wright contributes news and feature articles on science, technology, engineering and general-interest topics to a variety of publications, including Civil Engineering and Engineering News Record.*



Valerie Oke '88

“We are studying how the bacterial cells live within a plant and identifying the challenges for them. I am fascinated by genes and regulatory circuits — which groups of genes are turning on to enable the bacteria to survive there?”



## BRAIN STUDIES YIELD CLUES TO

# Desire + Motivati

BY BARBARA SPECTOR

**R**ecovering drug addicts who remain in their old neighborhoods often have trouble staying clean. Familiar sights spark the desire to return to old behaviors, they report. But how much exposure to visual stimuli is needed to trigger this kind of vulnerability?

Not much, according to studies by **Anna Rose Childress, M.A. '76, Ph.D. '79**, a Research Associate Professor of Psychology in Psychiatry at the University of Pennsylvania School of Medicine. Childress, who uses noninvasive, *in vivo* neuroimaging to observe brain activity, found that a mere 33-millisecond flash of an image can set the brain's ancient reward circuitry in motion. "The cues are coming in under the radar, before you have a chance to mount a defense," she says.

There is strong evolutionary pressure for the brain to respond rapidly to reward signals, Childress notes, as this — in the case of food and sex — promotes species survival. The mesocorticolimbic dopamine ("GO!") system is critical for processing rewards and their signals, including drug reward cues. Frontal lobe ("STOP!") circuits are responsible for modulating the downstream "GO!" regions, for weighing the consequences of reward pursuit.

Animal studies have shown that "repeated exposure to stimulants may further erode your frontal lobe 'brakes,'" Childress says. "Our cocaine patients have a double whammy — they have a powerful learned response to drug cues, and they may be poorly equipped to modulate it."

### A CAREER-LONG INTEREST

"My graduate training at Bryn Mawr shaped my interest in, and my approach to, the topic of reward and its pursuit," Childress says. "Addictions turned out to be a natural place to see this process gone awry."

Childress's doctoral research at Bryn Mawr investigated the neurotransmitters involved in the brain's reward system by

electrically stimulating the brains of rats. The animals "looked driven" as they pressed buttons, she says. "I was observing what looked like addictive behavior — before I had ever spoken with a cocaine-addicted person."

As a postdoctoral fellow at the University of Pennsylvania, Childress received clinical training in psychiatry. She first investigated a medication to blunt alcohol euphoria in social drinkers, and began studying opiate and cocaine addiction after joining the Penn faculty in 1982. From 1981 to 2006, she also had appointments at the VA Medical Center in Philadelphia, where she still sees a few longtime patients.

### CRAVING AND AROUSAL

Childress was inspired to test the response to "unseen" 33-millisecond drug cues after reading a pair of 1998 papers on the brain's response to fear cues presented outside awareness. She realized the techniques could be applied to cues for reward, including drug reward.

"When I saw the first article," she recalls, "It made my heart beat a little faster."

Childress was the first to document cue-induced cocaine craving and arousal. In her early work, she used short videos of (simulated) drug use shot with her own camcorder, later measuring skin temperature and other autonomic responses in her patients. As brain imaging became available, she pioneered the use of positron emission tomography (PET) and fMRI to map brain activity during craving induced by drug video cues.

Her recent imaging studies pushed the temporal envelope, using 33-millisecond drug and sexual cues presented by a technique that prevented their conscious recognition. The results offer "a peek into unconscious positive motivation," Childress says. "The notion of unconscious motivation has been around since Freud, but it has been hard to test." In



Anna Rose Childress,  
M.A. '76, Ph.D. '79



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Childress's studies, the brain activity in response to "unseen" cocaine cues strongly predicts future (two days later) affect to visible versions of the cues, underscoring the functional significance of the rapid brain response.

Childress's imaging work was featured in the recent HBO documentary, "Addiction." <[www.hbo.com/addiction/thefilm/](http://www.hbo.com/addiction/thefilm/)> Her segment is "The Science of Relapse."

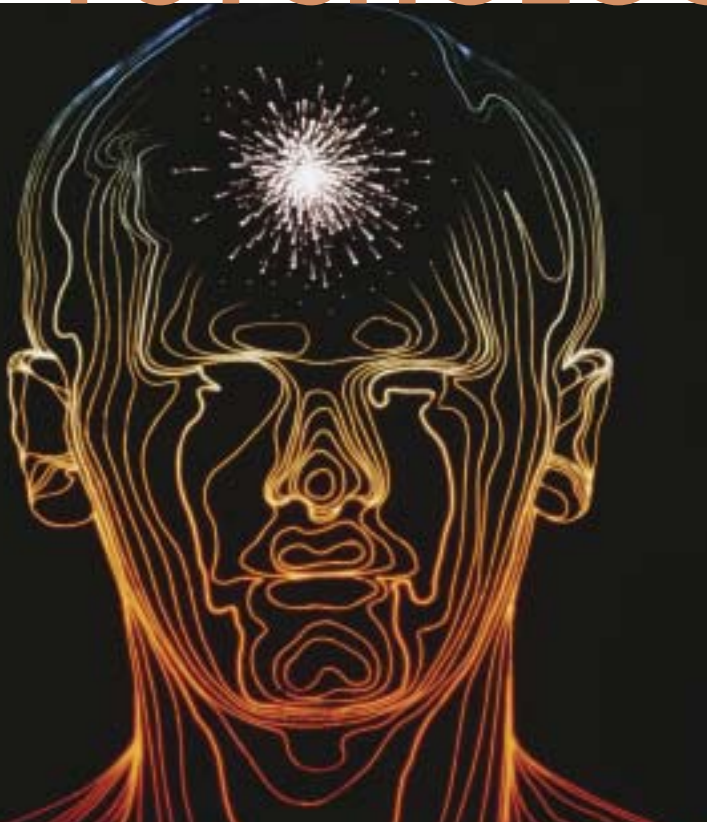
In her early clinical work, Childress developed a set of manualized behavioral strategies for "Coping with Cocaine Craving." The manual has been widely distributed by the National Institute on Drug Abuse; the tools were also modified for smoking cessation. "The behavioral tools make demands on the frontal "STOP!" regions, encouraging patients to consider the consequences of acting on craving," she explains. "However, our patients have great trouble using these "STOP!" tools when they're already in an intense craving state." For this reason, a medication that modulates the rapid response of the "GO!" system may be a critical partner for the behavioral strategies.

## SOLID BACKGROUND

Childress lauds the rigorous experimental training she received at Bryn Mawr. "People within the department had a passion for their science," she recalls. "They lived and breathed it, and they fully expected that their students would, too. What was lasting to me was the excitement of science — to think about what it would mean across species and on different scales." It was thrilling, she says, "to see broad-brush thinkers do translational science — decades before the term was to become the trademark of the 'NIH Roadmap.'"

Bryn Mawr faculty members such as her doctoral thesis adviser Professor Larry Stein (now at the University of California at Irvine), and Professor Earl Thomas, her master's adviser, Childress says, inspired within students a sense that the day's experimental result "could be really important; it could be helpful to people. It was a way of opening up your worldview...well beyond the walls of the laboratory."

## PSYCHOLOGY



"My graduate training at Bryn Mawr shaped my interest in, and my approach to, the topic of reward and its pursuit. Addictions turned out to be a natural place to see this process gone awry."

*Barbara Spector writes on science and technology as well as business topics. She is the editor-in-chief of Family Business magazine and former editor of The Scientist.*



## AAAS FELLOW

**Nancy L. Craig '73 (1)**, professor of molecular biology and genetics at Johns Hopkins University School of Medicine, was elected as a Fellow of the **American Academy of Arts and Sciences** on April 30. According to Academy President Emilio Bizzi, "Fellows are selected through a highly competitive process that recognizes individuals who have made preeminent contributions to their disciplines and to society at large." Craig was honored for her lifetime achievements in biochemistry and molecular biology

Craig's basic research focuses on transposons, discrete pieces of DNA that move to different locations within a cell and between cells. They are present in virtually all organisms and contribute to genome structure and function. She uses the Tn7 and Hermes transposons to examine, at a molecular level, how these "jumping genes" move, and to ascertain the functions of genes and the behavior of mutated genes. Her work has many applications — for example, to understand how retroviruses like HIV replicate or to tackle the problem of antibiotic resistance.

Craig is a fellow of the American Academy of Microbiology and a Howard Hughes Medical Institute investigator. She received her Ph.D. in biochemistry at Cornell University. Craig was profiled in the April 2002 issue of *Bryn Mawr S&T* <[www.bryn-mawr.edu/sandt/2002\\_april/mutation.html](http://www.bryn-mawr.edu/sandt/2002_april/mutation.html)>

## APS LEADER

Bryn Mawr College President Emeritus **Mary Patterson McPherson, Ph.D. '69 (2)**, took the reins as executive officer of the **American Philosophical Society** on July 1. In making the announcement of her appointment in May, APS President Baruch S. Blumberg said, "Her philosophy, her experience and her dedication will certainly continue the Society's tradition and strengthen its mission."

The APS is the nation's first learned society, founded in Philadelphia by Benjamin Franklin in 1743 with the goal of "promoting useful knowledge." Its more than 900 elected members are top

scholars from a variety of academic disciplines in the sciences, arts and humanities, including some 100 Nobel laureates. The society supports research, discovery and education through grants and fellowships, lectures, publications, prizes and exhibitions. It also serves scholars through a research library of more than 200,000 books and seven million manuscripts, as well as special collections of prints and maps.

McPherson succeeded **Mary Maples Dunn, M.A. '56, Ph.D. '59**, and Richard S. Dunn, who retired after serving as APS co-executive directors for five years. Mary Maples Dunn was the College's dean before she became president of Smith College. She had also served as interim director of the Radcliffe Institute and was succeeded by **Drew Gilpin Faust '68**, who became president of Harvard University in July.

Prior to joining the APS, McPherson was vice president of the Andrew W. Mellon Foundation and its program officer for liberal arts colleges from 1997 through March 2007. She served as the College's president from 1978 to 1997. She was elected a member of the APS in 1983 and is a fellow of the American Academy of Arts and Sciences. McPherson earned her A.B. at Smith College and an M.A. at the University of Delaware.

## EDGE HONORED

**EDGE — Enhancing Diversity in Graduate Education** was one of two programs nationwide to be designated Mathematics Programs That Make a Difference by the **American Mathematical Society** in 2007. EDGE was recognized for "its significant efforts to increase the presence of women, with a special focus on women of color, in the upper ranks of mathematical scientists."

EDGE was launched in 1998 as a collaborative effort between Bryn Mawr College and Spelman College. It's co-directors since its inception are the College's Helen Herrmann Professor of Mathematics **Rhonda J. Hughes (3)** and Spelman's Sylvia T. Bozeman. More than 100 women from diverse racial and educational backgrounds have participated in EDGE to date. Of these, the AMS points

out, more than 90 percent are either actively pursuing or have already completed graduate degrees in mathematics."

A cornerstone of the EDGE program is its four-week Summer Program, which has both academic and social components. The academic program, designed to provide intense exposure to advanced mathematics, includes two four-week core courses as well as a mini-course, guest lectures and presentations by program participants. The social program, which seeks to build a sense of community in a supportive environment, includes a diversity seminar, panel discussions about graduate school, dinners and reunions with past participants. EDGE also offers a Follow-Up Mentoring Program. The EDGE program was featured in the April 2001 issue of *Bryn Mawr S&T* <[www.bryn-mawr.edu/sandt/2001\\_april/index.html](http://www.bryn-mawr.edu/sandt/2001_april/index.html)>

## MAKING HAY

**Virginia "Ginger" McShane Warfield '63 (4)**, senior lecturer in mathematics at the University of Washington, Seattle, received the 17th annual **Louise Hay Award** from the **Association for Women in Mathematics** at its annual meeting in New Orleans, Jan. 5-7. The award recognized Warfield's "long career of dedicated service to mathematics and mathematics education" and her "contributions to education through her teaching, graduate student training and mentoring, work on the didactics of mathematics, and outreach and collaborations with K-16 communities."

The award citation highlighted Warfield's long association with Project SEED, a program designed to promote "sense-making" mathematical activities for fourth-through sixth-grade students, which was founded by her fourth-grade teacher, William F. Johntz. The citation also noted her leadership in three major teacher enhancement projects funded by the National Science Foundation — Creating a Community of Mathematics Learners, Extending the Community of Mathematics Learners, and Graduate Teaching Fellows in K-12 Education.

Warfield earned her M.A. and Ph.D. degrees from Brown University.

## Biostatistics: Science by the Numbers (continued from cover)

statistical and mathematical methods to data analysis in the biological sciences, according to the International Biometric Society, which counts almost 6,000 active members, including more than 2,000 in the United States alone. Biostatisticians work in a wide range of fields, including agriculture, biomedical science and public health, ecology, environmental sciences, forestry and allied disciplines.

For this issue of *S&T*, we talked to five Bryn Mawr alumnae working in several of these areas about the tools, challenges and rewards of their work.

### A SOLID FOUNDATION

Approximately two thirds of SCI's contracts involve presenting interim safety and efficacy analyses of clinical trial data to data monitoring committees, says Christ-Schmidt, and the remainder includes assistance in preparing final study reports, protocol development, meta-analyses and epidemiologic analysis.

Data monitoring committees and regulatory groups use the statistical reports generated at SCI to make important decisions about the future use of an experimental drug or device. "This is both exciting and nerve-racking!" Christ-Schmidt says. "We must strive to present data accurately and thoroughly, but also succinctly and quickly. So we are constantly struggling with the competing drives."

Unfortunately, clinical trial results may be inconclusive, not necessarily because a drug was ineffective, but because the sponsor designed the trial poorly, failed to collect the appropriate data, or failed to apply the correct analytical techniques. "They will then have a very difficult time defending their results to the FDA," Christ-Schmidt says. "It is particularly a problem when there are few patients, for example, in a study involving a rare disease. In these

cases, it is very difficult to conduct a confirmatory trial." SCI is often consulted after a study fails to demonstrate a statistically conclusive result in order to either advise on the design of a new trial or, when possible, to salvage the results from the original trial.

There is a lot at stake. "Increasingly, sponsors involve my colleagues and me when the research protocol is being written," Christ-Schmidt says.

The protocol not only describes how the trial will be conducted and the clinical questions that the trial is designed to answer, but also information about the main statistical analyses that will be used to answer these questions. The protocol also states how large the clinical trial will be and the justification of that sample size, which is another statistical component. "Often, clinical researchers think too much in the abstract," notes Christ-Schmidt. As a biostatistician, she can help them design a concrete, practical protocol that will generate clear results.

### A CRUCIAL ROLE

Multidisciplinary collaboration is crucial to the successful design of clinical trials, agrees **Wendy M. Leisenring '86**, a biostatistician who is a member of the Clinical Research Division (CRD) of the Fred Hutchinson Cancer Research Center in Seattle, a pioneer in bone marrow and other forms of stem-cell transplantation.

In collaboration with principal investigators in the CRD, Leisenring participates in the design and analysis of Phase I, II and III clinical trials, which aim to further expand and improve the center's ability to treat patients who are suffering with a wide range of diseases and prognoses. "My overall research goals are to ensure that scientific research is carried

(continued on page 12)

"Every study is slightly different, and so are the methods of collecting and analyzing the data. The actual research question sometimes gets lost in the sheer volume of information. The biggest challenge for a biostatistician is identifying precisely what question the researcher is trying to answer through the study." — **Rebecca K. Stellato '90**

Rebecca K. Stellato '90



out using appropriate statistical methodology,” she says. “Biostatisticians are a well-respected and integral part of the CRD team.”

Leisenring has developed new statistical methods that allow researchers to answer clinical questions about diagnostic tests. Because infection is a serious potential complication in patients undergoing stem-cell transplantation, accurate, early detection of infection is an important research topic at the CRD. “It is important that research leading to the development of new tests be rigorous in determining the tests’ accuracy,” she explains.

For example, Leisenring and her colleagues have developed new methods to compare multiple diagnostic tests, describe the degree to which the outcome of a diagnostic test revises the pre-test odds of disease, and compare predictive values of diagnostic tests when data are obtained under paired-study designs.

Collaboration also plays a crucial role in the design and analysis of large epidemiological studies, such as the Childhood Cancer Survivor Study (CCSS), a 13-year retrospective study of more than 10,000 five-year survivors of childhood and adolescent cancer and more than 3,000 siblings. Leisenring is the lead statistician for the study, which is supported by a grant from the National Cancer Institute and involves 27 institutions across the United States. The ongoing study involves an analysis of data from patient records and a 289-item questionnaire completed by survivors and siblings. A comprehensive summary of the chronic health conditions among these subjects was published in the *New England Journal of Medicine* in October 2006, showing that childhood cancer survivors are eight times more likely than a cohort of their siblings to have at least one severe or life-threatening condition.

“For this large study, the investigators work with us to write a proposal for each project we undertake,” Leisenring says. “We describe the importance of the study, its specific aims, the population, key data elements and analytical process, even going so far as to mock up tables of potential results. This level of planning does not always happen in clinical studies, but it is essential with so many people involved from all over the country. Throughout this process, lots of discussion between the clinical researchers and statisticians is necessary in order to make sure relevant questions are being answered with the existing data.”

### PUBLIC HEALTH

Large epidemiological public-health studies pose similar challenges, says **Rebecca K. Stellato '90**, a lecturer and statistical consultant to researchers and students in the Center for Biostatistics at the University of Utrecht in The Netherlands. Previously, as a biostatistician/researcher for the Center for Environmental Health Research of the Dutch National Institute for Public Health and the Environment, she was the lead statistician for a study of a 2000 fireworks disaster in the city of Enschede, in which a fire and subsequent explosion at a fireworks depot killed more than 20 persons, injured hundreds and destroyed adjacent properties. The study examined the physical and psychological health impacts on residents, visitors, passersby and first responders — police, firefighters and paramedics — at four weeks, 18 months and four years after the disaster.

“Every study is slightly different,” Stellato observes, “and so are the methods of collecting and analyzing the data. The actual research question sometimes gets lost in the sheer volume of information. The biggest challenge for a biostatistician is identifying precisely what question the researcher is trying to answer through the study.”

In this case, the data set comprised subjects’ responses to a 350-item questionnaire. Among the challenges were sporadic subject participation and drop-outs, associated missing data, and the confounding effects of the relationship between physical and psychological symptoms.

Missing data is a common problem with studies involving questionnaires. “If a questionnaire poses five questions to 20 people and we want to use all five of those variables, yet someone fails to answer one of the questions, then that subject generally will be thrown out of the model,” Stellato explains. “Every time a subject is missing a variable, they are eliminated. As a result, we can lose 20, 30 or even 40 percent of our subjects. In the past, statisticians tried to deal with that by taking the average response of all subjects who answered the question, and imputing it to all those who did not. One problem with that is we may be imputing a value to one subject based on subjects who are very different. For this study we used a newer technique, called multiple imputation, which imputes several plausible values, based on a model, *plus* a little random variation, which more accurately reflects reality.”

“We describe the importance of the study, its specific aims, the population, key data elements and analytical process, even going so far as to mock up tables of potential results. This level of planning does not always happen in clinical studies, but it is essential with so many people involved from all over the country.” — Wendy M. Leisenring '86

## ART AND SCIENCE

The workhorse for biostatistical analyses is SAS, a statistical software package developed by SAS Institute, but there are a number of different packages that can be used, including “R,” a free software environment for statistical computing and graphics, which runs on UNIX, Windows and MacOS platforms. “SAS incorporates the most widely used statistical techniques,” Stellato says. “The statistician writes the program for the data in the language of that software package, and then the software performs the analyses.”

The statistical tools run the gamut from simple descriptive statistics to more complicated methods to specialized techniques used for clinical trials, Christ-Schmidt says. “For example, ‘conditional power’ is the probability of seeing a statistically significant result at the end of the trial given the current results — that is, ‘conditional’ on the results from the data available now. Conditional power is a tool that allows the trial sponsor, usually through an independent data monitoring group, to determine whether a trial is very unlikely to show that the new treatment is beneficial.”

Like other biostatisticians, Stellato says, “Sometimes I have to write an independent program, either because there is no software for it or the software doesn’t give me *exactly* what I need.”

Leisenring agrees, “We may need to write a program to do something in a different or more innovative way. Also, a ‘canned’ statistical routine may not be the best approach to an analysis. For example, to some degree there is an art to building a good statistical model. There are statistical analysis packages that just ‘spit out’ a multivariable model that one might use, but it’s really important to go through a much more thoughtful process in developing those models.”

## ANIMAL-HUMAN CONNECTION

The health of more than a hundred million companion animals, plus millions of poultry, cattle, pigs and fish in the United States — and the people who dine on them — also depend on the work of biostatisticians. **Yoko Adachi '97** is a mathematical statistician in the Office of New Animal Drug Evaluation at the FDA’s Center for Veterinary Medicine (CVM), where she reviews study protocols and applications for approval of new animal drugs. The center is responsible for ensuring that animal drugs and medicated feeds are safe and effective, and that foods derived from treated animals are safe for human consumption.

For example, in FY 2005, the center approved a number of new animal drug applications, including an antimicrobial drug for control of mortality due to enteric septicemia in catfish, a drug feed ingredient to increase milk production in dairy cows, and an antiprotozoal drug for the treatment of horses with equine protozoal myeloencephalitis.

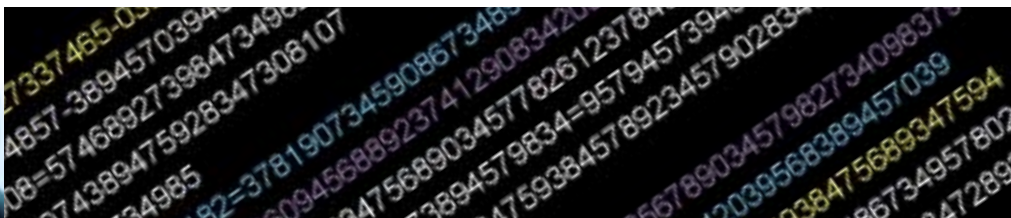
Pre-marketing reviewers study data submitted by drug sponsors to determine if they support a drug’s approval for commercial marketing. Biostatisticians, microbiologists and pharmacologists typically work closely with veterinarians, who are designated as primary reviewers. “The methods of statistical analyses for animal drug applications are fairly similar to those for human drugs,” Adachi says, “although sample sizes are typically smaller and we do not have clinical phases.”

As is the case with human clinical trials, however, the experimental design affects the statistical techniques used to analyze the data. “There was a case in which a sponsor was proposing to collect a blood sample once before and once after the treatment, but the primary reviewer requested more frequent sample collections,” Adachi recalls. “The study

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Yoko Adachi '97



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wound up having four post-treatment collections, and we determined that the statistical methods also needed to be changed to analyze these data.”

Animal pharmaceutical companies often submit study designs to FDA/CVM during the planning phases of developing a protocol. “For example, they may need input from a biostatistician as to the appropriate end-points and statistical procedures, and sample size for the study,” she says. “If we are consulted in advance, we can help prevent problems with study design and data analysis.”

### NATURAL SYSTEMS

There are unique challenges associated with the analysis of data from natural systems. Take the case of population decline among Steller sea lions. The largest of the “eared” seals, they can be found throughout the North Pacific Ocean, through the Aleutian Islands and Bering Sea, and south along the North American coast to central California, although 70 percent of the total population resides in Alaska. Counts of Steller sea lions on rookeries and major haul-outs between the mid-1970s and the present indicate a major population decline. The causes are unknown but may include disease, environmental changes and the effects of commercial fisheries, according to the Alaska Department of Fish and Game. Wildlife veterinarian **Camilla Lieske '91** is in Fairbanks studying the decline through biometric analysis of data that have been collected on the species over a period of 20 years.

“The biological systems I work with are not simple and they are not controlled,” Lieske says, “so the analyses are often complex both in how they are formed and in how they are interpreted. Rather than bringing an animal into a laboratory where we can control the variables and look at one variable

at a time, I am trying to allow all the variables that are in action to be working at the same time, and trying to find patterns and meaning in these natural biological systems.”

Lieske also encounters problems with data sets. “They are often incomplete, and they have been collected by various people, so I have to make sure there is consistency,” she says. “Analytical techniques have changed over the years, too, and that is one reason why I have focused on the more recent data sets in my work on Steller sea lions. “Although I have been looking primarily at data from the most recent five years, I am also trying to include as many data as possible for the last 10 years.”

The science of biostatistics brings order to the chaos. “It allows methods of interpretation and understanding,” Lieske says. “Using statistical methods, I can filter out the noise to get at the nuggets of truth.”

Since the initial decline in the Steller sea lion population as a whole, the western stock has continued to decline, while the eastern stock is rebounding. “There are a lot of questions about the difference in recovery between these two populations,” Lieske says. “A lot of scientists have been wondering about juvenile health differences between the two. My interest is in how to define health, so I am looking at the data that have been collected over the years, focusing on recent blood samples, to identify and compare health parameters.”

Thus far, Lieske has found little difference in juvenile health of the two populations. “My results suggest that if that was an issue when the population first began to decline in the 1970s, it is not necessarily the ongoing issue,” she says. “So we are now looking at other issues, such as reproductive health.”

Lieske will undertake a similar analysis of data pertaining to health and respiratory diseases in caribou.

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## COMPUTATIONAL POWER

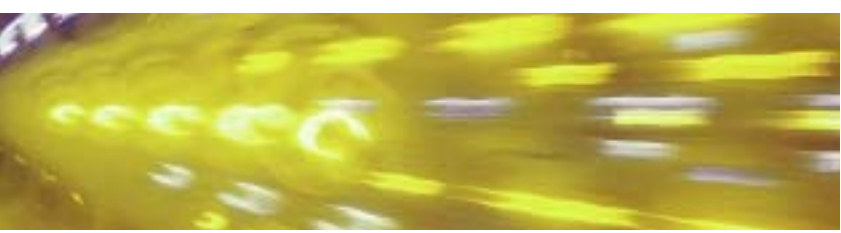
Like professionals in many other fields, biostatisticians have benefited from the enormous strides made in computer hardware and software technology over the past couple of decades. “The statistical software packages have all evolved enormously,” Leisenring observes. “There are many more options within those packages for carrying out a greater variety of analyses. When I first started in 1993, I had to write special programs more frequently, and now they are part of the software.”

For example, Stellato says, “There is much more available in the way of longitudinal and multi-level data analyses within standard software packages, largely, I think, because of the increasing power and speed of computers. An analysis that once required an overnight run on a mainframe computer might take only five minutes on a PC today. One exception is genetics research, which involves such enormous data sets that the analyses still sometimes have to be run overnight.”

The use of computer simulations has also grown. “Thirty years ago, it was difficult to do large simulation studies, in which you create a set of parameters and assumptions about how a population might behave, generate many data sets using random numbers and random variables, and see what happens when you tweak these parameters,” Leisenring explains. “Statisticians use modeling to predict what would happen in an epidemic, for example, increasing the number of people who are vaccinated to see how that might affect the spread of the epidemic.”

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“Sometimes I have to write an independent program, either because there is no software for it or the software doesn’t give me *exactly* what I need.” — **Rebecca K. Stellato ‘90**



## About Our Sources

**YOKO ADACHI ‘97** is a mathematical statistician in the Office of New Animal Drug Evaluation at the U.S. Food and Drug Administration Center for Veterinary Medicine. She reviews study protocols and data submissions that pharmaceutical companies submit to fulfill requirements that new animal drugs must be shown to be safe and effective. She has served as the center’s representative for the FDA Statistical Association, and she is a member of the 2007 FDA Science Symposium Planning Committee. Adachi earned a Master of Science in biostatistics from the School of Public Health at the University of Pittsburgh.

**CAMILLA LIESKE ‘91**, a wildlife veterinarian, is a biometrician for the Alaska Department of Fish and Game in Fairbanks, where she is analyzing data for the department’s Wildlife Conservation Sea Lion Program. Lieske is a doctoral candidate investigating the effects of environmental factors on amphibian health at the University of Illinois, Urbana, where she completed a residency in veterinary toxicology. She earned a Doctor of Veterinary Medicine, as well as a Master of Preventive Veterinary Medicine, from the School of Veterinary Medicine at the University of California, Davis. She is a Diplomate of the American Board of Veterinary Toxicology and serves on its testing committee.

**HEIDI CHRIST-SCHMIDT ‘91** is a biostatistician with the Statistics Collaborative, Inc., a biostatistical consulting firm serving pharmaceutical, biotechnical and government clients. A recipient of a three-year GAANN fellowship, she earned a Master of Science in Engineering in probability and statistics from the Department of Mathematical Sciences at Johns Hopkins University. She is a member of the American Statistical Association, the Association for Women in Mathematics and the Society for Clinical Trials.

**WENDY M. LEISENRING ‘86** is a full member of the Clinical Statistics faculty of the Clinical Research Division of Fred Hutchinson Cancer Research Center in Seattle. She serves as lead statistician and a member of the steering committee for the National Cancer Institute-funded Childhood Cancer Survivor Study. An affiliate professor in the Department of Biostatistics at the University of Washington, Seattle, Leisenring earned a Doctor of Science in biostatistics from Harvard University. She is a member of the American Statistical Association, the Biometrics Society and the Society for Clinical Trials.

**REBECCA K. STELLATO ‘90** is a lecturer and statistical consultant at the Center for Biostatistics, University of Utrecht, The Netherlands. Previously she was a biostatistician/researcher for the Center for Environmental Health Research, National Institute for Public Health and the Environment in Bilthoven, The Netherlands. She earned a Master of Science in biostatistics from the School of Public Health at Harvard University.



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### **PATTERNS EMERGE**

For all its challenges, the field of biostatistics offers many rewards. For Lieske, biostatistics is a means of understanding the effects of the environment on animal populations. “I love it when patterns emerge,” Lieske says. “It’s beautiful when you come up with an understanding of what’s going on. I’ve always been driven to understand the why and how. That’s what I find rewarding: the moment when I say, ‘Ah, *that’s* what’s driving it.’”

The work is challenging and rewarding, says Adachi, “especially since animal welfare may affect the welfare of humans. I also find it interesting to gain information about the latest research in biotechnology and medicine.”

In her role as a participant in the design and analysis of clinical research trials, Leisenring says, “One of the most rewarding things is that I have really gotten to know an area of medical research and that I have been able to help with the process of developing better treatments.”

Then there is the pleasure derived from solving a puzzle. “When somebody gives me a data set, an idea of their questions, and what they want to learn from their data, it is a puzzle for me,” Stellato says. “I get to mess around with the computer as long as I need to in order to get the answer.”

When Christ-Schmidt audits a colleague’s work for quality-control purposes, she says, “It is like detective work or doing a puzzle, trying to find out why my results, which I programmed independently, do not match someone else’s results.” Similarly, she says, “We have actually been hired by clients to check a competitor’s work because the clients were concerned about quality-control issues. We also often audit a trial’s randomization during the course of the trial to ensure that the randomizing company is carrying out the randomization as planned. I know that problems with the randomization are serious — and I still get a kick out of being the one to find them.”

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