After the double helix

The year was 1961 and geneticist Janet Rowley was setting up her chromosome research lab in what was then called the Argonne Cancer Research Hospital, having just moved to the University of Chicago.

Eight years earlier James Watson and Francis Crick had rocked the foundations of genetics with their discovery of DNA’s double helix structure, the architectural secret of life.

The discovery of DNA’s double helix is 50 years old.

But the ripples of their radical double helix discovery would come relatively late for Rowley and many other geneticists around the world. Even a decade after the double helix revelation, Rowley’s investigations into the genetic nature of cancer proceeded independently of the double helix structure.

“It took a while for the Watson-Crick discovery to actually percolate down into laboratory studies,” said Rowley, PhB ’45, SB ’46, MD ’49.

In 1978, a generation after Watson and Crick published their findings, new chromosome staining methods continued to emerge that were independent of any understanding of the structural basis of the double helix and heredity, according to Rowley.

“I would say that by the late 1980s we began to use our understanding of DNA and the pattern of the specific nucleotides within DNA to develop probes that could identify specific genes in cells,” she said.

“If we’d known the sequence of the gene, we could have prepared appropriate probes to synthesize them or have a company synthesize them. But I was using radioactively labeled material — precursors of DNA — to study the patterns in which chromosomes make copies of themselves, but that was a technique in use a while before we knew the structure of DNA,” Rowley told a Washington, D.C., audience at the April “Scientific Symposium: From Double Helix to Human Sequence — and Beyond.”

Both women said they felt honored to be included in the celebration.

“It was meaningful to participate in this celebration,” Cox said. “We have a lot to celebrate, not the least of which are the new challenges that we can tackle given the information infrastructure that has been generated.”

Rowley said she sees the genetic revolution gaining speed with the discovery of the human genome and the research that branches from that discovery.

“The challenge,” she said, “is to use all of the information that comes from sequencing the human genome to move much more quickly to identify the functional effects of the translocations and to find effective therapy.”

Chicago’s regional center will comprise researchers who study the detection, prevention and treatment of biological hazards such as anthrax, botulism, smallpox and the plague. A regional bioc containment laboratory, to be located at Argonne National Laboratory in Chicago’s southwest suburbs, would support the center by safely conducting research on microbes that cause potentially lethal diseases.

Rowley, the Blum-Riese Distinguished Service Professor of Hematology and Oncology, and Nancy Cox, PhD, associate professor of human genetics and of medicine, joined Watson, Crick and others as they spoke about their genetics research in a celebration of DNA’s 50th anniversary.

Rowley reviewed her 1972 discovery of the translocation of chromosomes 9 and 22 in chronic myeloid leukemia (CML). Her major scientific finding led to the development of Glivec — a drug that is bringing hope to those who suffer from CML. Rowley received the 1998 Lasker Award, the 1999 National Medal of Science and the 2003 Benjamin Franklin Medal for her work.

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“If we’d known the sequence of the gene, we could have prepared appropriate probes to synthesize them or have a company synthesize them.

“So knowing those sequences of genes was extremely important,” she continued, “because we knew that if we prepared a copy of that sequence we would then have a probe that was specific for the gene we were wanting to study.”

Cox, who uses statistical methods to analyze genetic data, spoke on what she believes are the short- and long-term challenges to gain a more complete understanding of the genetic component to diabetes. She also reviewed what those findings could mean for patient care and the prevention of diabetes and its complications.

In addition to conducting research, the center will train personnel to help respond to similar occurrences in the future.

“Soup’re absolutely what you need,” said Schneewind, who spent a year developing the proposals.

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Biodefense center proposed

The Roman Empire and Justinian’s plague. The Aztec empire and smallpox.

The Allied troops of WWII and trench fever. History repeatedly shows that even the most powerful nations can succumb to the spread of infectious diseases.

Lest anyone forget, the University of Chicago’s Old Snow sewed, MD, PhD, pointed out this fact of life in proposals worth $80 million that he recently submitted to the National Institutes of Health. The professor of molecular genetics and cell biology wants to establish a regional center for biodefense and emerging diseases and a related bioscience laboratory. More than 100 scientists from six states contributed intellectually to the proposals and would be affiliated with the new facilities.

“We bring a lot of expertise to the table,” said Schneewind, who spent a year developing the proposals.

“Still, this would be a daunting project.”

The proposals came in the wake of the fall 2001 anthrax attacks in the United States that killed five people and frightened thousands. The federal government responded with the largest funding increase in biomedical research history. NIH is expected to fund up to four regional centers and four to six regional laboratories, all focused on biodefense issues.

Chicago’s regional center will comprise researchers who study the detection, prevention and treatment of biological hazards such as anthrax, botulism, smallpox and the plague.

Plus there’s the proximity to Argonne’s advanced facilities in computation and proteomics, not to mention its Advanced Photon Source, the world’s most powerful source of X-rays and a leader in X-ray crystallography — a powerful tool for understanding proteins and other biologically important molecules. Stringent precautions would protect lab employees and people who live or work nearby.

Argonne National Laboratory, the site for a proposed biodefense center, is about 25 miles southwest of Chicago.
Postdocs find collective voice

University of Chicago postdoctoral students are joining their colleagues nationwide by stepping out of their laboratories and into the public arena to seek better working conditions, stipends and benefits.

In November 1999, postdocs from the Biological Sciences Division formed the BSD Post Doctoral Association (BSD-PDA), which now represents one of more than 70 campuses affiliated with the recently organized National Postdoctoral Association.

The NPA received a $450,000 grant from the Alfred P. Sloan Foundation and grants from other major scientific funding organizations to support the planning and development of the organization.

The BSD-PDA started its work by conducting a survey to find out what was on the minds of fellow BSD postdocs. More than 60 responded, indicating they wanted more voice in their institution’s administration and they needed more career guidance. Their “urgent issues” included a concern that postdoc salaries fell below national standards of fair compensation and the lack of “rational, equitable and university-wide benefits coverage.”

Orfeu Buxton, PhD, a fellow in the department of medicine, is a member of both the university and national organizations. He said that postdocs need a stronger sense of community and a network of support, which the BSD-PDA now is providing. “When you come to an institution as a postdoc, you’re a new person who is not part of a program or class of people who have arrived at the same time,” Buxton said. “We arrive at any time during the academic year, and we come to work not necessarily for the institution but for a mentor.”

Postdocs often find themselves isolated in their laboratories — cut off from a community and institutional resources or benefits. To make matters worse, this period of living on the fringe, according to Buxton, has grown over time. What used to be a transistor year or so of post-doctoral training has expanded to four years or more of serious and productive laboratory work.

Today, the university association communicates regularly with the 271 biology postdocs and research associates on campus and offers a roster of social and professional activities. BSD-PDA members now have opportunities to meet and discuss common issues, share their research and work together directly with administrators on improving those conditions.

One such administrator is Nancy Schwartz, PhD, professor of pediatrics and of biochemistry and molecular biology, and dean for graduate affairs. She is the association’s advisor and advocate within the BSD, as well as on the national level, where she is an NPA advisory board member and a postdoc affairs committee chairwoman for the Association of American Medical Colleges.

“Postdoctoral education and training play prominent roles in the national research enterprise and in the biomedical sciences at Chicago,” Schwartz said. “The importance of postdocs to the productivity of the scientific enterprise is profound, so their own efforts to improve the training environment can be expected to have a broad impact on biomedical science overall.

“Given the high level of education and professional skills of postdoctoral fellows and most research associates, these conditions could lead to a crisis in higher education if institutions do not respond to them in an organized and cooperative manner,” she said.

The BSD-PDA works closely with BSD Dean James Madara, MD, to improve conditions for postdocs. Madara appointed Schwartz to chair the postdoc advisory committee along with a postdoctoral researcher. The committee, composed of both faculty and postdocs, works to create policies and guidelines for improving the training environment for postdocs within the division.

The system has to be set up very precisely for surgery. But since the surgeon does not make direct contact with the patient, he can sit at the console in T-shirts and sneakers. “It’s a very comfortable position in which to do surgery,” Shalhav said. “You can stay in the position for hours without getting tired.”

Still relatively new, robotic surgery can take twice as long as conventional surgery to perform and costs $2,000 more per operation, but it requires shorter time in post-op.

Unlike ordinary laparoscopic techniques, the Da Vinci system provides the surgeon with a three-dimensional image of the surgical area, the result of two telescopes in the robot’s camera. The robotic system is easy to operate, enabling beginning surgeons to use it.

“The only handicap is that the system does not provide the surgeon with any tactile feedback,” Shalhav said. “For example, while suturing up an incision, you could break the string because you might be pulling it too hard without realizing it.”

Shalhav and his UCH colleagues are using the robot for a range of abdominal surgeries: to remove prostate glands in prostate cancer, to perform a radical nephrectomy by removing defective kidneys or to widen the urinary tract. They also are using the system for cardiac surgery.

“The system, it is possible to perform cardiac procedures without making a large skin incision and without splitting the chest bone [sternum] in half,” said Emile Bacha, MD, assistant professor of surgery and pediatrics. “This translates into less pain, shorter recovery times and better cosmetic results.”

The bacterium bursts open the host’s red blood cells, captures the hemoglobin inside and removes the iron-containing hemine groups. This transports the kidnapped heme groups across the bacterial membrane and extracts the iron.

The university finding, published in *Science* this past February, suggests new ways to combat this common pathogen. The researchers also found that anthrax and listeria use this same method. “It’s a beautiful system, a complete and very elegant pathway,” said Schneewind, professor of molecular genetics and cell biology. “It involves six different proteins, each with a specific function.”

“Our findings could be used to develop drugs that would disrupt the staphylococcal iron uptake systems, which could, in turn, prevent infection,” said co-author Eric Skaar, PhD, research associate in molecular genetics and cell biology. “Having the entire pathway provides us with multiple new drug targets.”

With one known exception (*Borrelia burgdorferi*), the bacterium that causes Lyme disease, pathogens must scavenge iron from their host in order to survive, grow and cause disease. Body fluids from humans and other mammals contain very little free iron, one of their most important defenses against infections. So bacteria have evolved specialized ways to obtain iron from a host’s body. In humans, hemoglobin is the most abundant iron source.

Schneewind and colleagues found that the *S. aureus* genome contains a family of iron-regulated surface determinants (Isd) genes, which encode factors that bind hemoglobin and transport the iron it contains across the cell wall and into the cell’s interior.

These genes are activated when the bacteria arrive in an iron-poor environment, such as a surgical wound, the gastrointestinal tract or virtually any other site in the human body.

The next step, the researchers said, is to find ways to inhibit this iron-gathering process. Since humans do not have an iron-gathering pathway, drugs that could disrupt the process might provide a safe and effective therapy.
Good Samaritan donates kidney

Since last June, Wilie Morris, 65, of Chicago, has been kept alive by a kidney donated “to whoever needed it” by Bill Van Pelt, 41, of Franklin, Ill.

The exchange commenced two years earlier when Van Pelt decided to donate one of his kidneys. But when he called a Chicago-area hospital, they “did not take me seriously” he said. On his third call, this time to the University of Chicago, he found doctors willing to listen.

“They took the time to understand and realized I really meant it,” said Van Pelt who was inspired to act after reading a newspaper account of a teacher in North Carolina who donated a kidney to one of her students. Also, in his job at Federal Express, Van Pelt made regular stops at a dialysis center where he saw dozens of people who depend on this technology to stay alive.

“It was sobering to see,” he recalled. “It did not seem like a fun kind of life.”

Transplant surgeon J. Richard Thistlethwaite, MD, PhD, worked with ethicist Laurie Ross, MD, PhD, to set up guidelines for how a “good-Samaritan” donation should be handled. The physicians agreed that if both donor and recipient were willing, the two patients could meet at least one month after the operation when the initial period of surgery and recovery were completed.

At the time of Van Pelt’s phone call, Morris, whose kidney had failed six years earlier, was at the top of the recipient list. His wife, two daughters and four sons had volunteered to donate but were ineligible.

After the procedure, Van Pelt recovered quickly and was back at work within six weeks. Morris also recovered well, and said he feels “fabulous, better every week.”

Finally, the two men met. Morris said he has been waiting a long time to thank Van Pelt.

“This was a marvelous thing he did” Morris said. “He’s like a Superman to me.”

Kidney recipient Willie Morris (left) recently met his good Samaritan donor, Bill Van Pelt.
Celiac disease is a digestive disorder triggered by the protein gluten, which is found in wheat, barley and rye. While symptoms vary among individuals, the most common are diarrhea, constipation and abdominal pain. Diagnosis can be difficult because symptoms also can include weight loss, anemia, osteoporosis, depression and sometimes, there are no symptoms.

In people who have genetic susceptibility to the disease, gluten can trigger an autoimmune reaction, preventing proper absorption of food and nutrients and leading to serious health consequences. By following a gluten-free diet, however, people with celiac disease can lead normal, healthy lives.

"When this disease is diagnosed and treated early we can prevent complications," said Stefano Guandalini, MD, director of the University of Chicago Celiac Disease Center and a professor of medicine at the University of Chicago.

"Equal recognition of celiac disease has been frustratingly slow to reach the U.S.,” said Guandalini, who worked in Italy. "In Europe, it typically takes a few weeks to go from the first symptoms to a diagnosis. In the U.S., the average lag time between onset and diagnosis is 11 years."

The disease's prevalence among Americans is far higher for those considered at risk. The study found that people who have first-degree relatives with the disease have one in 22 of having the disease. For second-degree relatives the chance decreases to one in 39. For those with the disease's symptoms but no diagnosed relative, the chances drop to one in 56 people.

"If physicians believe that (celiac disease) is rare," the authors noted, "they are less likely to test for it."

This study, the largest ever on the prevalence of celiac disease in the United States, took place over five years and tested blood samples from 13,145 adults and children from 32 states. Approximately 9,000 people were considered at risk because their relatives had the disease, and another 4,000 were not considered at risk because they had neither symptoms nor affected relatives.

Because celiac disease is an autoimmune disease, scientists now are beginning to suspect it may “set the stage” for other autoimmune disorders, such as type 1 diabetes or rheumatoid arthritis, Guandalini said. "People who are diagnosed late or who continue to eat gluten have a higher prevalence of autoimmune diseases."

The study supports the benefits of screening for the disease, and a blood test costs about $80. The study also found that insurance companies denied payment for an additional intestinal biopsy to confirm the diagnosis for 21 percent of the patients with positive blood tests. Such delays can complicate the disease’s health consequences.

"We are not ready to test the general population," Guandalini said, "but it now makes sense to screen those at risk."

AOA elects 15
The prestigious Alpha Omega Alpha Medical Honor Society welcomed 15 new members — all from the class of 2003 — at a campus reception in March. The inductees are: Benjamin Bryett, Scott Deede, Stephen Keeffe, Leah Kelley, Anjeli Krishnan, Nicholas Lerper, Tamara Levin, Jimmy Lu, Mecca Masey, Melissa Manuell, Claire Najim, Andrew Pennock, Daniel Refai, Elizabeth Suilhamer and Eric Serley.

Election to the society is based on U.S. Medical Licensing Board scores, third year clinical performance, and research and leadership accomplishments.

"It’s a very prestigious award,” said recent medical school graduate Daniel Refai, who started his neurosurgery residency at Washington University in St. Louis in July. "It’s an honor to be elected to AOA because you are joining a community of individuals who seek excellence in their academic pursuits, including their clinical work and researchs."

Exercising their privilege to name and induct additional members from among non-AOA residents and house staff, the new members selected: Elizabeth Oh, MD, third-year resident in obstetrics/gynecology; Joshua Robinson, MD, second-year resident in pediatrics; Maura Quinlan, MD, assistant professor of obstetrics/gynecology; and Monica Vela, MD, clinical associate of medicine.

John Asplin, MD, clinical associate in the department of medicine’s nephrology section, received the Volunteer Faculty Award.

The University of Chicago AOA chapter was established in December 1902.
The processes we studied are known to improve the quality of patient care.

“The results suggest that Americans are not receiving care that is as good as it could and should be,” said Stephen Shortell, PhD, the principal investigator of the study. “In many ways, physicians are still organized to practice medicine the way they did 100 years ago.” Shortell is professor and dean of UC-Berkeley’s School of Public Health.

The researchers found that physician groups on average use only one-third of 16 recommended care management processes. One physician group in six uses none.

“The processes we studied are known to improve the quality of patient care,” said Lawrence Casalino, MD, PhD, assistant professor of health studies at the University of Chicago and lead author of the paper. “Our research indicates that physician organizations are beginning to create effective processes to increase quality, but most still have a long way to go.”

The researchers focused on care for asthma, congestive heart failure, depression and diabetes, which together account for 140,000 deaths and $173 billion in costs each year in the United States. They surveyed 1,040 medical groups and independent practice associations with at least 20 physician members. The presidents, chief executive officers or medical directors of the groups took part in one-hour telephone surveys from September 2000 to September 2001.

Seven in 10 physician groups surveyed do not keep a list of patients who have serious chronic diseases such as diabetes. Half of the groups reported having no electronic data systems to track patients’ illnesses, medications and laboratory results.

Physician groups are more likely to use organized processes to improve care when they have clinical information technology in place and when they are given external incentives to provide high-quality care — such as financial rewards, public recognition or better contracts with health plans.

“We know incentives work, but for the most part they are not being used,” Casalino said. “The federal government and large employers have the most leverage to establish incentives. They have the opportunity and the responsibility to do so.”

Casalino pointed out that some Fortune 500 companies have set up successful programs to do just that, and that Medicare and Medicaid recently created demonstration projects that reward quality. In addition, six California health plans recently started a new pay-for-performance initiative designed to reward physician groups for achievements in documented performance measures.

But such programs remain the exception, and the use of organized processes to improve quality is still uncommon. Given the opportunity and the responsibility to do so, physicians should now act quickly to adopt the type of care management that has been proven to be effective.

That’s the latest finding from a nationwide survey of physician organizations published by researchers at the University of Chicago and the University of California-Berkeley in the January issue of the Journal of the American Medical Association.
**Healthy, wealthy and wise**

Extreme poverty has long been associated with reduced life span. Now more and more studies are showing that people in each socioeconomic category also have worse health than those in the group just above them. It’s not simply income or access to medical care. New studies have shown that personal, social and financial resources often determine the length and quality of life. It turns out deprivation, of any sort, can impair well being.

The pioneers in this emerging field — known as the social determinants of health — argue that people who work in public health should expand their focus beyond germs and genes. They also should include such factors as financial resources and social status, cognitive skills and educational background, racial attitudes and ethnic practices, personal behavior and lifestyle, even a person’s neighborhood and friends.

Many of these ideas can be traced to a handful of people, among them Alvin Tarlov, MD ’56, who chaired the department of medicine at the University of Chicago from 1968 to 1985. His protege, Mark Slegler, MD, a physician with a penchant for ethics, along with Richard Epstein, a lawyer with a taste for economics, pulled together a conference this past November to discuss the “Social Determinants of Health and Disease: Recognizing the Contributions of Dr. Alvin R. Tarlov.”

The conference was divided into six sessions:

- inequity and health,
- social connections and health,
- social and medical factors related to identity,
- how sex and gender affect health,
- the economics of medical innovation and
- the role of the legal system in public health and health care.

Speakers included distinguished faculty from business, economics, law, medicine, psychology, public health, public policy and sociology.

The idea is catching on. Three months after the Chicago conference, the president of the American Association for the Advancement of Science opened its annual meeting in Denver with a plea for more research of this type.

“The puzzles of better health promotion and disease prevention,” said former editor-in-chief of Science Floyd Bloom, PhD, “may be approached more rapidly and effectively through intensified social science research.”

**Daily dose**

Taking one aspirin a day can prevent the development of pre-cancerous polyps in people who have increased risk for colorectal cancer, according to a multi-center study published this past March in the New England Journal of Medicine.

Aspirin’s protective effect was so significant that the study was stopped early.

“Study had a significant protective effect,” said senior author Richard Schlisky, MD, a professor of medicine at the University of Chicago. “It clearly reduced the formation of polyps in this study of high-risk individuals, which is good news because it provides a new way to lower the risk of recurrence in patients who have had colon cancer.”

Conceived and organized by Cancer and Leukemia Group B (CALGB), this study and a related one published in the same issue provide a significant boost to the mounting evidence that aspirin and related drugs can reduce the risk of colon cancer — the second-leading cancer killer in the United States.

An aspirin a day, the researchers found, reduced the occurrence of adenomas, pre-cancerous polyps in the colon, by about one-third in patients with a history of colorectal cancer. Patients on aspirin who did get polyps took longer to develop them, and they had fewer polyps than those not taking aspirin.

“This suggests that aspirin and similar anti-inflammatory drugs may help prevent this disease in average-risk individuals,” said Schlisky, the CALGB chairman.

Although these drugs are not without risks, many people already take a daily aspirin to prevent cardiovascular disease. “Now we have one more reason to consider recommending aspirin for prevention in patients with no contraindications,” he said.

Despite the good news, the researchers caution that people need to consult their own physicians before beginning an aspirin regimen.

“We are not suggesting that even those with increased cancer risk take aspirin until they have discussed it with their doctors,” added Robert Sandler, MD, professor of medicine and epidemiology at the University of North Carolina, lead author of the CALGB paper and a co-author of the second study. “For those who have had polyps or previous colon cancer, regular colonoscopy and polyp removal remain the first step in prevention, possibly supplemented by aspirin.”

**Blocking the ills of painkillers**

A drug designed to relieve the intractable constipation associated with opioid pain relievers, such as morphine, codeine and OxyContin, entered phase III clinical trials in December. Methylaltrexone, or MXTN, was developed at the University of Chicago in 1979 and recently was acquired by Progenics Pharmaceuticals.

Cancer patients on heavy doses of opioid drugs can go a week without a bowel movement. The crippling state can make it difficult to eat, work or even walk. Laxatives are ineffective in such cases, and lacking other therapies, the only alternative is to cut off the painkillers.

Opioids relieve pain by interacting with receptors in the brain and spinal cord. However, they also affect other receptors in the body, including those in the digestive tract. MXTN blocks the digestive-tract receptors, and because the drug is unable to penetrate the brain, it doesn’t interfere with pain relief.

Methylaltrexone was invented by the late university pharmacologist Leon Goldberg who wanted to help a dying friend suffering from morphine-induced constipation. Goldberg started with naloxone, an established drug which completely blocks the effects of morphine. He altered the drug slightly by attaching a methyl group, which changed the charge of the molecule so that it could no longer cross the protective barrier that surrounds the brain. Consequently, the molecule did not interfere with morphine’s effect on pain, which is centered in the brain. But it did block morphine’s effects on gut motility, which is mediated by receptors in the peripheral gastrointestinal tract.

**Breaking ground for Collaboration**

With shovels in hand, University of Chicago officials gathered on the corner of Drexel Avenue and 57th Street this past November to break ground for one of the largest interdisciplinary science buildings on any Midwestern university campus. The 430,000-square-foot Interdisciplinary Research Building, slated for completion in 2005, will have seven floors covering nearly 10 acres.

The $200-million facility will enable biologists and physical scientists to work on projects that cross traditional boundaries of scientific inquiry, bringing together such diverse fields as condensed-matter physics and molecular biology. The IRB will house faculty from the Institute for Biophysical Dynamics, the Howard Hughes Medical Institute, the Ben May Institute for Cancer Research, the James Franck Institute and the chemistry department.

*It worked like a charm for his dying friend, who then shared the drug with several other friends who also were taking opioid drugs for cancer pain. The drug’s initial success in this compassionate-use setting drew notice from Goldberg’s colleagues. After Goldberg’s death, they continued to develop the compound, testing it in animals, performing the initial human safety trials and completing a series of pre-clinical studies in volunteers.”*