

## Tracking flying snakes

Ophidiophobia, the fear of snakes, traditionally has been among the most common phobias — and that was back when all we knew snakes could do was slither, burrow, swim and climb. Just imagine if snakes could fly.

In fact, some can. More precisely, they glide or parachute in the same fashion as a flying squirrel, frog, lizard or fish.

University of Chicago biologist Jake Socha has been studying the gliding patterns and biomechanics of these airborne creatures. In an August issue of *Nature*, the sixth-year graduate student described some of the aerodynamics of the *Chrysopelea paradisi*, or paradise tree snake — one of five snake species that are purported to “fly.”

Socha found that the aerial behavior of this snake is unlike any other glider. It exerts remarkable control over the direction it takes, despite an apparent lack of control surfaces. For example, while in flight the snake does not bank, or lean into, turns like most other flyers. Instead, the paradise tree snake turns as it undulates from side to side.

The *Nature* article, titled “Gliding flight in snakes,” also describes the three-dimensional kinematics of gliding by the paradise tree snake. More specifically, the

snake changes its undulation pattern while airborne: the amplitude, or height of the waves, is two to three times larger, and the frequency is one-third lower.

For the study, Socha videotaped and photographed various snakes taking off from a 33-foot-high tower in an open field at the Singapore Zoological Gardens. He positioned two video cameras to record in stereo, enabling the three-dimensional reconstruction of the head, midpoint and vent coordinates of the snake throughout its trajectory.

Socha found that *C. paradisi* prepares to take off by hanging from a branch looping its anterior body into the shape of a “J.” The snake then jumps by accelerating up and away from the branch. Using its ribs to change its body shape, it flattens from head to vent. (Snakes also flatten when threatened, to absorb more sunlight or when posturing, like a cobra does prior to attack.)

“But while in flight, it not only flattens its entire body, it moves at the same time,” Socha said. “It’s actually undulating in the air. So whatever muscles it’s using to flatten are probably decoupled from the muscles it’s using to undulate.”

Socha also found that its orientation changes throughout the trajectory. Before beginning to undulate, the snake pitches

its body downward, and then brings its head and vent together toward the midpoint to form an “S” shape.

The snake has some degree of control, undulating through the air as if swimming, moving the tail up and down and side to side. From the 33-foot platform, the snakes could glide as far as 70 feet, make turns up to 90 degrees and always seemed to land without injury.

The *Nature* article stems from a larger research project Socha conducted as part of his dissertation, which he defended this past November. His research also includes detailed analyses of takeoff and how body size relates to gliding ability.

But the young biologist had to start from zero.

“I didn’t know where to begin,” Socha admitted, since little was known about these snakes in general. He couldn’t use computer or physical models since the shape of the snake, its posture and how fast it undulates were unknown.

Instead, with the support of the National Geographic Committee for Research and Exploration, Socha traveled to Singapore twice and Thailand once to study the snakes. After six years of research, miles of film and videotape, and more than a hundred snake bites, Socha has emerged as rare as his subject: a flying snake expert.

Scientists have documented the existence of these animals for only a century, but legends of “winged snakes” go back as far as Herodotus, a Greek historian in the fifth century B.C. Most flying snakes grow three to four feet long and live in the trees in the lowland tropical rainforests of South and Southeast Asia.

Their temperament varies from species to species, and from individual to individual, but all five species of flying snakes are in the *Colubridae* family and officially are classified as harmless (although, according to Socha, some species will bite if they get the



PHOTO BY JAKE SOCHA/NATIONAL GEOGRAPHIC SOCIETY

**Just after takeoff, the flying *Chrysopelea paradisi*, or paradise tree snake, flattens its body, undulates into a wide-amplitude “S” posture and creates a slightly concave underside to glide from one tree to another. The heart makes a bulge in the snake’s flattened body, which measures nearly 28 inches and weighs approximately 1½ ounces.**

chance). Flying snakes secrete mild venom that is only dangerous to their small prey.

They are diurnal and opisthogyphous, or rear-fanged. These back teeth measure only 2 to 3 mm long and each has a small groove that runs along the fang's outer edge, where the venom drips down and into the prey.

Much still is not known about flying snakes, such as their predators, their sleep habits or how often they glide. There have been no studies that document their movement through the trees, but in general, animals that glide do so to travel more efficiently, to chase prey or to escape a predator.

There's no need to worry about snakes falling out of the skies, even if you live in Southeast Asia. There is no record — scientific or otherwise — of snakes landing on people. "Basically," Socha said, "they want to get away from you more than you want to escape them."

Try telling that to an ophidiophobe.

— Catherine Gianaro

## U.S. News lists best hospitals

For the sixth year in a row, *U.S. News & World Report* has named the University of Chicago Hospitals among the 17 best hospitals in the United States in its annual survey of America's 6,045 hospitals.

In the 2002 "Best Hospitals" issue published in July, UCH ranked 14th nationally overall and was ranked among the best in 11 specialty areas.

The areas ranked among the best include three in the top 10: cancer (#6), gastroenterology (#6) and orthopedics (#10).

Those in the top 20:

- geriatrics (#11),
- hormonal disorders (#14),
- respiratory disorders (#17),
- gynecology (#19) and
- kidney disease (#20).

Four other programs scored in the top 50: rheumatology (#22), ear/nose/throat (#35), urology (#38), and neurology and neurosurgery (#39).

UCH is the only Illinois hospital ever included in the survey's Honor Roll of the Best Hospitals in the United States.



For the sixth year in a row, *U.S. News & World Report* named the University of Chicago Hospitals among the nation's top 17.

The *U.S. News & World Report* rankings are based on a mathematical formula that takes into account each institution's reputation according to a poll of 150 specialists in each field, the ratio between actual and expected mortality at the hospital, and a group of factors such as available technology, procedure volume and nursing care.

— John Easton

## Leukemia gene found in Down children

University of Chicago researchers have identified a gene defect that causes the development of leukemia in children with Down syndrome.

The discovery, posted on *Nature Genetics*'s Web site in August, could speed diagnosis and provide a new target for therapy.

Children with Down syndrome are 10 to 20 times as likely as unaffected children to develop leukemia. They most commonly develop a type known as acute megakaryoblastic leukemia (AMKL), which is extremely rare in children without Down syndrome.

"This study, for the first time, defines a part of the molecular pathway leading to acute megakaryoblastic leukemia," said John Crispino, PhD, assistant professor in the Ben May Institute for Cancer Research and director of the study. "Having three copies of chromosome

21 places children with Down syndrome at increased risk for leukemia, then this abnormality tips the balance toward AMKL."

"This is a rare malignancy," added co-author Michelle Le Beau, PhD, professor of medicine, "but a great deal of what we now know about the molecular basis of cancer has come from disorders like this. Our finding pinpoints a specific pathway that leads to this kind of cancer, offers a method for rapid and precise diagnosis, and suggests more focused ways to treat this disease."

Unlike most studies, which begin with a disease and then search for the genetic trigger, this one began with a suspect gene. Crispino's laboratory had been interested in a gene called GATA1 for years because it played a role in the maturation of blood cells.

Our finding pinpoints a specific pathway that leads to this kind of cancer, offers a method for rapid and precise diagnosis, and suggests more focused ways to treat this disease.

— Michelle Le Beau  
Professor of Medicine

Crispino hypothesized that GATA1 might be mutated or dysregulated in leukemia. He contacted Le Beau, an expert on the genetics of leukemia. Having identified a patient with Down syndrome who had a mutation in GATA1 and had acute megakaryoblastic leukemia, they began searching for other patients with childhood leukemia and an abnormal copy of this gene.

When they looked at DNA from 75 patients with various types of myeloid

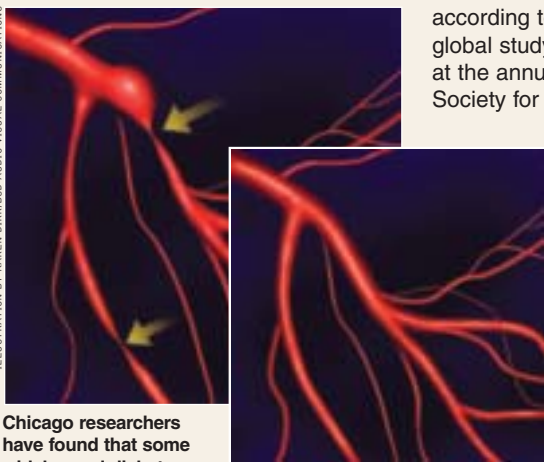
## InBrief

### Diabetes drug downfall

The oral medications most widely used to lower blood-sugar levels in patients with type 2 diabetes are likely to increase the risk of spasm of the coronary arteries, a University of Chicago-based research team reported this past July in *Journal of Clinical Investigation*. Constricted arteries increase blood pressure and decrease blood flow to the heart, causing chest pain and even sudden death, according to the study, which focused on mice with a genetic defect that duplicates the actions of these drugs.

Sulfonylurea drugs are the mainstay of therapy for non-insulin-dependent diabetes, which affects an estimated 15 million people in the United States. These

ILLUSTRATION BY KAREN DIRREBSO AUDIO-VISUAL COMMUNICATIONS



Chicago researchers have found that some widely used diabetes drugs may increase the risk of coronary artery spasms (shown by arrows above).

drugs stimulate the beta cells of the pancreas to squeeze out more insulin and also make insulin more effective.

Since the early 1970s, however, several studies have suggested that sulfonylurea drugs may increase cardiovascular problems in diabetic patients. The link between these drugs and heart damage has been disputed, because it was not clear — until now — exactly how such medications increased cardiovascular risk. The new study demonstrates a direct link between the receptor for sulfonylurea drugs and coronary arterial spasm, heart damage and death.

### Weiss joins Vanguard

The University of Chicago Hospitals and Health System and Vanguard Health Systems have established a joint venture to administer Louis A. Weiss Memorial

Hospital, UCHHS's north side affiliate. The arrangement brings new access to capital for investment as well as strengthened management expertise to the 369-licensed-bed Weiss Hospital.

Vanguard assumed 80 percent ownership of the joint venture. UCHHS retains a 20 percent stake. The partners maintain UCHHS's clinical and educational programs at Weiss. Responsibility for Weiss Hospital's administration, however, shifts to the joint venture.

### Pemetrexed's promise

Patients with cancer of the lining of the lung, known as pleural mesothelioma, live longer and have less pain and shortness of breath if they receive the new chemotherapy drug pemetrexed, according to the results of a phase III global study presented this past May at the annual meeting of the American Society for Clinical Oncology.

According to university researchers, mesothelioma patients who were treated with pemetrexed plus the commonly used chemotherapy drug cisplatin lived for about a year after their diagnosis, nearly three months longer than patients who received only cisplatin, the researchers found. The two-drug combination also caused the

cancer to shrink in 41 percent of patients, compared with 17 percent of patients who received only cisplatin, and was more effective at reducing pain and shortness of breath, symptoms commonly experienced by patients with this type of cancer.

### Biodiversity crucial

For more than half a century, ecologists have known the devastating effects of species loss within an ecosystem. How diverse the ecosystem is and how one species interacts with the rest of the system is perhaps more important than the actual number of species, according to a university study published this past April in *Nature*.

(Continued on page 6.)

leukemia and 21 healthy people, they found that six out of six patients with Down syndrome and acute megakaryoblastic leukemia had an alteration in GATA1. None of the other patients surveyed had an abnormal version of this gene.

GATA1 is a transcription factor; it controls the expression of other genes. It normally regulates genes that control the production of red blood cells and platelets, which enable the blood to carry oxygen and to clot. Previous studies in mice had shown that the loss of GATA1 caused the cells that give rise to platelets to proliferate excessively.

The abnormal GATA1 gene, found in the leukemia patients, produces a protein with a piece missing. The incomplete protein appears far less effective in regulating target genes, resulting in an outcome that is similar to having no GATA1 protein at all.

The researchers suspect that it requires several gene abnormalities working in tandem to cause full-fledged acute megakaryoblastic leukemia, and they are searching for the other genes that combine with GATA1 to trigger this disease.

"GATA1 is just part of the story," said Crispino, "but it is a crucial early step that should lead us to the rest of the pathway."

—J.E.

## Infliximab prolongs remissions of Crohn's

Sustained treatment with the monoclonal antibody infliximab can prolong remissions in patients with moderate to severe Crohn's disease, a multi-center research team reported this past May in *The Lancet*.

In the first large-scale trial of infliximab (marketed as Remicade) used as maintenance therapy instead of as a

Using 84 makeshift habitats, ecologist Mathew Leibold studied how diversity affects an ecosystem's productivity.



treatment for acute attacks, researchers found that patients who received infusions of infliximab every eight weeks were twice as likely to be in remission after 30 weeks of therapy as those who didn't receive the drug. Bi-monthly infusions kept patients in remission for twice as long, even longer at a higher dose.

"At last we have a therapy that truly allows us to manage this disease over time, rather than just treating flare ups," said lead investigator Stephen Hanauer, MD, professor of medicine at the University of Chicago and director of the study. "Ongoing treatment with infliximab decreased disease activity, prevented sudden attacks and enabled patients to reduce or, in many cases, completely eliminate steroids."

Crohn's disease, a chronic inflammatory bowel disorder, affects about 500,000 Americans, typically beginning in their teens and early 20s. The disease causes inflammation of the gastrointestinal tract. It causes diarrhea, fever, abdominal pain and weight loss. In up to 30 percent of patients, Crohn's disease causes fistulas — openings that burrow through the bowel wall into nearby organs or through the surface of the skin.

The researchers enrolled 573 patients with moderate to severe Crohn's disease at 55 centers in North America, Europe and Israel. All patients received an initial dose of infliximab. The 335 patients (58%) who responded to the initial dose within two weeks were randomized to one of three treatment groups.

Group I received placebo (an infusion containing no medication) at weeks two and six of the study, then every eight weeks. On the same schedule, group II received 5mg/kg of infliximab, and group III received 5 mg/kg of infliximab at weeks two and six followed by 10mg/kg beginning at week 14.

By week 30, patients who received infliximab were twice as likely to be in remission as those who didn't. Only 20 percent of the patients receiving placebo had no symptoms at 30 weeks. However, nearly 39 percent of those on the lower dose of infliximab and 45 percent of those on the higher dose were in complete remission.

Patients who had sustained treatment also had longer-lasting remissions. For patients receiving placebo, remissions lasted a median of 19 weeks. For those receiving 5mg/kg of infliximab, they lasted twice as long, a median of 38 weeks. For those receiving 10mg/kg, the average was greater than 54 weeks.

Infliximab also helped patients reduce their reliance on steroids. The majority of patients taking steroids at the beginning of the trial and who received the maintenance regimen of infliximab for 30 weeks were able to eliminate steroid use completely. Patients who had received only a single dose had to continue to use steroids.

Corticosteroids have been the first-line therapy for patients with moderate to severe Crohn's disease. Yet patients who use steroids for a long time often suffer a wide array of side effects, including osteoporosis, diabetes, difficulty sleeping, mood swings and possible dependency.

"It would make a real difference for patients if we had alternatives to steroids or better ways to reduce the steroid dose," Hanauer said.

Patients receiving infliximab also reported higher quality-of-life scores at week 30 than patients receiving the placebo.

"We also found that many patients who lost their response to the drug benefited from re-treatment at intervals shorter than every eight weeks," Hanauer said.

Reports of side effects were the same in all three groups.

Infliximab is a monoclonal antibody that blocks the activity of a key inflammatory mediator called tumor necrosis factor alpha. Overproduction of TNF-a leads to inflammation in conditions such as Crohn's, rheumatoid arthritis and other autoimmune diseases. Infliximab was designed to attach to and neutralize TNF-a on the cell membrane and in the blood.

Because it suppresses part of the immune response, infliximab may increase the risks of serious infections. There are also reports of serious infusion reactions with hives, difficulty breathing

## Noteworthy

**Janet Davison Rowley, PhD '45, SB '46, MD '49**, the Blum-Riese Distinguished Service Professor of Medicine and of Molecular Genetics and Cell Biology, has been recognized as one of the 50 most important women scientists in America (the only one from the state of Illinois) in the November issue of *Discover* magazine. Rowley also has been selected as one of 17 members of President Bush's Council on Bioethics, formed to advise the president on issues of scientific and ethical policy. **Leon Kass, BS '58, MD '62, PhD**, the Addie Clark Harding Professor in the Committee on Social Thought, heads the council.

**Richard L. Baron, MD**, a pioneer in abdominal imaging and in the gastrointestinal applications of magnetic resonance and computed tomography scans, has been appointed chairman of radiology. Baron comes to Chicago from the University of Pittsburgh, where he was founding president and CEO of the University of Pittsburgh Physicians Practice Plan and professor of radiology. He chaired the department of radiology there from 1992 to 1999.

**Bernard G. Ewigman, MD, MSPH**, a leader in the application of epidemiology and public health research in primary care and family practice, has been appointed chairman of the department of family medicine. Ewigman comes to Chicago from the University of Missouri-Columbia, where he was a professor and director of research in the department of family and community medicine, director of the Center for Family Medicine Science and director of the Child Injury Research Group.

**Richard G. Fessler, PhD '80, MD '83**, an authority on minimally invasive spine surgery and microendoscopic surgery and the first physician in the United States to perform a human embryonic spinal cord transplant, has been appointed professor and section chief of neurosurgery. Fessler comes to the university from the Chicago Institute of Neurosurgery and NeuroResearch, where he was founder and director of the Institute for Spine Care, and

*(Continued on page 7.)*

## more InBrief

Most previous studies focused on the effects of biodiversity in simple ecosystems. In this study, researchers used a more complex system involving a larger portion of the food web. They found a much bigger effect initially. Comparing it to a house of cards, the more stories that are built, the more severe the collapse when a card is plucked out.

### Med students on a mission

For the third year in a row, members of the REMEDY Medical Aid Mission — a student organization in the Pritzker School of Medicine concerned with international health issues — traveled to Havana, Cuba, this past June with more than \$70,000 worth of medical equipment and supplies. Various health care companies donated the items — everything from aspirin and syringes to cancer chemotherapy drugs — to help address supply shortages in Cuba.

U.S. embargoes prohibit medical equipment from being shipped to Cuba unless accompanied by personnel. The students raised funds, solicited donations and arranged all logistics for the trip. Once in Havana, the group traveled to local hospitals and clinics disbursing the supplies.



Pritzker medical students packed nearly \$70,000 worth of medical equipment and supplies to take to Cuba.

### Nicotine addiction

Brief exposure to low levels of nicotine not only boosts the brain's "reward" system but also blocks a rival system that limits the duration of such rewards, university researchers reported in the journal *Neuron* earlier this year. The finding helps scientists understand why nicotine addiction takes root so quickly and lasts so long.

In 2000, a team from the same laboratory demonstrated how the first exposure to nicotine can create an enduring

"memory trace," which instills the desire to repeat the experience and amplifies the pleasing effects of subsequent nicotine exposure. This recent study reveals how nicotine prolongs the reward period by disabling the system that counterbalances the drug's pleasant effects.

### A dietary risk

Popular low-carbohydrate, high-protein diets may result in rapid weight loss, but they also appear to pose serious health problems, including increased risk of kidney stones and bone loss, reported researchers from the universities of Chicago and Texas Southwestern.

In the study, published this past August in *The American Journal of Kidney Diseases*, 10 healthy subjects ate a regular diet for two weeks, followed by two weeks of a highly restrictive diet that included some vegetables but no fruits and fewer than 20 grams of carbohydrates. Participants then ate a slightly less-restrictive diet for the final four weeks.

A diet heavy on animal proteins and light on carbohydrates increases fat metabolism, which can increase the amount of acid in the blood. The researchers found that acid excretion — a marker for the acid load in the blood — increased as much as 90 percent while subjects were on diets that severely restricted carbohydrates. They also found that calcium absorption was unchanged but calcium excretion increased.

The diet also produced changes in urine chemistry — higher levels of uric acid and calcium — that enhanced the propensity to form stones. Increased acid in the blood also may suppress the function of cells that make new bone and stimulate the cells that break down bone, suggesting that much of the calcium being excreted was leached from bone.

"This short-term metabolic study stresses that a low-carbohydrate, high-protein diet may enhance the risk for stone formation and bone loss," the authors wrote. Patients who pursue such a course, they suggested, "should be made aware of a potential increase in risk for kidney stone formation and unknown long-term risk to bone health."

— J.E. and C.G.

and low blood pressure. In clinical studies, some people experienced upper respiratory infections, headache, cough, nausea, sinusitis or mild reactions such as rash or itchy skin. In rare cases, people with de-myelinating disease who were treated with infliximab have seen their symptoms intensify.

— J.E.

## Men regain evolutionary driver's seat

Are men fundamentally more flawed than women? Genetically speaking, yes.

University of Chicago researchers have estimated that genetic mutations — the raw material for evolution — occur 5.25 times more often in males than in females. This discovery should lay to rest any doubts raised by recent studies questioning the dominant role males play in producing mutations for molecular evolution.

The Chicago study, published this past April in *Nature*, also shows that these mutations are caused mainly by random errors that occur during cell divisions rather than by environmental factors.

"Mutation is the ultimate source of variation," said Wen-Hsiung Li, PhD, the George Wells Beadle Distinguished Service Professor in the ecology and evolution department. "Your ancestors and my ancestors accumulated different mutations, which is part of the reason why you and I look different."

For more than half a century, scientists have believed the main source of new mutations is in the male germ line. But two recent studies — one from the Whitehead Institute and the other from the International Human Genome Sequence Consortium — suggest the male-female ratio of mutation rate, or alpha, is only about 2-to-1, a drastic decrease from earlier estimates.

But Li and co-investigator Kateryna Makova, PhD, research associate in the ecology and evolution department, have restored the validity of a high alpha among humans and apes. They studied part of the DAZ locus, a non-coding genetic sequence present on chromosome 3 and the Y chromosome.

The researchers found a low male-female mutation rate when they compared closely related species, which involved a shorter evolutionary time span. For example, when they looked at humans, pygmy chimpanzees and gorillas, they found that alpha is only 1.4, which suggests there is only a slightly higher mutation rate in males than in females.

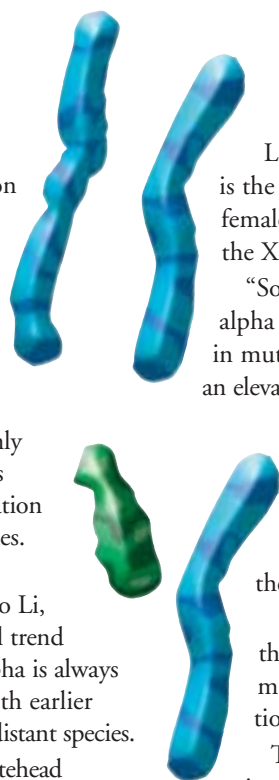
But for distantly related species, which, according to Li, better represent the general trend over evolutionary time, alpha is always high. This is consistent with earlier studies that also looked at distant species.

The study from the Whitehead Institute only compared closely related sequences from species that diverged after the point when human and chimpanzee split about 5 million years ago.

“One problem with this study is that they used a wrong gene genealogy,” Makova said. “Also, it’s inappropriate to use closely related species because of ancient-nucleotide polymorphism.” This means at the time of speciation, there already were mutations accumulating on chromosome 3. But the Y chromosome, which had virtually no polymorphism, did not start accumulating errors until the point of speciation. “When you account for ancient-nucleotide polymorphism, alpha increases drastically,” Makova said.

The results of the Whitehead and consortium studies also conflicted with the “generation-time effect” hypothesis, which suggests that the molecular clock runs faster in organisms with a shorter generation time because they undergo a larger number of cell divisions per unit of time. So, for example, rodents have a faster molecular clock than humans.

“We would expect alpha to be higher in primates than in carnivores and birds because in primates there is a larger difference in the number of cell divisions between egg cells and sperm cells than in carnivores and birds,” Makova said. “So these two new estimates didn’t make sense.”



Li and Makova’s study is the first to calculate the male-female mutation rate without using the X chromosome.

“Some have argued that the high alpha could be due to a reduction in mutation rate in X rather than an elevated rate in Y,” they noted in their paper. So in this study the researchers compared the Y chromosome with an autosome — an asexual chromosome — eliminating the X factor altogether.

“This is independent proof of the dominant male in producing mutations for molecular evolution,” Makova said.

The study also suggests mutations are “replication-driven” — caused mainly by cell divisions and not environmental factors. Since cell divisions are continuous during a man’s life, his sperm stem cells constantly accumulate errors — or mutations. In contrast, only 24 cell divisions occur in the egg cells of a woman, most of which take place before she is born.

“Since mutations seem to occur in the male germ line,” Li said, “then replication errors are important and environmental factors are less important.”

Since mutations in sperm cells accumulate as a man ages, does the biological clock tick faster for men than it does for women? Yes, but it’s not something worth worrying about, according to Li.

“The mutation rate is very low, so the increase in mutations in an individual male is not appreciable,” he said, “even if you were to double or triple the rate.”

Most mutations have no effect on a person’s health or survival, but merely accumulate within DNA, according to Li. “This is because more than 90 percent of the human genome is non-coding,” Li said. “But mutations — bad, good or neutral — accumulate in the genome of a species, whether it’s bird, chimp or human.”

— C.G.

## more Noteworthy

from Rush-Presbyterian-St. Luke’s Medical Center, where he was a professor of neurological surgery.

**Albert S. Bendelac, MD, PhD**, has been appointed professor in the department of pathology. Previously an associate professor in the department of molecular biology at Princeton University, Bendelac studies the immune system with particular emphasis on how the system recognizes markers other than proteins on the surface of cells.

**Ivy Bennett** has been appointed vice president and chief marketing officer at the University of Chicago Hospitals. Bennett came from Allstate Insurance Company in Northbrook, where she was assistant vice president of corporate marketing.

**Mayumi Fukui** has been appointed vice president for managed care. She will be responsible for leading managed care contracting for both the UCH and the University of Chicago Physicians Group, the largest such group in Chicago.

Six professors recently received the following appointments:

**J. Terry Ernest, MD ’61, PhD ’67**, professor and chairman of ophthalmology and visual science, as the first Cynthia Chow Professor.

**Richard P. Kraig, MD, PhD**, professor in the departments of neurology, and of neurobiology, pharmacology and physiology, as the William D. Mabie Professor.

**James L. Madara, MD**, dean of the Biological Sciences Division and Pritzker School of Medicine, as the Richard T. Crane Professor.

**Mark J. Ratain, MD**, professor of medicine and chairman of the Committee on Clinical Pharmacology, as the inaugural Leon O. Jacobson Professor. (See page 40 for story.)

**Jacob Rotmensch, MD**, professor of obstetrics and gynecology, as the Mary Campau Ryerson Professor.

**Julian Solway, MD**, professor of medicine and pediatrics, as the Walter L. Palmer Distinguished Service Professor.

## Gene therapy boosts cancer chemotherapy

University of Chicago researchers have found a way to combine cancer chemotherapy with gene therapy designed to disrupt the growth of blood vessels to a tumor. The combination, tested in mice, is far more effective than standard chemotherapy and has no additional side effects. This innovative approach is described in the August 2002 issue of *Journal of Clinical Investigation*.

The new approach evolved from a similar system, now entering phase II human trials, that combines gene therapy with radiation therapy.

The radiation therapy approach appears to be quite effective, aiming a powerful anticancer arsenal at the tumor.

— Ralph Weichselbaum  
Chairman of Radiation Oncology

“The radiation therapy approach appears to be quite effective, aiming a powerful anticancer arsenal at the tumor,” said Ralph Weichselbaum, MD, professor and chairman of radiation oncology and director of the study. “The new combination with chemotherapy, however, not only enables us to target the original tumor but also potentially to aim at the small clusters of cancer cells that may have spread to distant sites.”

The therapy uses a modified cold virus to insert the gene for tumor necrosis factor (TNF) into cells within a tumor. TNF is a potent biological substance that can kill cancer cells directly and disrupt their blood supply, but it can be very toxic when given systemically.

The researchers originally altered the

TNF gene so that it could be turned on by radiation therapy. Now they have produced a version of the gene that can be activated by exposure to the common anti-cancer drug cisplatin. So mice treated with both the gene injections and cisplatin have high concentrations of TNF within the injected tumors, but nowhere else.

The researchers found that the combined therapy was far more effective than either cisplatin or TNF-gene injections alone. Tumors treated with the combination of gene therapy and cisplatin had “significant regression,” noted the authors, with “no additional toxicity.”

Untreated tumors doubled in size within four days and grew to more than four times their original size in two weeks. Tumors treated with cisplatin alone or injected with the virus alone grew more slowly.

Cisplatin currently is used to treat many types of cancer, including lung, head and neck, ovarian and bladder cancers. Adding TNF increases the anti-cancer effects of cisplatin at the injection site. It also may interfere with the tumor’s ability to increase its blood supply. Since TNF was produced only at the injection sites, it did not increase toxicity.

Indirectly, TNF also may support cisplatin’s assault on distant metastases. Earlier this year Weichselbaum’s group showed that TNF stimulated the production of angiostatin, which inhibits a tumor’s efforts to grow new blood vessels.

This novel approach to combination cancer therapy grew out of a series of discoveries from Weichselbaum’s laboratory. In 1989, they discovered that radiation therapy could induce cancer cells to release small amounts of TNF, which in turn made the radiation more effective.

In 1998, Weichselbaum showed that radiation dramatically enhanced the effects of angiogenesis inhibitors — natural substances such as angiostatin or endostatin. These interfere with a tumor’s efforts to grow new blood vessels, which are necessary for tumor growth.

Since 1999, Weichselbaum has worked with colleagues and scientists at GenVec, a biotech company based in

Gaithersburg, Md., to develop safe and effective ways to insert a supercharged TNF gene into tumor cells. Infected cells produce high levels of TNF only when radiation or chemotherapy turns on the gene.

— J.E.

## Ginseng berry shows promise for diabetes, obesity

An extract from the ginseng berry shows promise in treating diabetes and obesity, according to a research team from the University of Chicago’s Tang Center for Herbal Medicine Research. In the June issue of *Diabetes*, they reported that the extract completely normalized blood glucose levels, improved sensitivity to insulin, lowered cholesterol levels and decreased weight by reducing appetite and increasing activity levels in mice bred to develop diabetes.

For more than 2000 years, traditional Chinese medicine has used ginseng root to treat a variety of ailments. This study focused instead on substances found in the ginseng berry, which has very different concentrations of ginsenosides, the substances thought to be medically useful.

“Ginseng berry has a distinctive chemical profile and has not previously been used for therapy,” said Chun-Su Yuan, MD, PhD, assistant professor of anesthesia and critical care and director of the study. “We were stunned by how different the berry is from the root and by how effective it is in correcting the multiple metabolic abnormalities associated with diabetes.”

Yuan’s team, which included researchers from the Tang Center and the departments of anesthesia, clinical pharmacology and medicine, studied the effects of the extract, made from the pulp of the berry. They also studied one

**Ginseng berries have a heavier concentration than ginseng roots of ginsenosides, the substances thought to be medically useful.**



particular substance known as ginsenoside Re, which is concentrated in ginseng berries but quite scarce in the root.

They tested the extract by injecting it once a day into mice with a gene defect that causes weight gain and type 2 diabetes. They found:

- Daily injections of 150 mg/kg of the ginseng berry extract restored normal blood-sugar levels in diabetic mice. Blood-glucose levels fell from 222 mg/dl (quite high for a mouse) to 137 mg/dl (normal) within 12 days. Treated mice also had better scores on a glucose tolerance test, which measures how quickly the mice could remove excess glucose from the blood.
- The extract caused diabetic mice, which were also obese, to lose more than 10 percent of their body weight in 12 days. Untreated mice gained 5 percent of their weight in 12 days. The treated mice ate 15 percent less and were 35 percent more active than untreated mice. Once the injections stopped, weight gain gradually resumed.
- The extract improved insulin secretion and insulin sensitivity, both of which were abnormal in mice with diabetes.
- Treated diabetic mice had 30 percent lower cholesterol levels than untreated diabetic mice (117mg/dl versus 169mg/dl).
- The extract had no detectable effect on normal mice.

Tests using ginsenoside Re alone found that it had all of the anti-diabetic but none of the obesity-fighting activities of the extract. "This novel compound could serve as the basis for a whole new class of anti-diabetic medications," said Yuan, who also is working to isolate other substances from the extract that contributed to the weight loss.

"Since this berry contains agents that are effective against both obesity and diabetes," Yuan said, "the ginseng fruit has enormous promise as a source of new drugs."

—J.E.

## Bookmark

Alumni affiliations are indicated by degree and year; University of Chicago faculty affiliations, by asterisk.

### Medicine and Health

*Basic Pathology*  
Ramzi Cotran, Vinay Kumar\*,  
Stanley Robbins, eds.  
W.B. Saunders, 2002



*Big Doctoring in America: Profiles in Primary Care*  
Fitzhugh Mullan, MD '68  
University of California Press, 2002

*Building on Bion — Roots: Origins and Context of Bion's Contributions to Theory and Practice and Building on Bion — Branches: Contemporary Developments and Applications of Bion's Contributions to Theory and Practice*

Robert M. Lipgar\*, Malcolm Pines, eds.  
Jessica Kingsley Publishers, 2002

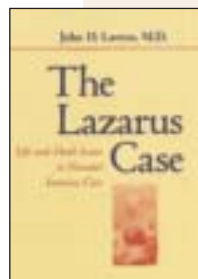
*Disorders of Bone and Mineral Metabolism*  
Fred Coe\*, Murray Favus\*, eds.  
Lippincott Williams & Wilkins, 2002



*Endocrinology*  
Leslie J. De Groot\*,  
J. Larry Jameson, eds.  
W.B. Saunders, 2001

*Great Sex for Moms: Ten Steps to Nurturing Passion While Raising Kids*  
Valerie Davis Raskin\*  
Simon & Schuster Trade Paperbacks, 2002

*The Lazarus Case*  
John Lantos\*  
Johns Hopkins University Press, 2001



*Motor Neuron Disease*  
Ralph W. Kuncl, PhD '75,  
MD '77  
W.B. Saunders, 2002

*Neural Plasticity*  
P.R. Huttenlocher\*  
Harvard University Press, 2002

*Pathology*  
Arthur S. Schneider,  
Philip A. Szanto,  
SB '57, AB '57  
Lippincott Williams & Wilkins, 2002

*Endotext.com: Your Endocrine Source*  
A complete, constantly updated, downloadable, free source on endocrine disease.  
Leslie J. De Groot\*, Lorraine Fitzpatrick, MD '80, et al., eds.  
www.endotext.org

*Thyroid Disease Manager*  
A complete, constantly updated, downloadable, free source on the thyroid.  
Leslie J. De Groot\*, Edwin Kaplan\*, Samuel Refetoff\*, Roy Weiss\*, Fred Wondisford\* et al., eds.  
www.thyroidmanager.org

### Psychiatry and Psychology

*Don't Call Me Nuts: Coping with the Stigma of Mental Illness*  
Pat Corrigan\*, Robert Lundin\*  
Recovery Press, 2001

*Dreams: A Reader on Religious, Cultural and Psychological Dimensions of Dreaming*  
Kelly Bulkeley, PhD '92, ed.  
Palgrave, 2001

*The Einstein Syndrome: Bright Children Who Talk Late*  
Thomas Sowell, PhD '68  
Basic Books, 2001

*Empirical Direction in Design and Analysis*  
Norman H. Anderson, SB '46, SM '49  
Lawrence Erlbaum Associates, 2001

*Family, Self and Psychotherapy: A Person-Centered Perspective*  
Ned L. Gaylin, AB '56, AM '61, PhD '65  
PCCS Books, 2001

*Using Groups to Help People*  
Dorothy Stock Whitaker, PhD '44,  
AM '48, PhD '52  
Brunner-Routledge, 2001

### Science and Technology

*Craniofacial Surgery: Science and Surgical Technique*  
John A. Jane Sr., AB '51, MD '56, PhD '67,  
Kant Y. Lin, Roy C. Ogle  
W.B. Saunders, 2001

*Genetic Engineering: Science and Ethics on the New Frontier*  
Michael Boylan, AM '76, PhD '79,  
Kevin Brown  
Prentice Hall, 2001

*Guide to Standard Floras of the World*  
David G. Frodin, SB '63  
Cambridge University Press, 2001