Genomic changes reveal evolution of SARS

Careful study of genetic changes in the SARS virus during the 2003 epidemic has enabled researchers from China and the University of Chicago to chart three phases of the virus’s molecular evolution as it gradually adapted from animal to human hosts and became more infectious.

“What we see is the virus fine-tuning itself to enhance its access to a new host: humans,” said study co-author Chung-I Wu, PhD, professor and chairman of ecology and evolution at Chicago. “This is a disturbing process to watch, as the virus improves itself under selective pressure, learning to spread from person to person, then sticking with the version that is most effective.”

In the journal *Science*, researchers reported how the SARS virus (above) quickly adapted to infect humans during the 2003 epidemic. The earliest phase involved cases that appeared to be independent and featured viral genomes identical to those found in animal hosts, the researchers reported in the journal *Science*. The 11 early cases had documented contact with wild animals.

The middle phase began with the first “super-spread event,” the major SARS outbreak in a hospital in Guangzhou beginning Jan. 31, 2003. This outbreak produced 130 cases, including 106 acquired in the hospital. A doctor from this hospital carried the virus to Metropole Hotel in Hong Kong on Feb. 21. Other hotel guests became infected and spread the virus further.

Cases originating after the hotel cluster fall into the late phase.

Although most of the known SARS virus genomes have come from the epidemic’s earliest stages, this study focused on 29 genomic sequences obtained from 22 patients from Guangdong Province who experienced onset of the disease in all three phases of the epidemic, plus two patients from the late phase in Hong Kong.

Two genotypes dominated the early phase of the epidemic. Both differed from later viral samples in a region known as ORF. Five early isolates contained a short sequence of 29 nucleotides that is missing from most of the previously known virus sequences. Four other early isolates showed a previously unreported 82-nucleotide deletion.

By the middle phase, the version with the 29-nucleotide deletion had become dominant.

Besides the large deletions, the researchers found 259 smaller variations, changing just a single piece of the virus’s genetic code. Because SARS, like HIV, uses RNA instead of DNA to store its genetic information, it has a high mutation rate.

The researchers discovered a series of genetic motifs, like molecular fingerprints, that enabled them to distinguish between different lineages. Early-phase viruses have a characteristic motif that is shared by the viruses isolated from animals.

The middle-phase viruses show a slightly different fingerprint, with two variations: one tied to the majority of the cases in the hospital outbreak and a different version associated with Hong Kong. From the hotel cluster to the end of the epidemic in August, viruses with a different motif dominate. “Surprisingly few genotypes predominated in the late phase,” the authors wrote.

The researchers tentatively trace this late-phase virus back to one patient infected with an unusual variation in the hospital in February. She began having symptoms Feb. 7 and subsequently had contact with the physician who carried the virus to Hong Kong Feb. 21.

The researchers also looked closely at the history of mutations in one gene, which produces the spike protein that is thought to be involved in the process the virus uses to enter cells. This gene underwent rapid mutation in the epidemic’s earliest stages, but that rate slowed in the later stages after the virus had adapted to infect humans rather than other animals.

“The genetic fingerprints add a whole new layer to our understanding of the course of events in this epidemic,” Wu said, “but this work could not have been done without a remarkable effort by our Chinese colleagues in the field and in the lab to unravel the precise history of hundreds of patients affected by this epidemic.”

MidwayNews

Preserving China’s biodiversity

A new International Center for Studies of Evolution and Biodiversity headquartered in Beijing will train China’s next generation of conservation biologists.

Co-founded by University of Chicago evolutionary geneticist Chung-I Wu, PhD, in collaboration with biodiversity specialists in China and Germany, the center will foster scientific discussion of such topics as genetics, biodiversity and extinction. Wu said he expects the center to serve as “a model for all conservation efforts worldwide by addressing the need for theoretical development and by fostering greater cross- and interdisciplinary research.”

Based at the Chinese Academy of Sciences Kungming Institute of Zoology, the center also will work to increase conservation awareness and action in China.
The research also revealed serious concerns with current asthma practice. In only 18 of the 70 studies, people with more than mild asthma were taking anti-inflammatory medications prior to joining the study. Although 22 of the studies required all subjects to begin or continue to take appropriate medications, 48 of the studies did not. In six trials, subjects who had been on appropriate anti-inflammatory therapy prior to the study were taken off these medications.

“These children aren’t taking medications before the study for a variety of reasons,” Ross said. “It may be a lack of access to medications and pediatric care, a lack of family education and understanding regarding the need for daily medication, and/or a failure of health care providers to prescribe appropriate treatment.”

“Children aren’t taking medications because the very medication they depend on is being withheld from them during these studies.”

Whatever the reason, Ross said, it’s “unconscionable” that children are not properly treated when joining these studies. “Those who don’t get the experimental drug should get standard treatment,” she said.

The researchers chose to scrutinize asthma research because the disease is one of the most common chronic conditions of childhood. Nearly 4.5 million U.S. children have asthma. In 1998, asthma resulted in more than 200 deaths, 174,000 hospitalizations, more than 867,000 emergency room exams, and 5.8 million visits to doctors’ offices and 10 million missed school days. Many patients suffer severe discomfort from anxiety that may be associated with the disease.

The researchers examined the impact that 1998 policy initiatives have had on the inclusion of children in clinical trials. The NIH and the Food and Drug Administration have attempted to involve more children earlier in the drug development process to ensure that new treatments are effective and appropriately dosed. But the researchers noted that only one of 52 studies involving both children and adults analyzed the effects of the experimental medication on the pediatric subjects.

“The goal of the policies is to place some children at risk for the benefit of children as a class, but unless researchers do subpop analyses, we are not getting any benefit to children as a class,” Ross said.

Many of the asthma studies examined approval, so they were scrutinized for their research ethics. Ross explained that IRBs have two functions: to protect subjects and to ensure that subjects are informed to give consent. She argues that “IRBs do a better job ensuring consent than protecting subjects, in part because of our cultural attitude that individuals can decide what is in their best interest.” But, Ross said, IRBs should place greater focus on protection, particularly for vulnerable populations like children.

Ross described the criteria used in many clinical asthma trials involving children as “flawed.” She said researchers and IRBs need to re-evaluate how these types of clinical asthma trials are conducted. Ross’ work on children in research was funded by an NIH grant. Additional authors of the paper are Benjamin Wölfend, MD, a bioethicist at the National Human Genome Research Institute, and M. Justin Coffey, a University of Chicago medical student.

— Kerry Odboy

Children with asthma who were placed in clinical-trial control groups were more than twice as likely to be harmed because they did not receive standard asthma therapy than children in the same studies who continued to receive appropriate medications.

Clinical trials put children with asthma at risk

Enrolling children with asthma in the placebo arm of a clinical trial is common, harmful and ethically unjustified, researchers from the University of Chicago and the National Institutes of Health (NIH) argued in the journal Pediatrics.

A systematic review of all U.S. pediatric clinical asthma trials published between 1998 and 2001 showed that children with asthma were more than twice as likely to be harmed — defined as forced exacerbation — if they did not receive standard asthma therapy as compared to children as a class, but unless researchers do subpop analyses, we are not getting any benefit to children as a class,” Ross said.

Many of the asthma studies examined Genes linked to evolution of human brain Researchers have identified two genes that were involved in the dramatic expansion of the human cerebral cortex — considered to be a hallmark of human evolution. The finding comes on the heels of recent studies by the same group, which also discovered a genetic difference that may account for the variation in brain size between humans and other primates.

Led by Bruce Lahn, PhD, assistant professor in human genetics and molecular genetics and cell biology, the researchers presented evidence in the journal Human Molecular Genetics that natural selection pressure led to the evolution of a version of a gene called microcephalin found in humans. Co-authors Patrick Evans, Jeffrey Anderson, Eric Vaillender and Sun Shim Choi work in Lahn’s laboratory.

In an earlier article published in the same journal, Lahn and his colleagues showed that the pressure of natural selection similarly affected the abnormal spindle-like microcephaly associated (ASPM) gene, a gene also linked to brain size.

People have studied the evolution of the brain for a long time, but they have traditionally focused on the comparative anatomy and physiology of brain evolution,” said Lahn, who also is an assistant investigator at the Howard Hughes Medical Institute. “I would venture, however, that there really hasn’t been any convincing evidence until now of any gene whose changes might have contributed to the evolution of the brain.”

Chicago scientists made the cover of Cell for their identification of two genes involved in the evolution of the human brain.

The researchers chose to explore microcephalin because a mutant form of the gene is among those thought to be responsible for microcephaly, a developmental defect in humans. This disorder is marked by reduced brain size, particularly the cerebral cortex — the part of the brain responsible for planning, abstract reasoning and other higher brain functions. The brains of people with microcephaly are otherwise normal and other brain functions seem unaffected.

For monkeys, it’s nature, not nurture

For infant rhesus macaques, heredity for outwith the socialization when it comes to behavioral traits like aggression and sociability. Monkeys taken from their mothers at birth and raised by foster mothers behaved more like their birth mothers, according to a study by behavioral biologist Daris Maestripieri, PhD. During a three-year period, Maestripieri and his team observed how often the offspring had bodily contact with other group members and how many times they expressed aggression, such as threats, slaps, bites and chases. The team found that an offspring’s behavior mirrored that of its biological mother and that practically no behavioral differences were seen between offspring and its foster mother. Maestripieri’s work, published in Developmental Psychobiology, may help other researchers understand the biological origins and evolutionary impacts of characteristics that promote socialization among humans and other primates.

Alcohol and chronic back pain don’t mix

The first study of the relationship between chronic back pain and consumption of alcohol has sent up red flags for doctors. The findings, published in the journal Disability and Rehabilitation, suggest that physicians need to be more careful about prescribing pain relievers that can cause serious liver damage or respiratory depression when combined with alcohol. Co-authors by emergency medicine resident Sihan Boulter, MD, the study assessed patients’ health, psychological state and alcohol consumption. It showed that drinking can improve physical performance in men experiencing similar levels of pain. But drinking appears not to decrease pain and in fact the study suggests that heavy drinkers could be at greater risk for disability. Analysis of data from 137 male patients showed no difference in the use of narcotic pain relievers between people who claimed heavy alcohol use and those who reported light drinking.

9
A new weapon against parasites

The first effective, non-toxic method of combating toxoplasmosis—one of humankind’s most common, chronic parasitic diseases—was reported in the Proceedings of the National Academy of Sciences. Ophthalmologist and visual scientist Rosa McLaid, MD, led the multicenter study that successfully transported drugs across multiple membrane barrières and into cysts of Toxoplasma gondii, the single-celled microorganism that causes toxoplasmosis. Prior to this study, researchers were unable to access the microbe in its latent stage. The study also described a new therapeutic target within the parasite: an enzyme involved in synthesizing fatty acids necessary for survival. Each year in the United States, toxoplasmosis affects approximately 3,000 infants, causing severe eye damage, mental retardation and death. In its latent stage, the disease infects the nervous system causing lifelong infection. Although three billion people worldwide are infected, including about 30 percent of Americas, most cases are asymptomatic.

Promising treatment for kidney cancer patients

A newly discovered treatment for patients with advanced renal cancer shows promising results for markable short-term benefits. The drug under investigation, BAY 43-9006, produced positive results in 21 of 50 patients (42 percent), whose tumors shrank at least 25 percent within the study’s first 13 weeks. Six of the 21 patients experienced a reduction of 50 percent or more, according to clinical pharmacologist Mark Ratain, MD. In 13 patients (25 percent) tumors stabilized within 25 percent of pretreatment size. A third of the patients left the study because of adverse effects, such as painful rash or diarrhea. Study BAY 43-9006 is believed to inhibit an enzyme known as Raf kinase, which regulates tumor cell proliferation and also may play a role in the growth of new blood vessels to feed the tumor. Only 10 percent to 15 percent of patients with metastatic kidney cancer respond to standard immunotherapy.

It’s a great opportunity for students and residents to appreciate the gift of plastic surgery in transforming children with deformities and to see what a phenomenal impact their intervention can have in somebody’s life.

— Robert L. Walton, MD, Chief of Plastic Surgery

Predicting insect outbreaks

Sudden population increases occur in many species: butterflies and moths, voles, lemmings and other small mammals. Such outbreaks, which occur at irregular, hard-to-predict intervals, can devastate huge areas of forest. A new mathematical model predicts unpredictable gypsy moth outbreaks better than any model yet. Greg Dwyer, PhD, associate professor of ecology and evolution, lead author of the study published in Nature, combined elements from two prevailing but flawed insect-outbreak theories: one based on host-parasite and host-pathogens, the other based on “general” predators. Dwyer introduced a host-parasite-plus-predator model that combines the stabilizing effects of dependable predators with effects of disease to account more accurately for the gypsy moth outbreaks.

— Laura Bodner

A new mathematical model better predicts devastating outbreaks of the gypsy moth.
Although the studies are preliminary, the evidence of evolutionary pressure on the two genes offers a hint at how the large human brain evolved.

— Bruce Lahn, PhD, Assistant Professor of Human Genetics

As with ASPM, the researchers traced the evolution of microcephalin by comparing the gene’s sequence in a range of primates, including humans, as well as nonprimate mammals. Specifically, the researchers sequenced the human, chimpanzee, gorilla, orangutan, gibbons, colobus monkey, squirrel monkey and lemur forms of the microcephalin gene.

“We chose these species because they were progressively more closely related to humans,” Lahn said. “For example, the closest relatives to humans are the colobus monkey, squirrel monkey and chimpanzee, gorilla, orangutan, gibbon, and the next closest are gorillas and the rest go down the ladder to the most primitive.”

For each species, the researchers identified changes in both the microcephalin and the ASPM genes that altered the structure of the resulting protein as well as changes that did not affect protein structure. Only those genetic changes that alter protein structure are likely to be subject to evolutionary pressure, Lahn said.

While changes in the ASPM gene showed the most dramatic acceleration in the later lineage from ape ancestors to humans, the greatest acceleration in the evolution of microcephalin gene occurred early in the primate lineage, Lahn said.

“This provides strong evidence that the evolution of the microcephalin gene is highly accelerated, specifically along the lineage leading to humans, but not necessarily in a terminal human branch,” he said. “Accelerating certain genes — such as the evolution of microcephalin — is likely the result of competition among genes that control brain size or gross morphology during development will be disproportionately involved in brain evolution.”

— Catherine Gianaro

Human genome data overturned

University of Chicago researchers have discovered extensive gene “traffic” on the X chromosome in mammals, overturning a conventional theory about how the genes evolved on the sex chromosome.

The study, published in Science, shows that excess genes on the X chromosome “jump” to a non-sex chromosome, or autosome, during germline cell division. This finding contradicts the historic view that the sex chromosome is not the ‘hot bed’ of sex-related genes that was once thought.

“An X-linked gene spends two-thirds of its time in females compared with one-half for an autosomal gene, so that the X chromosome becomes ‘demasculinized,’” the researchers wrote.

Long’s laboratory first discovered this phenomenon itself,” said J.J. Emerson, a fourth-year graduate student in Long’s lab and one of the paper’s lead authors. “We can see very clearly that the X is an unusual case. Through the evolution of gene duplication, the X chromosome seems to have an excess of traffic.”

Researchers located at retropos genes — those genes that are copied and pasted repeatedly into the genome — simply because scientists can map the direction of those genes (whether individual genes left or joined the chromosome). The team looked at the “expected levels of traffic” by plotting pseudo genes — those genes that lose their function after being duplicated and which natural selection ignores.

The researchers compared the rate of gene traffic on the X to all the autosomes and found the X chromosome exports four times as many genes as the average autosome and imports 3.5 times as many. They did not look at the traffic rate of the Y chromosome. “It’s such a small chromosome that any excess or decrease is miniscule,” Emerson said. They found that 77 percent of the genes leaving the X chromosome have testis expression, compared with 44 percent of genes that jump from autosomes to autosomes.

The researchers noted that this Darwinian process has evolved slowly since both mice and humans share the same excess traffic characteristics on the X chromosome. It was, therefore, present prior to the mouse-human split.

The study also shows that although about 71 percent of those genes leaving the X chromosome are to be expressed in a male germline cell, only about 14 percent of the genes being imported to the X are female expressed.

No old idea that the X chromosome is a major contributor of sexual genes is also not true.

— MaryJan Long, PhD, Associate Professor of Ecology and Evolution

New generation of scanners brings power and speed

The second ever clinical chest tomography scanner ever produced by Philips Medical Imaging, and the first to reach the United States, has been installed and is now in clinical use at the University of Chicago Hospital. The scanner, which has four times as many detectors as a typical multi-detector CT scanner, combines uniview and multiplanar image quality with remarkable speed. It can produce detailed pictures of any organ in a few seconds and provide sharp, clear, three-dimensional images, including 3-D views of the blood vessels, in an instant.

Researchers discovered that the X chromosome is not a major contributor of sex-related genes. Rather, excess genes on the chromosome “jump” to a non-autosome chromosome before being expressed, which contradicts claims in the historic human genome project paper.

Long and his colleagues propose that sexual xenogamy also may cause this high traffic volume on the X. Since females have two X chromosomes and males have only one, the X is more likely to end up in a female. And if there is a beneficial gene mutation on the X, there is a higher chance that it would help the female, despite its effect on the male. The researchers suggest that male-expressed genes leave the X for an autosome, where each gene would have the same share of the chromosome and, therefore, a better environment to carry out its function more effectively.

The scientists looked at retropos genes — those genes that are copied by being reinserted randomly into the genome — simply because scientists can map the direction of those genes (whether individual genes left or joined the chromosome). The team looked at the “expected levels of traffic” by plotting pseudo genes — those genes that lose their function after being duplicated and which natural selection ignores.

The researchers compared the rate of gene traffic on the X to all the autosomes and found the X chromosome exports four times as many genes as the average autosome and imports 3.5 times as many. They did not look at the traffic rate of the Y chromosome. “It’s such a small chromosome that any excess or decrease is miniscule,” Emerson said. They found that 77 percent of the genes leaving the X chromosome have testis expression, compared with 44 percent of genes that jump from autosomes to autosomes.

The researchers noted that this Darwinian process has evolved slowly since both mice and humans share the same excess traffic characteristics on the X chromosome. It was, therefore, present prior to the mouse-human split.

The study also shows that although about 71 percent of those genes leaving the X chromosome are to be expressed in a male germline cell, only about 14 percent of the genes being imported to the X are female expressed.

“No old idea that the X chromosome is a major contributor of sexual genes is also not true.”

— Catherine Gianaro

So the old idea that the X chromosome is a major contributor of sexual genes is also not true.

— MaryJan Long, PhD, Associate Professor of Ecology and Evolution

Defying the odds, twice

Plastic surgeons McKay McKinnon, MD, gained worldwide attention in 2000 after he successfully removed a 200-pound tumor from a Filipino student. The student’s chances of surviving the operation were one in 10.

Patient Loti Hoogewind’s story received international coverage, including a spot on the Discovery Channel, and caught the attention of a Romanian family with a similar problem. Lucius Bunghes, 48, of Brasov, had the same disease that caused Hoogewind’s tumor – neurofibromatosis, or NF, a progressive nervous system disorder that causes disfiguring tumors. Because the Romanian government said it could not afford to pay the $300,000 needed for Bunghes to receive treatment in the United States, McKinnon and a team of doctors traveled to Bucharest, Romania, in January 2004 to perform the 16-hour surgery for free. Doctors successfully removed the benign tumor that weighed 176 pounds and covered most of Bunghes’s back and thighs.

Sexy tentacles

While observing the mating ritual of a pair of two-spot octopus, evolutionary biologist Janet Voight, PhD, saw something she didn’t expect. One of the male’s eight tentacles was longer than the other. The male two-spot octopus passes spermatophores — tubular packets filled with millions of sperm — from the tip of the longer tentacle to a female during mating. Voight discovered that the tentacle involved in mating was engorged with erectile tissue not unlike that of the mammalian penis. The finding is intriguing because even though octopi and mammals do not share recent common ancestry, they have evolved similar ways of solving a problem of reproduction.

Understanding how erectile tissue works in a castrated invertebrate could someday lead to new chemical treatments for such human ailments as erectile dysfunction and high blood pressure, Voight said. The study appeared in the Journal of Zoology.

Similar problem. Lucius Bunghes, 48, of Brasov, had the same disease that caused Hoogewind’s tumor – neurofibromatosis, or NF, a progressive nervous system disorder that causes disfiguring tumors. Because the Romanian government said it could not afford to pay the $300,000 needed for Bunghes to receive treatment in the United States, McKinnon and a team of doctors traveled to Bucharest, Romania, in January 2004 to perform the 16-hour surgery for free. Doctors successfully removed the benign tumor that weighed 176 pounds and covered most of Bunghes’s back and thighs.

While observing the mating ritual of a pair of two-spot octopus, evolutionary biologist Janet Voight, PhD, saw something she didn’t expect. One of the male’s eight tentacles was longer than the other. The male two-spot octopus passes spermatophores — tubular packets filled with millions of sperm — from the tip of the longer tentacle to a female during mating. Voight discovered that the tentacle involved in mating was engorged with erectile tissue not unlike that of the mammalian penis. The finding is intriguing because even though octopi and mammals do not share recent common ancestry, they have evolved similar ways of solving a problem of reproduction.

Understanding how erectile tissue works in a castrated invertebrate could someday lead to new chemical treatments for such human ailments as erectile dysfunction and high blood pressure, Voight said. The study appeared in the Journal of Zoology.

Similar problem. Lucius Bunghes, 48, of Brasov, had the same disease that caused Hoogewind’s tumor – neurofibromatosis, or NF, a progressive nervous system disorder that causes disfiguring tumors. Because the Romanian government said it could not afford to pay the $300,000 needed for Bunghes to receive treatment in the United States, McKinnon and a team of doctors traveled to Bucharest, Romania, in January 2004 to perform the 16-hour surgery for free. Doctors successfully removed the benign tumor that weighed 176 pounds and covered most of Bunghes’s back and thighs.

While observing the mating ritual of a pair of two-spot octopus, evolutionary biologist Janet Voight, PhD, saw something she didn’t expect. One of the male’s eight tentacles was longer than the other. The male two-spot octopus passes spermatophores — tubular packets filled with millions of sperm — from the tip of the longer tentacle to a female during mating. Voight discovered that the tentacle involved in mating was engorged with erectile tissue not unlike that of the mammalian penis. The finding is intriguing because even though octopi and mammals do not share recent common ancestry, they have evolved similar ways of solving a problem of reproduction.

Understanding how erectile tissue works in a castrated invertebrate could someday lead to new chemical treatments for such human ailments as erectile dysfunction and high blood pressure, Voight said. The study appeared in the Journal of Zoology.

Similar problem. Lucius Bunghes, 48, of Brasov, had the same disease that caused Hoogewind’s tumor – neurofibromatosis, or NF, a progressive nervous system disorder that causes disfiguring tumors. Because the Romanian government said it could not afford to pay the $300,000 needed for Bunghes to receive treatment in the United States, McKinnon and a team of doctors traveled to Bucharest, Romania, in January 2004 to perform the 16-hour surgery for free. Doctors successfully removed the benign tumor that weighed 176 pounds and covered most of Bunghes’s back and thighs.
Chicago biochemist features retired University of commercialization of a number of studies that tell of the discovery, award-winning journalist, uses case of basic scientific research. To reap huge profits from the sale taxpayer ends up paying twice research at taxpayer-funded institutes of Health. But the research at taxpayer-funded 25 years actually originated from important new drugs of the past demonstrates that almost all the drug industry and the high costs litigation, political deals and "sordid tale of endless patent prices for the drug," Goozner said. The Goldwasser-Amgen story is a "world tale of endless patent litigation, political deals and marketing schemes, all designed to discourage rival drug companies and promote the overuse of the drug to maintain its high price, most of which was paid by the federal government's Medicare program." Goozner states that tax-paying citizens already are being "robbed blind" and does this all relate to a drug's action? This Side of Doctoring: Reflections From Women in Medicine Eliza Lo Chin, MD, MPH Oxford Press, 2003 Chin reveals an intimate collection of stories, poems, essays and quotations about the joys and heartbreaks of being a woman and a physician. More than 130 stories speak to the trials, rewards and surprises of practicing medicine, starting with the writings of early medical pioneers. University alumni Stephanie Nagy-Agren, MD '87, and Florence Sheehan, MD '79, are featured in the book.

Merrill Goozner
The $800 Million Pill: The Truth Behind the Cost of New Drugs Merril Goozner
University of California Press, 2003 This is an informative and practical source book for professionals and parents concerned about Fragile X Syndrome. Fast and Harris-Schmidt explore the nature of this genetic condition from birth to age 01 and its link to developmental delays, speech-language disorders and learning disabilities. Topics covered include physical characteristics, cognitive development, sensory issues, speech and language development, behavior and emotional issues, academic intervention, biological basis, future directions, and education placements and programming. Fast is a neurologist of biology at St. Xavier University Harris-Schmidt is an associate professor of communication sciences at St. Xavier, whose son has Fragile X syndrome.

MidwayNews

Drug Localization in Tissues and Cells: A Basis for Tissue and Cellular Pharmacokinetics, Drug Targeting, Delivery, and Prediction Walter E. Stumpf, PhD '67 IDDC Press, 2003 This book answers important questions about in vivo drug disposition, such as: Where do drugs act in the body? Are the targets reached? Which receptors lead to side effects or engender toxicity? What are the routes of drug delivery? How much of a certain drug is bound to receptors? For how long does it bind? And how does this all relate to a drug's action? This Side of Doctoring: Reflections From Women in Medicine Eliza Lo Chin, MD, MPH Oxford Press, 2003 Chin reveals an intimate collection of stories, poems, essays and quotations about the joys and heartbreaks of being a woman and a physician. More than 130 stories speak to the trials, rewards and surprises of practicing medicine, starting with the writings of early medical pioneers. University alumni Stephanie Nagy-Agren, MD ‘87, and Florence Sheehan, MD ‘79, are featured in the book.

Merrill Goozner
The $800 Million Pill: The Truth Behind the Cost of New Drugs Merril Goozner
University of California Press, 2003 This is an informative and practical source book for professionals and parents concerned about Fragile X Syndrome. Fast and Harris-Schmidt explore the nature of this genetic condition from birth to age 01 and its link to developmental delays, speech-language disorders and learning disabilities. Topics covered include physical characteristics, cognitive development, sensory issues, speech and language development, behavior and emotional issues, academic intervention, biological basis, future directions, and education placements and programming. Fast is a neurologist of biology at St. Xavier University Harris-Schmidt is an associate professor of communication sciences at St. Xavier, whose son has Fragile X syndrome.

HIPAA Plain and Simple: A Compliance Guide for Health Care Professionals
Edward D. Jones, AB ’66, and Carolyn P. Hartley, AM ’88, PhD ’95
American Medical Association Press, 2003

This guide provides simple explanations of the eight types of transactions standards, definitions of electronic terms and analyses of the pros and cons of alternative electronic transaction methods. A step-by-step plan helps readers implement electronic transactions and return-on-investment analyses.

HIPAA Transactions: A Non-Technical Business Guide for Health Care Professionals
Edward D. Jones, AB ’66, and Carolyn P. Hartley, AM ’88, PhD ’95
American Medical Association Press, 2003

This guide provides simple explanations of the eight types of transactions standards, definitions of electronic terms and analyses of the pros and cons of alternative electronic transaction methods. A step-by-step plan helps readers implement electronic transactions and return-on-investment analyses.
Chemotherapy improves survival in early-stage lung cancer

Chemotherapy following surgery dramatically improves survival rates for patients with early-stage lung cancer, according to research presented at the annual June meeting of the American Society for Clinical Oncology.

It is the first study to demonstrate a substantial benefit from chemotherapy for patients with stage IB non-small-cell lung cancer — just as for breast and colorectal cancer.” Schilsky said. The study of 344 patients found that three months of adjuvant chemotherapy using paclitaxel (Taxol) and carboplatin decreased the risk of lung-cancer death by 49 percent. After four years, 15 percent of the chemotherapy patients had died of lung cancer compared with 26 percent of those in the observation group. Those who received chemotherapy had a higher overall four-year survival rate of 71 percent — compared with 59 percent in the observation group — and were 38 percent less likely to die from all causes.

Adjuvant chemotherapy should now be considered standard treatment for patients with early-stage lung cancer just as for breast and colorectal cancer.

— Richard Schilsky, MD, Professor of Medicine

Gary Strauss, MD, MPH, of Rhode Island Hospital and Brown Medical School, led the study and now recommends adjuvant chemotherapy to patients with high-risk, early-stage disease. “These figures solidify adjuvant chemotherapy as a proven way to improve cure rates for patients with early-stage lung cancer,” he said.

Lung cancer specialist Everett Vokes, MD, a professor of medicine and chief of hematology/oncology at the University of Chicago, called the findings “a major breakthrough” after several decades of research. “Many of the previous chemotherapy regimens were effective but they were toxic that patients left the trial,” Vokes said. “This regimen not only increased the cure rate, but was also well-tolerated. The next step is to find better ways to detect lung cancer at this early stage when it is still curable.”

Stage IB involves a tumor at least 3 centimeters in diameter or one of any size that invades the surface lining of the lung, but without regional lymph-node involvement. Previous studies of adjuvant chemotherapy after surgical removal of a tumor in this stage produced inconsistent results.

In this study, half of the patients received chemotherapy for three months of chemotherapy after surgery and the other half received none. The chemotherapy was well-tolerated, with no deaths related to drug toxicity. The most serious side effect was neutropenia, a temporary reduction in white blood cells that places the patient at high risk for infections. Future studies will compare the effectiveness of chemotherapy in early-stage lung cancer based on different drug combinations.

This trial was coordinated by CALGB. Also participating were the Radiation Therapy Oncology Group and the North Central Cancer Treatment Group, large cooperative groups that conduct clinical trials focusing on new cancer treatments.

— John Easton

Ginseng reduces effects of anti-clotting drug

University of Chicago researchers have found that ginseng, a popular, over-the-counter supplement, interferes with warfarin, also known as Coumadin, a drug commonly used to prevent blood clots. Ginseng is among the best-selling herbal supplements in the United States.

The scientists, who reported their findings in the Annals of Internal Medicine, encourage people who take both ginseng and warfarin to notify their doctors and urge doctors to ask patients who take warfarin whether they also take ginseng. A “blood-thinning” drug, warfarin prevents blood clots from forming or growing larger. It is prescribed for people who have certain types of irregular heartbeat, have had a heart attack or have undergone heart-valve replacement surgery.

“Precise dosing is crucial. With too small a dose, the risk of clots increases, but too much can cause serious bleeding,” said lead author Chun-Su Yuan, MD, PhD. “So a substance such as ginseng that alters warfarin’s effects even slightly can have significant consequences.”

Yuan is the Cyrus Tang Professor of Anesthesiology and Critical Care and directs the Tang Centre for Herbal Medicine Research at the University of Chicago.

For four weeks, Yuan’s team studied 20 healthy volunteers. During the first week and again during the fourth, all subjects received 5 milligrams of warfarin daily for three days. Beginning in the second week, 12 subjects took 2 grams of powdered ginseng in capsules while the others received a placebo. The researchers found that after two weeks, daily doses of ginseng significantly reduced the blood levels and anti-clotting effects of warfarin.

Since ginseng alone can promote bleeding and delay clot formation, the researchers were surprised to find that it reduced the anti-clotting effect of warfarin compared with those who took the placebo. The researchers said they suspect that substances in ginseng may enhance the function of enzymes that break down warfarin, clearing it from the blood stream more rapidly.

The National Institutes of Health and the Tang Center for Herbal Medicine Research funded the study.

— John Easton

Home-based dialysis

Home-based hemodialysis may become the healthiest way to treat people with end-stage renal disease. Dadi Ding, former dialysis nurse and long-term dialysis patient, recently became the first person in the Chicago area to use the system. “I feel so much better,” Ding said. “I hate to skip a day. I dialyze seven times a week.”

Traditional dialysis — a few hours three times a week — has been linked to health problems, lower quality of life and increased chance of death. Patients who dialyze daily say they have more energy, better appetites, improved blood pressure and less fatigue, said Chicago nephrologist Orly Kohn, MD. Unlike previous home systems, this new one is compact, low-maintenance and highly automated.

Can’t beat ‘em? Pacify ‘em.

Researchers working with lab mice have discovered a way to control Pseudomonas, a genus of bacteria that can cause some of the most lethal post-operative infections known. Instead of using antibiotics to kill Pseudomonas, the researchers injected a protective coating into mice. Pseudomonas occurs in the intestines of about 1 percent of healthy people and often can turn deadly, according to general surgeon John Alverdy, MD. The mice underwent major surgery and then Alverdy’s research team injected the mice’s bowels with PEG 15-20 at the time of infection. The team found the mice were fully protected and showed no ill effects. Repeated use of this approach could prevent hospital infections among patients without using antibiotics.

Chemo effects blocked

A routinely prescribed anti-nausea drug, dexamethasone, may interfere with the effectiveness of paclitaxel and doxorubicin, two drugs commonly used in breast cancer chemotherapy. Hematologist Suzanne Conzen, MD, directed a study that found that pre-treatment of breast cancer cells with dexamethasone reduced by more than 25 percent the effectiveness of both chemotherapeutic drugs in killing cancer cells. The two drugs under investigation rely on different mechanisms to reduce the number of tumor cells. Conzen also identified genes that play a major role in dexamethasone’s effects by shunting cancer cells from the affects of chemotherapy. By blocking protein produced by these genes, Conzen reversed the anti-nausea drug’s unwanted effects.
Research. Jensen shares the award three scientists to receive the 2004 Institute for Cancer Research, is among Professor Emeritus for the Ben May B. Huggins Distinguished Service Award. The Charles Elwood Jensen, PhD ’44, has been named the Alice Hogge and Distinguished Service Professor in Medicine, as well as the Sara and Harold Lincoln Thompson Distinguished Service Professor in Pathology.

Jill J. Mohr, PhD, assistant professor of medicine, has been appointed to the 2004 Board of Examiners for the Malcolm Baldridge National Quality Award.

Jonathan Pritchard, assistant professor of human genetics, received the inaugural Lancet Paper of the Year Award. The paper, titled “Genetic Structure of Human Populations,” was published in December 2002 with the help of his colleagues from the University of Oxford.

Kathleen Kelley, MD, associate professor of clinical psychiatry and pediatrics, has been named a Harvard Macy Fellow by the American Academy of Child and Adolescent Psychiatry.

Joseph B. Kirnser, MD, PhD ’42, the Louis Block Distinguished Service Professor of Medicine, received the first Lifetime Achievement Award from the Institute of Medicine of Chicago.

Vinay Kumar, MD, FRCPath, chairman of the department of pathology, has been named the Alice Higgins and Arthur A. Baer Professor.

Wen-Hsiung Li, PhD, the George Beadle Distinguished Service Professor in Ecology and Evolution, has been named the first James D. Watson Distinguished Service Professor.

James Madda, MD, dean of the Biological Sciences Division and Pritzker School of Medicine, was named the Richard T. Crane Distinguished Service Professor in Pathology, as well as the Sara and Harold Lincoln Thompson Distinguished Service Professor in Pathology. The study follows a paper published in Nature four years ago in which Ramírez and colleagues showed that the same network of respiratory cells in the brainstem controls different forms of breathing; the sigh, the gasp and normal rhythm. Shortly after that groundbreaking paper, scientists overcame conventional theory that pacemaker neurons drive the entire network of cells. Researchers found that riluzole, a drug that blocks the cell’s sodium channel, could silence pacemaker neurons yet the rhythm of the network remained active. But riluzole didn’t disable all of the pacemakers, Ramírez said, which is why the rhythm continued. He found that two groups of pacemaker neurons exist: One group operates on sodium channels and the other on calcium. Only four of the 172 pacemaker cells were not affected by riluzole.

“You have to have a perfect recording in order to get those cells,” Ramírez says. “It’s not that these neurons are more powerful, just more elusive.”

To test the new theory, the researchers applied not only riluzole to silence sodium-driven pacemakers but also the drug cadmium to silence calcium-driven pacemakers. The rhythm stopped, confirming that pacemaker neurons actually do drive the network.

To take their investigation a step further, the researchers tested the network in a hypoxic state, an oxygen-deprived condition. According to the researchers, during hypoxia, the body shuts down most of the cellular respiratory network and focuses its energy on gasping, which is modulated solely by the sodium-driven pacemaker neurons. If those neurons are blocked, for whatever reason, the body cannot gasp.

This means there may be nothing wrong with a baby’s breathing under normal conditions, but if the baby goes into hypoxia — either from a blocked airway or because the baby sleeps on the stomach and does not receive sufficient oxygen — then the baby needs the sodium-driven pacemakers in order to gasp. Gasping wakes the baby and initiates movement or crying.

New weapons against anthrax bacteria

Chicago researchers have discovered three unrelated compounds that inhibit two toxins in the deadly anthrax bacterium Bacillus anthracis. Cancer biologist Wei-Jen Tang, PhD, discovered years ago that anthrax, which is caused by the deadly bacterium Bacillus anthracis, can be treated with calcium channel blockers. The researchers were able to discover the toxins in the deadly anthrax bacterium.

The researchers have identified the group of neurons responsible for gasping. Their discovery one day could help prevent SIDS.

Researchers have identified the group of neurons responsible for gasping. Their discovery one day could help prevent SIDS.

Researchers have identified the group of neurons responsible for gasping. Their discovery one day could help prevent SIDS.

Researchers have identified the group of neurons responsible for gasping. Their discovery one day could help prevent SIDS.
**Gassing resets a baby’s normal breathing rhythm and also alerts the baby as well as the parent that something is wrong.**

---

By replacing a single gene in fruit flies, two University of Chicago researchers have discovered a mechanism by which two different “races” begin to become different species, with one group adapting to the tropics and the other becoming more suited to cooler climates. Chang-I Wu, PhD, chairman of ecology and evolution, used a new technique to knock out one gene in fruit flies and then replace it with one of two slightly different versions of the same gene. Wu and postdoctoral student Tony Greenberg, focused on a gene called desaturate2, which plays a role in fat metabolism. Watching what they called “the essential event in Darwinian evolution,” the researchers observed how the two flies adapted to new environments and how their patterns of sexual attraction changed as a result. Their findings suggest that a small genetic change, already taking place in nature, can cause sexual isolation.

---

**Onion satire lands in researcher’s lap**

Imitation is the sincerest form of flattery, the saying goes. But it’s not true. Satire is even more sincere. And you know you’ve arrived when satirists at The Onion, whose three million weekly readers make it arguably the world’s most popular humor periodical, throw the spotlight on you. Seong-Hun Kim, MD, PhD, a research associate and assistant professor in the University of Chicago’s department of neuroscience, pharmacology and physiology, knows that kind of flattery.

Kim found himself so complimented last July when he appeared as a source for an Onion spoof of obesity research lamenting the lack of a “cure” for obesity.

“We’ve pursued every avenue—pills, topical creams, nutritional shakes, even holistic cures like vitamin regimens and massage—but nothing has worked,” Kim is quoted in the tabloid article, which lampoons recent science news. But Kim had never heard of The Onion—much less been interviewed by one of its writers—when the article hit newstands. In fact, Kim’s research has nothing to do with obesity. “I don’t know much about obesity at all,” he said. “I research senile dementia.”

Kim studies the genetic mechanisms that cause degenerative diseases such as Alzheimer’s and familial British dementia (FBD). By looking closely at how certain cells work to facilitate FBD, Kim and his research team hope to get to the root of dementia itself. “If we could identify these mechanisms more clearly,” he said, “we could prevent or treat dementia.”

In real life, Kim has received several grants for his research on how proteins interact to catalyze early-onset Alzheimer’s disease.

Meanwhile, the scientists is hard at work on another investigation: figuring out just how he made it into The Onion. “If it’s such a popular newspaper, it could easily get a real researcher,” he reasoned. Kim briefly entertained the notion that he simply shared the same name as another researcher who actually does study obesity, but then the South Korean-born neurobiologist pointed out just how uncommon his name is in the United States.

The Onion, founded at the University of Wisconsin in 1988, has published six books and earned 10 Webby Awards for its popular Web site www.theonion.com. The obesity article mocks traditional science stories, faux-quoting Kim: “The other researchers will say ‘Come have dinner with us,’ but I’m so busy that I have to just grab some yogurt from the vending machine. I’m just too busy running over to the research facility on the west side of campus or carrying samples to the lab up on the fourth floor. I’ve lost 20 pounds since starting this project in January.”

“It’s totally not me; it’s totally untrue,” the real Kim said. Though, he added, “I wouldn’t mind losing 20 pounds.”

---

**Relief for bowel diseases**

New compounds may provide significant relief for people with chronic inflammatory bowel diseases, such as Crohn’s disease. Gastroenterologist Steve Hanauer, MD, and colleagues conducted a Phase II safety and efficacy trial of an oral dose (once daily) of an experimental compound called OPC-65696. Patients with severe ulcerative colitis showed significant improvement. In another study, Hanauer demonstrated that 30 percent of 20 patients treated with adalimumab (sold as Humira) achieved remission within four weeks compared with 1.8 percent taking a placebo. A smaller, related clinical trial found that adalimumab was a safe, effective treatment option for Crohn’s disease patients who failed to improve on, or became intolerant to, infliximab (sold as Remicade). Also, in a related maintenance trial, 64 percent of 265 Crohn’s patients who received metolazolubam remained in remission at six months compared with 36 percent who did not get the drug.

---

**Premies benefit from NO**

Premature infants with respiratory distress syndrome may benefit from a study that found low doses of inhaled nitric oxide decrease risks of chronic lung disease and death by one-fourth. Pediatrician Michael Schreiber, MD, also showed that administering nitric oxide to premature infants cut by almost half the risk of severe bleeding into the brain and loss of brain tissue. Sixty-four percent of infants who received standard therapy died or developed chronic lung disease compared with 49 percent who also received nitric oxide. Schreiber said nitric oxide may have a significant impact on premature infants’ long-term health.

---

**Spinal cord regeneration**

Chicago scientists have discovered a signaling pathway that controls neural growth within the spinal cord and guides nerves toward the brain. The research presents a new model for how spinal cord injuries may be cured someday. Neurobiologist Yimin Zou, PhD, and colleagues showed in rat experiments that the signaling molecule nitric oxide can cause the spinal cord to regenerate and that extending axons to the brain may be beneficial for spinal cord injuries.

---

**A new view of science**

The Center for Integrative Science (formerly known as the International Research Buildings), scheduled to open this fall, will wrap around the John C. Furman Library along Drexel Avenue and 57th Street. Clockwise from top left: a north view from Drexel Avenue; a construction worker amid building scaffolding; a rooftop view from Drexel Avenue with the roof of Crear in the foreground, inside the new center.