

Researchers identify gene linked to the leading cause of age-related blindness

Turning an eye blind

BY JOSEPH BONNER

Eye wear. A slice of human retina ravaged by age-related macular degeneration, a common cause of blindness, is stained to show where the complement factor H protein (green) accumulates.

IMAGE: NATIONAL EYE INSTITUTE

It takes a sharp eye to catch a single error in the 3 billion letter long genetic sequence of human DNA. But by using a combination of high-throughput biology and statistical genetics, researchers led by Rockefeller University's **Jürg Ott** and colleagues at Yale University have spotted a tiny mutation that confers susceptibility to a highly prevalent form of blindness.

"We have shown that a variant, or polymorphism, of the complement factor H gene, which alters a protein whose normal function is to regulate the immune system's attack of foreign invaders and abnormal cells, is involved in the development of age-related macular degeneration, the most common form of blindness in the United States for those over 60," says Ott, professor and head of the Laboratory of

Statistical Genetics at Rockefeller. "We believe this polymorphism is a strong risk factor for the disease."

Age-related macular degeneration causes a loss of the central visual field necessary for detailed sight, reading, driving, sports participation and watching TV and movies. A characteristic of the disease is the build up of fatty deposits called drusen in the macu-

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Honoring obesity

Rockefeller's Jeffrey Friedman wins Gairdner and Passano awards for research on how hormones regulate body weight

BY JOSEPH BONNER

Considering he's a scientist, **Jeffrey Friedman** has quite a following among average Joes, especially the overweight ones. After public events he's approached by grateful attendees eager to thank him for relieving a bit of the stigma they experience regarding their weight, which Friedman's research has shown is more a product of genetics than bad habits.

This spring, Friedman also received some unexpected attention from his scientific colleagues. On April 5, it was announced that he had won the prestigious Gairdner Award, one of the top international prizes in biomedical science. A few weeks later, at a banquet in Baltimore, he was presented with the highly selective Passano Foundation Award.

Both awards have a history of recognizing truly outstanding scientists. Founded by a Toronto businessman, James Gairdner, in 1959, Gairdners are awarded to between three and six scientists each year to recognize the achievements of medical researchers whose work contributes significantly to improving the quality of human life. Of the 274 Gairdner winners, 64 have gone on to win the Nobel Prize.

The Passano Foundation Award has been given since 1945 to just one exceptional scientist each year who has done outstanding research in the United States. More than 20 Passano award winners have gone on to win the Nobel Prize.

Prior to Friedman's research, little was known about the components of the biologic system that controls weight. Many scientists, in fact, questioned

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Boosting immunity via vaccine

A therapy based on dendritic cells is tested in cancer patients

BY LYNN LOVE

When scientists began treating advanced cancer patients with an experimental vaccine in July 2003, they hoped their formula would boost the patients' natural killer T cells, fast-responding components of the immune system that are thought to attack some viruses and tumors and quickly alert the immune system to danger.

Not only did natural killer T cells proliferate, but they also spurred other, slower-responding immune system cells into action. And the effects lasted for more than three months in each of the five patients in whom the vaccine has been tried over the past two years, far longer than the typical short-lived natural killer T cell response.

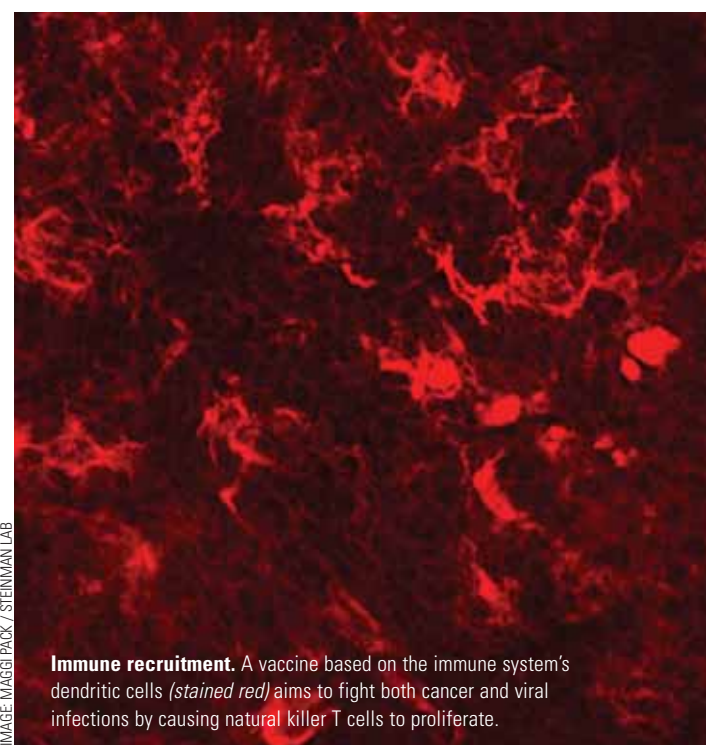
The surprisingly positive findings, which were

published in the May 2 issue of the *Journal of Experimental Medicine*, are encouraging Rockefeller University researchers to pursue additional clinical studies using vaccines based on natural killer T cells against both cancer and viral infections.

"This study clearly demonstrates the feasibility to specifically boost this important immune cell in humans and therefore opens the door for targeting the innate arm of the immune system against pathogens and cancer," says study senior author **Madhav Dhodapkar**, who is the Irene Diamond Associate Professor and head of the Laboratory of Tumor Immunology and Immunotherapy.

Natural killer T cells are part of what's known

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Immune recruitment. A vaccine based on the immune system's dendritic cells (stained red) aims to fight both cancer and viral infections by causing natural killer T cells to proliferate.

IMAGE: MAGGI PACK / STEINMAN LAB

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Doubled development. A mutant zebrafish has twice the normal number of neuromasts, sensory receptors that appear as a row of dots on each side of the six-day-old animal.

IMAGE: HUDSPETH LAB

Aquatic motion detectors. Fish detect the motion of water with a sensory system called the lateral line, a row of clustered sensory receptors known as neuromasts. Each sensory cell is innervated by a nerve fiber that extends from a ganglion located near the ear. Neuromasts form from a stream of cells that migrates along the animal from the ear to the tail. This stream of cells also serves during the organism's development as a scaffold that guides the migration of the nerve fibers and supporting cells called glia. Studying zebrafish, Hernán López-Schier and **A. James Hudspeth** have discovered that mutant animals that lack glia develop twice the usual number of neuromasts, suggesting that glia play a role in inhibiting the overproduction of neuromasts. The finding provides insight into the genetic basis for changes in developmental timing — inherited sensory alterations that might allow a fish to colonize new niches, avoid predators, or capture novel prey. Hudspeth is F.M. Kirby Professor and head of the Laboratory of Sensory Neuroscience.

Proceedings of the National Academy of Sciences, February 1, 2005

Old bottle, new vaccine. Just one dose of the vaccine against yellow fever protects against the disease for 30 years or more, a fact that is crucial in tropical Africa and South America, where the virus is endemic and few people have the chance to be vaccinated more than once. Now **Charles Rice** and colleagues at the NYU School of Medicine have taken an important step toward using the yellow fever vaccine against another tropical disease — malaria. They placed a gene from the malaria parasite into 17D, as the yellow fever vaccine is known, and then injected malaria-infected mice with the hybrid. The single injection greatly reduced the level of malaria parasites in the livers of the mice and conferred lasting resistance against later exposure. The study opens the door to using 17D as the basis for vaccines against many other infections, including AIDS. Rice is Maurice R. and Corinne P. Greenberg Professor and head of the Laboratory of Virology and Infectious Disease.

Journal of Experimental Medicine, January 17, 2005

Changing channels. Two new studies by **David Gadsby's** laboratory provide some hints on what does, and does not, regulate the activity of the cystic fibrosis chloride channel (CFTR), which allows salts to move in and out of the body's cells. By deleting different segments of the protein, Gadsby and colleagues showed that two unique parts of the CFTR that were thought to regulate the channel, first seen in a crystal structure published last year, actually do not. However, when Gadsby and Rockefeller's **Brian Chait** examined several of the sites in the CFTR where signal-mediated phosphorylation occurs, they found that one amino acid in particular is important for helping the channel distinguish signals from noise. When this site is phosphorylated — when a phosphate group is attached to it — only a strong stimulus can activate the CFTR. Mutations to the site, meanwhile, cause the channel to become much more sensitive. The CFTR is one member of a family that also includes proteins involved in cancer multi-drug resistance and hypoglycemia, and an understanding of how the CFTR protein works may shed light on how other members of the family function. Gadsby is head of the Laboratory of Cardiac and Membrane Physiology.

Journal of General Physiology, January 2005, February 2005

Short stopper. A recent paper by **Titia de Lange** and Jacqueline J. L. Jacobs shows that a protein called p16INK4a is important for detecting when strands of DNA called telomeres have become too short. Telomeres act as caps that get shorter with every cell division, as chromosomes lose a small amount of DNA each time a cell replicates. They protect important genetic sequences from getting lost. However, extremely short telomeres can destabilize the structure of a chromosome, making breaks and rearrangements that lead to cancer more likely. de Lange and Jacobs found that p16INK4a can cause a cell to stop growing when it senses very short telomeres. The role of p16INK4a in this process, called telomere-directed senescence, has been controversial, and de Lange and Jacobs hope the new data will aid in the understanding of the genetics behind tumorigenesis. de Lange is Leon Hess Professor and head of the Laboratory of Cell Biology and Genetics.

Current Biology, December 29th, 2004

Understanding blood clots

How monoclonal antibodies first produced decades ago are helping scientists develop drugs for cardiovascular disease

BY LYNN LOVE

Fine wine and single malt scotch are well known to improve with age, but rarely do scientific discoveries have much staying power, usually being supplanted by the next big thing in weeks to months. But two monoclonal antibodies produced by **Barry Collier** 25 years ago are still providing valuable new information.

A pair of recently published studies from Collier's Rockefeller lab have yielded new knowledge about deadly blood clots that trigger heart attacks and strokes, with potential new implications on how an entire family of receptors change shape with activation.

"Somebody told me about monoclonal antibodies over lunch one day while I was at Stony Brook University in the late 1970s, and I knew immediately what I wanted to do," Collier recalls. Normally, antibodies are manufactured in breathtaking variety by the body's immune system, and function to help the body fight diseases. Unlike their naturally occurring counterparts, however, monoclonal antibodies are derived in the lab, from just one mouse spleen cell making an antibody to a molecule of interest. Thus, they usually bind to just one site on a protein. If the site is important in receptor function, they can be highly useful tools due to their specific ability to block the receptor's normal function. And they can be used to study proteins anywhere in the body, not just those of the immune system.

The only problem with developing monoclonal antibodies is their sheer randomness: "Researchers easily can create hundreds of monoclonal antibodies. But systematically testing each one to determine if it binds to a target protein you are studying is painstaking work. Many researchers frankly don't have the infinite patience to stay with this task," says Sarah Schlesinger, associate research professor with appointments to both David Ho and Ralph Steinman's Rockefeller labs. (Schlesinger should know; her first project as a summer intern in Steinman's laboratory in 1977 was to assist in creating a monoclonal antibody that could bind to dendritic cells.)

Collier, who is today Rockefeller's physician-in-chief and David Rockefeller Professor, created and tried hundreds of monoclonal antibodies in the 1970s and 1980s before striking gold. In 1994 he successfully converted one to medical use as the

basis for the drug abciximab, which has been administered to more than 2 million people worldwide. Abciximab, known in the marketplace as ReoPro, keeps coronary arteries open in patients who've undergone angioplasty and stent replacement to clear blockages from their arteries, often as part of the treatment for a heart attack. By connecting to and blocking the platelet integrin receptor, $\alpha IIb\beta 3$, which normally binds fibrinogen, abciximab prevents platelets from aggregating one with another, thus preventing unwanted clotting.

Yet despite this success, the integrin receptor has continued to vex scientists. Now in two recent publications, one in *The Proceedings of the National Academy of Sciences* and one in *Nature*, two of Collier's early monoclonal antibodies, known as 7E3 and 10E5, are helping explain the secret of how the fibrinogen receptor functions, and are hinting at how even more effective drugs to treat cardiovascular disease could be designed.

Collier and his colleagues in the Laboratory of Blood and Vascular Biology localized the binding site for 7E3 to a region on one of the two subunits of the receptor. This site undergoes a major change in conformation when platelets are activated and detailed studies of the binding of 7E3 report this change. These new data help to confirm crystallography.

Many years ago Collier used another one of his antibodies, 10E5, to hold the two subunits of the receptor together. More recently, in collaboration with Timothy Springer and his group at Harvard Medical School, they used 10E5 to hold the subunits of a fragment of the receptor together during purification for crystallography. This led to the first crystallographic structure of the $\alpha IIb\beta 3$ receptor — published in *Nature* — and defined precisely where 10E5 binds on the other subunit of the receptor. They also produced the first crystal structures of the receptor in complex with several existing drugs used to treat cardiovascular disease. In addition, the data localized sites of conformational changes associated with ligand binding and thus open the door for more precise drug tailoring for life-threatening vascular events.

"Many people make monoclonal antibodies, but they don't always study the details of their binding properties," says Collier. "When we made ours, we made the decision to characterize them in great detail. And it paid off. It helped to obtain this aesthetically beautiful crystal structure, which has generated exciting new information."



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the very existence of such a system. Then, in December 1994, Friedman, who is Marilyn M. Simpson Professor and director of the Starr Center for Human Genetics at Rockefeller, and his colleagues published a landmark paper in the journal *Nature* in which they identified a gene in mice and humans called *obese* (*ob*) that codes for a hormone he later named leptin, after the Greek word leptos, for thin. Friedman and colleagues showed that leptin is a hormonal signal made by the body's fat cells that regulates food intake and energy expenditure.

Over the last decade, as his research has progressed, Friedman has learned much about leptin. Mice that lack *ob*, and thus do not produce leptin, are massively obese. So are humans — those lacking leptin eat copious amounts of food and often weigh several times what normal adults do. In patients with leptin mutations and in a subset of obese patients in the general population, treatment with leptin can lead to substantial weight loss. But the majority of obese individuals have high, not low, levels of leptin in their blood. Friedman's studies have indicated that such high levels are associated with leptin resistance, and further evidence suggests that animals destined to become obese increase their production of leptin in order to satisfy a higher set point for weight.

Leptin has also proven to be an effective therapy for a number of conditions, including several forms of human diabetes and hypothalamic amenorrhea, a condition which develops in extremely thin women — often ballet dancers and long-distance runners — that is one of the most common causes of infertility in women. More recently, Friedman and his colleagues at Rockefeller and the University of Wisconsin at Madison have begun to understand how leptin functions at a molecular level; in 2002 they showed that an enzyme called SCD-1 works through leptin to signal the body to either store fat or burn it. They believe leptin acts in part by suppressing SCD-1's activity, which in turn activates a metabolic pathway that promotes the burning of fat.

What has made Friedman something of a celebrity for the overweight, however, is his fight against the stigmatization of the heavy-set. Friedman's long experience with the genetics of obesity — including his clinical research of obese patients in The Rockefeller University Hospital and his collaboration in a long-term study of obesity-related health problems among the remote population of the south Pacific island of Kosrae — have in recent years led him to become an outspoken advocate for the obese. In editorials published in scientific journals and the lay press, Friedman has argued that obesity cannot be simply ascribed to a breakdown in willpower or poor lifestyle choices, as many of the world's thin would have us believe. It is primarily genes modified by environmental factors, he explains, that determine a person's weight. (See **A War on Obesity, Not the Obese**, right.)

"While answers are beginning to emerge as to why so many of us are obese, there can be no meaningful discussion on this subject until we resist the impulse to assign blame," Friedman says. "Nor can we hold to the simple belief that with willpower alone, one can consciously resist the allure of food and precisely control one's weight."

A war on obesity, not the obese

In their efforts to lose weight, obese individuals are fighting biology, evolution and a culture that misunderstands them

Food consumes our interest. To the hungry, it is the focal point of every thought and action. To hundreds of millions of obese and overweight individuals, it is the siren's song, a constant temptation that must be avoided lest one suffer health consequences and stigmatization. To the non-obese, it is a source of sustenance and often pleasure. To the food and diet industries, it is big business. And to those interested in public health, it is at the root of one of the most pressing public health problems in the developed and developing world.

Alarm about the health crisis associated with an emerging "obesity epidemic" is sounded almost weekly in response to reports that its incidence has greatly increased over the past decade. Many argue that this explosive increase over a short period of time indicates that the obesity problem is primarily a result of our modern lifestyle. The facts, however, do not support this conclusion. For example this argument fails to take into account that the increasing incidence of obesity in the population, from 23.3 percent in 1991 to 30.9 percent today, is not reflected by a proportionate increase in the weight of the average American, which grew by just 7 to 10 pounds.

Thus while we can't minimize the importance of the fact that more than half of the U.S. population is now overweight or obese, we should highlight the fact that the change in weight attributable to any recent change in our environment, such as a change in diet or a more sedentary lifestyle, is much smaller than the enormous differences in weight, often numbering in the hundreds of pounds, that can be observed among individuals. The question might as well be, in our current environment where almost everyone has essentially free access to unrestricted calories, why is anyone thin?

The answer appears to reside in our genes and the way in which they interact with environmental factors. Numerous studies have shown that the heritability of obesity is equivalent to that of height and exceeds that of many disorders for which a genetic basis is generally accepted.

Consider the case of a 200-pound, 9-year-old English girl whose legs were so large she could barely walk. She was found to lack a weight-regulating hormone called leptin, and often consumed as much as 1100 calories in a single meal, approximately half the amount an average adult would require in an entire day. After leptin treatment, this was reduced to 180 calories, the typical intake for a child her age. Her weight is now normal. About five percent of severely obese children have been shown to carry defects in known single genes, and there are likely to be other forms of genetic obesity that have yet to be identified.

In general, obesity genes encode the molecular components of the system that regulates energy balance, matching food intake to energy expenditure and maintaining constant energy stores in the form of fat. Normally, the system is incredibly precise. Over the course of a decade, a typical person consumes approximately 10 million calories, gener-

ally with only a modest change in weight. To accomplish this, energy intake and output must match with just a 0.17 percent margin for error. This extraordinary level of precision exceeds by several orders of magnitude the ability of nutritionists to accurately count calories and suggests that conscious factors alone are incapable of precisely regulating caloric intake.

So why are some individuals obese and others not? Feeding is a complex motivational behavior, and many factors influence when we start eating and when we stop. These factors include the unconscious urge to eat that is regulated by leptin and other hormones, the conscious desire to eat less (or more), sensory factors such as smell and taste, emotional state, and others. The brain somehow processes this diverse information. Though there is clearly cross-talk between brain regions that produce a basic drive to eat and those that express your conscious wishes, the feeling of hunger is intense and, even if not as potent as other basic drives, such as the drive to breathe, it is the powerful force that the obese must resist in order to sustain weight loss. For most dieters, sooner or later a primal hunger trumps the conscious desire to be thin.

There's also an environmental component. As a species, we carry the genetic legacy of two environments. One is passed down from hunter-gatherers, who had only sporadic access to food. In such an environment, genes that predispose to obesity increase energy stores and provide a survival advantage in times of famine. The second, passed down from more recent societies, is the result of a decreased risk of starvation but a higher risk of obesity related health problems. In this environment, genes that resist obesity and its complications would have a selective advantage. It may be that it is the obese who carry the hunter-gatherer genes and the lean that carry the Western genes, an idea supported by the observation that populations that were historically more prone to starvation (Pima Indians, Pacific Islanders and others) become the most obese when exposed to a Western diet and lifestyle.

The challenge we face now is to build a molecular framework for the system that regulates weight and to identify these genes and genetic variants that cause obesity. As we learn more about the physiologic system that balances energy, the impact of the environment on its function will also become better understood and new therapeutic approaches will be developed.

In the meantime, a different kind of understanding is called for. Obesity is not a personal failing. In trying to lose weight, the obese are fighting a difficult battle. It is a battle against biology, a battle that only the intrepid take on and one in which only a few prevail.

Adapted with permission from "A War on Obesity, Not the Obese," *Science*, 299:856, February 7, 2003. ©2003 AAAS. To read the article in its entirety, visit www.rockefeller.edu/scientist.



Boosting immunity *continued*

scientifically as the innate immune response, or that part of the immune response that should, under normal circumstances, respond quickly. Most prior cancer vaccines have focused on the adaptive immune system. What's more, prior attempts to mobilize natural killer T cells in humans have met with limited success.

But the vaccine designed by Dhodapkar and his colleagues also led to an enhancement in adaptive immunity, the delayed immune response that is more fine-tuned to specific foreign invaders like microbes or mutated cells. The result suggests a successful link between innate and adaptive immune response prompted by the new vaccine.

"Early events of the immune system may determine what happens down the line," says Dhodapkar. "In cancer, we've learned that both arms of the immune system are defective." The absence of a coordinated immune response may allow cancer cells to grow and spread.

The process for creating the vaccine used in this investigation is known as *ex vivo* amplification. Scientists at Rockefeller University and elsewhere have devised methods to expand patients' own dendritic cells, specialized cells that are at the heart of the body's immune system, outside of their

bodies, then expose the cells to antigen or load them with powerful drugs and send them back inside the body to deliver emphatic messages or finely tailored treatments.

Because the dendritic cell is central to the immune system's operations, it is capable of more precise control of immune mechanisms and better delivery than traditional treatments that send antigen or drugs randomly into the bloodstream. KRN-7000 (manufactured by Kirin Breweries, Japan), the drug used in this study, is known to be safe, but was not effective at expanding natural killer T cells in prior trials when used alone. Specialized delivery via dendritic cells arguably makes the difference in the drug's efficiency.

Using mature, rather than developing, dendritic cells likely also contributed to the consistent results, says coauthor **Ralph Steinman**, a senior Rockefeller University scientist who discovered the dendritic cell in 1973. Naturally occurring mature dendritic cells are known to do two things. One is to process and present antigen, or material considered foreign to the body, allowing other immune system cells to recognize foreign material and tumor cells. The other is to deliver "accessory" signals to immune system cells so that they develop into helpers or killers focused on removing an

antigen. Among these accessory signals are cytokines.

"The interaction of mature dendritic cells with natural killer T cells results in the production of many immune-enhancing cytokines," Steinman says. When scientists elsewhere carried out an experiment similar to the current study, but used immature dendritic cells, results were limited and not consistent.

The Rockefeller researchers now are planning another clinical study, in a larger population, to build on the current approach both by improving the function of the natural killer T cells and the downstream recruitment of other immune system cells. "This study is an important first step and provides some new clues about how the immune system works, but we need to build on this to improve clinical efficacy. Fortunately, we already have several new insights from the bench along these lines that are ready to be translated to the bedside," says Dhodapkar. "The next challenge is to test these approaches in our patients."

"The principle of this vaccine is valid for both cancer and infectious disease," says Dhodapkar. "These findings therefore support testing this approach in chronic viral infections such as HIV or hepatitis C."

Overcoming addiction, step by step

'Contingency management' study rekindles interest in a deceptively low-tech treatment for heroin users

BY KRISTINE KELLY

Before Rockefeller's Scott Kellogg got involved, many of the clinics that treat New York City's 200,000 heroin addicts were struggling to come up with better ways to motivate their patients.

Methadone, a drug developed at Rockefeller in the 1960s, helps eliminate the need for heroin, but for many it's only one part of their recovery process. Though the clinics rely on methadone to counter the biology of addiction, sometimes they need something more.

"For years, there has been just such a system, one that, like methadone, has been scientifically tested and documented over a period of decades," says Kellogg, who is a clinical psychologist and research associate in **Mary Jeanne Kreek's** Laboratory of the Biology of Addiction. "It just hadn't ever been widely adopted by clinics."

It's known as contingency management, and it works by giving patients a series of immediate rewards to encourage small steps towards recovery. Now a new study, one of the largest ever done to examine the role of motivational incentives in drug users, has convinced many in New York's clinics that contingency management works.

Contingency management, or, as it is increasingly called, motivational incentives, was first used in the 1960s, and is based on the work of behaviorist B. F. Skinner's idea of operant conditioning, which proposes that behavior is more likely to continue if it is reinforced. At its core, the contingency management approach to drug addiction is based on the idea that people use drugs because they are reinforcing — they provide pleasure. The way to counter this and to help people recover is to provide reinforcements for not using drugs.

In the mid 1970s, Maxine Stitzer from Johns Hopkins University began to test its effectiveness on patients addicted to drugs. "Dr. Stitzer started to look at drug addictions, methadone patients in particular, to see if she could make changes in their behavior," says Kellogg. "She consistently worked throughout the late 1970s and 1980s, doing this research and publishing papers; this was basically ignored by the mainstream addiction treatment field."

The history of contingency management underlines a basic rift in addiction treatment between the scientists and the treatment specialists. Addiction, said the specialists, is a disease and, as such, would be unresponsive to external conditions.

But study after study, published by Stitzer and others, argued that this was not the case. Addicts could change their behavior if given the right incentive or set of incentives. The National Institute of Drug Abuse (NIDA) saw that contingency management, as well as other science-based addiction treatments, were being under-utilized. In response, they developed the Clinical Trials Network to both test and publicize the various treatment approaches.

In 2002, Kellogg, who is scientific director for the NIDA contingency management intervention in New York, joined with the New York City Health and Hospitals Corporation to launch contingency management programs in seven city addiction clinics, one of the largest contingency management adoptions ever attempted.

"Scott developed the concept of a modified, practical but formal contingency management intervention within a community-based treatment setting," says Kreek, the Patrick E. and Beatrice M. Haggerty Professor, "and he educated people at the HHC so they could implement it."

"Clinics, including New York's, have experimented with rewards systems over the years, but they have tended to focus on long-term rewards — giving out prizes only to those who achieve major milestones which may take weeks or months of consistent effort to reach," says Kellogg. "But that sets the bar too high and runs the risk of rewarding only the best patients, when it's the struggling patients that need the most motivation."

Kellogg suggested to them that they could achieve a better outcome if they didn't simply reward the attainment of goals, but, instead, reinforced each of the steps along the way.

Those steps include celebrating each attendance at a group meeting or each drug-free test result. Later, larger achievements like stable housing are rewarded. The prizes are easy-to-earn material goods, such as movie passes and food vouchers; and they help to both initiate and maintain positive changes. It is the reinforcement of the small steps that is the key for tapping into the power of the approach, especially with patients who have not been doing well in treatment. The program is not a substitute for counseling or pharmacotherapy, but it serves to keep the patients motivated and reaffirm the benefits they make in treatment.

Kellogg's study, published in the January issue of *The Journal of Substance Abuse Treatment*, is based on clinical data and progress reports submitted by each of the seven clinics involved, as well as staff interviews and patient testimonials. The paper shows that combining contingency management with other treatments increases patient motivation to stay in treatment and enhances their therapeutic progress. In addition, the staff and administrators observed increased attendance at group and individual counseling sessions, more drug-free tests, higher levels of employment-related activities, better school attendance, and a markedly improved treatment atmosphere.

It was not always a smooth collaboration. Many staff were at first hesitant to even try contingency management treatment. Eventually, however, most changed their minds, spurred on by the sight of positive and, in some cases, dramatic changes in their patients.

"I remember one patient saying 'I felt like I was going down the drain with drug use, that I was going to die soon. And this got me connected, got me involved in groups and back into things. Now I'm clean and sober,'" says Kellogg. "It is so powerful to hear, so powerful to witness. I would love to see the whole treatment system adopt this intervention."

Thanks in large part to Kellogg's work, the use of contingency management has already been extended to several additional treatment centers and plans are in the works for further expansion in New York City and beyond.

Mutations and temptations

How tiny alterations in the genetic code are linked to a vulnerability to addiction

BY KRISTINE KELLY

Central to the study of addiction is why one person can walk away from a drug while another can't. There is a solid base of research demonstrating that people's genes can help make the decision to say no easy, or tough, and Mary Jeanne Kreek and her laboratory have been exploring the genetic basis of addiction for many years. But in new research published in the December issue of *Pharmacogenetics*, she is taking her studies beyond the simple question of which genes are involved in addiction. She's focusing on tiny mutations within those genes.

"What we wanted to know was if small changes in DNA have any effect on an individual's vulnerability to develop heroin addiction," Kreek says.

Kreek and colleagues were looking for small mutations called single nucleotide polymorphisms (SNPs). These are DNA sequence variations between different people, where only a single nucleotide building block — A, T, G or C — is altered. Some SNPs do not alter the sequence of the protein, but can affect aspects like its stability and regulation, perhaps enough to change an individual's susceptibility to addiction.

"The human kappa opioid receptor has a role in both opiate withdrawal and responses to cocaine," says Vadim Yufarov, the study's first author and a senior research associate in Kreek's lab. "But its full structure hadn't been studied, so that's where we started."

"After we clarified the sequence of the kappa gene," says Kreek, "we looked at the groups of people represented in New York. We sequenced the kappa gene in close to 300 people from different ethnic backgrounds and thus far have found 12 SNPs."

Three had already been identified during Yufarov's initial sequencing. Of the remaining nine, however, one stood out from the rest. A small nucleotide change from a G to a T resulted in a statistically significant increase in an individual's vulnerability to heroin addiction. While significant across all ethnic groups, some had stronger associations than others.

"The study needs to be replicated, but the results of this study and others already tell us that SNPs have a role in addiction," says Kreek. "If you consider that there are multiple SNPs in multiple genes, all interacting with environmental factors, an individual's vulnerability could be greatly increased or decreased."

Understanding how SNPs affect addiction will eventually lead to the design of more effective pharmacotherapies, as well as tools for better preventative measures for individuals at risk."

Turning an eye blind *continued*

la, the central region of the retina.

The gene variant identified by the researchers is known as a single nucleotide polymorphism (SNP), as it is derived from a single letter difference in the genetic sequence of DNA. Some of these differences may change a gene's protein products in ways that may confer susceptibility to — or protection from — diseases. In this case, the complement factor H (CFH) SNP associated with age-related macular degeneration encodes for a different amino acid, as histidine substitutes for tyrosine at a specific position. The CFH gene lies in a region of human chromosome 1 that had been linked previously to age-related macular degeneration through family studies by other researchers.

Josephine Hoh, a former research assistant in Ott's lab, now assistant professor in

the division of chronic disease epidemiology at Yale's School of Public Health, analyzed DNA taken from the blood samples of 146 unrelated patients, collected for the National Eye Institute-sponsored Age-Related Eye Disease Study (AREDS), designed to learn more about the natural history and risk factors of AMD and cataract and evaluate the effect of high doses of antioxidants and zinc on the progression of these conditions. She then compared the DNA from 96 patients with an advanced form of age-related macular degeneration with that from 50 healthy people who had little or no drusen deposits in their retinas.

The researchers genotyped more than 116,000 SNPs using the most advanced microarray technology and compared the frequency of each of them between the

two groups of patients.

Then, under the supervision of Hoh and Ott, Ott lab member Robert Klein analyzed the data, and the CFH SNP was located.

Biochemical analysis of drusen by other researchers has shown that the deposits are largely composed of lipids, but also contain components of the immune system called complement. The complement system is a collection of related proteins that are the body's front-line defense system — the innate system — that attacks foreign invaders while usually avoiding any attacks against healthy cells. One of the known properties of factor H is that it regulates the activation of complement components.

The researchers examined the eyes of four patients with age-related macular degeneration and found complement

debris in the drusen, as well as in eye components called Bruch's membrane and the intercapillary pillars. Other researchers also have detected complement components in the drusen of humans.

"The polymorphism produces a change in a specific amino acid in the complement factor H protein, which is located in the region that interacts with C-reactive protein and heparin," says Hoh. C-reactive protein is associated with heart disease and high cholesterol levels and both C-reactive protein and heparin are associated with age-related macular degeneration.

The team reported their findings in the April 14 issue of *Science*, and say the work opens the door for new investigations of the role of genes in developing age-related macular degeneration, as well as suggesting possible treatments for the disease.