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Gene Doping

Science and sport converge once again as medical research charts the complexities of genetic treatment. A look at the facts, and the dangers of gene doping, and at what WADA is doing to fight this new threat.

> A genetic delivery device, or *vector* (in this case an adapted virus), delivers its payload to the nucleus of a muscle cell. See full feature on Page 2 and more detailed explanation on Page 5

play true

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CONTACT:

THE WORLD ANTI-DOPING AGENCY E-MAIL: info@wada-ama.org

URL: www.wada-ama.org

HEADQUARTERS

800 PLACE VICTORIA - SUITE 1700 P.O. BOX 120, MONTREAL, QC CANADA H4Z 1B7 TEL: +1.514.904.9232 FAX: +1.514.904.8650

AFRICAN REGIONAL OFFICE

PROTEA ASSURANCE BUILDING 8TH FLOOR GREENMARKET SQUARE CAPE TOWN 8001 SOUTH AFRICA TEL: +27.21.483.9790 FAX: +27.21.483.9791

ASIA/OCEANIA REGIONAL OFFICE

C/O JAPAN INSTITUTE OF SPORTS SCIENCES 3-15-1 NISHIGAOKA, KITA-KU TOKYO 115-0056 JAPAN TEL: +81.3.5963.4321 FAX: +81.3.5963.4320

EUROPEAN REGIONAL OFFICE

AVENUE DU TRIBUNAL-FÉDÉRAL 34 1005 LAUSANNE SWITZERLAND TEL.: +41 21 343 43 40 FAX: +41 21 343 43 41

PHOTOS APPEAR COURTESY OF:

STACY SPLETZER (WADA) GETTY IMAGES IPC OWI DOMINIC FUIZZOTTO

GRAPHIC DESIGN & ILLUSTRATIONS

ANTHONY PHILBIN COMMUNICATIONS, MONTREAL E-MAIL: philbin@sympatico.ca

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Taking the Lead

Gene therapy represents an exciting and promising step forward in medical research, but its use to enhance athletic ability is as wrong as any type of traditional doping.

As the Olympic Games in Athens wrapped up last summer, I was frequently asked one question by journalists who were already thinking ahead to the Beijing Games: Could there be genetic doping by 2008?

The idea that genetically-altered athletes could be competing at the Olympics in Beijing is disturbing but not out of the realm of possibility. WADA has, for some time, considered genetic doping to be a looming threat. We have taken the lead in focusing the attention of the scientific and sport communities on the challenge this new method presents for enhancing performance. As you will read in the following pages, our scientists do not believe that genetic doping is a reality - yet. But that could very well change in the next few years and we have to be ready with new weapons in our arsenal to deal directly with this new threat.

In 2002, WADA brought together, for the first time, leaders in sport and in science to discuss the issue of gene doping at the Banbury Conference in New York. The conference was exactly what we needed to place gene doping on the map for those who could do something to prevent it before it ever gets off the ground. Those involved in sport learned just how far science has come in the field of gene therapy. Cures for many devastating diseases now sit tantalizingly within our reach. The scientists learned just how far some athletes will go to be the best. They heard directly from some of their colleagues who had already had calls from coaches and trainers, asking how gene therapy could be applied to their athletes solely to enhance performance.

It was an eye-opening event for all of us and led to the inclusion of gene doping as a prohibited method on the 2003 Prohibited List of Substances and Methods. Since that time, we have done quite a bit to get ahead of the cheaters in this field. We have partnered up with some of the best scientists in the world to fund research projects into how gene doping can ultimately be detected. We have created a gene doping panel, whose members will continually advise us on cutting edge technology in gene-doping detection. And we have undertaken education efforts to let athletes and their entourages know that gene doping is still an imperfect science and quite

studies. But there is still much that needs to be done in this area. Some disreputable labs would be willing to replicate the technology for performance enhancement – for the right price. As dangerous and wrong as traditional doping is, it is hard to conceive what the consequences could be of altering a person's genetic makeup just to make them better in sports. This is a slippery slope we do not ever want to go down.

We should all keep in mind one important point: gene therapy is an incredible step forward in the field of medicine and a testament to human ingenuity and ability. The fact that science now allows us to tinker with

As dangerous and wrong as traditional doping is, it is hard to conceive what the consequences could be of altering a person's genetic makeup just to make them better in sports. This is a slippery slope we do not ever want to go down.

dangerous. In addition to being as morally wrong as traditional doping, gene doping can present a significant risk to health.

Last winter, I spoke to the annual meeting of the American Association for the Advancement of Science on this topic. One point I stressed to them is the need for governments and regulatory bodies to create a framework for regulating the application of gene transfer technology. Some of that is already in place. In the U.S., for example, there are stringent rules regarding oversight of gene transfer our genetic codes in order to be healthier human beings is a remarkable achievement. While we have a long way to go, I am confident science will get us to the point where gene transfer technology can be applied safely and effectively. But to misuse this advancement to create super athletes is not acceptable. WADA will fight gene doping as vigorously as it has traditional doping. Competitions should still be won through hard work, training, and dedication.

Special Feature: Gene Doping

Gene Doping

Gene therapy for a number of diseases may be just around the corner, but those who would seek to use these advances for athletic gain should take note: the science of detecting gene doping is rapidly advancing to meet this new challenge.

Imagine a day when we will no longer worry about Parkinson's Disease. Or cystic fibrosis. Or some cancers.

There may come a day, in the not too distant future, when diseases such as these and others that have plagued mankind become a distant memory, thanks to research into genetics. Gene therapy - the ability to manipulate the human genome to prevent or cure diseases - is still a highly experimental procedure performed by very few research and clinical centers. Science has not advanced to the point where we can go to the doctor's office, get a shot, and be cured of an assortment of ailments caused by defects or mistakes in our genetic code.

But soon, we may be able to do just that.

Unfortunately, advancements in this field of science also may someday be used by athletes to try to better their performance on the playing field. For some, the lure of becoming better, stronger and faster than their competitors through tinkering with their genes may be too strong a temptation to resist.

"Most doping is the misuse and abuse of medicines normally used for therapeutic purposes," said Dr. Olivier Rabin, WADA's science director. "Many of the substances used for doping actually represent great steps forward in the fields of science and medicine. But they are being wrongly used to enhance athletic performance. The same may become true of gene doping." While it is doubtful that gene doping is already a reality, WADA and its partners in the fight against doping have already made it a top research priority. In 2003, the Prohibited List of Substances and Methods was amended to include gene doping as a prohibited method. WADA brought together experts in the field of genetics, as well as representatives from the sporting world, in 2002 to look at the problem. And the Agency continues to take a leading role in the fight against gene doping by forming a panel of experts to continuously advise the agency on the most recent progress in this area.

"We know the threat of gene doping is very real," said Richard W. Pound, WADA's president. "We need to start fighting this threat now, before it becomes a reality. It is easier to prevent a problem than it is to solve it."

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Anatomy of a muscle

The cells that make up our muscles are unlike most found in the body. To understand how gene doping may one day affect the human musculature, it is useful to first understand how our muscles are made and how they work.

What is gene therapy?

To understand what gene doping is, one must first understand the concept of gene therapy. Most of what we are, from the way we look, to how good we are in athletics, to what diseases we might one day develop, comes to a certain degree from our genes. Some of our traits are predominantly determined by our genes with a minor contribution from our environment. For other traits, the environment plays a bigger part. Usually, the two work in tandem to make us who we are. In 1990, the U.S. Department of Energy and National Institutes of Health began the Human Genome Project, a 13-year effort to identify all of the approximately 20,000 to 25,000 genes in human DNA.

Genes are composed of segments of our DNA and can best be thought of as the instruction sheet for what the genes ultimately produce– proteins. These proteins build our cells and instruct them how to function.

But what happens if a particular gene is defective and not working properly? What if the gene is missing or is mutated through inheritance from our parents, by exposure to chemical products or to radiation? When the gene cannot carry out its proper function to regulate the production of certain proteins, disease can result. For example, muscular dystrophy, a disease that causes progressive wasting of the muscles in the body, is a genetic disorder. The genes that create proteins for the growth and function of muscles are missing or defective.

One day, gene therapy may eliminate diseases such as muscular dystrophy. Scientists are studying various ways in which gene therapy can work. In some cases, a normal gene may be inserted into cells of patients or directly into the patient's genome to replace or repair a gene that does not work properly. In cases where a new, normal gene is inserted, scientists must use a gene transport method, known as a vector, to deliver the gene into the genome. The most common way to get the gene into the body is to use a disabled virus that has been altered to not be harmful in itself but simply to act as a moving van to deliver normal DNA to the cell.

"The viruses are like Trojan horses," said Dr. Theodore Friedmann, director of the Gene Therapy Program at the University of California San Diego and chair of WADA's gene doping panel. "The virus carries the genes into the targeted cells and unloads the normal genes, which can then begin to function and produce the necessary proteins and enzymes."

While the process sounds fairly straightforward, it has proven extremely difficult, with no real evidence of therapeutic effect in many hundreds of attempts. However there has been a notable recent success. In France, scientists have carried out gene transfers on several children who suffer from severe combined immune deficiency (SCID), or "Bubble Boy Disease." These children have a single malfunctioning gene that produces non-functioning form of a critical protein involved in the creation of a normal immune system. They must, therefore, live in isolation to protect them from the outside world. When treated with a virus vector carrying the normal copy of the gene, their bodies were able to produce the necessary protein to create a normal immune system. Unfortunately, three of the children treated later developed leukemia (see article by Dr. Thomas Murray, pages 9-12).

The realities of gene doping

In gene doping, an athlete would not be suffering from any disease. Instead, normal genes would be injected into the body to increase the function of a normal cell. Scientists, including Dr. Lee Sweeney, have experimented with genes that produce insulin-growth factor 1 (IGF-1), which helps muscles grow and repair themselves. The genes, carried into the body by a harmless virus, produce more IGF-1 than the body would normally produce, stimulating muscle growth.

Friedmann envisions a scenario in which some athletes with injuries in a particular part of the body could use IGF-1 to speed healing and repair of the damaged muscles. Others might use gene doping to strengthen, for instance, a weakened knee or other damaged joint or injured tissue, which would give them a significant advantage on the playing field.

For athletes who use erythropoietin, or EPO, to enhance performance, gene doping would represent the next step. Instead of injecting themselves with the EPO itself, they would inject with the gene that produces the EPO, allowing the body to naturally produce more red blood cells.

The dangers of gene doping

Of course, gene therapy is not quite as easy as it seems on paper.

"Gene therapy is far from being mastered," Rabin said. "The chances of success are very low and the risks are still very high."

Indeed, gene therapy can be quite dangerous (see interview with Friedmann, page 7). It is therefore strictly regulated in the United States and now in other countries in which these kinds of experimental clinical studies are being carried out – England, Germany, France, Italy, Sweden, Japan, China, Australia and others. In the U.S., all gene transfer studies in humans must be approved at the local level by hospitals and institutional committees, as well as at the national level by the Food and Drug Administration (FDA) and, in most cases, also by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health, which Friedmann has chaired.

Nevertheless, most experts predict that rogue labs will pop up, in the U.S. and elsewhere around the world, which would be willing to make experimental gene doping, no matter how dangerous, available to athletes for the right price.

What WADA is doing

WADA became involved in the fight against genetic doping in 2002. The Agency convened a two-and-a-half day conference called "Genetic Enhancement of Athletic Performance" at the Banbury Center on Long Island. The Banbury Conference, as it came to be known, was the first time experts from both the scientific and athletic worlds came together to tackle this issue (see Friedmann interview, page 7).

Conference participants issued a series of conclusions, including a call for the inclusion of gene doping on the Prohibited List, which occurred a year later. They also called for governments to "expedite the development of a global social framework for the application of genetic transfer technologies that address the potential misuse of these technologies in sport and a publicly stated deadline for the adoption of that framework."

At that conference, WADA also pledged to devote more resources to research projects dedicated to gene doping. To that end, WADA is now sponsoring five distinct projects on how best to detect gene doping. (See table on page 6).

Enhancing with genes

Genes can theoretically be used to build muscles, alter and adjust muscle composition, or boost endurance levels. Simulating injury (see explanation below), energizing dormant genes, inhibiting specific proteins, or adding new genetic material are all possible methods that may one day be used to achieve these medical procedures.

Normal muscle growth due to repair

Small microscopic injuries caused by exercise and training are thought to provide the signal for satellite cell division and growth, but other factors may also be at work.

Under normal circumstances a localized 'factory' of a protein known as IGF-1 causes growth and hypertrophy of the muscle, at least partly by causing nearby satellite cells to divide, grow and fuse with existing cells. This process leaves the repaired cell with more nuclei and myofibrils - thus bigger than before the injury. A protein called myostatin is one of several that can tell the satellite cells when to stop.

Mimicking injury with genes

One method of enhancing muscle fiber size through gene therapy could possibly involve introducing an IGF-I gene with a vector (see page 5) to increase stem cell attraction and proliferation, or else by bringing in a gene for a protein to inhibit myostatin.

Can it be Detected?

Many athletes and their entourages may have a false sense of security about whether gene doping can be detected. After all, when a gene is inserted into the body, it becomes part of the genome. How can you tell if a gene is new or if it has always been there?

"Those who think they can cheat using gene transfer technology will be in for a rude surprise," said David Howman, WADA's director general. "It is a priority for WADA and for our partners to make sure gene doping is as detectable as any form of traditional doping."

The projects WADA is funding in this field give a good indication of the type of methods researchers are examining for the detection of gene doping. It might be difficult to see that a particular gene has been added to the

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body, but there will be consequences to that addition that can be seen and measured. For example, the gene will express itself and produce more of a particular protein or enzyme, which can be detected and measured just as in the case of drug-based doping. The effects of that new and foreign substance will have an effect on the body that also can be detected. For example, there could be increased production of red blood cells.

Special delivery

Fia. 1

Researchers have coined the term 'vector' to refer to any of a number of possible systems for delivering genes to target cells.

In one example in the illustration below, a packet of free DNA that might have been injected directly is represented as a bare double-helix entering the cell nucleus upper left (Fig. 1).

Any of a number of disabled virus classes (represented by the yellow figure, above right) may also be used to deliver DNA.

Researchers will strip the harmful genetic material in the virus and then replace it with the helpful DNA that they wish to introduce into the target cell. The virus then simply does what nature designed it to do: penetrates the cell and delivers its genetic payload.

Furthermore, the addition of a new gene can have an effect on a number of other genes, causing them to "turn on" or "turn off," creating specific genomic, proteomic or metabonomic signatures that could also be detected. This method of detection would be similar to how astronomers find new planets: they cannot see the planet but know that it is there by observing the effect its gravitation has on nearby objects that are visible. Researchers are looking at ways in which these changes to the genome can be detected through blood testing. Another unique idea being looked at is imaging, where a process similar to magnetic resonance imaging would be used to scan the body and search for unusual locations of gene expression.

Bottom line? Detection is possible and probable.

"I would like to send a shot across the bow of those who think we will not be able to detect gene doping," Friedmann said. "My advice to them is: don't be so sure—this is a very dangerous road to proceed on, and we will be ready to halt the traffic." *

GENE DOPING PROJECTS FUNDED BY WADA AS OF JANUARY 2005

Investigator	Project	Location	Started	Short summary
Dr. Geoffrey Goldspink	Manipulation of muscle mass via the growth hormone (GH)/insulin-like growth factor (IGF-1) axis	Royal Free and University College Medical School University College London, UK	2002	Both GH and IGF-1 are human peptides involved in muscle growth. These factors are naturally upregulated during athletic training. Therefore, the distinction between endogenous and exogenously administered GH and IGF-1 is difficult. It has been shown that intake of GH, but not exercise, modifies the expression of a muscle-specific variant of IGF-1. This property is being used to design a test allowing the ability to distinguish between the introduced and the endogenous substances.
Dr. Günter Gmeiner	Application of microarray technology for the detection of changes in gene expression after doping with recombinant human growth hormone (hGH)	ARC Seibersdorf Research Seibersdorf, Austria	2004	Microarray technology will be used to search for changes in white blood cell gene expression following application of human growth hormone. Gene expression profiles of treated and untreated cells will be compared, with the objective of defining a set of genes modulated after hGH treatment.
	Microarray detection methods for growth hormone and insulin-like IGF-1	University of California San Diego, CA, USA		Administration of growth hormone and IGF-1 or of the genes expressing them will be associated with reproducible and detectable secondary changes in gene expression in many affected tissues, including peripheral blood. New methods for gene expression screening, such as global microarray techniques, will be used to detect such changes in cells from peripheral blood of mice exposed to GH and IGF-1 and to gene transfer vectors expressing them.
Dr. Jordi Segura	IMAGENE: non-invasive molecular imaging of gene expression useful for doping control: pilot study in animals after erythropoietin gene transfer	Pharmacology Research Unit Institut Municipal d'Investigació Mèdica (IMAS-IMIM) Barcelona, Spain	2005	An important field of application of imaging will be the prevention of the prohibited misuse of gene therapy in athletes. For this purpose, imaging will be used to detect the RNA being formed in unusual tissues after the gene transfer process. This approach is applicable to any gene transfected to tissues not usually expressing the "doping" protein, such as muscle for EPO. Imaging of mRNA will be carried out by the use of antisense peptide nucleic acids oligonucleotide probes labeled for tomographic detection. A pilot project will be carried out to image the presence of transfected EPO genes into muscle of mice.
Dr. Jane Roberts	The application of cellular chemistry and proteomic approaches to the detection of gene doping	HFL Laboratory Inc. Fordham, Cambridgeshire UK	2005	A different and more global approach for the detection of doping is proposed. Following doping with doping substances or the use of genetic manipulation, the expression of one or more genes and/or proteins will be altered in several accessible tissues, such as blood cells or bucal mucosa cells. These changes in gene/protein expression will be detected through the application of high performance transcriptomic or proteomic techniques. Ultimately, this will lead to the identification of abnormal RNA/protein patterns, representing molecular signatures associated to the use of doping substances, such as IGF-1 or growth hormone.

Dr. Theodore Friedmann, professor of pediatrics and the director of the gene therapy program at the University of California, San Diego, is a foremost expert in genetic research. He has worked with WADA on the issue of gene doping since shortly after the Agency's inception and was instrumental in organizing WADA's conference on gene doping at the Banbury Center in March of 2002. He is also the head of WADA's new panel on genetic doping. He shares some of his thoughts on gene therapy, why the Banbury Conference was so important, and whether gene doping is already a reality.

04

Interview: Dr. Theodore Friedmann

What were the concrete results from WADA's conference on gene doping in Banbury, Long Island, in 2002?

Before Banbury, there really wasn't much in the way of interest or publicity about the application of gene therapy in sport. What came out of Banbury was an awareness in both the athletic and scientific communities that there was a problem. It was clear that the scientists were only marginally aware of what was happening in sport. At the same time, the sports world was hearing in the lay press about gene therapy and other advances in genetics but was not up to date on its true promise, problems and potential impact on sport. After this conference, the scientists became interested very quickly in the models of the application of gene therapy in sport. And the athletic community took away a level of sophistication about the advances science was making in this field.

I think that the meeting was a kind of epiphany for most or all of the participants. The conference put a level of credibility and importance on the issue that wasn't there before. It was a very effective moment in the history of this issue. Special Feature: Gene Doping

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How advanced is gene therapy? Is it already a reality in the medical world?

The technology is evolving very rapidly. The science is not all that difficult and can be reproduced by well-trained people in many thousands of laboratories all over the world. The research results in the field are rapidly and widely published in the open medical and scientific literature and therefore are available to any and all to learn. What is extremely difficult is to transfer the underlying basic scientific technology into human beings, whether they be sick people or athletes, and to do so safely and efficaciously.

For humans, gene therapy remains very immature, experimental and highly risky. In the United States, thousands of patients have been enrolled in clinical trials in the last decade and most of these studies have not shown any striking therapeutic benefit to patients. In fact, some serious adverse events, including death, have occurred. The bottom line is that everything gets complicated when you move from the laboratory into a human being. We don't have the technology yet in hand to ensure a predictable and adequate level of safety to feel comfortable using gene transfer technology in anyone other than in a patient with a serious or untreatable disease.

Such a use would be frivolous, dangerous and, in my mind, would constitute medical malpractice or professional misconduct.

Do you believe gene doping is already a reality?

The simple answer is that we don't know. We have no proof that it has happened yet, but we think it is likely

to happen. Gene doping won't replace traditional drug doping because genebased approaches will be more difficult. But as the technology advances, there will be those with means and motivation who will be willing to try.

The frightening thing is that rogue, unregulated laboratories will not be concerned about safety and will not be concerned about informed consent from athletes.

Can gene doping really be detected?

I think there is a very good chance that scientists will discover techniques for detecting gene doping. There are many avenues of research to pursue. Those who will try it, thinking it is undetectable, will be in for quite a surprise.

WADA's new gene doping panel, from left to right: Dr. Alain Garnier, WADA medical director, Professor Odile Cohen-Haguenauer, Dr. Lee Sweeney, Dr. Theodore Friedmann, Dr. Ann-Muriel Steff, WADA manager for scientific research, Dr. Kurt Zinn, and WADA science director Dr. Olivier Rabin. Not pictured: Professor Doug Wallace.

WADA Forms Gene Doping Panel

WADA is using all resources at its disposal to battle gene doping, and that includes bringing together some of the top scientists in the field for advice.

Late last year, the Agency formed a gene doping panel, which is composed of five of the top researchers in various fields of genetics. The panel is headed by Dr. Theodore Friedmann, from the University of California at San Diego, and includes other experts in the fields of energy utilization and imaging: Professor Odile Cohen-Haguenauer, of the Laboratoire de biotechnologies et pharmacologie génétique appliquée de l'École normale supérieure de Cachan, France; Professor Lee Sweeney, of the physiology department of the University of Pennsylvania, United States; Professor Douglas Wallace, of the evolutionary biology department of the University of California at Irvine, United States; and Dr. Kurt Zinn, of the molecular imagery department of the University of Alabama at Birmingham, United States.

Panel members will advise WADA's Health, Medical and Research Committee on gene-based doping to ensure the Agency has the latest information on advances in this field. The panel will also encourage promising research in the field of detecting gene doping.

"The gene doping panel is meant to expand the horizons of WADA," Friedmann said. "It's a way of bringing attention to new concerns in this field and new areas of expertise. This is something no one person can do alone."

The panel met for the first time in February at WADA's headquarters in Montreal.

Gene Doping and

Article contributor Thomas H. Murray is an expert in bioethics and the President of The Hastings Center (www.thehastingscenter.org). He also chairs WADA's Ethical Issues Review Panel.

Will the Olympic Games soon be dominated by genetically transformed athletes? With all the recent attention to genetically manipulated animals, one could be forgiven for thinking that the future of sport will belong to genetic engineers and their human guinea pigs. But the reality does not yet match the hype.

H. Lee Sweeney, a scientist at the University of Pennsylvania and a member of WADA's Gene Doping Panel, has indeed created genetically modified mice and rats with larger and stronger muscles than their unmanipulated peers. How soon will the Olympic movement have to worry about human analogs of these unnaturally muscular rodents? How soon will gene "doping" have a discernible impact on athletes' abilities to run faster, leap higher, or throw farther? The hoopla over genetically supercharged mice and rats worries—or excites—many people over the prospect that genetically enhanced human athletes will soon be here. For people who care about the meaning and integrity of sport and about fair competition, there is no time to lose in responding to the challenge of gene doping.

But we do have time.

A sober and realistic assessment is needed to shoulder aside the sensation-mongering that has dominated public discussion of gene

Olympic Sport

doping. One question helps to throw the cold water of reality on overheated speculations about genetically enhanced humans: For how many human diseases has gene transfer the scientific term for inserting new genes into cells, such as with Sweeney's mice—been clearly demonstrated to be an effective therapy?

The answer is, one—a very rare inherited disorder known as X-linked Severe Combined Immune Deficiency or X-SCID for short. It is "X-linked" because the disease is caused by an abnormal gene on the X chromosome. Similar to what happens in hemophilia, girls inherit two copies of the X chromosome. A normal copy of the gene on one X chromosome compensates for the unhealthy one, so female children escape the ravages of the disease. Boys, however, get only one X chromosome to pair with their Y, or male, chromosome. If their only copy of the gene is defective, their ability to fight off infection is severely compromised. Clinically, having X-SCID is like being born with an untreatable case of AIDS. These children have to be protected against even the mildest infection or they will die.

Researchers found the gene responsible and devised a way to insert healthy copies of it into the genome of these children's bloodproducing cells. In a clinical trial conducted in France, eleven boys received the experimental gene therapy. The initial news was wonderful: most of the boys treated were able to make enough of the missing protein for their immune systems to function for the first time. As we have subsequently learned, while the gene transfer was effective, it was far from safe. When the first boy developed leukemia, knowledgeable scientists treated it as an instance of colossally bad luck. Picture gene transfer in this admittedly crude way: Imagine millions of targets (human cells), each with its genome, like thin spaghetti tangled inside it. Then imagine blasting away at these targets with a shotgun. Most of the pellets pass harmlessly through. Some targets are obliterated. In other instances, though, a few pellets lodge in one of the spaghetti strands, but not enough to destroy the cell's ability to function. The new genes become integrated into the genome of that cell. The first boy's misfortune occurred because in one of those celltargets, a gene-pellet came to rest in a sensitive spot close to another gene. That other gene began to function incorrectly, causing the disease known as leukemia.

" DOING GENE TRANSFER IS NOT LIKE TOSSING A BEAN INTO A BEANBAG WITH PREDICTABLE EFFECTS. OUR GENOMES ARE MORE LIKE INTRICATE ECOSYSTEMS, WITH COMPLEX INTERACTIONS AND FEEDBACK LOOPS INVOLVING THE GENES THEMSELVES AND THE INTERNAL AND EXTERNAL ENVIRONMENTS."

Special Feature: Gene Doping 🦂

Scientists knew that the methods of gene transfer—so technically sophisticated and yet at the same time so imprecise—could result in a cell going haywire. But most likely the cell would simply die, or cease to function. In this unfortunate boy, instead the cell became a kind of bully, proliferating faster than its peers and ultimately taking over – as cancerous cells do.

Several months later another of the eleven boys in the experiment also developed leukemia. What was almost universally regarded as an astonishing coincidence became instead an ominous pattern. In January 2005 the researchers announced yet a third case, similar to the first two. That same announcement included the news that one of the two boys diagnosed earlier had died; the other appears to be recovering.

Scientists have learned to get genes into a cell, and how to prompt them to produce the protein, enzyme or hormone the gene is programmed to make. But that is not enough. The newly-inserted gene has to make just enough of its product—not too little, not too much—and to make it at the right time, for it to be optimally effective. But the X-SCID experiment shows that where the gene lands in a cell's genome may be just as important to the health of the person undergoing gene transfer.

The more we learn about our genomes, the more complexities we uncover. The central dogma of 1960s molecular biology was: one gene, one protein. Now we know that in some cases an individual gene can make multiple proteins that can affect different parts of our physiology. Doing gene transfer is not like tossing a bean into a beanbag with predictable effects. Our genomes are more like intricate ecosystems, with complex interactions and feedback loops involving the genes themselves and the internal and external environments.

It is also worth remembering that while a mouse's lifespan is roughly

two years, a human's can easily exceed eighty. A genetically engineered mouse might die of old age well before long-term complications of gene transfer emerge. A twenty-year-old athlete, on the other hand, can look forward to many decades of uncertainty during which unpredictable, possibly catastrophic, consequences might appear. Drugs are more or less rapidly metabolized and excreted from the body-although in some cases they can result in permanent changes. If new genes become stably integrated into the genomes of long-lived cells or cell lines, they can continue to exert a powerful influence on the person's health for a lifetime.

Although the technology of genetic manipulation has come a long way, it is still very early days with respect to our understanding of how to make it work-and not malfunction-in people. Sadly, the history of performance-enhancing technologies in sport suggests that these uncertainties and risks will not deter unscrupulous entrepreneurs-or desperate, gullible athletes. Coaches and trainers indifferent to the health of the athletes under their influence may collude with unethical scientists who have the skills, knowledge, and access to raw materials necessary to attempt genetic modification.

The renowned physicist Niels Bohr is credited with saying "Prediction is very difficult, especially about the future." How true. Nevertheless, I will offer a few educated guesses about what the next several years will offer for gene doping in sport:

- There will be people offering what they will claim is genetic enhancement to athletes.
- Some athletes will take them up on their offer.
- Rumors will fly around the world of Olympic sport about gene-doped super-athletes.
- Those rumors will be half-true: True about some athletes subjecting

themselves to genetic manipulation; false about them becoming superathletes. The rumors will grossly overestimate the effectiveness of gene doping and its impact on sport.

 Of the athletes who try gene doping, most will experience no performance boost beyond the placebo effect, while others will find their abilities diminished and possibly their health damaged. There is the possibility—exceedingly remote at this time—that some few athletes may experience a temporary increase in performance. But this is very, very unlikely to affect the competitive balance in Olympic sport—at least not for a good many years.

For those who love the Olympics and want to preserve its dignity and integrity, complacency is not an option. Gene doping is not an imminent threat to sport, but it has the potential to dramatically affect the Games many years hence unless steps are taken now.

Education is vital. Athletes and the people athletes rely on for advice need to understand the complexities and uncertainties around gene transfer—not least, our enormous ignorance about the risks of gene transfer in humans, risks that the X-SCID experiment demonstrates can be unexpected and grave.

Research is also crucial. We need to devise strategies to deter and detect gene doping. We also must refine our understanding of the ethics of genetic enhancement. Does gene-doping challenge our conception of *natural talents*? In what ways is it similar to or different from using performanceenhancing drugs?

Meanwhile, if you find someone hyperventilating about the Olympics being on the verge of ruin because of gene transfer, encourage the person to take a deep, slow breath, and then set about the work necessary to insure that what you love and value about Olympic competition is preserved. *

Newly-elected WADA VP Brian Mikkelsen (above and with Richard Pound bottom-left) hosting the World Conference on Doping in Sport in Copenhagen in 2003.

A Vice President for WADA Brian Mikkelsen, the Danish Minister for Sport, newly elected as WADA vice president by the Foundation Board

For the first time since the Agency's inception, WADA has a vice president. At its November 2004 meeting, the Foundation Board unanimously elected Brian Mikkelsen, the Danish Minister for Sport, to this position. Since that time, Mikkelsen has been working closely with WADA President Richard Pound and Director General David Howman.

Mikkelsen is no stranger to WADA. In fact, he was responsible for hosting the 2003 World Conference on Doping in Sport in Copenhagen, where the World Anti-Doping Code was unanimously approved. He has also served Europe on WADA's Executive Committee since 2002 and has been working hard on placing the fight against doping on the European Union agenda.

Mikkelsen, who holds a Masters degree in political science, was elected to the Danish Parliament as a representative of the Conservative People's Party at only age 28. He became Minister of Culture in November 2001 and was reappointed following the February 2005 Danish election.

Since responsibility for sport falls under the cultural minister, Mikkelsen also holds the title of Minister of Sport, a topic for which he has a great passion. Despite a busy schedule, he finds time each morning to jog, likes to play tennis and attends sporting events as often as possible. Mikkelsen has been elected WADA's vice president for a period of one year.

"WADA is built upon a partnership between the Olympic Movement and governments of the world," Mikkelsen said. "This partnership is reflected in all the work the Agency carries out and it is now evident in WADA's leadership, as well."

Pound, who was re-elected to a three-year term, is pleased to have Mikkelsen on board.

"Denmark has always been a stalwart supporter of the antidoping fight and Brian has shown his commitment to WADA many times," Pound said. "I am happy to be able to collaborate even more closely with him."

State of the Nations

Our continuing series on government representatives who are particularly active in the fight against doping in sport.

Jean-François Lamour (FRANCE)

Jean-François Lamour is a well known sports figure in France. A talented fencer, he has won two Olympic titles, in Los Angeles in 1984 and in Seoul in 1988, as well as three other Olympic medals and a world championship in 1987. He was the flag bearer for the French Olympic team in Barcelona in 1992 and retired from sports competition at the age of 36. He then took up again his trade of physiotherapist, which he put aside in 1993, when then Paris Mayor Jacques Chirac asked him to be his counselor on youth and sport. He held the same position at the national level from 1995 to 2002, when Chirac became president of the republic, before being named France's Minister for Sport.

Today, Lamour is one of Europe's most active ministers in the fight against doping in sport. He has helped coordinate this fight internationally for years and in 2004, became a member of WADA's Executive Committee. As Minister in France, he has prepared a law that will put French legislation completely in line with the International Convention Against Doping in Sport, being prepared under the auspices of UNESCO.

Under Lamour's guidance, France has intensified the fight against doping in many areas, including education, doping control tests and international cooperation in the area of substances trafficking. France also continues to make one of the largest contributions among governments to WADA's annual budget (approximately US\$593,000 in 2004).

Humberto Rodriguez Gonzalez (CUBA)

Humberto Rodriguez Gonzalez holds a dual role in Cuba, as president of the Cuban National Insitute for Sport, Physical Education and Recreation and as president of his country's national anti-doping commission, which was created in 1999. In this role, he plays an important role in the fight against doping at both a national and international level.

Gonzalez, who holds a degree in law, was the chief of mission of his country's delegations to the Olympic Games in both Sydney and Athens and is quite familiar with the world of elite sport. His role with the antidoping commission gives him responsibility for putting in place educational campaigns, warning athletes about the dangers of doping and putting in place various programs, in collaboration with the Cuban Olympic Committee, to ensure clean sport.

In recent years, Cuba has stepped up its efforts in the fight against doping, particularly since the opening of an accredited laboratory in Havana in 2001. In addition, more than 2000 doping controls will be carried out in Cuba this year as part of the antidoping program and Cuban sports authorities continue to put in place various programs for educating athletes and their entourages.

Datuk Azalina Othman Said (MALAYSIA)

Datuk Azalina Othman Saidi is a pioneer. She is the first woman to serve as Minister for Youth and Sport in Malaysia and is also the first woman to serve the Asian region on WADA's Foundation Board.

A lawyer by trade, she has undertaken her role as minister with the same fervor that she used to create "Women, Sport and Health," an organization dedicated to promoting physical activity among women. She entered politics in 2000 and has served as minister since March 2004. She has launched a national campaign "Sport for All," and has created a council on physical activity, opened athletic centers to the public and has invited the Malaysian population to contact her directly with their thoughts and suggestions.

A fifth-dan black belt in taekwondo and a sport enthusiast, she is passionate about the concept of sport without doping and has put in place several measures in this regard. Her election to WADA's Foundation Board allows her to pursue more anti-doping activities in her country, which is one of two nations in Southeast Asia to have a WADA-accredited anti-doping laboratory.

A proven champion and certified lover of life on the edge, Jacqui Cooper has become one of Australia's most vocal advocates of how the greatest thrills come from an honest and dedicated pursuit of athletic excellence.

He told her she would be good at freestyle and she took it from there.

Now 32, Cooper's career highlights include 15 career World Cup wins and 27 World Cup medals (15 gold, 8 silver and 3 bronze). Cooper was 1999 World Champion and she was World Cup Freestyle Overall Champion in 1999, 2000 and 2001. Cooper was the first woman in the world to compete Full Tuck Full (Complex double twisting somersault). She was also the first woman in the world to do a Full Full on snow and compete it (triple twisting triple somersault).

Cooper is one of several high-profile Olympians spearheading the "Live Clean, Play Clean" Drug Education Program, which is an initiative of the Australian Olympic Committee (AOC).

"I really believe that education is vital, and that education about drugs in sport is very important for individuals that compete in sport," Cooper said. "Being a role model brings certain responsibilities. I feel it is my responsibility to help inform and educate people about drugs in sport. Olympians can be a huge asset to these types of programs; they can raise the awareness of drug issues because Olympians have to deal with drugs in sport everyday."

This program targets young athletes involved in Olympic and non-Olympic sports throughout Australia. The program highlights the dangers of taking performance-enhancing drugs. It also deals with the use of food supplements, recreational drugs and explains in detail the penalties for any athlete who returns a positive test. The program travels to schools and sporting institutes throughout Australia. (For more information on the program see the spring 2003 issue of Play True.)

"I think all national federations (NFs) should run similar programs in line with the AOC "Live Clean, Play Clean" initiative," Cooper said. "I think that educating everyone (all young people) is an enormous job. All NFs need to be responsible for their athletes and an education program for drugs in sport should be out in place. Too many times people say that they weren't aware of the banned substances."

The program outlines the AOC's strict anti-doping policy, which all athletes

must sign before they are accepted onto the Australian Olympic Team. Cooper's role as deputy chairperson on the AOC's Athletes Commission allows her to help formulate that policy. It stresses the need for all athletes to take full responsibility for what they take.

"Given the information out there, I don't think there is any excuse for what we take as athletes," she said. "Anything "I think WADA, the Australian Sports Drug Agency (ASDA) and the NFs are doing a great job targeting drug cheats," she added "The harshest penalty should be in place for people that cheat the system. Taking drugs is breaking the "sport" laws and punishment should be very tough."

Last year, Cooper made a successful return to aerial skiing competition at

I really believe that education is vital, and that education about drugs in sport is very important for individuals that compete in sport. Being a role model brings certain responsibilities. I feel it is my responsibility to help inform and educate people about drugs in sport. Olympians can be a huge asset to these types of programs.

we put in our mouth is our responsibility. As long as the education is there for the younger and up-andcoming athletes, a lack of knowledge is not an excuse anymore."

When asked what she thinks of athletes who cheat and the adequacy of penalties in reference to cheaters Cooper said, "Athletes that cheat are really just cheating themselves. Winning is so important but it should be honest and it should be a display of a person's natural abilities, hard work and talent. I have no respect for athletes that cheat. I'd rather see a mediocre performance that wins, than an outstanding performance that only won because the performance was enhanced by drugs."

Mt Buller's Alpine Exposure World Aerials in September 2004, more than two and a half years after the injury that ended her gold medal campaign at the Salt Lake 2002 Olympic Games. She came back not only intent on rejoining the World Cup circuit and getting to the Olympic Games in Turin in 2006, but also on completely rebuilding her technique step by step, making sure fundamentals were bedded down in low degree of difficulty routines.

Cooper was still only part way through the process of re-building her routine, performing double somersaults rather than her trademark triples, but she executed them superbly, not only making the podium, but also qualifying for selection to the Australian team for the Turin Games.

When the 2004/05 World Cup circuit resumed in Mont Tremblant (Canada) in January, Cooper maintained her focus on rebuilding her technique, opting for a double twisting and single twisting double somersault routine. She placed sixth, but more importantly, she earned a perfect form score on her lay full from one of the judges, and was just 1.7 points off a perfect points score for the jump. ■

Cooper was 1999 World Champion and World Cup Freestyle Overall Champion in 1999, 2000 and 2001. Her career highlights include 15 career World Cup wins and 27 World Cup medals (15 gold, 8 silver and 3 bronze).

🚺 🛯 🗌 Partner Profile

Ever vigilant in its stance against doping, the IPC's priorities remain focused on the education of athletes and the implementation of a comprehensive registered testing pool

By Miriam Wilkens, IPC Media and Communication Director

The International Paralympic Committee (IPC) is the international governing body of sport for athletes with a disability. The IPC supervises and co-ordinates the Paralympic Summer and Winter Games and also acts as the international federation (IF) for 13 sports. For these 13 IPC sports, the IPC supervises and coordinates multi-disability competitions, such as world and regional championships, and provides the administrative and policy development services, including in the area of anti-doping. The IPC also supports the recruitment and development of all athletes across all performance levels.

The IPC was founded in 1989 as an international non-profit organization and is formed and run by 161 National Paralympic Committees (NPCs) and four disability specific international sports federations. The IPC headquarters, situated in Bonn, Germany, includes approximately 20 professional staff, the first employed in 1998, who manage the daily operations of the organization. Previously, the organization was run almost exclusively by volunteers.

Andy Parkinson, who will be joined by an anti-doping and classification manager in the near future, currently heads the IPC medical and scientific department. The department manages anti-doping, classification and sport science issues and is supported by the Anti-Doping Committee and the Therapeutic Use Exemption (TUE) Committee. The Anti-Doping Committee supports test planning and manages results whereas the TUE Committee is responsible for the TUE process (applications, decisions, etc). International level athletes with specific medical conditions requiring medication that are prohibited may apply for TUE. The IPC works closely with WADA through its representation on the WADA Foundation Board (Phil Craven), Health, Medical and Research Committee (Dr. Björn Hedman), and the Education Working Group (Andy Parkinson).

The Code

In March 2003, the IPC became a signatory of the World Anti-Doping Code. Thereafter, the IPC Anti-Doping Code was revised to comply with the WADA Code and corresponding International Standards, and was officially launched on February 1, 2004. The IPC Anti-Doping Code is a unique code as it applies at all IPC sanctioned competitions, meaning at all 13 IPC sports' competitions (championships, cups, etc) and at Paralympic Games. This is in contrast to, for example, the IAAF Code, which only applies for one sport, namely athletics, or the IOC Code, which only applies at Olympic Games. The IPC was the second organisation, in its capacity as an IF, to release a WADAcompliant Code.

To protect the athletes' fundamental right to participate in doping-free sport, the IPC in mid-2003 ruled that all NPCs and sports wishing to take part in the Paralympics must declare their acceptance and recognition of the WADA Code. This obligation has now been expanded; today one requirement for IPC membership is to sign a declaration to abide by the WADA Code and to implement appropriate rules and regulations. It is believed that this is the strongest message that the IPC can send to its members signalling that doping will not be tolerated.

In-Competition Testing

The IPC negotiates the number of tests to be taken with each organizing committee of an IPC sanctioned competition. Generally, no less than 15 percent of the accredited athletes at world championships are tested and at regional championships and other sanctioned competitions, approximately 10 percent are tested. Last year, tests were carried out at a variety of world championships (eg, IPC 2004 Bowls World Championships), regional championships (eg, IPC 2004 Archery Asia & South Pacific Championships) and world cups (eg, IPC 2004 Nordic Skiing World Cup). The IPC plans to increase the number of competitions with in-competition testing significantly in 2005.

Paralympic Games

The Paralympic Games provide the IPC with the greatest single opportunity to test athletes across a wide variety of sports. A total of 680 urine tests, including EPO tests, were carried out at the Athens 2004 Paralympic Games. For the Turin 2006 Paralympic Winter Games, approximately 250 urine tests are planned including EPO, and blood tests for hGH and other substances.

Partner Profile 🗌 🛛 🕄

Photo courtesy IPC

Out-of-Competition Testing

In 2004, the IPC signed an agreement with WADA on out-ofcompetition testing, ensuring that the 13 IPC sports are subject to out-ofcompetition testing; in the past, testing has only taken place at sanctioned competitions. WADA, in consultation with the IPC, manages the out-of-competition testing and sample analysis with national antidoping organizations or third parties carrying out the testing on behalf of WADA. All athletes competing at an international level may be subject to out-of-competition testing. It is expected that the number of tests will increase in 2005.

Registered Testing Pool/ADAMS

Since 2004, the IPC has been working on refining the criteria for and management of the IPC's registered testing pool, which currently includes all athletes participating at Paralympic Games. Being the IF for 13 sports complicates the already hard-tohandle matter of athletes' whereabouts. At present, there is no internal solution for tracking athletes' whereabouts but it is hoped that the WADA Anti-Doping Administration and Management System (ADAMS), once implemented in mid 2005, will assist significantly in the IPC's ability

to track athletes' whereabouts and implement an effective out-ofcompetition testing program. Together with other organizations, such as UK Sport and the International Rugby Board, the IPC is involved as part of the ADAMS implementation group to assist with the first phase of operations of ADAMS. Another area, which ADAMS will hopefully simplify, is the TUE procedure. The IPC has had a TUE process in place since 1994 (formerly known as the Medications Advisory Panel) and the number of applications has, over the years, grown. In 2004, approximately 350 TUE applications were managed. While the number of applications is not expected to decrease, it is hoped that ADAMS will assist both athletes and the IPC in the TUE process, from application to approval, through an online solution.

Education

During 2005, another priority will be education. In the past, the WADA Athlete Outreach program has successfully assisted the IPC in educating athletes through its presence at the Salt Lake 2002 and the Athens 2004 Paralympic Games, and at the IPC 2004 Alpine Skiing World Championships. The Outreach program will also be present at the Turin 2006 Paralympic Winter Games and is a successful means of educating athletes. However, the IPC plans to implement greater initiatives for education and is presently developing web-based educational tools and investigating possibilities to develop an IPC Athlete Outreach program in line with WADA's strategy.

Contact

For further information visit the IPC website: www.paralympic.org or contact us at:

International Paralympic Committee (IPC) Adenauerallee 212 - 214 53113 Bonn, Germany

Tel.: +49-228-2097-200 Fax: +49-228-2097-209 E-mail: info@paralympic.org ■

WADA Funds available for Social Science Research

US \$60,000 earmarked for 2005 pilot program

Anti-doping education remains a high priority for WADA. To this end, the Agency will award grants in the social sciences to encourage research in this area. The objective is to gain more information into the most effective way to put in place anti-doping education programs.

In the 2005 pilot program, US \$60,000 in funds will be available as grants. Future funding of this program will depend largely on the interest shown by the research community in this field and by the quality of proposals submitted for grants this year.

All proposed research projects must be related to one or more of the stated

program priorities. Priorities will be assigned on an annual basis to certain topics, research subjects and protocols. More detailed information is available in the "Guidelines for Applicants 2005," which are available, along with the "Call for Proposals," on WADA's website under the education section.

WADA will dispense research grants to all types of organizations (universities, small businesses, forprofit organizations, etc.) Deadline for submissions for consideration for the pilot program is March 31, 2005. Those interested in obtaining further information can contact: info@wada-ama.org

WADA Launches Poster Series

WADA has launched a poster series to promote the values of sport (respect, dedication, character, solidarity and excellence). The series - available for now only in English - is titled "Spirit of Sport" and features five athletes in the fight against doping: Canadian basketball player Tracey Ferguson; Brazilian swimmer Gustavo Borges; Japanese judo competitor Yoko Tanabe; German rower Roland Baar; and English runner Paula Radcliffe. Interested stakeholders can contact WADA at *info@wada-ama.org*

Education Symposium held in Uruguay

WADA has launched its education symposia program February 22 and 23 in Montevideo, Uruguay. The symposium brought together approximately 50 participants, including representatives from the sporting world, anti-doping agencies, athletes, trainers and other interested parties from Latin America.

WADA was represented by Director General David Howman and others at the event in Uruguay. The Agency has developed this symposia program with a particular focus on developing countries and regions worldwide. The program has a fundamental objective of assisting WADA's stakeholders in implementing effective education programs and ensuring the provision of relevant information on doping-free sport, with particular emphasis on athletes and their support personnel.

More educational symposia will be organized in other regions of the world in the coming months.

2005 Prohibited List and Third Edition Athlete's Guide now available in print

WADA's 2005 List of Prohibited Substances and Methods, which went into effect January 1, is now available in print form in English and French.

The Agency has also published a third edition of the Athlete's Guide, which gives an over view of the World Anti-Doping Code and describes athletes' rights and responsibilities in the doping control process.

These two publications can be found on WADA's website at: www.wada-ama.org

International Convention Reaches New Stage

The UNESCO Headquarters in Paris. The objective remains to have the convention ratified prior to the Turin Games in February of next year.

Draft final text sent to member states, will be presented to UNESCO General Conference in October

The International Convention Against Doping in Sport, being prepared under the auspices of UNESCO, the United Nations body for education, science and culture, reached an important milestone in January.

The final text of the document was drafted during a Category II meeting of UNESCO member countries in Paris. WADA representatives, including Director General David Howman, participated in the meeting. This draft final text was sent in early March by UNESCO Director General Koïchiro Matsuura to all member states and will be presented to the UNESCO General Conference during its session, which will take place October 3 to 21 in Paris.

The objective remains to have the convention ratified by governments and the World Anti-Doping Code thus formally recognized by them prior to the Olympic Games in Turin in February 2006.

III I WADA Updates

NEW ARRIVALS

WADA has new Communications Director

WADA has hired Elizabeth Hunter as its new director of communications. Hunter was senior director of communications and member services, Federation Relations, for

Elizabeth Hunter

the United States Chamber of Commerce, the world's largest business federation. In that capacity, she was responsible for the organization's relationship with 3,000 state and local chambers and 800 business associations, garnering their support for U.S. Chamber legislative and regulatory priorities.

From 1999 to 2001, she served as marketing director for the U.S. Chamber's joint venture ChamberBiz.com, a business-tobusiness web portal providing grassroots advocacy services and business information to the small business market. Prior to joining the U.S. Chamber, Hunter was the government affairs officer for a U.S. business association in the blood products and services industry. She has also worked as a legislative aid to a member of the United States Congress. She holds a master's degree in French from Middlebury College in Middlebury, Vermont. Hunter will start at WADA in early April.

In addition, WADA welcomes new legal manager Julien Sieveking, who previously worked for the European Football Union (UEFA) in Nyon, Switzerland. WADA's regional office in Lausanne has also grown with the addition of Nicole Frey, who assumes the role of medical coordinator. Frey will assist medical director Dr. Alain Garnier in the review of therapeutic use exemptions.

New booklet on Athletes and Medications now available

WADA has published a new question and answer booklet entitled *Athletes and Medications*.

The booklet, available in English, French and Spanish, gives athletes information on how to be cautious when taking medications in order to avoid a positive doping test. This publication is the latest in a series produced by WADA in multiple languages. Other *Q* & *As* produced focus on the World Anti-Doping Code, therapeutic use exemptions (TUEs) and nutritional supplements. All of these publications can be found in PDF format on the Agency's website.

Funding

94 percent received for 2004, Oceania contribution paid in full for 2005

WADA has already received several contributions from the Olympic Movement and world governments to its budget beginning this year.

By the end of January, WADA had received 25.5 percent of its budget for 2005, US \$3.7 million

of which was an advance from the International Olympic Committee.

The Oceania region has paid in full for this year. WADA has also received contributions due from previous years, which brings the total received for 2004 to 94 percent.