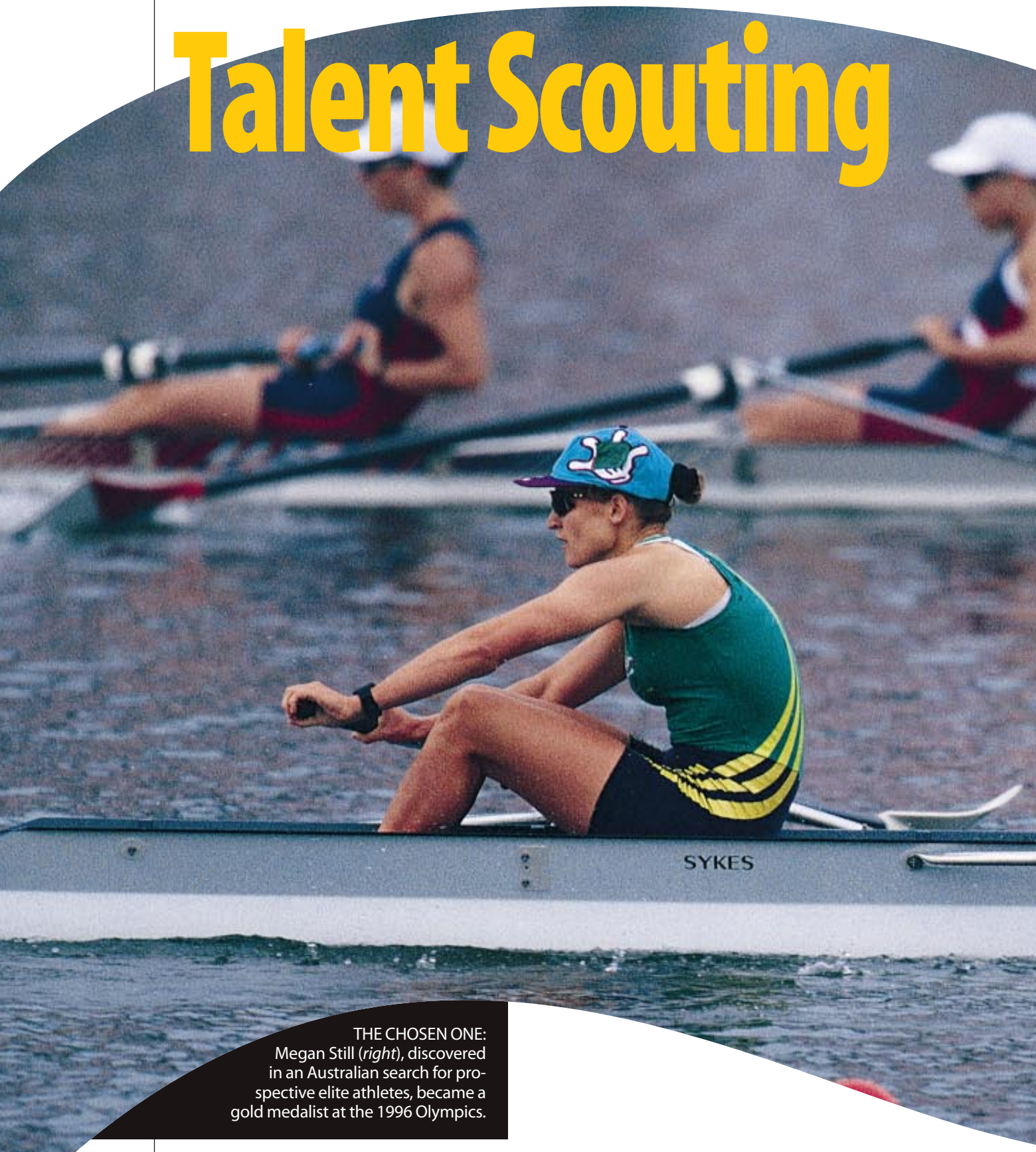
Toward Molecular Talent Scouting



THE CHOSEN ONE: Megan Still (*right*), discovered in an Australian search for prospective elite athletes, became a gold medalist at the 1996 Olympics.

Scientists are engaged in a frustrating search for genes to identify future Olympians

by Gary Taubes

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Thirteen years ago the Australian Institute of Sport (AIS) set out to level the Olympic playing field, to make it possible for a country of fewer than 20 million inhabitants to compete against nations with 10 or 50 times the talent pool. The result was the national Talent Search Program, which would scour the high schools of Australia for 14- to 16-year-olds who had the potential to be elite athletes and might not even know it. Once identified, these kids would be given the opportunity to engage in the sports in which they were most likely to excel, given their physical attributes and skills.

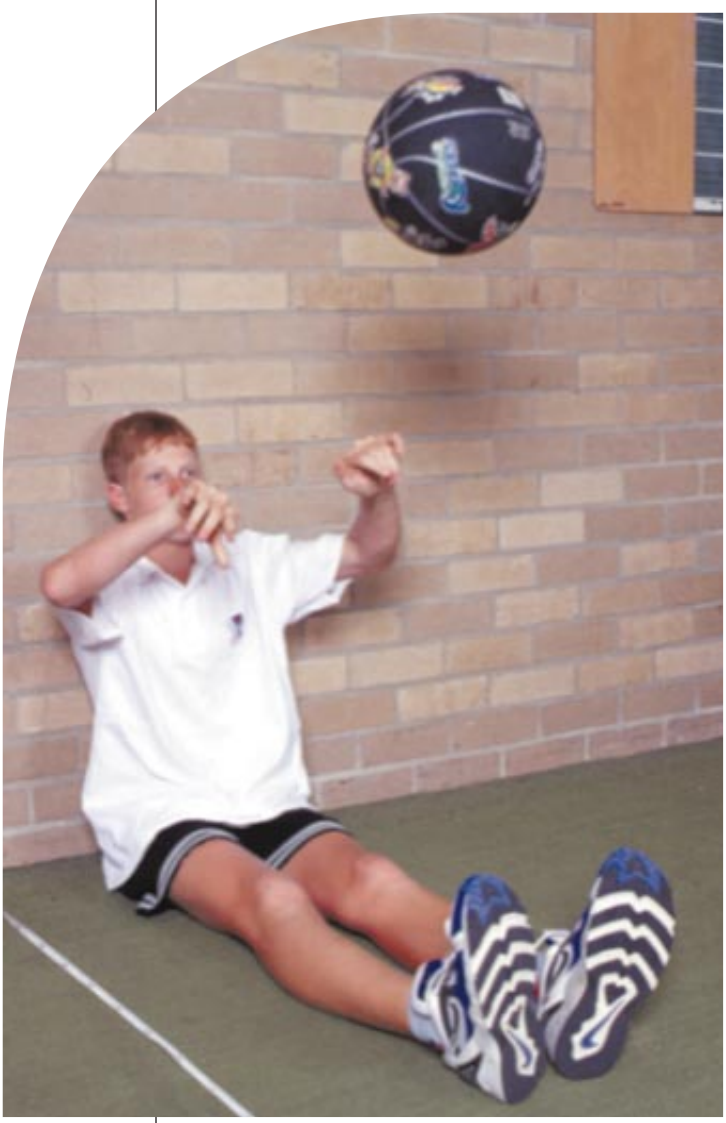
The program began in 1987 by searching for rowers to compete in a sport in which the Australians had failed to qualify a single athlete for the 1988 Olympics. The Talent Search team described the physical and physiological characteristics that appeared to differentiate elite rowers from their less successful competitors and then went off to test Australian high school students and se-

SELECTION PRESSURES: Teenagers in Australian high schools went through a battery of tests to determine their potential to become top athletes.

lect those who possessed the winning attributes—people who were tall with broad shoulders relative to their hips, long limbs, good musculature and a relatively high level of both strength and endurance. That the program and the philosophy could pay off was demonstrated in the 1996 Atlanta Olympics, when Megan Still took home a gold medal in women's rowing. Still had been running track as a 16-year-old before Talent Search handed her an oar.

TRAINABILITY GENES

In 1994 Talent Search was extended to eight different sports, from cycling and canoeing to water polo and weight lifting, and the program's researchers concocted a series of tests to measure coordination, endurance, strength and aerobic fitness. That left one critical attribute, however, for which they've yet to develop a test: how to differentiate the young athlete who will improve greatly from one who has, in effect, peaked. "We know that you can give two people the same training program, and one will respond to it with enormous improvement in performance capabilities, and the other will show hardly any improvement at all," says Allan Hahn, director of the physiology program at the AIS.



Over the years, researchers have demonstrated that the difference in "trainability" is mostly in the genes: some of us have an innate ability to respond to exercise and others don't, and the ability runs in families. So the AIS has launched a project to identify those genes and put them to work. "The aim is to see if we can maybe use some of these genetic characteristics to work out who will respond to a particular training program," Hahn comments, "although it is a very long-term goal."

Call it the search for performance genes. Someday researchers hope to pinpoint those genes that not only ensure trainability but perhaps endow athletes with the flashing speed of a sprinter or the endurance of a marathoner or that differentiate a power lifter from a power forward. In the past decade researchers have found at least two gene mutations—one in horses and one in humans—that will bestow a winning edge on those who possess them, but they have yet to locate those genes in the general population that differentiate winners from losers or the trainable from the untrainable.

Meanwhile the bulk of the research is done not in pursuit of Olympic glory but with the hopes of curing or ameliorating chronic diseases and the deterioration that comes with aging. The logic: find the genes that are crucial to muscle growth, and you have a handle on how to restore muscle growth to the elderly, to forestall the physical frailty and debilitation that comes with aging. Identify a gene that explains why some individuals are especially efficient at putting oxygen to work in their cells, and you might be on the way to creating a drug that makes cells work more efficiently with the limited oxygen and nutrients those cells receive when heart disease or cancer strikes.

AN EQUINE SCHWARZENEGGER

That a single gene can make a difference was demonstrated unambiguously by a quarter horse, aptly named Impressive. Purchased at the Indiana State Fair in 1969, Impressive went on to become the most famous progenitor of quarter-horse show winners for decades to come. He had the perfect physique, the ideal blend of muscle mass and tone for his frame, which is what it takes to win in quarter-horse competitions. By 1992, 13 of the top 15 quarter horses in the world were his descendants.

Impressive, however, had a single flaw in a single gene—a one-letter abnormality in the three billion letters that constitute the horse genome. The result of this mutation was a defect in the molecular channels that controlled the flow of sodium into and out of Impressive's muscle cells. It was discovered because this flaw also induced a type of temporary paralysis often fatal to the afflicted horses. On the

PHOTOGRAPHS COURTESY OF THE AUSTRALIAN NATIONAL TALENT SEARCH UNIT

other hand, it led directly to the extraordinary musculature of Impressive and his progeny. "This caused some furor within the horse community," explains geneticist Eric P. Hoffman of George Washington University, "because this single nucleotide change definitely makes you win. There is absolutely no question. You look like Arnold Schwarzenegger in a horse if you have this single base change."

Hoffman and his colleagues have now discovered a host of genetic mutations in animals and humans that lead to excessive musculature. Muscle growth is spurred first by damage to the muscle cell membranes caused, for example, by lifting weights. The muscle responds to damage by growing back stronger and larger. These mutations result in muscle cells that are more easily stimulated to contract and so, in effect, are constantly exercised—as is the case with the sodium channel defect of Impressive and his offspring in muscle cells that are easily damaged and so more easily spurred to grow back stronger.

One example is Duchenne's muscular dystrophy, the most common lethal childhood disorder. In Duchenne's, a single genetic defect results in the complete absence of a protein, called dystrophin, that is critical to the structural integrity of muscle cell membranes. In cats, the absence of the dystrophin protein is relatively benign but still leads to Schwarzenegger-esque musculature. "A lot of their muscle groups are double the size of [those of] normal cats," Hoffman remarks. And children lacking the dystrophin protein often "look like professional body builders at five and six, and they don't lift any weights." In children, however, the muscle soon turns into scar tissue, resulting in the gradual wasting away that characterizes the disease in its later stages. "It's like the muscle tries to keep growing back and [dies and grows] back and, in time, just gives up." In less severe forms of muscular dystrophy, such as Becker muscular dystrophy, the dystrophin gene is defective but not missing. The result often manifests itself as the abnormal muscle growth without the fatal consequences. "We found patients with [this abnormal] dystrophin," Hoffman says, "who are professional athletes. Some are professional tennis players; some are weight lifters; some are quarterbacks on football teams."

Now Hoffman and his colleagues are comparing the genes of average individuals with those of world-class body builders, weight lifters and football players to see if the genes that code for dystrophin and other structural proteins of the muscle cell membranes play an important role. Specifically, they wonder whether these athletes have a particular variation in the gene—as opposed to a rare mutation—that might predispose them to muscular development and lead to success in their chosen events. In another study, Hoffmann and his collaborators are putting 1,600 students through an exercise program to see if those who come out of it with extraordinary muscle growth will turn out to share the same variants of specific genes. "Hopefully," he observes, "we'll find a lot of muscle strength and size genes out of a large study like this."

ELIMINATING COUCH POTATOES

While Hoffmann and his colleagues pursue the genetics of musculature, the bulk of the research in performance genes aims at tracking down those involved with endurance performance, if for no other reason than that athletic endurance correlates well with a physiological characteristic known as maximal oxygen uptake. This is your body's capacity to take in oxygen and put it to work in your muscles, and it is easy to quantify. "We know what we are measuring here," says Claude Bouchard, a geneticist and exercise physiologist who directs the Pennington Biomedical Research Center in Baton Rouge. "This is not the case, for example, in a sport that requires a lot of coordina-

IMPRESSIVE: The descendants of this quarter horse, which bore a genetic mutation that gave it extraordinary musculature, accounted for 13 of 15 top show winners by 1992.

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tion—basketball or archery or whatever—where we don't have a good laboratory measurement." Elite endurance athletes have a maximal oxygen uptake twice as high as that of the rest of us and perhaps three times that of elite couch potatoes.

This ability to use oxygen efficiently is determined by an enormous number of physiological variables, from the volume of blood that the heart can pump in and out to the efficiency with which the body can convert oxygen from the blood into fuel that powers muscle motion. As with muscle growth, however, there is one outstanding example that genetic mutations can succeed in providing a winning edge. In this case it's a mutation in a gene that codes for a protein known as EPOR, or the erythropoeitin receptor.

Erythropoeitin is a growth hormone that regulates the production of red blood cells, which carry oxygen through the blood to the muscles. EPOR is the protein with which erythropoietin interacts to initiate the process of red blood cell production. In this type of mutation, the EPOR protein is truncated. It can still turn on in response to erythropoietin, but turning off is a problem. Individuals with this rare mutation generate an abnormal amount of red blood cells. This excess should give them an advantage in endurance sports, in which keeping oxygen flowing copiously to the muscles is critical.

That it does so was realized a decade ago, when Finnish researchers identified an entire family with the EPOR mutation, several members of which were championship endurance athletes, including one Olympic gold medalist, cross-country skier Eero Maentyranta. The Olympic champion, says Gregory D. Longmore, a biologist at Washington University, turned out to have an extraordinarily high red blood cell count, higher than could be achieved artificially by athletes who enhance their red blood cell count by injecting themselves with erythropoietin. "[The erythropoeitin receptor gene] is clearly a performance-enhancing gene," Longmore says.

CONTRADICTORY EVIDENCE

But researchers have been unable to show unambiguously that naturally occurring variations in EPOR or any other genes confer athletic advantages that might be predicted in advance through genetic testing. This is trickier than it might seem, as illustrated by the results so far of the two largest studies in the field. One, the Heritage Family Study, is a collaboration of four universities and Bouchard's Pennington center. The Heritage researchers recruited 200 families, encompassing some 750 sedentary subjects. They put them through a rigorous training program and then looked for genes that might relate to trainability, in this case the ability to increase maximal oxygen uptake with exercise. The second study, known as GENATHLETE, was begun 15 years ago by Bouchard and an international collaboration. The GENATHLETE researchers banked the DNA from more than 350 male Olympic-caliber endurance athletes and 350 sedentary controls, assuming that if any particular gene variants or mutations were critical to elite endurance performance, they would show up more frequently in the Olympic DNA than in that of the sedentary controls.

The Heritage researchers have been able to isolate four chromosomal regions—comprising millions and millions of base pairs of the double helix of DNA—that appear to be linked to maximal oxygen uptake while at rest among these sedentary individuals and another five different regions that are linked to trainability. When they tested specific genes, however, the results were discouraging. "We've probably looked at about 40 different genes," Bouchard says, "and we have a few we can clearly exclude." The GENATHLETE researchers have tested 30 candidate genes and come up effectively empty. "Nothing so far is striking," Bouchard says. As for EPOR, it seemed to show some small relation to trainability in the Heritage study but no relation to elite athletic performance in GENATHLETE.

The most controversial research and the most highly publicized candidate for a performance gene is one known as ACE, which stands for angiotensin-

converting enzyme. It appears to play a role in regulating blood pressure, cell growth and the growth of heart muscle. In the early 1990s French researchers discovered that the ACE gene can be found in the general population in two distinct variations: one with an extra fragment of DNA (called the Insertion, or I, variant) and the other without it (called the Deletion, or D, variant). The two variants evidently influence the amount of ACE that can be found in tissue. Individuals with two I variants, one from their mother and one from their father, have significantly less ACE activity than do individuals with one I and one D, who in turn have less ACE activity than do individuals who have two D variants.

At University College London, physiologist Hugh E. Montgomery and his colleagues studied the effect of ACE variants first on young army recruits, then on elite endurance runners and finally on high-altitude mountain climbers. They found that individuals with two I variants (known as II) were, on average, more efficient at endurance exercise than either ID or DD individuals were and also seemed to be more trainable. Their bodies became considerably more efficient with exercise.

All this information strongly indicates that if you want to be an endurance athlete, it might help to check your ACE genes first and see if you have two I variants. Indeed, when Australian researchers from the University of Sydney compared Olympic rowers with the Australian population at large, they found that the II variant was overrepresented in the rowers. The Australian and English results might have settled the issue of ACE as a definitive performance gene, but several studies since, including GENATHLETE and Heritage, have not confirmed it. If anything, Bouchard says, the Heritage results suggest the opposite of the English and Australian results—that the DD variant is more common in individuals who respond well to exercise. To Bouchard, the idea of ACE as a performance gene is at best controversial and at worst wrong.

Most researchers in this field are confident that unambiguous performance genes will eventually be found, but they expect that the search will be difficult and that the benefit of having particular variants of these genes, unlike the rare mutations, will be very subtle. After all, even the simplest biological systems are excruciatingly complicated, full of protective redundancies and regulating mechanisms. University of Missouri biologists Marc T. Hamilton and Frank Booth recently demonstrated that some 100 genes are involved in regulating an activity as basic as taking the weight off your legs—at least in mice. It's what the Missouri researchers call an unloading experiment, which is the opposite of lifting weights and a much easier experiment to do with mice. They freed the rear legs of the mice from their usual job of supporting the body's weight. "Within 12 hours," Booth asserts, "almost 100 different genes either turned on or off. It's kind of striking—it means you only have to lie down for 12 hours and you'll see huge changes in gene expression."

This result strongly implies that even if researchers could make sense of what all these 100 genes are doing, they would find that no single gene is making a crucial difference. Rather they are all having some small interrelated effect. And that's just for the equivalent of lying down for 12 hours—which, last we heard, was not an Olympic sport.

GARY TAUBES is a science writer based in California.

FURTHER INFORMATION

FAMILIAL RESEMBLANCE FOR VO_2MAX IN THE SEDENTARY STATE: THE HERITAGE FAMILY STUDY. Claude Bouchard et al. in *Medicine & Science in Sports & Exercise,* Vol. 30, No. 2; February 1998.

FATAL BUILD: A child with Duchenne's muscular dystrophy looked like a professional body builder, but signs of muscle wasting were already present.

LUCKY FLAW: Olympic cross-country skier Eero Maentyranta came from a Finnish family with a mutation that gives its members unusually high counts of oxygen-bearing red blood cells.

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