

by Glenn Zorpette, staff writer

The Mystery of Muscle

A little over two decades ago a grinning, oiled Arnold Schwarzenegger, with the motion picture *Pumping Iron*, hauled bodybuilding out of the dingy gyms and into the mainstream of U.S. popular culture. During more or less the same period, anabolic steroids started infiltrating bodybuilding, turning musclemen into big-jawed, moon-faced freaks, and strength-training machines began making weight training safer and more appealing to the masses.

The U.S. has not been the same since. Strength training has persisted as few movements have in recent U.S. history, reshaping popular views of physical beauty and male feelings of self-esteem. In 1994 an article in *Psychology Today* declared that “there seems to be emerging a single standard of beauty for men today: a hypermasculine, muscled, powerfully shaped body.” Since then, the trend has only intensified.

In 1995 weight training replaced riding a stationary bicycle as the most popular kind of exercise among American adults. The same year the number of males in the U.S. who worked out with weights at least 100 days a year reached 11.6 million, up from 7.4 million in 1987, according to American Sports Data in Hartsdale, N.Y. And more recently, the market for dietary supplements aimed at weight lifters and bodybuilders has grown explosively, led by a chalky powder called creatine monohydrate [see “Sports Supplements: Bigger Muscles without the Acne,” on page 52].

Although the number of women who regularly use weights has roughly tripled in the past decade, the superior ability of men to add muscle to their bodies has ensured that weight training remains inextricably linked to the male image and feelings of self-worth. And in recent years, several disturbing aspects of this link have become clear. Use of anabolic steroids is up, as are cases of muscle dysmorphia, a puzzling disorder in which abundantly muscled people see themselves as scrawny and become increasingly obsessed with weight training [see “You See Brawny, I See Scrawny,” on page 54].

Along with the cultural appreciation of muscle has come a surge of work aimed at understanding the biology of muscles. The vast majority of researchers in this area are study-

ing anatomical or physiological aspects of exercise related to aging, the effects of diet, dietary supplements and so on. A large group is also studying heart muscle tissue, a subject that bears strongly on cardiac diseases. Oddly enough, what might seem to be the most compelling issue in muscle science in this physique-obsessed era—the biochemistry of bulking up—has but a tiny band of full-time devotees.

Nevertheless, their research has yielded some impressive and even startling results of late. For example, researchers at the Royal Free and University College Medical School of University College London recently cloned a kind of hormone, which they call mechano-growth factor, that appears to be a significant link in the still largely mysterious ways in which muscle cells respond biochemically to mechanical stress by becoming stronger and thicker.

The University College researchers themselves view their discovery with a mixture of enthusiasm and uneasiness. On the one hand, the findings could be invaluable for treating muscular dystrophy and possibly age-related muscle loss. At the same time, the discovery seems likely to usher in a new age in performance-enhancing drugs, one that sports officials have anticipated with dread.

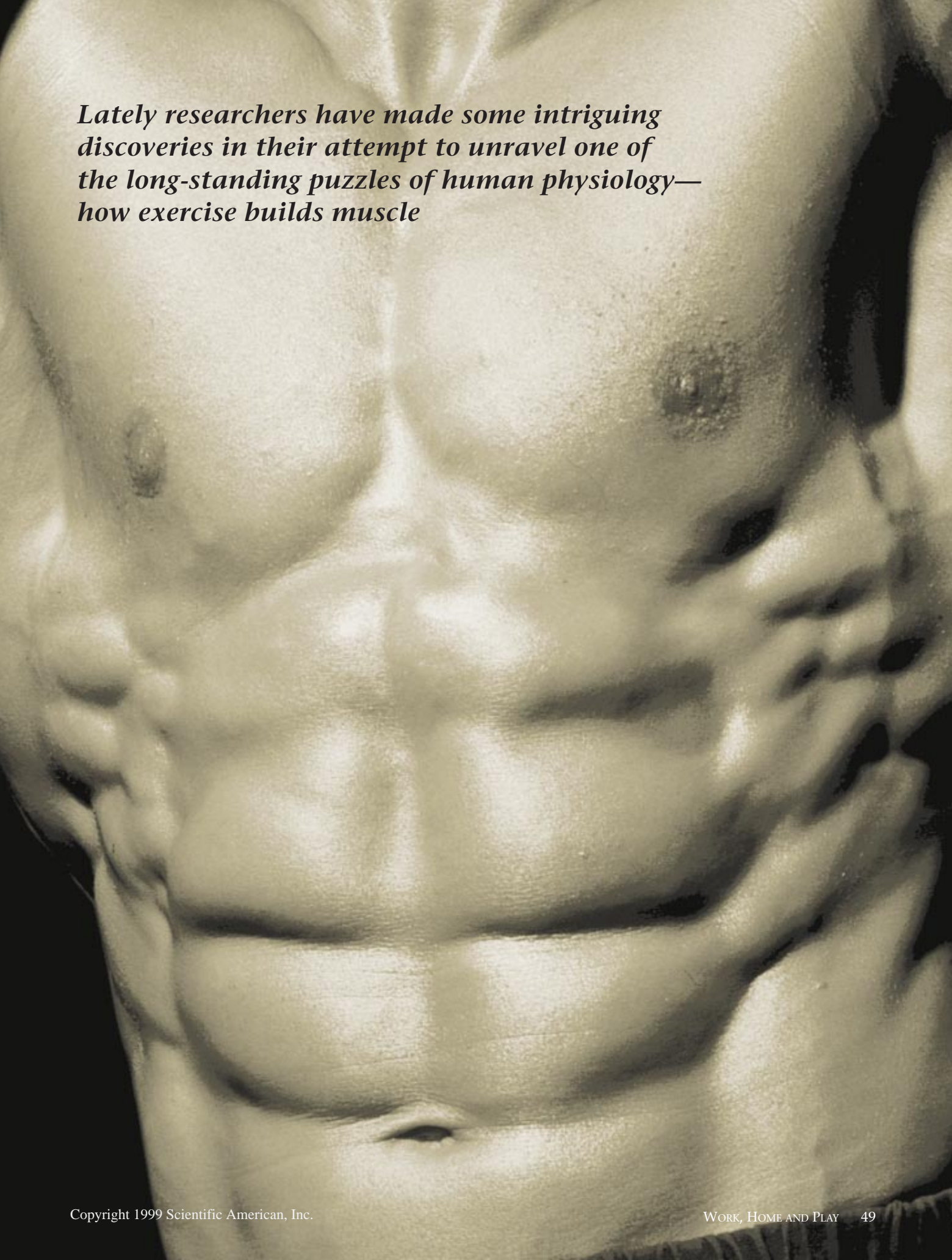
Stimulating the production of mechano-growth factor in specific muscles would increase their mass. Doing so would require only the injection of bits of human DNA into the muscles. Because the muscle cells would have already contained the DNA naturally, sports officials would find it difficult, if not impossible, to detect the injections. Thus, the development promises to create the ultimate muscle-building drug—one that, like anabolic steroids, could build muscles even without strenuous exercise.

“We’ve cloned the magic substance that makes muscles grow,” says Geoffrey Goldspink, the leader of the University College group that identified and reproduced the growth factor. In the not too distant future, he adds, “American footballers and athletes in all countries will probably be using this method. It will be abused, I’m sure. It is a great worry to me.”

How Muscles Contract

The recent findings at University College and elsewhere on skeletal muscle are the latest in a chain of discoveries stretching back at least to the 1950s. Researchers have laid out a detailed if incomplete understanding of skeletal muscle: what it is, how it works, how it grows and develops, and—most intriguingly—how it alters itself in response to exercise.

Although it is only one of three categories of muscle in the human body, skeletal muscle is what most people think of as “muscle.” The other two kinds are cardiac muscle, which



Lately researchers have made some intriguing discoveries in their attempt to unravel one of the long-standing puzzles of human physiology—how exercise builds muscle

powers the heart, and smooth muscle, which lines the arteries and parts of the stomach, intestine, uterus and other bodily components (its relatively slow, sustained contractions move food through the digestive system, for example).

Groups of skeletal muscles contracting against a scaffold of bone, all coordinated by the nervous system, do the work of lifting, playing the piano, moving an eyeball or throwing a right cross. Muscle is the most abundant tissue in the body, a distinction that makes it the body's largest store of a variety of key substances, such as amino acids, which are the building blocks of protein. For this reason, among others, the consequences of muscle loss in the elderly go beyond frailty to include such problems as weakened immune systems.

Skeletal muscle cells, also known as muscle fibers, are rather unusual in many respects, not least of which is that they have multiple nuclei. They are also comparatively huge, at approximately 50 microns in diameter and up to tens of centimeters long. Most of the cells' cytoplasm (the gelatinous part outside the nucleus but within the membrane) consists of elements called myofibrils [see illustration below]. Organized by the hundreds or thousands inside the muscle fiber, myofibrils are often about the same length as the muscle cells but only one to two microns in diameter.

Myofibrils are the contractile elements of muscle. In other words, a muscle contracts—and does work—when the lengths of all its myofibrils shrink forcefully in response to nerve impulses. To understand how the myofibrils do this requires an understanding of yet smaller elements within the

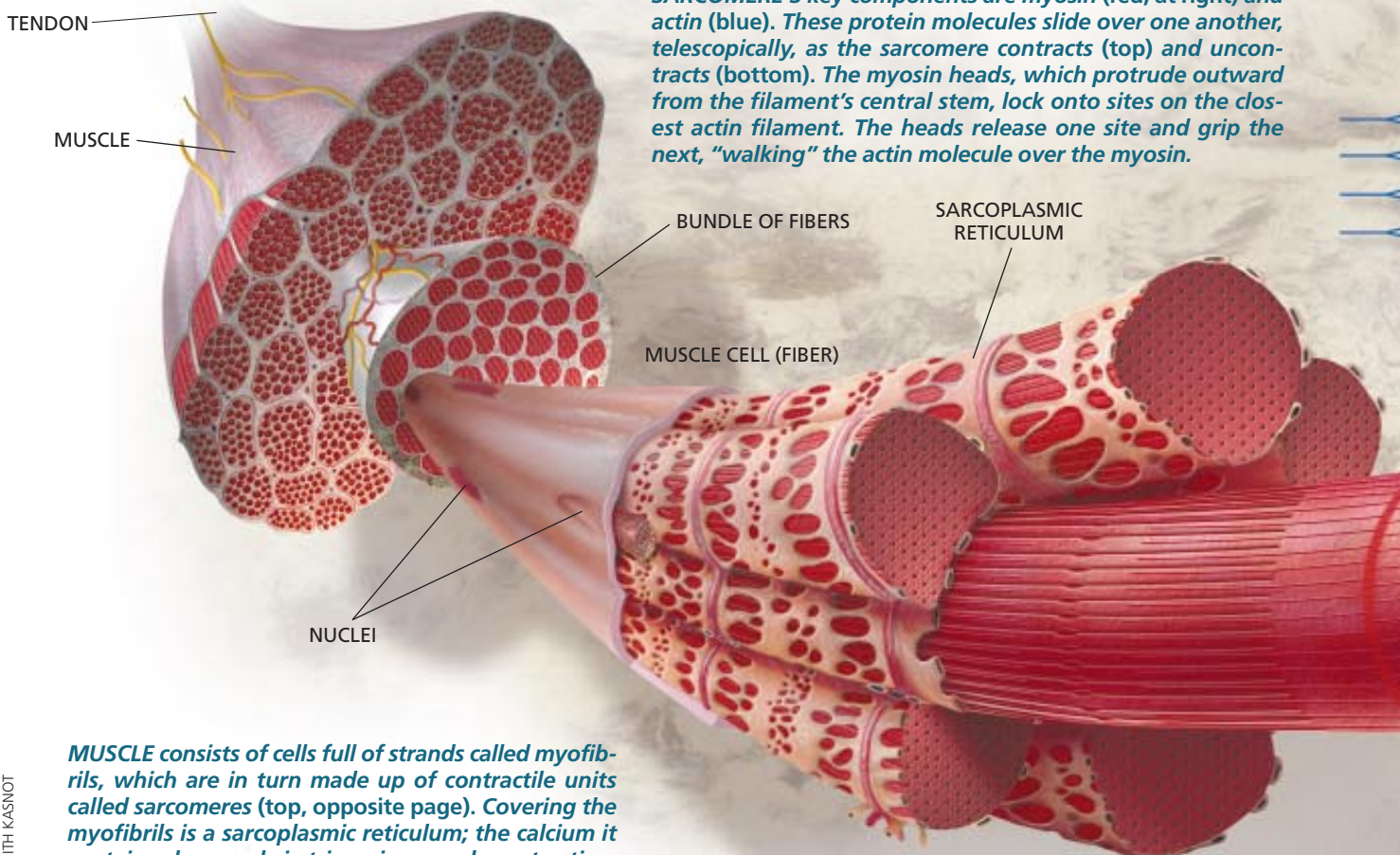
myofibrils. These components, called sarcomeres, are the contractile units of muscle; a myofibril contracts when all its sarcomeres do so. Sarcomeres are about 2.2 microns long and are linked end to end to make up a myofibril.

Like Russian nesting dolls, muscle's components keep getting smaller: within each sarcomere are two protein molecules, known as myosin and actin. It is the interaction of these two molecules, primarily, that makes a sarcomere contract.

Myosin, the most abundant protein in muscle, is shaped like a tadpole, with a large head and a long, thin tail. Many of these proteins make up what is known as a myosin thick filament, the central component of a sarcomere. In a thick filament the many myosin proteins are arranged with their tails bundled together, like a bunch of pencils held in a fist and with the heads sticking out to the side.

In the sarcomere the ends of the thick filament are surrounded by molecules of actin, also elongated and helical, and parallel to the myosin [see illustration below]. During muscle contraction, a sarcomere shortens like a collapsing telescope as the actin filaments at each end of the myosin thick filament slide toward the thick filament's center.

The motive force that pulls the actins inward is exerted by the myosin heads. Each myosin head locks onto specific sites on the actin molecule. The head "walks" the actin molecule over the bundles of myosin tails, step by step, by relinquishing its grip on one site on the actin and grabbing and pulling the adjacent site [see illustration below, right]. In effect, the myosin heads are like so many oars that, marvelously



SARCOMERE'S key components are myosin (red, at right) and actin (blue). These protein molecules slide over one another, telescopically, as the sarcomere contracts (top) and uncontracts (bottom). The myosin heads, which protrude outward from the filament's central stem, lock onto sites on the closest actin filament. The heads release one site and grip the next, "walking" the actin molecule over the myosin.

MUSCLE consists of cells full of strands called myofibrils, which are in turn made up of contractile units called sarcomeres (top, opposite page). Covering the myofibrils is a sarcoplasmic reticulum; the calcium it contains plays a role in triggering muscle contraction.

KEITH KASNOT

synchronized, paddle the actin filaments to move them.

The fuel for this molecular motor is adenosine triphosphate (ATP). In a contracting sarcomere, an ATP molecule combines with a myosin head and breaks down into adenosine diphosphate (ADP) and a phosphate ion. From this reaction comes the energy necessary to release the myosin head from the actin molecule, to move the head to the next binding site and to help pull the actin molecule that distance. The ratchetlike cycle can happen five times a second in a rapidly contracting muscle. As the cycles occur, various reactions convert the ADP back to ATP to keep fueling the contraction.

Three Kinds of Skeletal Muscle

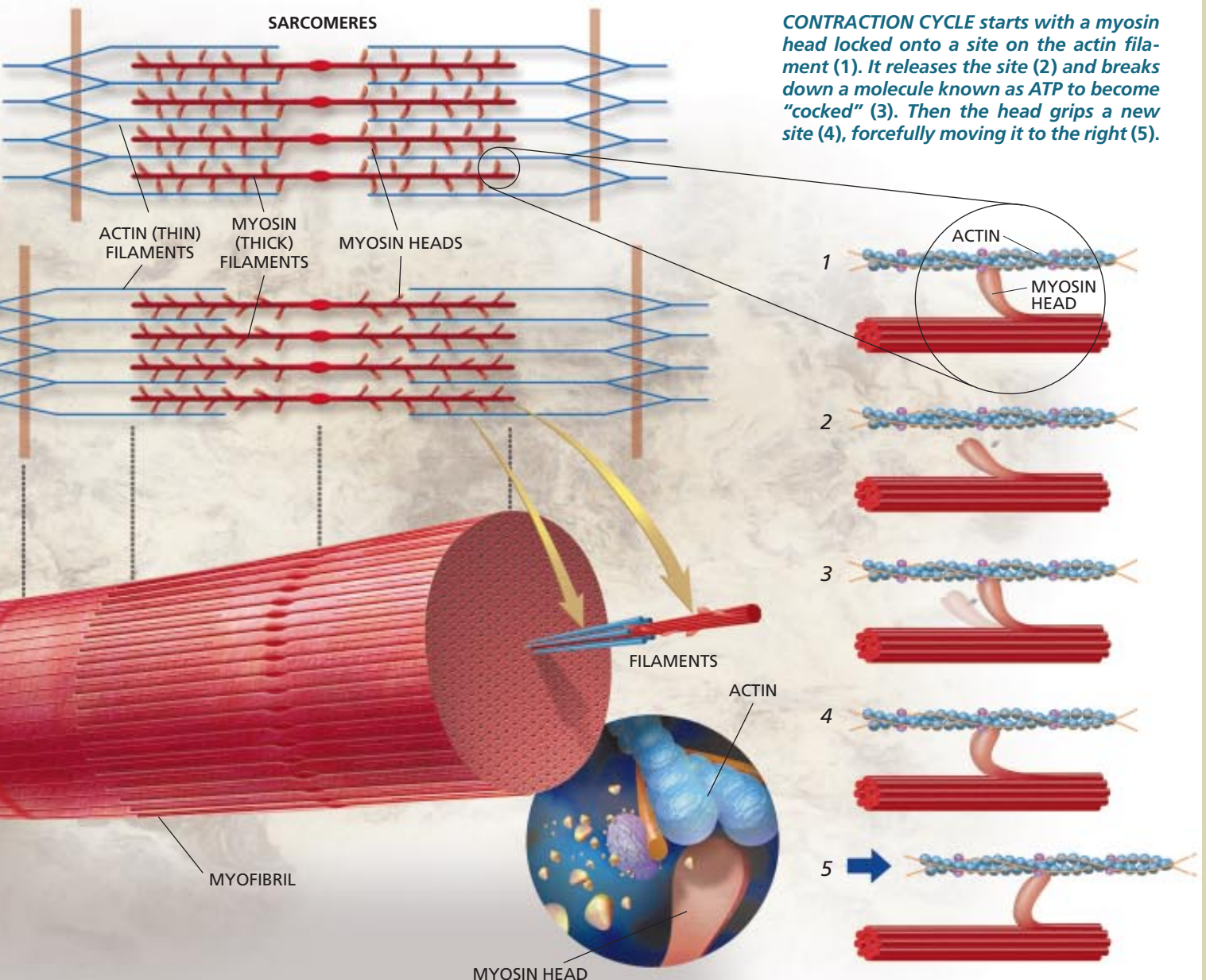
Healthy adults have at least three main types of skeletal muscle cells, which differ primarily in the kind of myosin at the core of their sarcomeres. These three cell types, like the myosin variants they contain, are designated I, IIa and IIx (also known as IIc).

Type I muscle cells are also known as slow fibers, because their kind of myosin converts ATP to ADP relatively slowly

and derives energy from the reaction efficiently. Muscles that must contract repeatedly for long periods, such as those of the back and legs, are rich in type I fibers. For example, the soleus, which extends from the central calf area to the ankle, is almost entirely type I. It comes into play not only for walking and running but even for simply standing.

Type I muscle cells, which are critical for any kind of aerobic exertion, have large numbers of mitochondria, specialized cellular functionaries that use nutrients and oxygen to convert ADP back into ATP. Type I muscle fibers are therefore the narrowest, because their constant need to feed the mitochondria with nutrients and oxygen and to remove their waste limits how wide the fiber can be. These fibers also have a great deal of myoglobin, a protein that acts as a short-term store of oxygen for the cells. (The leg and thigh meat of a chicken, rich in type I muscle, gets its dark coloration from the myoglobin.)

The other two myosin varieties are "fast." They predominate in muscles, such as those of the biceps, capable of more powerful but less frequent contractions. One of the key necessities for sustaining high-power output even briefly is a method of rapidly replenishing ATP, the cells' energy source.



CONTRACTION CYCLE starts with a myosin head locked onto a site on the actin filament (1). It releases the site (2) and breaks down a molecule known as ATP to become "cocked" (3). Then the head grips a new site (4), forcefully moving it to the right (5).

Sports Supplements: Bigger Muscles without the Acne

Steroid alternatives have become an \$800-million market

Weight lifting used to be pretty simple. You went to a dingy, seedy room on the other side of the railroad tracks, you put on ragged cotton clothes, and you hoisted, heaved and herniated to your heart's content. Of course, in those days, Burt Lancaster and Jack LaLanne were paragons of physical masculinity.

Today better understanding of nutrition and muscular development has complicated life for weight lifters. Most notably, it has given rise to so-called sports supplements, a category comprising hundreds of different pills, powders and the odd potion that supposedly enhance physical performance. Last year Americans spent



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SPORTS SUPPLEMENTS line the walls at the *Elite Value Center* in New York City, where acting student *John Ostensoe, 26*, shopped recently.

some \$800 million on sports supplements, not including sports nutrition bars and electrolyte replacement drinks, according to Grant Ferrier, editor of the *Nutrition Business Journal* in San Diego.

Sports supplements aimed at weight lifters are doing particularly well, thanks in part to clinical trials that have proved that at least a few of the supplements actually do help increase strength and muscle mass or promote the repair of muscle tissue.

"Supplements are a tool for making an exercise program work," says Bill Phillips, the relentlessly motivational 34-year-old CEO of Experimental and Applied Sciences, the largest marketer of sports supplements. "And when an exercise program works, it is one of the most empowering things an adult can experience."

At best, supplements provide the elevated energy levels and possibly the tissue-repairing help that lets weight lifters lift a little more weight, do a few more

repetitions or train a little more often. The muscle-mass gains possible are not on a par with those of anabolic steroids. But supplements have the advantages of being legal, much less expensive and a lot less harmful.

No two weight lifters seem to have the same supplement regimen. But the one thing almost all of them have in common is creatine, which accounted for \$180 million of the \$800 million spent on all sports supplements in 1998, according to Ferrier. Most weight lifters are also consuming some kind of protein supplement, such as whey powder or ordinary sports nutrition bars.

Creatine occurs naturally in the body. It plays a role in muscle contraction, which is energized by a molecule called adenosine triphosphate (ATP). When ATP breaks down, giving up one of its three phosphates, it releases the energy used by the muscle cell to contract. The small amount of ATP stored in a muscle is used up instantaneously during strenuous exertion. Fortunately, muscles contain creatine phosphate, which donates its phosphate and the necessary energy to replenish the ATP.

Eventually you tire out when, among other things, your supply of creatine phosphate dwindles. But by taking creatine supplements, weight lifters and sprinters can at least marginally increase the amount of creatine phosphate in their muscles, enabling them to exert themselves a little harder. Although no one has been able to prove that creatine has any harmful side effects, no study has lasted more than a few years.

The biggest seller in the prohormone category is 4-androstenedione, which became one of the longest and strangest household words in history after Mark McGwire's admission that he was using it. The substance is just one of a growing family of over-the-counter steroids; other products in this category include 5-androstenedione, 4-androstenediol, 5-androstenediol, 19-4-norandrostenedione and 19-5-norandrostenediol. Yet another product, DHEA (dehydroepiandrosterone), like 4-androstenedione, is often used by people seeking to boost their sex drive.

The main difference between these prohormones and traditional anabolic steroids is that the prohormones are converted in the liver and testes to testosterone, the body's key hormone for muscle building. Anabolic steroids, in contrast, are nothing more than synthetic versions of testosterone. Because of this hormonal action, prohormones can have mildly steroidal side effects, such as acne, a swollen prostate and hair growth in unusual places. Some evidence suggests that prohormones temporarily elevate testosterone levels, at least marginally, but no one knows if these higher levels translate into greater muscle mass. —G.Z.

Type II fibers have variable amounts of mitochondria, but they also exploit a much faster process, called glycolysis, to provide the energy the muscle needs. Basically, glycolysis releases energy for making ATP by breaking down sugars only partially but without need for oxygen.

The type II fibers differ mainly in their oxidative properties. Type IIa fibers have more mitochondria and are thus more similar to type I. Because of the extra mitochondria, type IIa can sustain an output of power longer than can the type IIx fibers, which are “faster,” more powerful and more quickly fatigued.

Injections of genes will increase muscle mass— without exercise and almost undetectably.

The bodily distribution of the different muscle fiber types is not fixed. It depends on the body’s regular activities, and it changes if they do. This ability of the body to alter itself is an important part of its complex, genetically based response to mechanical stressors and signals. Take an extreme example: a fitness enthusiast who gives up doing squat thrusts and begins training to run a marathon. According to Brenda Russell of the University of Illinois at Chicago, who did pioneering investigation in this area in the early 1980s, the runner would gradually replace much of the fast, type IIx fibers in his quadriceps and calves with the slower, more oxidative type IIa fiber. The change would occur because the nuclei of the muscle cells in his legs would stop specifying production of type IIx myosin and start prompting for the type IIa myosin. In more technical terms, the nuclei would stop “expressing” the gene that through a chain of events triggers the cell to assemble amino acids into the type IIx myosin. Instead the nuclei would express the gene that specifies the IIa type.

Bulking Up

Researchers know relatively little about how the body translates mechanical stresses into increased muscle mass. Recent findings, however, have shed light on parts of the process while generating some intriguing theories and a few controversies.

One of those areas of contention is whether the number of muscle cells in a body is fixed for life. Although a small group of researchers disagrees, the widely accepted view is that the number of muscle cells cannot increase significantly, because the cells cannot split apart to form completely new fibers. (Their multiple nuclei may make the process infeasible.) Because a muscle cannot produce more fibers, the only way it can grow in response to exercise is for the individual fibers to become thicker. This thickening can be thought of as the body defending itself against a mechanical stress by enlarging the structural members so that they can generate more contractile force.

With continued weight training, the type II muscle fibers grow ever thicker by adding more myofibrils. This thickening initially involves the longitudinal splitting of myofibrils into two daughter myofibrils, a process that occurs over and over if the mechanical stresses continue. Enormous amounts of myosin, actin and myriad other proteins are needed to create entirely new myofibrils. But the amount of protein, and therefore the number of myofibrils, that the existing muscle cell nuclei can help create and maintain is limited.

In cardiac muscle, that limit is absolute. In skeletal muscle,

it is not. Scattered among the many nuclei on the surface of a skeletal muscle fiber are so-called satellite cells. They are largely separate from the muscle cell and, unlike it, have only the usual one nucleus apiece. Thus, they can replicate by dividing. In the mid-1970s Věra Hanzliková and her colleagues at the Czechoslovak Academy of Sciences in Prague discovered that these satellite cells proliferate in response to the stresses of muscle growth.

As they multiply, some of these cells remain as satellites on the fiber, but others, incredibly, become incorporated into it. Their

nuclei become indistinguishable from the muscle cell’s other nuclei. With these additional nuclei, the fiber is able to churn out more proteins and create more myofibrils. Most researchers now believe that this recruitment of satellite cells is a significant factor in the muscle growth that comes from weight lifting.

Satellite cells figure in another controversy: whether damage to muscles is necessary for enlargement (a phenomenon known as hypertrophy). A popular theory contends that it is: according to this view, rigorous exercise inflicts tiny “microtears” in muscle fibers. Calcium ions enter the ripped area, initiating biochemical cascades that break down the existing proteins to leave a less ragged gap. The tiny opening, meanwhile, releases a specific protein—the very same one that Goldspink has dubbed mechano-growth factor but that others have called hepatocyte growth factor or scatter factor. In the mid-1990s Richard Bischoff of Washington University found that at least in cultured cells, this growth factor attracts satellite cells to its source, which in muscle would be the damaged area.

Some of these satellite cells incorporate themselves into the muscle tissue and begin producing proteins to fill the gap. Significantly, the number of nuclei passing from the satellite cells into the damaged area of the fiber is greater than the number of nuclei lost when the gap opened up. As a result, in that part of the fiber, more protein can be produced and supported. Gradually, as more microtears are repaired, the overall number of nuclei grows—as does the fiber itself.

Muscle-Making Machinery

This “damage” model of muscle cell growth is by no means the only one that can explain hypertrophy; it is at best only one of many, perhaps dozens, of processes at work in exercise-induced muscle growth. For example, a fair amount of speculation, and at least a modest amount of research, focuses on the mechanical connections between muscle cells and surrounding tissue. These connectors are the tendons and the focal adhesion complex, a series of some 30 proteins that connects the cell’s skeleton (the “cytoskeleton”) with its exterior supportive “scaffolding,” the extracellular matrix.

Mechanical stresses on the tendons and focal adhesion complex are believed to initiate intricate processes that affect the protein-making machinery of muscle cells. Understanding these theories requires some background on the machinery.

One of the key steps in the creation of a protein is transcription. It occurs in a cell’s nucleus when a gene’s information (encoded in DNA, the “blueprint” for protein production) is copied as a kind of molecule called messenger RNA

You See **Brawny,** I See **Scrawny**

Big bruisers with a self-image problem

The ascendance of muscle as a key ingredient of male allure has had ramifications both good and bad. Take the countless aging squires and he-men who've turned to weight training mainly out of vanity: they have unwittingly improved their metabolic rates, bone strength, connective tissue and other important bodily components. At the same time, though, a distressing self-image disorder—which afflicts men disproportionately—has become pervasive enough of late to be the subject of dozens of articles in the academic and general-interest press.

At first description, the malady seems almost comical: imagine a 250-pound bruiser with rippling, rocky muscles and a body-fat percentage hovering around 7.5. Now imagine that the guy thinks he is so scrawny that he only wears loose-fitting clothes to cover up what he sees as a shamefully skinny body. But muscle dysmorphia, as the condition is known, is not very funny. Like anorexia nervosa, the disproportionately feminine disorder to which it is often compared, muscle dysmorphia can lead to complete social withdrawal and, in the most extreme cases, to suicide.

Muscle dysmorphia and anorexia are both part of a larger group of disorders in which the afflicted fixate despairingly on a facial feature, body part or their entire bodies. Harrison G. Pope, Jr., the psychiatrist who has done more than anyone else to uncover and describe the condition, says you can spot muscle dysmorphics by their "pathological preoccupation with their degree of muscularity." Pope, who is probably the only Harvard Medical School professor who can squat 400 pounds, pumps iron six days a week. He himself does not have muscle dysmorphia, he says. (But he did ask *SCIENTIFIC AMERICAN PRESENTS* not to disclose his height, weight and body-fat percentage.)

In his studies with volunteers recruited from Boston-area weight rooms, Pope has encountered people "who had not dined in a restaurant in years, because they could not tolerate eating something for which they did not know the precise protein, fat and carbohydrate content." Although use of anabolic steroids is not at all universal among muscle

dysmorphics, Pope found "many who would persist in taking anabolic steroids or drugs for fat loss even if they were getting pronounced side effects." Such as? Well, high cholesterol, hard arteries and teeny testicles in men, and beards and rich baritone voices in women.

The anecdotes go on. Pope and his colleagues have encountered dysmorphics who left high-powered jobs in law or business because their careers were taking away too much time from the gym. They've come across muscle dysmorphics in the 230- to 290-pound range who were so ashamed of their puniness that they hardly ever left their homes, preferring instead to adhere to an indoor regimen of weight lifting in the basement interrupted mainly for periodic protein consumption. The underground nature of the condition makes it virtually impossible to estimate how many people have it, Pope says.

How do you distinguish muscle dysmorphia from good old hormone-fueled enthusiasm? One of Pope's experiences suggests a method. To recruit volunteers for a study a couple years back, he put up handbills in Boston-area weight rooms seeking out people who could bench press their own weight 10 times. Hardly any of the respondents had dysmorphia. He then repeated the procedure, again asking for people who could bench their own weight 10 times—but who also thought they were "small." This time, almost all the 24 respondents were dysmorphic. —G.Z.



DAVID TILLINGHAST

(mRNA). The mRNA then carries this information outside the nucleus to structures called ribosomes, which assemble amino acids into the protein—myosin or actin, say—specified by that gene. This latter process is called translation.

But what triggers transcription? For muscle and many other tissues, the answer is an array of extraordinarily complex biochemical pathways involving a dizzying number of proteins. Some of the key proteins are sex hormones, such as testosterone, thyroid hormones, insulinlike growth factors, fibroblast growth factor and transcription factors. Some of these proteins are produced in organs such as the liver and circulate throughout the body; others are created locally, in specific muscle tissue, in response to exercise or stretching of that tissue.

These hormones, growth factors and transcription factors act in a variety of ways, often in conjunction with one another, to promote protein production. For example, sex hormones appear to work with particular transcription factors to turn on certain genes. These transcription factors are generally in the cytoplasm or in the nucleus itself. Their combination with a testosterone molecule enables them to bind to locations on the chromosome, called promoter regions, that “turn on” a nearby gene and trigger transcription. Because anabolic steroids are merely synthetic versions of testosterone, this pathway is the one they initiate and exploit to build muscle.

Other factors work by doubling up. In 1995 Frank W. Booth

According to Goldspink, mechano-growth factor is one of the most important of these locally acting factors. The University College researchers cloned the gene that leads to the production of mechano-growth factor, using a standard biological technique to insert the gene into muscle cells. The gene for mechano-growth factor was incorporated into a plasmid, a circular piece of DNA, which acted like a teeny Trojan horse. Injected into a mouse’s leg, the engineered gene infiltrated muscle cells and induced them to produce more of the growth factor. Within two weeks, the muscle mass in the mouse’s leg increased by 15 percent—without exercise.

Goldspink’s interest is in treating degenerative diseases such as muscular dystrophy. But he notes ruefully of his accomplishment: “This will be the way they reshape athletes in the future.”

Mechanical-Chemical Link

Researchers know very little about the mechanical-chemical link that translates stress on muscle fibers into locally higher levels of mechano-growth factor and countless other biochemicals. But earlier this year Booth and Martin Flück, now at the University of Bern in Switzerland, made a significant discovery. The finding involved focal adhesion kinase, one of the 30 proteins in the focal adhesion complex that

Anabolic steroids combine with transcription factors to turn on genes and make more protein.

and James Carson of the University of Texas–Houston Health Science Center found that when two identical molecules of serum response factor combine in a muscle cell, they form a kind of biochemical “key.” The keyhole in this case is a gene in the nucleus. When the double molecule attaches itself, the gene becomes active and begins producing more mRNA for a certain protein. In this case, the protein is actin. “It’s a pretty novel finding,” Booth says. “It’s only the seventh transcription factor described in hypertrophy.”

Other pathways are more complex. Some crucial ones begin with the binding of growth factors to receptors. Receptors are specialized proteins that poke through a cell’s membrane. When the part outside the cell binds with a specific molecule, it activates a series of chemical reactions inside the cell. For example, the binding of a growth factor to a receptor activates cascades of enzymes, called kinases, that modify other proteins in the cytoplasm that in turn bind to promoter regions on the chromosome and otherwise regulate the expression of genes.

One of the most important growth factors is insulinlike growth factor-1 (IGF-1). During the first few years of life, IGF-1 produced by the liver circulates throughout the body, rapidly expanding essentially all its muscle fibers. The amount of this circulating, liver-produced IGF-1 eventually declines sharply, ending the early-life spurt. For hypertrophy, the free ride is then over, and only exercise can add (and, eventually, merely maintain) muscle mass. According to University College’s Goldspink, IGF-1 and other growth factors continue to play a major role, but they are released only locally in muscle during exercise. For example, IGF-1 concentrations are high around muscle-fiber microtears caused by exercise.

connects the structural elements inside cells with the matrix outside them. In muscle cells undergoing hypertrophy, the researchers learned, the amount of this enzyme doubled. “It could be the mechanical-chemical link,” Booth speculates, “because the stress on the kinases could release signaling factors, which could go to the nucleus to trigger the production of more messenger RNA” and therefore more protein.

Perhaps more important, the kinase could also trigger a cascade of biochemical reactions that ultimately signal ribosomes directly to produce proteins. These proteins would be the product of translation alone, without any immediately prior gene activity in the nucleus. “We think, and a lot of others think, that the initial response when a muscle is loaded is to increase translation,” Booth says. He adds that this more efficient process would, instead of transcribing new mRNA “templates” from the genes, simply reuse existing mRNA already in the cytoplasm to direct protein production.

Although their numbers are small, researchers studying the cellular and molecular biology of skeletal muscle are making important gains as they attempt to unravel the complex mystery of muscle. Over the next decade or so, their work will produce a more complete picture of how one of the most basic of human systems grows, develops and alters itself in response to changing stimuli. In addition to intellectual satisfaction, there will almost certainly be treatments, if not cures, for a host of degenerative diseases.

And if the history of anabolic steroids is a guide, there will also be a new kind of drug abuse problem—one that will be exceedingly difficult to monitor. Science will soon bring high-stakes athletics to a troubling threshold, beyond which the ground rules of competition could be forever altered. SA