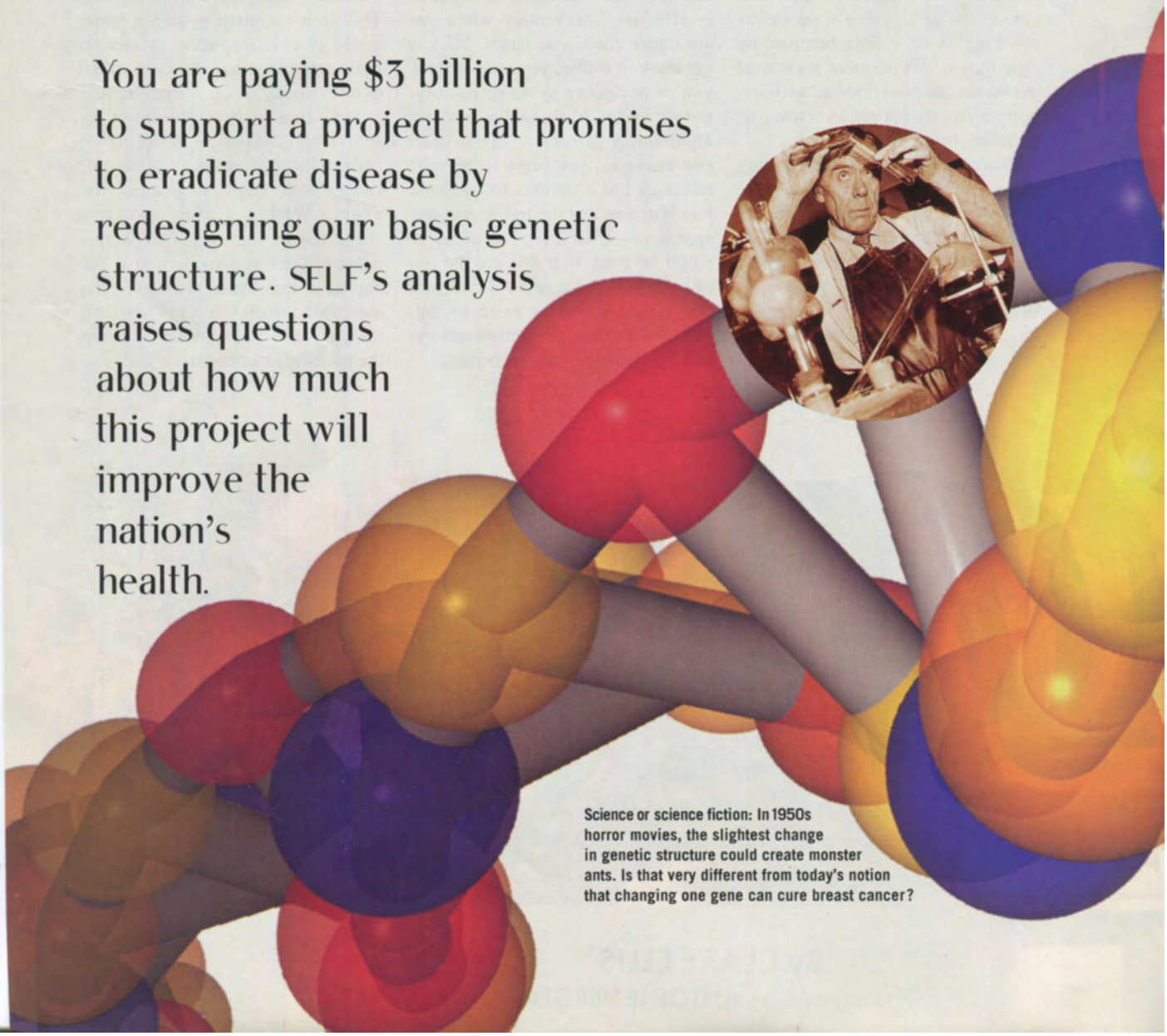
genes 'R' us

—maybe

You are paying $3 billion to support a project that promises to eradicate disease by redesigning our basic genetic structure. SELF's analysis raises questions about how much this project will improve the nation's health.



Science or science fiction: In 1950s horror movies, the slightest change in genetic structure could create monster ants. Is that very different from today's notion that changing one gene can cure breast cancer?

PHOTOGRAPHS, LEFT TO RIGHT, EVERETT COLLECTION; ARCHIVE PHOTOS; ARCHIVE PHOTOS/LAMBERT

It would have made a great premise for one of those giant-grasshopper-eats-Chicago horror movies that were so popular in the 1950s. You know the ones, where a top-secret government project leaks radiation and causes a genetic mutation in some insect that happens to go hopping by at just the wrong moment. The not-so-subtle implication of these B-movie catastrophes is that the slightest rejiggering of a single gene could change the future of an organism—and of life itself.

Outlandish as it may seem, this is the basic concept behind the genetic revolution that has captured the fancy—and money—of the nation. In a scenario worthy of Greek mythology, its proponents claim that our fates are written not in the stars or on our palms, but in our genes. The slender, twisting threads of DNA woven into our cells at conception foretell our lives and our deaths; they dictate everything we are and everything we will become.

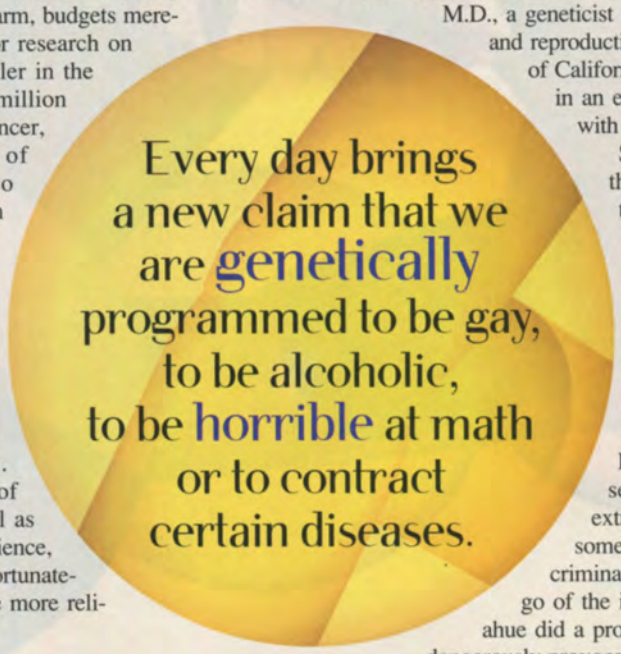
But we go the Greeks one better. This new geneticism holds out the promise that we can alter our fates by changing our genes. All we have to do to eliminate disease, for individuals and for society, is to find out which genes cause us trouble and change them. Sounds pretty nifty, doesn't it? The amazing part is that, in an era strewn with the wreckage of high-tech delusions like cheap nuclear power and a Star Wars defense system that could provide an impenetrable shield against nuclear attack, so many people believe in this proposition so deeply.

It seems that every day brings a new claim about how we are genetically programmed to be gay, to be alcoholic, to be horrible at math, to watch too much TV or, more menacingly, to contract certain diseases, including breast

By JOHN SEDGWICK

cancer, schizophrenia and hypertension. Indeed, the biggest single biological undertaking in history, the 15-year, $3 billion Human Genome Project, is largely intended to isolate the individual genes that account for some of these traits, and about 100,000 others as well. The logic is powerful: DNA creates RNA creates proteins create us. So, to fix whatever is wrong with us, go back to the DNA.

By bankrolling the Human Genome Project so heavily, the U.S. government is placing a very large bet on a rather risky venture. Furthermore, in doing so it is taking money away from other medical research that has a lot better potential to improve people's lives. The National Institutes of Health, the government's major research arm, budgets merely $784.5 million per year for research on heart disease, the leading killer in the United States, and just $99 million more for research on lung cancer, the second-leading killer of women. Is genetic theory so compelling that it should drain funds away from these other projects? Admittedly, the whole idea that our DNA shapes our destiny has a certain appeal. It marks a considerable advance over the mysticism our ancestors relied on to divine what the future had in store for them. Genetics provides a means of influencing the future as well as seeing it. It is, also, a real science, with measurable results. Unfortunately, at present it is only a little more reliable than palm reading.



The basics of genetic inheritance were first uncovered by the Augustinian monk Gregor Mendel in the middle of the nineteenth century. Tinkering in his abbey garden, he traced particular traits in peas—specifically their shape, color and wrinkledness—through various generations and postulated a convincing relationship between a single gene and an individual pea characteristic. His theories of genetic inheritance were models of scientific elegance and clarity, and they have served as the basis for much of modern thinking about the genetic transmission of traits.

More recent research, however, has shown his laws to have distressingly limited application. While single genes do influence some of the simpler human characteristics, such as the color of our eyes, skin and hair, when it comes to anything complicated, like the prospect of contracting a particular disease, individual genes tell only part of the story. "The community of basic scientists will have to reexamine the notion of one gene causing one effect," says Richard C. Strohman, Ph.D., professor emeritus of cell and molecular biology at the University of California, Berkeley, and a leading critic of what has come to be called the Genes 'Я' Us theory. "This straight-line thinking is terribly misguided."

The essential reasoning of naysayers like Dr. Strohman has to do with the laws of evolution: If diseases are formed so easily, through the operation of a single-gene defect, then we would all have been wiped out years ago. "We've evolved for 2 million years," says Charles Sing, Ph.D., professor of human genetics at the University of Michigan. "You wouldn't expect to flip just one switch and see the lights go out." Instead, many factors contribute to disease formation—some of them genetic, some of them environmental—in a complex process. "Genes don't operate in a vacuum," says Michael Kaback, M.D., a geneticist who is professor of pediatrics and reproductive medicine at the University of California, San Diego. "They operate in an environment, and they interact with other genes."

Sensible as it might sound, that idea runs directly counter to the view that many geneticists are putting forward, as one gene after another is heralded as the source for X, Y or Z trait. This has been particularly outrageous in the case of behavioral genetics, a topic that the media have always found enthralling. Back in the Sixties, there were serious reports that having an extra copy of the male Y chromosome was supposed to make you a criminal, and the culture still can't let go of the idea. Not long ago, Phil Donahue did a program on the extra Y with the dangerously provocative title "How to Tell If Your Child's a Serial Killer!" Actually, as the National Academy of Sciences recently concluded, there is no known link between that extra Y chromosome and violent behavior.

But such extravagant claims aren't solely the product of tabloid television. Researchers have been publishing a steady stream of articles arguing that certain behaviors can be passed down from parent to child. Manic-depression was reported to be inheritable, and two groups in 1987 claimed to have found the gene responsible. The reports have since been quietly retracted. In 1990, a group located what was quickly dubbed the "alcoholism gene," which was said to operate by producing a receptor for the neurotransmitter dopamine. Well, not exactly. No one has been able to corroborate the claim. In 1991, researchers declared they had detected anatomical differences between the brains of homosexuals and heterosexuals—differences that, presumably, were created by genes. These reports are much in dispute.

To be fair, most geneticists would not propose a direct link between a gene and a complicated behavior like alcoholism, which appears to draw on as many social factors as biological

ones. But many do seem more optimistic about the medical claims that have been getting attention lately. As evidence of the great strides being made in the field, geneticists usually cite the progress made in the handful of diseases that actually are caused by a single gene: Huntington's disease, retinoblastoma, cystic fibrosis, sickle-cell anemia and Tay-Sachs disease. But these examples are much more the exception than the rule. The afflictions that kill the vast majority of Americans—heart disease and cancer, to name the two most rapacious—are not caused by single genes, nor are most others. According to the best-known catalog of genetic disorders, Victor A. McKusick's *Mendelian Inheritance in Man*, no more than 2 percent of all diseases stem from single-gene causes. "So we're spending 98 percent of our resources on 2 percent of diseases," Strohman says, referring to the immense cost of the Human Genome Project, "and only 2 percent of our resources on 98 percent of diseases."

This is not to say that cancer and heart disease don't have a heritable component. Epidemiologists have long known that these illnesses, or at least a propensity for them, run in families. But it has never been clear what, precisely, has been inherited, and how likely it is to manifest itself as disease.

Furthermore, even the diseases that have been shown to be monogenic are proving to be considerably more nuanced than Mendelian laws would have predicted. Genes are not all equal. Some genes are especially long, containing up to a million base pairs of nucleotides; the more of these pairs there are, the more opportunities there are for something to go wrong, for the gene to mutate. Each different mutation produces what amounts to a different disease. For instance, the gene for cystic fibrosis, which has been located on chromosome 7, undergoes at least 350 different mutations—with more being discovered every day. The exact site of each of those mutations can so gravely affect the outcome of the disease that it is hard to say that all of them cause the same cystic fibrosis. In its purest form, this disorder produces a severe malfunctioning of the mucous membranes and sweat glands, which in turn leads to an early death. Yet some of the mutations result only in infertility, asthma or chronic bronchitis, and some don't cause any disease at all. "There is almost a full spectrum of syndromes in patients carrying that gene," says Strohman.

The gene for Huntington's, which was found on chromosome 4 after a feverish 10-year search, has now been dubbed a "stuttering gene" because, in a flouting of the normal laws of Mendelian genetics, it contains a sequence of three nucleotides that repeats anywhere from 37 to 100 times. Scientists now believe that the more this triad repeats, the fiercer the disease and the earlier its onset.

Finally, Tay-Sachs, one of the first genetic disorders that could be screened for, is likewise proving to have a wide range of manifestations. Classically, it is a fatal neurodegenerative disease that strikes children in the very first years of life, which is why an effective prenatal test was considered so important. But scientists are now discovering that Tay-Sachs also appears in the twenties and thirties as a much less severe neuromuscular disorder. "That's a lot different from being completely paralyzed at age one," notes Dr. Kaback, who helped develop the first genetic tests for Tay-Sachs. "It's the same gene, but different mutations and manifestations."

Geneticists may be able to predict that an unborn baby girl is at risk for developing breast cancer by age 50. What could anyone possibly do with that information?

Again, these are the diseases that are believed to be monogenic. If the record regarding the genes for which scientists have the clearest picture is so undistinguished, and if there is little evidence that such an approach will be at all useful for the vast majority of diseases that are recognized to be polygenic, then why the mad scramble to decode the chromosomes? "It's like the old joke of the drunk looking for his keys under the lamplight," Strohman says. "He can't see to find them anywhere else." Partly, he believes, this is due to the researchers' training, partly to what one scientist calls the "industrial-genetic complex," which has linked researchers to biotech firms and upped the ante for genetic claims, and partly to the technological imperative. Now that microbiologists are equipped with powerful tools like the clone-producing polymerase chain reaction technology, they can't resist using it. Even if a disease isn't caused by a single gene, but by a few with demonstrable effects, geneticists argue, then surely it is worth investigating to see what turns up.

As any number of epidemiological studies have shown, a genetic contribution to the development of many diseases is undeniable. The woman whose mother, grandmother and two sisters all died of ovarian cancer is obviously at a greater than average risk of developing it, too. But that is quite different from knowing precisely how, if and when that risk will lead to cancer. The Human Genome Project is hoping to resolve these questions, but by focusing so

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exclusively on single genes, it probably won't tell us much about most diseases. And by shifting the attention of the public, if only inadvertently, onto the genetic component, the geneticism rage has encouraged individuals to overlook other disease ingredients, like poor nutrition, that are at least as significant.

The genetics of breast cancer provides a good example of the hazards of wishful thinking. Although the public has been led to believe that BRCA1, which has recently been localized to chromosome 17, is the breast cancer gene, researchers now recognize that in all likelihood it will simply turn out to be, as Stephen H. Friend, M.D., a cancer researcher at the Massachusetts General Hospital in Boston, puts it, "a" breast cancer gene. There will probably be BRCA1, 2, 3 and so on all the way up to 10, and possibly more. And all of them will play an important role in the formation of the disease.

Yet, as Dr. Friend points out, having a mother or sister with breast cancer—that is, having a genetic link to the disease—is still "the highest risk factor. It just wipes out the other factors." So everyone thinks that the fastest route to a cure is through genetics. Maybe so, but if there are even a few genes involved, the interaction can become too tangled to straighten out using what we currently know. With just six genes, for example, Strohman calculates that the possible outcomes total 6,000 plus.

It is true that for some less complicated species, a relatively small number of genes come into play for individual traits, which is why Mendel worked out his laws on peas. But to make that assumption for higher orders like humans requires, says Strohman, "a leap of faith." Indeed, one reason that higher organisms emerged to be higher organisms is that they don't rely so much on single genes. Instead, they rely on what some geneticists are calling "redundancy," a term used here in much the same way it is in NASA's flight program to describe backup systems that keep everything running should any one system fail.

Instead of a tidy linear sequence, then, from gene to protein to trait, Strohman proposes a far more complicated system in which genes interact with other genes and the environment. He calls it an epigenetic system, a term that sounds more forbidding than it is. In his view, determining the likelihood of coming down with a disease is like predicting how many squirrels you will find in your backyard on a given afternoon, where such ever-changing factors as the amount of food, number of predators, density of the trees, degree of sunlight and the individual characteristics of the squirrels themselves all combine in complicated ways to dictate the answer. "The epigenetic system is complex, interacting, self-regulating," he says, "and it takes on a life of its own." Strohman is convinced that, just as the colony of squirrels will probably survive the loss of any individual squirrel, the epigenetic system is usually able to withstand defects in individual genes for reasons that conventional geneticists cannot begin to explain. "If you have a mutation that inserts a flawed protein into this network," he once told an interviewer, "the result will be unpredictable. The network might break down or it might simply switch on other genes or it might produce different products to substitute for the mutant protein. This epigenetic system is adaptive and will often overrule genetic changes like mutations."

It is, in fact, a kind of living organism. It may draw from the genes, but it operates independently of them for the most part. In fact, Strohman would reverse the commonly accepted gene-leads-to-trait sequence. He believes the epigenetic system actually feeds back to and regulates the genes. Even more controversial is his notion that some of the genetic defects that are discovered on individual chromosomes might not be the cause of an illness but a result of it. This is viewed as rank heresy in genetic circles. If the organism changed in response to the environment and was somehow able to pass that change on to its offspring—if, for example, an individual giraffe's neck grew long as the animal reached ever higher in its search for food and this longer neck was passed on to future giraffes—individual members of a species would presumably be far more varied than they are. Still, Strohman notes that Barbara McClintock, Ph.D., the late Nobel Prize–winning geneticist, believed that changes did occur at the level of the cell, that these very small entities were capable of transforming themselves in response to dangers posed by their environments. Strohman says that this transformation could work its way back to the genes over time. "So the mutation might be an indicator of illness," he concludes, "not a cause." If Strohman is right, the Human Genome Project is mistakenly examining the consequences, not the sources, of disease.

Strohman would turn the direction of medical research around. To him, disease doesn't work from the inside out, but from the outside in; its cause is not to be found in our genes, but in our environment. He notes that the cancers and heart disease and hypertension that are now ravaging the populations of industrialized nations are relatively recent arrivals on the casualty charts. While most epidemiologists argue that they have been there all along and only show up now because improvements in nutrition have allowed humans to live long enough to die from them, Strohman believes these killer diseases are a consequence of our inability to adapt to a radically changed environment. Which changes are causing the problems? "Probably everything that falls under the heading of the Industrial Revolution," he says. "I'd guess that psychological stress plays as big a role as any."

That may be going too far in the environmental direction, but there is currently too heavy a financial emphasis on the genetic end. As it is, the geneticists are not only sucking up billions for their investigations into molecular biology, but also leading the country down a path that will require billions more for genetic screening of the general population—a screening that, if the present is any guide, may well prove useless. For instance, it isn't so helpful to learn that your child has a genetic mutation for cystic fibrosis if the disease ranges as widely in severity as it now appears to, depending on precisely which mutation. Should anxious parents still abort fetuses carrying cystic fibrosis? No one knows.

In the future, geneticists hold out the possibility of being able to say that, based on DNA samples, an unborn baby girl has a 60 percent chance of developing breast cancer by age 50. What could anyone possibly do with that information? There are already ethical wrangles developing over whether insurance companies and employers have the right to certain kinds of genetic information, as if it held some absolute truth.

And there are more questions to come. If the wildest dreams of geneticists really

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do prove true, do we ask Presidential candidates to submit a DNA sample to see if they carry the gene for, say, manic-depression? (If it isn't given freely, it would be easy to obtain, since a single hair or fingernail clipping would be enough.) Would accused murderers be asked to submit DNA samples along with their fingerprints, so that the court could determine if violent behavior was in their genes? No wonder the Human Genome Project has reserved 4 percent of its budget to study ethical issues.

Right now, most of the screening mechanisms expose defects that medical science can do precious little about and many that may never develop into full-blown illnesses. Even if the tests eventually prove to be worthwhile, they could be terrifically expensive to institute nationally. Assuming, by a conservative estimate, it costs $50 to screen an individual for a single disease, the bill to test the American population would run over $12.5 billion, or nearly 2 percent of the current health budget. Then there are those futuristic billion-dollar plans for treatments that would fix any errant genes—another costly idea with no guarantees. It is true that researchers have recently published promising results about their efforts to cure an inherited cholesterol disorder called familial hypercholesterolemia by providing one patient with a critical gene she lacked. But it is important to note that despite the expensive, arduous and hazardous series of operations that were undertaken to repair the genetic defect, the woman's cholesterol remains at more than twice the level recommended by most doctors.

Obviously, there is nothing inherently wrong with a scientific quest for knowledge. But it does lead to problems if it raises expectations unduly. As it is, people are all too inclined to believe in genetic predispositions, if only because it frees them from personal responsibility for their circumstances. In a time of federal austerity, it seems expensive to spend $3 billion to validate geneticism. At that price, surely some hedging of bets is in order. Otherwise, we might be seeing yet another horror movie, one about the amazing genetic theory that ate the American health care budget.

COOKBOOKS

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World Cookbook, published this past April, contains even less butter and cream. "Nonfat yogurt is my staple now," she told me. "Where before I would have used a cup of mayonnaise, now it'll be drained nonfat yogurt." Lukins, who is the food editor of *Parade Magazine,* which reaches millions of people as a Sunday supplement in newspapers, says that readers are *begging* for more healthy recipes. "They want the cream-style soups without the cream. Vegetables, grains and beans are where it's at and where it will continue to be. Even men feel this way: Their food no longer has to be roast beef."

There is no better barometer of this trend—and proof that it has reached the mainstream—than one of the bestselling cookbooks of all times, *Betty Crocker's Picture Cook Book,* which has sold more than 55 million copies since it was first published in 1950 by General Mills. In the foreword to the sixth edition, published in 1986, the editors wrote: "We monitored your new food tastes and discovered that what was once exotic is now mainstream....Your growing awareness of the need for good nutrition became evident—you choose poultry and fish over red meat, eat more fresh fruits and vegetables, and use less fat in cooking." The 1993 *Betty Crocker's New Choices Cookbook* is a loose-leaf binder with "over 500 recipes for eating right," including a chapter with some light meatless main dishes. All of the recipes are followed by nutritional data.

This is not to say that the cream-and-butter-laden books aren't still selling like hotcakes drenched with maple syrup. Workman Publishing brought out *Rosie's Bakery All-Butter Fresh Cream Sugar-Packed No Holds Barred Baking Book* in 1991, and it has sold 101,500 copies to date. Sales of the early *Silver Palate* books and *The New Basics Cookbook* continue to soar. But today, when a cookbook makes the bestseller list, it's more likely to be Dean Ornish's *Eat More, Weigh Less.* Paul Prudhomme's *A Fork in the Road,* a low-fat book by a notoriously high-fat Louisiana chef, and Julee Rosso's *Great Good Food* are following close behind. Let's face it: Americans are schizophrenic when it comes to food. But judging from today's cookbooks, we would like to be healthy schizophrenics.

FASHION DETAILS

CROSSOVER CHIC PAGE 92 OMO GYM Norma Kamali spandex star top, $62, and logo bodysuit, $122. At OMO Norma Kamali, NYC. Zero.4 sunglasses by Oakley, $90. For information, call 714-951-0991. **PAGE 94** Cotton/Lycra sleeveless top by Anne Cole Locker. At Bloomingdale's, select stores. Brief, $20, by Crunch. At Crunch gyms, NYC. For information, call 212-620-7867.

A SUITABLE ATTITUDE PAGE 146 Navy and white pin-striped suit, $965, and suspenders; both by Emporio Armani. At Emporio Armani boutiques, New York City, San Francisco, Beverly Hills. White tank top, $9, by Calvin Klein Underwear. At department stores nationwide. Black suede/leather bucks, $380, by Robert Clergerie. At Robert Clergerie, L.A. **PAGE 147** Charcoal pin-striped blazer, $325, and wide-leg pants, $185; both by DKNY. At Barneys New York, Neiman Marcus, Nordstrom. Men's pajama top with navy trim, $55, by Brooks Brothers. At Brooks Brothers stores nationwide or, to order, call 800-274-1815. Black crocodile belt, $40, by Wathne. To order, call 800-942-1166. **PAGE 148** Charcoal pin-striped trousers, $185, by DKNY. At Barneys New York, Neiman Marcus, Nordstrom. White cotton button-down shirt, $80, and black cotton ribbed knit top, $72; both by CK Calvin Klein. At Calvin Klein stores, Boston, South Coast Plaza, Cleveland; Charivari. Black belt with silver buckle, $68, by A/X Armani Exchange. At A/X Armani Exchange stores nationwide. **PAGE 149** Black cotton vest, $160, multistriped T-shirt, $49, and ivory seersucker pants, $275; all by Ralph by Ralph Lauren. At Polo/Ralph Lauren, NYC; Bloomingdale's, NYC. White bucks, $85.95, by Walkover. At Nordstrom, Dillard's, and fine shoe stores nationwide. Blue silk print pochette by Etro. Natural striped suspenders from Ralph by Ralph Lauren.

THE TIGHTEST THIGHS EVER—GUARANTEED PAGE 162 Two-piece bathing suit, $60, by Anne Cole Locker. At Bloomingdale's, select stores. **PAGE 163** Orange and pink French twist shorts, $28, and top, $26; both by J. Crew. To order, call 800-562-0258.

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