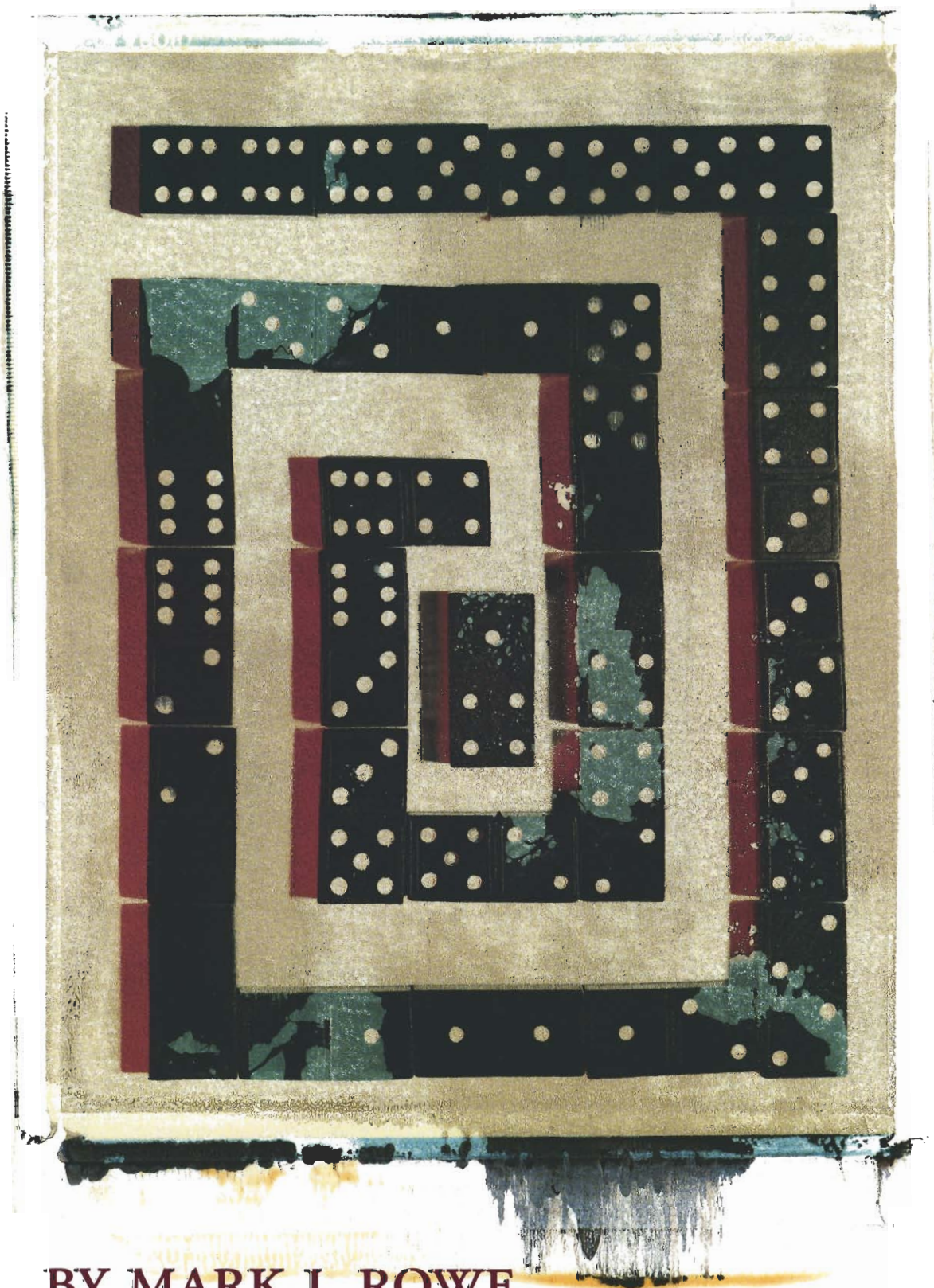

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PHOTOGRAPHY BY JOHN SNYDER

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"It can be rationally argued that biologically we are the sum result of genetic and nutritional events, other than of accidental (pathological or physical) intrusions."

—Donald B. McCormick, *President, American Institute of Nutrition*

fitting into your genes

For decades, physicians and biologists have debated the roles of "nature vs. nurture" or "genetics vs. environment." We are all largely products of genetic expression and environmental impact. Our ability (or lack of it) to manipulate either is important in health and disease. Even with our stunning new knowledge of molecular genetics, we still are not in control of individual genetic makeup. Therefore, every individual would do well to learn ways to "fit" his environment to his "genes." He should be aware of the impact of his controllable environments on his health, as well as the suitability of his individual genetic makeup to the environments determined by his lifestyle choices.

The concepts that follow include several ideas meant to be conveyed by the statement "fitting into your genes." First, the nutrition we choose to provide our bodies is an environment that will interact with the expression of our genetic makeup. In an expanding body of important information in nutritional sciences, it is becoming clear that each of us has a unique set of genes and should adapt our nutritional environment to make the genes and the environment fit better together. Second, and as a specific example, the interaction of genes related to thinness and obesity with the nutritional environments defined by dietary composition and caloric intake could be productively pondered.

NUTRITIONAL GENETIC INDIVIDUALITY

The implications of genetic individuality are surprisingly important in nutrition, where food choices determine the environment. It is significant that nutrition is one of the few fronts in the "nature vs. nurture" debate where an individual can control or change his environment to make it more compatible with his genes. This can be done by more "individually appropriate" food choices.

A simple genetic test provides a thought-provoking example of genetic individualities and their nutritional implications. The test involves the use of the compound phenylthiocarbamide, or PTC, usually impregnated in paper. It very clearly illustrates our diversity with regard to taste and demonstrates one important reason why individually tailoring our nutritional environment to match our genes may be important.

Phenylthiocarbamide tastes extremely bitter to a portion of the population. It is surprisingly tasteless to the rest of the population.[1] Furthermore, those who can taste PTC show a greater sensitivity to bitterness in other substances. They are more sensitive to the sharp taste of cruciferous vegetables and dislike cabbage, brussels sprouts, and broccoli. The ability to taste PTC, or to be spared that genetic distinction, is inherited. It follows classical Mendelian dominant genetics. Therefore, there is most likely a genetic reason why President Bush disliked broccoli, and those of us who enjoy broccoli should be tolerant (in a genetically intelligent sort of way) of him, or of our children or our patients. We must come to recognize how different one person can be from another on such a simple matter as ability to taste a specific bitter molecule, or how one person can be repelled by a taste that another person cannot even experience.

This PTC genetic test deals with taste only, but it can serve as a beginning point to and understanding of genetic nutritional individuality in areas dealing with more important issues such as heart disease, cancer, obesity, etc. The results of genetic individuality span a spectrum of science and practicality, ranging from physiological and health implications, to food choice and marketing implications.

A FAMILIAR EXAMPLE: THE SPRATS

The concept of "fitting into our genes" by adapting our nutritional environment to our genetic individuality has considerable health-related practicality. To illustrate, consider two individuals in the literature (not scientific) with whom we are all familiar. It is not known why "Jack Sprat could eat no fat," nor why his wife, Joan Cole Sprat, "could eat no lean." We only know that because of the difference in food choices "betwixt them both they lick'd the platter clean." It is entirely possible that genetic individuality, such as a difference in ability to taste specific molecules in the various parts of the food on the platter, was the basis for the differing food choices. However, there is an important extension of the putative genetic individuality of Jack's and Joan's taste, that is, the potential for additional genetic individuality that may allow their food choices to trigger the expression of a variety of chronic degenerative diseases that have dietary etiologic components.

Further research revealed that when Joan Cole became Jack Sprat's bride, no coach could take her, so he took her home in a wheelbarrow. Further, while "Jack Sprat was wheeling his wife by the ditch, the barrow turned over, and in she did pitch"; and from which she could not remove herself.[2]

We must conclude that Jack and Joan are very different individuals and that these differences, over time, resulted in some physical expression of the genetic differences in taste, metabolism, or appetite. We must also conclude from the available records that perhaps Joan Cole Sprat would have benefitted from genetically intelligent nutrition counseling to help her "fit into her genes" more compatibly. If the genetic differences between Joan and her husband were known in detail, perhaps her counseling could focus on her tastes, food choice behavior, or propensity toward obesity.

MOLECULAR GENETIC INDIVIDUALITY

How different is Jack from Joan Sprat in the DNA encoding the enzymes and proteins that catalyze their metabolic reactions? How genetically different is each individual of the human species from others?

Genetic information is encoded in the nucleotide base pairs of the familiar DNA double helix. The nucleotides

are arranged in precise sequences to encode information dictating the amino acid sequences of the many proteins and enzymes that result in the structure, function, and metabolism of each cell in an individual. The whole of these proteins and this metabolism makes the cells (and the individual) do what they do and look like what they look like.

The chromosomes in the nucleus of each of our cells have about three billion nucleotide base pairs of encoded information. In the human species, there is a nucleotide substitution on the average of every 200–300 base pairs in this sequence that distinguishes 1 percent to 50 percent of the population. Therefore, there *can* be as many as 6,000,000 genetic informational differences between Jack and Joan. (By the way, in 1990 Congress appropriated the first $90 million to begin a controversial $3 billion, 10-year project to map the human genome. This means decoding the sequence of the three billion base pairs. (Note that this is only one dollar per base pair, one of our better tax bargains.)

What will be the effect of this new information about individuality on nutrition? Knowledge of the human genomic sequence will revolutionize human biology and medicine and will impact the fundamentals of our understanding of the role of nutrition in health. Nutrition professionals will recommend food choices according to individually determined needs based on individual genetic characteristics. Artemis Simopoulos concluded, "The impact of genetic variation on nutrition advice will expand as genes are located, gene alterations noted, gene sequences described, and regulation of gene expression delineated."[3]

Members of Collegium Aesculapium are well aware that even with the limited genetic knowledge available (without a three billion nucleotide base pair map of each individual), we already know that genetic patterns have a significant role in heart disease, cancer, diabetes, and other chronic illnesses. In many of these, diet can play an important role in disease etiology or an effective role in therapy. Imagine what nutritional counsel we can give when we know all three billion base pairs and can identify specific differences that result in diseases preventable by dietary counseling. Such knowledge will help us tailor diets to individuals and avoid "general recommendations" (which result in, for example, the current fear of food resulting from the cholesterol education campaign). Too often general recommendations are twisted and exploited by unscrupulous marketers. When we can individualize "genetically intelligent nutrition counseling," such problems can be avoided.

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GENETIC AND ENVIRONMENTAL COMPATIBILITY

If there is good compatibility between an individual's genetic makeup and the myriad of nutritional environmental conditions to which he or she is exposed, everything works well. In other words, the population that is genetically susceptible to a chronic degenerative disease impacted by food choice environment and the population exposed to the offending environment do not overlap. However, if the genetic makeup of an individual is incompatible with the environment to which he or she is exposed, then eventually poor health or disease may result. In fact, Childs has noted that the greater the incompatibility, the worse the disease.[4]

Making genetic individuality compatible with nutritional environment is the essence of "fitting into your genes" and the goal of "genetically intelligent nutrition counselling." The point is that certain genes can put an individual at risk for chronic diseases if our environment is not appropriately chosen to be compatible with the genes inherited. Whether the chronic disease potentially resulting from the presence of certain genes is expressed is determined by environmental factors, and diet is a very important (and controllable) environment in many genetic conditions, such as the obesity resulting from Joan's taste or metabolism.

HELPING JOAN FIT INTO HER GENES

With the blossoming tools of molecular biology, can we learn enough about the specific genetic makeup of an individual to benefit him or her by helping make the genes and environment more compatible, especially by affecting food choices? Can we help Jack and Joan and others "fit into their genes" nutritionally? Will nutritionists, dieticians, and physicians be able to give genetically intelligent nutrition counseling to help people "fit into their genes"?

We have moved toward this process in significant ways in the three centuries since the *Melody Collection of Nursery Rhymes* described the Sprat case. While we, as yet, do not have the entire human genome on which to base our genetically intelligent nutrition counseling, we do have considerable genetic and molecular information. Let me describe our attempts in the area of obesity.

GENETICS OF "FITTING INTO YOUR 'JEANS'"

There have been many and varied attempts to relate such genetic concepts to obesity. The research is not easy. Obesity is one of those individual characteristics for which there is evidence that genetics plays a significant role. But it should be noted that obesity has many causes beyond genetics; the issue is not only a biological but also an emotional and psychological one. And even genetically determined obesity is probably rooted in many genes.

A very difficult aspect of studying genes in obesity is separating the environment from genetics in determining the role of genetics. Several types of studies have attempted to do this. One uses adult adoptees who, when they were infants, were adopted by another family and raised apart from their biological parents. These studies compare the weight class of the adoptee with the Body Mass Index (BMI, which is the weight in kilograms divided by the height in meters squared and is a method of expressing body mass that removes the effect of stature and correlates very well with body fat) of their adoptive parents and of their biological parents. There is no correlation of adoptee weight class with adoptive parents' BMI. Obese adoptees did not have obese adoptive parents. But there is significant correlation of adoptee weight class with biological parents' BMI, especially the mother's. That is, as the biological parents increase in BMI, so does the offspring's weight class. Since they were removed from the parents' environment, the correlation shows a significant genetic component.[5] Similar studies show a significant correlation between separately adopted sib's BMI, which removes generation and economic differences.[6]

At the metabolic level, adjusted resting metabolic rate (RMR) was shown to be familially determined to a large degree.[7] Resting metabolic rate can be grouped according to families, and the variation *within* a family is much less than the variation between families. These studies also show that some families have low, some have median, and some have high resting metabolic rates. Furthermore, the studies demonstrate prospectively that individuals in those families with low RMR have a four-fold greater incidence of becoming obese five years later. Therefore, low RMR is a risk factor for obesity, and it is inherited.[8]

The bottom line with regard to current thinking on the source of some obesity then is this: In obese families the environment acts on a genetic susceptibility to determine the extent of obesity in individuals who are genetically vulnerable. That is, genetics determines the presence of obesity, environment determines the extent of the obesity.

WHICH GENES SHOULD WE FIT INTO?

If we want to understand how risk factors for obesity are rooted in the genes, it is clear that studies aimed at finding specific gene alterations related to obesity are justified using the tools of molecular biology. Because RMR is a risk factor for obesity, I have recently examined genes related to energy expenditure using the tools of molecular biology. Those who struggle with obesity know that some people can seemingly eat all they want and remain slim, partly because they burn the calories by an apparently inefficient metabolic system. Others seem to walk by the kitchen and absorb all the calories on the top of the stove simply by smelling the aroma, because they have a very energy-conserving, efficient metabolism.

While this is an obvious exaggeration, the expression of some obesities makes it clear that some individuals inherit genetic factors that contribute to less or more efficient burning of metabolic fuel. Generally, the *less* fuel efficient are thin, because more calories become heat. The *more* fuel efficient are at much greater risk for obesity. Therefore, we should examine genes for proteins and enzymes involved in efficiency of energy utilization.

GENES RELATED TO ENERGY EFFICIENCY

Genes regulating use of metabolic fuel, and therefore those that may be altered in some families to become less or more efficient, are located in two places in the cell: the nucleus and the mitochondria. Several years ago I became impressed with the importance of studying mitochondrial genes to relate the efficiency of energy utilization to the genetic roots of some forms of obesity.

Mitochondria are centrally involved in energy conversion in the cell. Mitochondrial DNA and nuclear DNA cooperate to make all of the enzymes involved in processes related to energy utilization in the organelle. Thirteen genes centrally involved in the efficiency of energy utilization are encoded in mitochondrial DNA.

Metabolic energy from food fuels is converted in mitochondria to ATP by the electron transport system (ETS) and oxidative phosphorylation. This process is driven by chemosmotic pressure from pumping protons out of the matrix and bringing them back through ATP synthetase. The efficiency of this process is determined by how effectively protons are pushed out through ETS channels and whether they are allowed to leak back through channels *other* than ATP synthetase. This efficiency is determined in part by the proteins and enzymes in the membranes that make up the channels. Some of these membrane proteins are encoded in mitochondrial DNA and translated on mitochondrial ribosomes. The overall process can be less or more efficient depending on alterations in these gene products.

"In an expanding body of important information in nutritional sciences, it is becoming clear that each of us has a unique set of genes and should adapt our nutritional environment to make the genes and the environment fit better together."

What kind of genetic pattern could we expect if alteration in one of these genes caused changes in efficiency of energy utilization resulting in obesity or thinness? Interestingly, mitochondrial genes are *only* maternally inherited. Only offspring of daughters in a given generation will have the family gene. Therefore, in the next generation of a pedigree we know exactly who has and who does not have a given alteration. Offspring of the females do. Offspring of the males do not.

I have used this fact to calculate a "generation Body Mass Index ratio." In this generation BMI ratio, the BMI of the offspring of females (that is, those who share common mitochondrial genes) is divided by the BMI of the offspring of males (those who do not share the same mitochondrial genes). There are not many places other than Utah where families are large enough and have enough information about each other to give statistical significance to such calculations. If this ratio is significantly greater than one, then a pattern of maternally inherited obesity, related to a mitochondrial gene, may be suspected. If significantly less than one, we may suspect maternally inherited thinness.

If either of these cases exist in a pedigree, then we may be justified in using tools of molecular biology to look for altered mitochondrial genes that have affected efficiency of energy utilization.

Our studies have shown two types of evidence that the 13 mitochondrial genes may have an impact in some genetic obesities. First, 26 families recently were screened for mitochondrial DNA alterations. By calculating a "generation BMI ratio," one family was shown to have a statistically significant maternal inheritance of greater BMI. Several alterations in mitochondrial energy efficiency-related genes were found, but all have so far been shown to be silent mutations.[9] The search continues in this family among the remaining genes.

Secondly, families who exhibit consistently low RMRs or consistently high RMRs are being studied. After sequencing a portion of the DNA from several mitochondrial genes in 40 families with low and high RMRs, we now have statistically significant evidence that certain DNA alterations in these genes contribute to a low RMR, possibly by increasing the efficiency of energy utilization. One difference between those with low and high RMR is a nonsilent point mutation in the gene for a membrane protein used by mitochondria to efficiently convert and store energy.[10,11] As already noted, a low RMR has been shown to be a considerable risk factor for weight gain and obesity.

We are clearly just beginning this task. Much more must be done to correlate specific gene alterations with maternally inherited variation in efficiency of energy utilization, but the potential is obviously great for developing processes that could lead to genetically intelligent nutrition counselling. This is a beginning to helping people "fit into their genes."

A CAUTION AND A PERSPECTIVE CHECK

I cannot finish without commenting on an obvious trap related to blaming some obesity on genes. The trap will be, and indeed has already been, the temptation to give up hope, feeling that weight maintenance is *wholly* genetically controlled, and therefore beyond the individual's control. The erroneous conclusion may be to disregard encouragement to follow sound dietary principles.

Increased knowledge of genetic individuality *will surely come.* The knowledge given an individual that he or she carries certain genes that may put him or her at increased risk for obesity (or for any genetic disorder), sensibly construed, should add to—and definitely not detract from—the value of or motivation to heed and practice sound nutritional principles. Indeed, the motivation should be at least as strong as that experienced by a patient with a dramatic family history of heart disease who is also hypercholesterolemic.

Lastly, let me put in perspective the risk factors stemming from genetic individuality and how they may fit into the overall picture of obesity. There are many causes of obesity, only some of which are genetic. There are many genetic causes of obesity, only a portion of which are the result of alterations in genes related to energy metabolism. There are many energy-related genes that could be altered to put an individual at risk for obesity, only a portion of which are the 13 included in mitochondrial DNA, which we have discussed. Therefore, we are probably looking at a small percentage of the genetic causes of obesity by examining a few specific genes. However, this is an important starting place, because we know exactly what kind of genetic pattern of obesity will be present if these genes are the root, and therefore we can focus on the right genes in the right families. □

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