

Chapter Thirteen

DEMENTIA, CANCER, AND AGING

The bottom line is pretty irrefutable: What is good for the heart is good for the brain.

RUDOLPH TANZI AND ANN PARSON,
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WHEN IT COMES TO THE CAUSE of chronic disease, as we discussed earlier, the carbohydrate hypothesis rests upon two simple propositions. First, if our likelihood of contracting a particular disease increases once we already have Type 2 diabetes or metabolic syndrome, then it's a reasonable assumption that high blood sugar and/or insulin is involved in the disease process. Second, if blood sugar and insulin are involved, then we have to accept the possibility that refined and easily digestible carbohydrates are as well.

This applies to Alzheimer's disease and cancer, too, since both diabetes and metabolic syndrome are associated with an increased incidence of these two illnesses. In both cases, critical steps in the disease process have been linked unambiguously to insulin and blood sugar, and the relevant research is now beginning to influence the mainstream thinking in these fields.

Though the characteristic dementia and brain lesions of Alzheimer's were first described a century ago, the disease only recently captured the attention of the research community. In 1975, when the NIH was supporting hundreds of research projects on atherosclerosis and cholesterol metabolism, it was funding fewer than a dozen on Alzheimer's and what was then called senile dementia. This number rose gradually through the end of the 1970s. Between 1982 and 1985, the number of Alzheimer's-related research projects funded by the NIH quintupled.

It took another decade for researchers to begin reporting that heart disease and Alzheimer's seem to share risk factors: hypertension, atherosclerosis, and smoking are all associated with an increased risk of Alzheimer's, as is the inheritance of a particular variant of a gene called

apolipoprotein E4 (apo E4) that also increases the risk of cardiovascular disease.* This in turn led to the notion that what's good for the heart is good for the brain, but that, of course, depends on our understanding of what exactly is good for the heart. Because Alzheimer's researchers, like dietologists, assume that Keys's fat-cholesterol hypothesis is supported by compelling evidence, they will often suggest that cholesterol and saturated fat play a role in Alzheimer's as well. But if coronary heart disease is mostly a product of the physiological abnormalities of metabolic syndrome, as the evidence suggests, then this implicates insulin, blood sugar, and refined carbohydrates instead, a conclusion supported by several lines of research that began to converge in the last decade.

A handful of studies have suggested that Alzheimer's is another disease of civilization, with a pattern of distribution similar, if not identical, to heart disease, diabetes, and obesity. Japanese Americans, for instance, develop a pattern of dementia—the ratio of Alzheimer's dementia to the stroke-related condition known as vascular dementia—that is typically American; when Japanese immigrate to the United States, their likelihood of developing Alzheimer's disease increases considerably, while their risk of developing vascular dementia decreases. The incidence of Alzheimer's dementia in African Americans, according to research published in *JAMA* in 2001, is twice that of rural Africans, and they are three times as likely to suffer vascular dementia, again suggesting that dietary or lifestyle factors play a role in both dementias.

Studies in large populations—6,000 elderly subjects in Rotterdam, 1,500 in Minnesota, 1,300 in Manhattan, 800 Catholic nuns, priests, and brothers in the American Midwest, and 2,500 Japanese Americans in Honolulu—have suggested that Type 2 diabetes have roughly twice as much risk of contracting Alzheimer's disease as nondiabetics. Diabetics on insulin therapy, according to the Rotterdam study, had a fourfold increase in risk. Hyperinsulinemia and metabolic syndrome are also associated with an increased risk of Alzheimer's disease. And so one interpretation of these results, as the Rotterdam investigators noted in 1999, is

* Individuals with a single copy of this apo E4 gene are nearly three times as likely to have both heart disease and Alzheimer's than those with none. Apo E4 is a cousin of apo B, the protein component of LDL and VLDL, and it is also found in the lipoproteins that transport triglycerides and cholesterol. Because heart-disease researchers have focused on cholesterol as the cause of heart disease, Alzheimer's researchers tend also to refer to apo E4 as involved in cholesterol transport as though that were all it did, thus "pointing to a link between cholesterol and Alzheimer's." But this took the overly simplistic 1960s view of heart disease and used it to misdirect the Alzheimer's research.

that "direct or indirect effects of insulin could contribute to the risk of dementia."

One complicating factor in this research is that the underlying cause of dementia is exceedingly difficult to diagnose, even on autopsy. For this reason, it's possible that the research linking diabetes to a higher incidence of Alzheimer's does so because it confuses the consequences of a known complication of diabetes—vascular dementia—with an apparently increased incidence of Alzheimer's dementia. These are the two most common causes of dementia, but the actual diagnoses are not clear-cut.

Alzheimer's dementia is typically perceived as a slow, insidious process that can be identified on autopsy by the presence of neurofibrillary tangles, which are twisted protein fibers located within neurons, and amyloid plaques, which accumulate outside the neurons. Vascular dementia, a recognized complication of diabetes, is perceived as a more abrupt cognitive decline that is caused by small strokes in the blood vessels of the brain. Vascular dementia is usually diagnosed because the dementia appeared shortly after a stroke, or because an autopsy revealed the characteristic stroke-related signs of vascular damage. That vascular dementia is a complication of diabetes means that diabetics are far more likely to be diagnosed someday with vascular dementia than nondiabetics.

In cases of dementia, however, the determination of the actual cause is likely to be arbitrary. Most of us, if we live long enough, will accumulate both vascular damage and Alzheimer's plaques and tangles in our brains, even if we don't manifest any perceptible symptoms of dementia. (Similarly, most of us will have plaques in our arteries even if we don't manifest clinical signs of heart disease.) Vascular dementia and Alzheimer's dementia appear to coexist frequently, a condition known as *mixed dementia*. When dementia is present, the diagnosis of its ultimate cause is a matter of clinical judgment. This gray zone of mixed dementia was examined in a seminal study of nearly seven hundred elderly members of the Sisters of Notre Dame congregation, led by the University of Kentucky epidemiologist David Snowdon. The results suggest that, the less vascular damage we have in our brains, the more easily we can tolerate the lesions of Alzheimer's without exhibiting signs of dementia. It's the extent and location of the vascular damage in the brain, according to Snowdon, that appears to be the determining factor.

The implication is that the accumulation of damage to neurons and blood vessels is one unavoidable process of aging. There is a point when the slow accumulation of Alzheimer's lesions and vascular damage passes some threshold and manifests itself as dementia, and diabetics are always likely to reach that threshold sooner than nondiabetics, if only because

they accumulate vascular damage more rapidly, even if the diabetes bestows on them no special predisposition to develop Alzheimer's plaques and tangles. So whatever dietary factors or lifestyle factors lead to Type 2 diabetes will always increase the likelihood of manifesting dementia.

Two other lines of evidence linking insulin and high blood sugar to Alzheimer's disease are directly related to the amyloid-plaque buildup that is now thought to result in the degeneration and death of neurons in the Alzheimer's-affected brain. The primary component of these plaques is a protein known as *beta-amyloid*—or just amyloid, for short—and this protein is what's left after a larger protein, a *precursor* protein, is cleaved in two. The amyloid precursor protein exists naturally in brain neurons, according to the Harvard neurologist Rudolph Tanzi, and the act of cutting it down in size to the amyloid protein appears to be a normal cellular process. A healthy brain, however, clears away amyloid efficiently after the cleavage occurs; this does not happen in Alzheimer's. The question is, why not?

One phenomenon now implicated in the process of amyloid-plaque accumulation is the accumulation of AGEs, the conglomerations of haphazardly linked proteins and sugars that are found to excess in the organs and tissues of diabetics. Because neurons ideally last a lifetime, they seem to be prime candidates for the slow accumulation of AGEs and the toxic damage they inflict. The proteins that make up the plaques and tangles of Alzheimer's are particularly long-lived themselves and so particularly susceptible. And AGEs can indeed be found buried in both the plaques and tangles of Alzheimer's and even in immature plaques, suggesting that they are involved from the very beginning of the process.

Investigators studying AGEs have proposed that Alzheimer's starts with glycation—the haphazard binding of reactive blood sugars to these brain proteins. Because the sugars stick randomly to the fine filaments of the proteins, this in turn causes the proteins to stick to themselves and to other proteins. This impairs their function and, at least occasionally, leaves them impervious to the usual disposal mechanisms, causing them to accumulate in the spaces between neurons. There they cross-link with other nearby proteins, and eventually become advanced glycation end-products. All of this would then be exacerbated by the fact that the glycation process itself generates more and more toxic reactive oxygen species (free radicals), which in turn causes even more damage to the neurons. In theory, this is what causes the amyloid plaques and leads to the degeneration of neurons, the cell loss, and the dementia of Alzheimer's. The theory is controversial, but the identification of AGEs in the plaques and tangles of Alzheimer's is not.

The involvement of insulin in Alzheimer's can be considered the sim-

plest possible explanation for the slow, relentless development of Alzheimer's plaques in the aging brain. Insulin (in a test tube) will monopolize the attention of the *insulin-degrading enzyme (IDE)*, which normally degrades and clears both amyloid proteins and insulin from around the neurons. The more insulin available in the brain, by this scenario, the less IDE is available to clean up amyloid, which then accumulates excessively and clumps into plaques. In animal experiments, the less IDE available, the greater the concentration of amyloid in the brain. Mice that lack the gene to produce IDE develop versions of both Alzheimer's disease and Type 2 diabetes.*

Much of the relevant research in humans on insulin and Alzheimer's has been done by Suzanne Craft, a neuropsychiatrist at the University of Washington. In 1996, Craft and her colleagues reported that boosting insulin levels, at least in the short term, seems to enhance memory and mental prowess, even in Alzheimer's patients. This linked insulin to the biochemical regulation of memory in the brain, but it said nothing about the long-term, chronic effects of hyperinsulinemia. In 2003, Craft reported that when insulin was infused into the veins of elderly volunteers, the amount of amyloid in their cerebral spinal fluid increased proportionately. This implied that the level of amyloid protein in their brain had increased as well. The older the patient, the greater the increase in amyloid protein. As Craft sees it, if insulin levels are chronically elevated (hyperinsulinemia), then brain neurons will be excessively stimulated to produce amyloid proteins, and IDE will be preoccupied with removing the insulin, so that less will be available to clean up the amyloid. "We're not saying this is the mechanism for all of Alzheimer's disease," Craft says. But "it may have a role in a significant number of people."

This evidence linking insulin, amyloid, and Alzheimer's has now evolved to the point where it has "attendant therapeutic implications," as the Harvard neurologists Dennis Selkoe and Rudolph Tanzi wrote in a 2004 article. "Compounds that subtly increase IDE activity," they suggested, "could chronically decrease [amyloid] levels in the human brain." This implies that anything that decreases insulin levels over the long term (and so increases the amount of IDE available to clean up amyloid)—

* Harvard neurologist Dennis Selkoe and others have been working to track down a gene that seems to predispose individuals to age-related Alzheimer's, rather than the inherited early-onset form. By February 2007, they had not found it, but they had localized it, in the lingo, to a chunk of a single chromosome that was known to include the gene for insulin-degrading enzyme. This made IDE the obvious candidate and suggested that anyone who inherited a particularly unlucky variant of the IDE gene would have an increased likelihood of getting Alzheimer's.

including such dietary approaches as eating less carbohydrates—will achieve the same effect. This isn't to say that eating carbohydrate foods to excess is a cause of Alzheimer's, only that mechanisms have now been identified to make the hypothesis plausible.

To discuss cancer, we need to first return to the subject of cancer in isolated populations eating traditional diets. The modern incarnation of these observations begins with John Higginson, who was the founding director of the World Health Organization's International Agency for Research on Cancer (IARC), a position he would hold for two decades. In the 1950s, Higginson studied cancer incidence in native African populations and compared them with incidence in the United States and Denmark, the two nations for which equivalent data existed. With a few exceptions, Higginson reported, cancer in African natives was remarkably uncommon. This led Higginson to conclude that most human cancers were caused by environmental factors, and that diet and lifestyle factors were the primary suspects. "It would seem, therefore, that the majority of human cancer is potentially preventable," as the World Health Organization concluded in 1964, a view that evolved into the new orthodoxy.

Cancer epidemiologists then tried to establish what proportion of cancers these might be. Higginson suggested 70 to 80 percent of all cancers could be prevented; others said as many as 90 percent. In 1981, the Oxford epidemiologists Richard Doll and Richard Peto published the seminal work on this subject: a 120-page analysis in the *Journal of the National Cancer Institute* that reviewed the existing evidence on changes in cancer incidence over time, changes upon migration from one region of the world to another, and differences in cancer rates between communities and nations. (Colon cancer, for example, was ten times more common in rural Connecticut than in Nigeria; breast cancer was diagnosed eight times more often in British Columbia than in the non-Jewish population of Israel.) Based on this evidence, Doll and Peto concluded that at least 75 to 80 percent of cancers in the United States might be avoidable with appropriate changes in diet and lifestyle.

In the quarter-century since Doll and Peto published their analysis, it has been cited in nearly two thousand journal articles, and yet the fundamental implications have been largely lost. The two most important conclusions in their analysis were that man-made chemicals—in pollution, food additives, and occupational exposure—play a minimal role in human cancers, and that diet played the largest role—causing 35 percent of all can-

cers, though the uncertainties were considered so vast that the number could be as low as 10 percent or as high as 70 percent.

Higginson had repeatedly remarked on these two points during his tenure as director of IARC. In early reports, Higginson and the World Health Organization had referred to "extrinsic factors" and "environmental factors" as the cause of most cancers, by which they meant lifestyle and diet. The public and the environmental movement had perceived this to mean almost exclusively "man-made chemicals"—the "carcinogenic soup," as it was known in the 1960s and 1970s. "It appears that only a very small part of the total cancer burden can be directly related to industrialization," Higginson wrote. The release of industrial chemicals into the environment could not explain, for example, why the nonindustrial city of Geneva had more cancer than Birmingham, "in the polluted central valleys of England," or why prostate cancer was ten times more frequent in Sweden than in Japan.*

Nonetheless, this focus on carcinogenic chemicals as the primary cancer-causing agents in the environment also carried over to nutrition-related cancer research in the laboratory. It was assumed that whatever components of diet were responsible for cancer worked the same way that chemicals did: by inducing mutations and genetic damage in cells. When cancer researchers from around the world met in September 1976 at the Cold Spring Harbor Laboratory to discuss the origins of human cancer, the talks focused on those chemicals shown to be carcinogens in animals, and the possibility that they might be found in infinitesimal or greater amounts in human diets, drinking water, or pharmaceuticals.

By the mid-1970s, when cancer epidemiologists began to convince politicians and the public that many cancers were caused by what Peto and Doll had called the "gross aspects of diet," rather than "ingestion of traces of powerful carcinogens or precarcinogens," the focus was almost exclusively on fat, fiber, and red meat, or smoked- or salt-cured meat, as well as the possibly protective nature of vitamins, vegetables, and fruits. The low incidence of cancer in vegetarians and Seventh-day Adventists was often cited as evidence that meat is carcinogenic and that green vegetables and fruit are protective. (Although the incidence of colon cancer, for instance,

* Higginson held the environmental movement responsible for what he considered a willful misinterpretation of the epidemiologic observations: "If they could possibly make people believe that cancer was going to result from pollution, this would enable them to facilitate the clean-up of water, of the air, or whatever it is," he told *Science* in 1979. He was all for cleaning up the environment, he added, but "to make cancer the whipping boy for every environmental evil may prevent effective action when it does matter."

among Seventh-day Adventists was no lower than among Mormons, described by Doll and his colleague Bruce Armstrong as "among the biggest beefeaters in the United States.") For the next twenty years, conferences, textbooks, and expert reports on nutrition and cancer continued to focus exclusively on these factors, although now aided by the advances in molecular biology.

By the end of the 1990s, clinical trials and large-scale prospective studies had demonstrated that the dietary fat and fiber hypotheses of cancer were almost assuredly wrong, and similar investigations had repeatedly failed to confirm that red meat played any role.* Meanwhile, cancer researchers had failed to identify any diet-related carcinogens or mutagens that could account for any of the major cancers. But cancer epidemiologists made little attempt to derive alternative explanations for those 10 to 70 percent of diet-induced cancers, other than to suggest that overnutrition, physical inactivity, and obesity perhaps played a role.

Throughout these decades, refined carbohydrates and sugars received little or no attention in discussions of cancer causation. Peter Cleave had suggested in *The Saccharine Disease* that the refining of carbohydrates might be involved in colon cancer. John Yudkin had noted that the five nations with the highest breast-cancer mortality in women in the late 1970s (in descending order: the United Kingdom, the Netherlands, Ireland, Denmark, and Canada) had the highest sugar consumption (in descending order: the United Kingdom, the Netherlands, Ireland, Canada, and Denmark), and those with the lowest mortality rates (Japan, Yugoslavia, Portugal, Spain, and Italy) had the lowest sugar consumption (Japan, Portugal, Spain, Yugoslavia, and Italy). But in 1989, when the National Academy of Sciences published its 750-page report on *Diet and Health*, the authors spent only a single page evaluating the proposition that carbohydrates might cause cancer. "There is little epidemiologic evidence to support a role for carbohydrates *per se* in the etiology of cancer," they noted. They did add two caveats. One was that "no definitive conclusion is justified . . . because carbohydrates have often been reported in epidemiologic studies only as a component of total energy and not analyzed separately." The other was that Richard Doll and Bruce Armstrong had found sugar intake in international comparisons to be "positively correlated with both the incidence of and mortality from" colon, rectal, breast,

* Those clinical trials that tested the dietary-fat-and-fiber hypotheses of cancer, as we discussed earlier, replaced red meat in the experimental diets with fruits, vegetables, and whole grains. When these trials failed to confirm that fat causes breast cancer, or that fiber prevents colon cancer, they also failed to confirm the hypothesis that red-meat consumption plays a role in either.

ovarian, prostate, kidney, nervous-system, and testicular cancer, and that "other investigators have produced similar findings."

The patterns of cancer incidence, for many cancers, are similar to those of heart disease, diabetes, and obesity, which alone suggests an association between these diseases that is more than coincidental. This was the basis of Cleave's speculation, of Dennis Burkitt's, and of those cancer epidemiologists who argued that dietary fat caused breast cancer. But if dietary fat, red meat, man-made chemicals, or even the absence of fiber cannot explain the "strikingly similar" patterns of disease distribution, as the Harvard epidemiologist Edward Giovannucci remarked about colon cancer and Type 2 diabetes in 2001, then something else most likely does.

Those cancers apparently caused by diet or lifestyle and not related to tobacco use are either cancers of the gastrointestinal tract, including colon and rectal cancer, or cancers of what are technically known as *endocrine-dependent organs*—breast, uterus, ovaries, and prostate—the functions of which are regulated by hormones. This connection between these diet- and life-style-related cancers and hormones has been reinforced by the number of hormone-dependent factors linked to cancers of the breast and the endometrium (the lining of the uterus). All suggest that estrogen plays an important role. All these cancers, with the possible exception of pancreatic and prostate cancer, appear to increase in incidence with weight gain. These associations together imply both a metabolic and a hormonal connection between diet and cancer. This in turn led breast-cancer researchers to focus their attention on the likely possibility that obesity increases the incidence of breast cancer by increasing estrogen production.

The most direct evidence linking overweight or overnutrition to cancer comes from animal experiments. These date back to the eve of World War I, when Peyton Rous, who would later win a Nobel Prize, demonstrated that tumors grow remarkably slowly in semi-starved animals. This line of research lapsed until 1935, when the Cornell University nutritionist Clive McCay reported that feeding rats just barely enough to avoid starvation ultimately extended their lifespan by as much as 50 percent. Seven years later, Albert Tannenbaum, a Chicago pathologist, launched a cottage research industry after demonstrating that underfeeding mice on very low-calorie diets, as McCay had, resulted in a dramatic inhibition of "many types of tumors of divergent tissue origin." In one experiment, twenty-six of fifty well-fed mice developed mammary tumors by a hundred weeks of age—the typical lifespan of lab mice—compared with none of fifty that

were allowed only minimal calories. Tannenbaum's semi-starved animals not only lived longer, but were more active, he reported, and had fewer "pathologic changes in the heart, kidneys, liver, and other organs."*

To explain this inhibitory effect, Tannenbaum considered an idea that had originated in the 1920s with Otto Warburg, a German biochemist and later Nobel Prize winner. Warburg had demonstrated that tumor cells quickly develop the ability to survive without oxygen and to generate energy by a process of fermentation rather than respiration. Fermentation is considerably less efficient, and so tumors will burn perhaps thirty times as much blood sugar as normal cells. Incipient tumors in these calorie-restricted lab animals, it was thought, cannot obtain the huge amounts of blood sugar they need to fuel mitosis—division of the nucleus—and continue proliferating.

Insulin was not considered a primary suspect until just recently, but the evidence has existed for a while. The earliest such link between a dysfunction in carbohydrate metabolism and cancer dates to 1885, when a German clinician reported that sixty-two of seventy cancer patients were glucose-intolerant. One common observation by clinical investigators over the years was that women with adult-onset (Type 2) diabetes or glucose intolerance had a higher-than-average incidence of breast cancer. By the mid-1960s, researchers were reporting that insulin acts as a promoter of growth and proliferation in both healthy and malignant tissues. Howard Temin, who later won a Nobel Prize for his cancer research, reported that cells turned malignant by a chicken virus would cease to proliferate in the laboratory unless insulin was added to the serum in which they were growing. This growth-factor effect of insulin was also demonstrated in adrenal and liver-cell cancers. Insulin "intensely stimulated cell proliferation in certain tumors," noted one 1967 report. In 1976, Kent Osborne and his colleagues at the National Cancer Institute reported that one line of particularly aggressive breast-cancer cells were "exquisitely sensitive to insulin."

By the late 1970s, researchers had also reported that malignant breast tumors had more receptors for insulin than did healthy tissue. The more insulin receptors on the surface of a cell, the more sensitive it will be to the insulin in its environment. Having a greater number of insulin receptors than healthy cells, as one report noted, might confer "a selective growth advantage to tumor cells."

* Tannenbaum actually compared his chronically underfed mice with control mice fed the identical diet but supplemented with cornstarch. The inhibition of cancer, as Tannenbaum noted, could have been due to "carbohydrate-restriction" rather than restriction of all calories.

"Selective growth advantage" speaks directly to the process of Darwinian evolution that is considered the controlling force in tumor development. We can think of human cells as existing in a microscopic ecosystem, living in harmony with their environment, and balanced, as are all species, between the opportunities for growth and proliferation and the processes that lead to aging and death. In such an environment, the billions of cells that eventually constitute a tumor will be the descendants of a single cell that has accumulated a series of genetic mutations, each adding to its proclivity to proliferate unfettered by any of the normal inhibitions to growth. The process in which a healthy cell eventually results in malignancy is a gradual evolution driven by a series of mutations in the DNA of the genes, each bestowing on the cell either the inclination to multiply or a breakdown in the control and repair mechanisms that have evolved to counter precisely such potentially deleterious mutations. The descendants of such a mutant cell would inherit this fitness advantage over other cells in the tissue, and so, within a few years, a single such mutant cell will leave millions of descendants. As one of those descendants in turn gains, purely by chance, yet another advantageous error or mutation, its descendants will now come to dominate.

Each new mutation-bearing cell constitutes a new species, in effect, that is better suited to prevail in its local cellular environment. Eventually, with this continued accumulation of what to the body as a whole is simply bad luck, a single cell will come to possess precisely that set of mutant genes that drive it and allow it to grow and proliferate without limit. Because each single *hit* of genetic damage alone is not sufficient to produce a cancer cell, the accumulation of just the right half-dozen hits (actually, the *wrong* half-dozen hits) takes years or decades, which is why virtually all cancers become more common as we age.

Cancer researchers now believe that these cancer-causing mutations occur as errors in the replication of DNA during the process of cell division and multiplication. Each one of us is likely to experience some ten thousand trillion cell divisions over the course of our lives, constituting an "enormous opportunity for disaster," in the words of the MIT molecular biologist Robert Weinberg, author of the textbook *The Biology of Cancer*. This suggests that cancer-causing mutations are another unavoidable side effect of aging, which is why our cells have also evolved to be exceedingly resistant to genetic damage. They have sophisticated mechanisms to search out defects in newly replicated DNA and repair them, and other mechanisms that actually prompt a cell to commit suicide—programmed cell death, in the technical terminology—if the repair mechanisms are

incapable of fixing the damage that occurred during replication. Alas, with time, these programs, too, can be disabled by the proper mutations.

Within this Darwinian environment, insulin provides fuel and growth signals to incipient cancer cells. Its more lethal effects, however, might come through the actions of insulin-like growth factor (IGF). Growth hormone itself is secreted by the pituitary gland and works throughout the body; IGF is secreted both by the liver and by tissues and cells throughout the body, and it then works locally, where concentrations are highest. Most tissues require at least two growth factors to grow at an optimal rate, and IGF is almost invariably one of the two, and perhaps the primary regulator. Insulin-like growth factor is sufficiently similar in structure to insulin that it can actually mimic its effects. IGF can stimulate muscle cells to take up blood sugar, just as insulin does, though not as well. Researchers now believe that IGF serves as the necessary intermediary between the growth hormone secreted by the pituitary gland, and the actual amount of food that is available to build new cells and tissues. If insufficient food is available, then IGF levels will stay low even if growth-hormone levels are high, and so cell and tissue growth will proceed slowly if at all. Add the necessary food and IGF levels increase, and so will the rate of growth. Unlike insulin, which responds immediately to the appearance of glucose in the bloodstream and so varies considerably from hour to hour, IGF concentrations in the circulation change only slowly over days or weeks, and thus better reflect the *long-term* availability of food in the environment.

Since the mid-1970s, researchers have identified many of the molecules that play a role in regulating the strength of the growth and proliferation signals that IGF communicates to the cells themselves. There are several different insulin-like growth factors, for instance, and they bind to specific IGF receptors on the surfaces of cells. The more IGF receptors on a cell's surface, the stronger the IGF signal to the cell. If insulin levels are high enough, insulin will stimulate the IGF receptors and send IGF signals into cells as well as insulin signals.*

IGF and its receptors appear to play a critical role in cancer. In mice, functioning IGF receptors are a virtual necessity for cancer growth, a discovery that Renato Baserga of Thomas Jefferson University says he "stumbled" upon in the late 1980s, after nearly forty years spent studying the growth processes of normal and cancerous cells. Shutting down the IGF

* Different IGFs have different effects. To keep the following discussion reasonably simple, I'll refer to IGF and IGF receptors as though there were only one species of each, although I'm oversimplifying the science by doing so.

receptor in mice will lead to what Baserga calls "strong inhibition, if not total suppression of [tumor] growth"; it is particularly lethal to those tumors that have already metastasized from a primary site elsewhere in the body.

In the bloodstream, virtually all insulin-like growth factors are attached to small proteins that ferry them around to various tissues where they might be needed. But the IGFs, when attached to these proteins, are too large and unwieldy to pass through the walls of blood vessels and get to the tissues and cells where the IGF might be used. At any one time, only a small percentage of IGF in the circulation is left unbound to stimulate the growth of cells.

These *binding proteins* constitute yet another of the mechanisms used by the body to regulate hormonal signals and growth factors. Insulin appears to depress the concentration of IGF-binding proteins, and so high levels of insulin mean more IGF itself is available to effect cell growth—including that of malignant cells. Anything that increases insulin levels will therefore increase the availability of IGF to the cells, and so increase the strength of the IGF proliferation signals. (Insulin has been shown to affect estrogen this way, too, one way in which elevated levels of insulin may potentially cause breast cancer.)

The role of IGF in cancer appears to be fundamental, albeit still controversial. As is the case with insulin, IGF has been found in the laboratory to enhance the growth and formation of tumor cells directly; IGF signals prompt cells to divide and multiply. (This effect seems to be particularly forceful with breast-cancer cells when IGF and estrogen are acting in concert.) IGF has an advantage over other growth factors that might play a role in cancer because it can reach tumors either through the bloodstream—after being secreted by the liver—or as a result of production by nearby tissue. There's even evidence that tumors can stimulate their own further growth and proliferation by secreting their own insulin-like growth factors. In the early 1980s, cancer researchers discovered that tumor cells also *overexpress* IGF receptors, just as they overexpress insulin receptors. The surfaces of tumor cells have two to three times as many IGF receptors as healthy cells, which makes them all that much more responsive to the IGF in their immediate environment.

This is another way in which cancer cells gain their all-important survival growth advantage, suggests Derek LeRoith, whose laboratory at the National Institute of Diabetes and Digestive and Kidney Diseases did much of this research. The extra insulin receptors will cause cancerous cells to receive more than their share of insulin from the environment,

which will convey to the cell more blood sugar for fueling growth and proliferation; the extra IGF receptors will assure that these cells are supplied with particularly forceful commands to proliferate. Another critical role of IGF in the development of cancer may be its ability to inhibit or override the cell suicide program that serves as the ultimate fail-safe mechanism to prevent damaged cells from proliferating.

In the past decade, LeRoith and others have demonstrated that the various molecules involved in the communication of the IGF signal from the bloodstream to the nucleus of cells—the insulin-like growth factors themselves, their receptors, and their binding proteins—work together with insulin to regulate both the growth and metastasis (the spread of tumors to secondary sites) of colon and breast cancer. LeRoith has done a series of experiments with mice genetically engineered so that their livers do not secrete IGF. As a result, these mice have only a quarter as much IGF in their circulation as normal mice. When colon or mammary tumors are transplanted into these mice, both tumor growth and metastasis are significantly slower than when identical tumors are implanted in normal mice with normal IGF levels. When insulin-like growth factor is injected back into these genetically engineered mice, tumor growth and metastasis accelerate. David Cheresch, a cancer researcher at the Scripps Institute in La Jolla, California, has demonstrated that both insulin and insulin-like growth factor will prompt otherwise benign tumors to metastasize and migrate through the bloodstream to secondary sites.

The working hypothesis of cancer researchers who study IGF is not that these molecules initiate cancer, a process that occurs through the accumulation of genetic errors, but, rather, that they accelerate the process by which a cell becomes cancerous, and then they work to keep the cells alive and multiplying. At a 2003 meeting in London to discuss the latest work on IGF, researchers speculated that the development of cancerous cells and even benign tumors is a natural side effect of aging. What's not natural is the progression of these cells and tumors to lethal malignancies. Such a transformation requires the chronically high levels of insulin and IGF induced by modern diets. This hypothesis is supported by epidemiological studies linking hyperinsulinemia and elevated levels of IGF to an increased risk of breast, prostate, colorectal, and endometrial cancer.

This hypothesis, if not refuted, would constitute a significant shift in our understanding of the development of malignant cancer. It would mean that the decisive factor in malignant cancer is not the accumulation of genetic damage in cells, much of which is unavoidable, but how diets change the environment around cells and tissues to promote the survival,

growth, and then metastasis of the cancer cells that do appear. "People were thinking a bit too much that diet could be a risk factor for cancer almost exclusively based on the idea that it contained carcinogenic substances," explains Rudolf Kaaks, director of the Hormones and Cancer Group at the International Agency for Cancer Research. "Now the idea is that there is a change in the endocrine and growth-factor environment of cells that pushes cells to proliferate further and grow more easily and skip the programmed cell-death events."

IGF and insulin can be viewed as providing fuel to the incipient fire of cancerous cells and the freedom to grow without limit. The critical factor is not that diet changes the *nature* of cells—the mutations that lead to cancer—but that it changes the *nurturing* of those cells; it changes the environment into one in which cancerous and precancerous cells can flourish. Simply by creating "an environment that favored, even slightly, survival (rather than programmed cell death)," says the McGill University oncologist Michael Pollak, insulin and IGF would increase the number of cells that accumulate some genetic damage, and that would increase the number of their progeny that were likely to incur more damage, and so on, until cancer is eventually achieved. "When applied simultaneously to large numbers of at-risk cells over many years," notes Pollak, "even a small influence in this direction would serve to accelerate carcinogenesis."

All of this leads us back to the spectacular benefits of semi-starvation on the health and longevity of laboratory animals. If we take a young rat and restrict its eating to less than two-thirds the calories of its preferred diet, and if we keep this up for its entire life, our rat will likely live 30 to 50 percent longer than had we let it eat to satiation, and any age-related diseases—cancer in particular—will be delayed in their onset and slowed in their progression. This has been shown to hold true for mice and other rodents, and for yeast, protozoans, fruit flies, and worms (and maybe even monkeys).

Two possibilities for how these diets work are that the animals live longer because they are less encumbered by body fat, or because they're leaner all around and so weigh less. Neither of these can explain the evidence, however. Consider a strain of mice known as ob/ob mice. These have a mutation in a single gene that results in such extreme obesity that a mouse ends up looking like a loaf of bread with fur, eyes, whiskers, and a mouth. Nonetheless, these mice can be kept at a normal weight by restricting their food consumption to half of what they would naturally prefer to

eat. They are normally short-lived, which supports the idea that the greater the body fat the shorter the lifespan, but on a lifelong very low-calorie diet they will live as long as or longer than lean mice of a similar genetic inheritance but without the mutation that causes obesity. They will do this even though they still have more than twice the body fat of the lean mice. Indeed, when these experiments were done in the early 1980s by David Harrison of the Jackson Laboratory in Bar Harbor, Maine, these calorically restricted ob/ob mice lived just as long as calorically restricted lean mice, even though the former were nearly four times as fat as the latter. "Longevities," Harrison concluded, "were related to food consumption rather than to the degree of adiposity." This has inevitably been the case, whenever these experiments are done. The calorie-restricted animals live longer because of some metabolic or hormonal consequence of semi-starvation, not because they are necessarily leaner or lighter.

So what does eating less do physiologically that leanness does not? With each new study, researchers have honed their hypothesis of why semi-starvation leads to these anti-aging and disease-delaying processes, and what this says about human aging and disease. This has led to some remarkable revelations about insulin and insulin-like growth factor, and what is likely to happen when these two hormone/growth factors are perturbed by modern diets.

One hypothesis proposes that calorie restriction reduces the creation of toxic reactive oxygen species—free radicals—which are considered to be crucial factors in the aging of cells and tissues. Eat less food and the cells burn less fuel, and so generate fewer free radicals. Oxidative stress proceeds at a slower pace, and we live longer, just as a car will last longer in a dry climate that doesn't promote rust. Certainly, calorie restriction suppresses free-radical production. And if fruit flies are either fed antioxidants or genetically transformed to overproduce their own antioxidants, they will live up to 50 percent longer. But similar experimental interventions seem to do nothing for rodents. The genetic evidence suggests that something more profound is happening, although this reduction in oxidative stress likely plays some role.

The characteristics that all these long-lived organisms seem to share definitively are reduced insulin resistance, and abnormally low levels of blood sugar, insulin, and insulin-like growth factor. As a result, the current thinking is that a lifelong reduction in blood sugar, insulin, and IGF bestows a longer and healthier life. The reduction in blood sugar also leads to reduced oxidative stress and to a decrease in glycation, the haphazard binding of sugars to proteins, and glycation end-products and all the toxic

sequelae that follow. The decrease in insulin and IGF also apparently bestows on the organism an enhanced ability to protect against oxidative stress and to ward off other pathogens.

The most compelling evidence now supporting this hypothesis has emerged since the early 1990s from genetic studies of yeast, worms, and fruit flies, and it has recently been confirmed in mice. In all four cases, the mutations that bestow extreme longevity on these organisms are mutations in the genes that control both insulin and IGF signaling.

Geneticists and developmental biologists refer to yeast, worms, fruit flies, and mice as *model* organisms because they're easy to study in the laboratory and what we learn from them about genetics will almost assuredly apply to humans as well. This is considered the fundamental principle underlying modern genetic research: once evolution comes upon a genetic mechanism that works, it reuses it again and again. Those genes that regulate the development and the existence of any single living organism will likely be used in some similar fashion in *all* of them. "When reduced to essentials," as the cancer researcher J. Michael Bishop suggested in his 1989 Nobel Prize lecture, "the fruit fly and *Homo sapiens* are not very different."

Consider, for instance, the mutations that control longevity in nematodes, which are the particular type of microscopic worms favored by modern researchers. These mutations, as Cynthia Kenyon and her colleagues from the University of California, San Francisco, reported in *Nature* in 1993, are in a gene that was known to regulate the passage of young worms into a state known as *dauer* that is similar to hibernation in mammals. The worms will enter this dauer state, explains Kenyon, only if they have insufficient food to survive. "The way these worms work," she explains, "is that the worm hatches from the egg, and if there's not a lot of food around, it goes through various larval stages and ends up in this dauer state. . . . It doesn't eat or do anything else. Then, if you give it food, it will exit the state and reproduce and have a normal lifespan." The particular genetic mutation that Kenyon discovered resulted in worms that lived twice as long as normal worms, and this was, at the time, the longest lifespan extension ever reported in an organism. Kenyon then demonstrated that this increased longevity was not simply a consequence of some kind of developmental arrest—as though the mutation had somehow trapped a young worm in a dauerlike limbo—but was actually the result of the mutation's triggering a lifespan-extension mechanism in adult worms. In other words, this mutation was keyed into a genetic program that actually regulates longevity, and does it in a way that would be evolutionarily advantageous.

In 1997, the Harvard geneticist Gary Ruvkun reported that the gene in question was the single worm-equivalent of a trio of insulin-related genes in humans. In retrospect, this wasn't surprising, noted Ruvkun, because here was a gene in worms that regulated a process—dauer—that depended on the presence or absence of food in the environment, and insulin and IGF are the genes in more sophisticated organisms that respond specifically to food availability. As it turns out, particularly long-lived fruit-fly mutants have also been found to have defects in this same insulin-like gene pathway, which serves to regulate in the fly a condition very similar to dauer and hibernation.

The ultimate evidence, at least so far, that insulin and insulin-like growth factor affect longevity and disease comes from a type of transgenic animal experiment known as a *knockout*. The working assumption of such experiments is that the function of a gene can be elucidated by creating an animal that lacks the gene entirely—the gene has been *knocked out*—or has only one copy instead of the usual two. In January 2003, Martin Holzenberger and his colleagues from the Institut National de la Santé et de la Recherche Médicale in Paris reported that they had created mice with only a single copy of the gene for the IGF receptor, which meant that the cells of such mice would be comparatively unresponsive to any IGF that might be available in the circulation. The result was that these mice lived 25 percent longer than their littermates who had both copies of the gene, despite the fact that their weights were effectively identical. That same month, C. Ronald Kahn and his colleagues at the Joslin Diabetes Center published the results of their research on mice that they had genetically engineered to lack the insulin receptor only on their fat cells. With their fat tissue immune to the effect of insulin, Kahn's mice weighed 25 percent less than normal mice. These mice remained lean, even when forced to overeat. They were simply incapable of putting on fat. As Kahn later explained, this wasn't surprising, since fat cells require insulin for fat synthesis. If they have no receptor to detect the insulin that's present, then no fat can accumulate. The transgenic mice lived almost 20 percent longer than normal mice.

These experiments have led to the working hypothesis that insulin and insulin-like growth factor emerged in simple organisms in part to promote the survival of the species when food is hard to come by. These hormone/growth factors regulate metabolism and fat storage and reproduction. The IGF regulates cell division and growth, while the insulin regulates metabolism by apportioning or partitioning the food we consume into those calories that will be used immediately for fuel and those that will be stored for use at a later time. When food is plentiful, activity in the

insulin and IGF pathways increases and pushes the animal to grow, mature, and reproduce. When food is scarce, activity in these pathways is reduced, and this shifts the organism into a mode that favors long-term survival over immediate reproduction. As Cynthia Kenyon explains:

When food becomes limiting, an animal lacking this system would either die of starvation, or produce progeny that die of starvation. In contrast, with this food-sensing system in place, as food declines, the animal begins to build up fat and/or glycogen [the molecular storage form of glucose] reserves, elaborates stress-resistance mechanisms, and delays or suspends reproduction until food is restored. It also activates pathways that extend lifespan, which increases the organism's chance of being alive and still youthful enough to reproduce if it takes a long time for conditions to improve.

If we accept the evolutionary argument that genetic mechanisms are conserved from simple organisms to humans, then we have at least to contemplate the implications: if a regulatory system as fundamental as that of insulin and IGF is capable of influencing longevity and susceptibility to disease in flies, worms, and mice, then it is likely to do so in humans as well. This research supports the hypothesis that elevations of insulin and IGF will increase the risk of disease and shorten life, and so any diet or lifestyle that elevates insulin and makes IGF more available to the cells and tissues is likely to be detrimental.

To accept these implications at face value, however, we have to be capable of dismissing the conventional wisdom on diet and chronic disease—that an excess of saturated fat, all fat, or perhaps all calories is responsible. Few researchers are willing to take this approach. One who has is Cynthia Kenyon. Once it became clear that the mutations that prolonged longevity in worms were those that reduced the level of activity in the worms' insulin-IGF pathway, Kenyon began a series of experiments based on a single question: what would happen if she fed worms glucose, in addition to their preferred diet of bacteria? Kenyon added 2 percent glucose to the bacterial medium in which the worms lived, and the lifespan of the worms was reduced by a quarter. Kenyon is still working to establish the nature of this adverse effect of glucose. Her hypothesis: just as mutations increase lifespan in worms by decreasing activity in their insulin-IGF pathway, glucose *shortens* the lifespan of worms by *increasing* activity in the same pathway. In October 2004, when Kenyon presented the results of these experiments at a conference on the molecular genetics of aging, she con-

cluded her presentation with a simple, albeit radical question: "Could a low-carb (i.e., low-glycemic-index) diet lengthen lifespan in humans?"

Kenyon is unusual in this kind of laboratory research in that she had already interpreted the results of her research as relevant to her own life. As Kenyon tells it, the day she realized that glucose shortened the lives of her worms, she decided to restrict her own consumption of carbohydrates to a bare minimum. She lost thirty pounds, she says; her blood pressure, triglycerides, and blood-sugar levels all dropped; and her HDL increased. Kenyon recognizes her experience as anecdotal, but it certainly influenced her suspicion that carbohydrates would also cause chronic disease in humans through their effect on insulin and insulin-like growth factor.

A more common approach to this research implicating insulin and IGF in the causation of chronic disease is to avoid any possible dietary implications and focus solely on the connotations for drug or gene therapies. This was the approach used by Dennis Selkoe and Rudolph Tanzi, who concluded their April 2004 report on insulin and Alzheimer's by suggesting that the results "have attendant therapeutic implications." The only therapeutic implication they discussed was the possibility of creating "compounds" that increase the activity of insulin-degrading enzyme—the equivalent of reducing insulin levels—and so inhibiting the accumulation of Alzheimer's plaques in the brain.

This same approach was used by Ronald Kahn and his collaborators when they discussed the lean, long-lived transgenic mice they had created by knocking out the insulin receptors on the fat cells of the mice. The publication of the research in *Science* was accompanied by a press release from the Joslin Diabetes Center, of which Kahn is president, focused almost exclusively on the "dream of 60 million overweight American adults," which it described as the desire to "throw away those diet books and eat whatever you want without becoming fat, and—as a bonus—not develop diabetes and live longer as well." The press release implied that this dream might be accomplished by the insights gleaned from these transgenic mice, and Kahn was quoted discussing therapeutic implications, although once again diet was not one of them. "Perhaps one day if we are able to find a drug to reduce or block insulin action in fat cells in humans, we might be able to prevent obesity, as well as Type 2 diabetes and other metabolic diseases," Kahn wrote. "And who knows, they might also live longer too." Diabetologists implicitly take the same tack whenever they discuss the need for their diabetic patients to "normalize" blood sugar, while recommending that this be accomplished primarily with "intensive insulin therapy" rather than restricting the carbohydrate content of their diets.

years, after all, is not just associated with chronic diseases of civilization, it is a disease of civilization, and so it, too, may be a symptom of an underlying disorder. In this hypothesis, it is the *quality* of the calories consumed that regulates weight, and the *quantity*—more calories consumed than expended—is a secondary phenomenon. Whatever causes weight gain is at the heart of this tangled web, and that is the question we must now address.

THE CARBOHYDRATE HYPOTHESIS

Another common approach today is to accept the chronic elevation of insulin, and so IGF, as a likely cause of chronic disease, but then assume that the hyperinsulinemia is caused by insulin resistance, which in turn is induced by a combination of high-fat, energy-dense, high-calorie diets, physical inactivity, and excess weight. By this logic, any research that implicates increased insulin activity in disease only confirms that too much food and too little exercise are the true bane of our existence. This approach is the one employed by those clinicians and public-health authorities who now acknowledge that hyperinsulinemia, insulin resistance, and the associated physiological abnormalities of metabolic syndrome are important risk factors for heart disease, but then blame the syndrome itself on excess weight or, if the patient happens to be lean, on physical inactivity. The guidelines from the National Cholesterol Education Program manage to merge both of the latter two approaches, by first enumerating the causes of metabolic syndrome as overweight, physical inactivity, and an "atherogenic diet"—defined as a diet high in saturated fat and calories—and then suggesting that "pharmacological modification of the associated risk factors" is the most effective treatment.

In this approach, high-calorie, high-fat diets and sedentary lifestyles are seen as the causes of all the diseases of civilization. The causal link in this chain from diet and lifestyle to disease is excess weight. "Weight sits like a spider at the center of an intricate, tangled web of health and disease," as the Harvard epidemiologist Walter Willett has described it in *Eat, Drink, and Be Healthy: The Harvard Medical School Guide to Healthy Eating*. Or, as Jeremiah Stamler suggested back in 1961, about heart disease in particular, "Excess weight and the common American pattern of gain in weight from young adulthood into middle age are highly prevalent and serious risk factors. . . . The problem is not the severe, marked, huge, circus-type of obesity, but rather the 25 or 40 pounds put on gradually over the years—the moderate, creeping obesity so common among middle-aged American men."

That excess weight is accompanied by an elevated risk of chronic disease is a given. The questionable assumption is that it is an excess of calories of *all* types, and the dense calories of dietary fat in particular, combined with a relative lack of physical activity, that causes weight gain. In the prevailing wisdom, a simple caloric imbalance is the culprit: we get fat because we consume more calories than we expend.

The alternative is that excess weight and obesity, like all diseases of civilization, are caused by the singular hormonal effects of a diet rich in refined and easily digestible carbohydrates. The fattening of our adult