A BRIGHT IDEA?:
THE PROMISE AND PERIL OF A MEMORY DRUG

by

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B.A. English
Boston College, 2002

SUBMITTED TO THE PROGRAM IN WRITING AND HUMANISTIC STUDIES IN
PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE IN SCIENCE WRITING
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

SEPTEMBER 2007

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Submitted to the Program in Writing and Humanistic Studies on June 11, 2007 in Partial Fulfillment of the Requirements for the Degree of Master of Science in Science Writing

ABSTRACT

In the MIT lab of neuropharmacologist Richard Wurtman, rodents that received a new Alzheimer’s drug have shown a marked improvement in learning and memory. They are able to master elaborate mazes in half the time of their all-natural counterparts. Wurtman theorizes that the memory loss and dementia associated with Alzheimer’s disease is caused not by amyloid plaques and tangles but by a gradual deterioration of the brain’s synapses. Wurtman’s drug—a cocktail of three dietary supplements including uridine, choline, and an omega-3 fatty acid called DHA—is designed to generate more synapses. The three ingredients deliver the stimulus and raw material needed to create more phosphatidylcholine, a major component of neuronal membrane. More membrane, the thinking goes, means more neuronal encounters, more synapses, and more relayed messages. Wurtman’s cocktail has just entered a massive clinical trial involving 10,000 Alzheimer’s patients spread across 10 European countries.

The same drug that could preserve brain function in Alzheimer’s patients also has potential as a memory drug for healthy people. This thesis explores the ethical questions surrounding such biotechnological enhancement. What might be the benefits and drawbacks of taking a memory booster? Could a class-like division eventually arise between those who get the drug and those who do not? Could the molecular manipulations of a smart drug—what some call “cosmetic pharmacology”—change qualities that are inextricable from who we are?

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On an early Saturday morning in November, Sarah Holguin, a petite, fourth-year graduate student, was harvesting brains.

It was “Sac Day” in the lab of MIT neuropharmacologist Richard Wurtman and, judging by an incessant clamor from the cages, the dozens of laboratory rodents slated to be “sacrificed” seemed to know what was coming.

Holguin, who looked like she could be twelve-years-old in her oversized lab coat, was jovial and industrious. She plucked gerbils two at a time from their bed of wood shavings, or else a single Chihuahua-sized rat, and dropped them in a glass container. A tube, snaking from a nearby tank, pumped in a suffocating flow of carbon dioxide. The gerbils and rats threw their heads back as if howling, then collapsed. Holguin slid the limp rodents one-by-one into a guillotine the size of a large paper cutter and, with a tiny leap, brought all her weight down on the blade. The bodies were discarded in a shopping bag at her feet (“My bag of horrors,” she called it). The heads, and the all-important brains, were passed down the long metal table, a make-shift assembly line, to three undergraduate assistants.

While steeled to the task at hand, the undergrads were less cheerful than Holguin. They looked up regularly from the steady stream of heads to take in the view: the tortuous, almost byzantine pipes sprouting from the nearby power plant; a sheer steeple rising from Cambridge’s Central Square, its apex just visible from the fifth floor animal surgery room of the Picower Institute for Learning and Memory.

It was the undergraduates’ job to cut away the rodents’ scalps with miniature scissors, crack and peel away the skull like a peanut shell, and spoon out the brain. With a razor blade, they easily sliced apart the left and right hemispheres of the brains,
separating them like lobes of cauliflower. Wrapped in a square of tinfoil, each half was deposited in a bucket filled with chips of dry ice. Once collected, all the brains were moved to an industrial freezer to be preserved for later analysis.

These rodent brains, each a mere 2 grams of pale tissue, were handled like precious stones. Over the past few months, half of the rodents had received Dr. Wurtman’s new drug, a cocktail of dietary supplements including uridine, choline, and an omega-3 fatty acid called DHA. Holguin studied the behavioral effects of the cocktail, putting the rodents through a series of mazes that tested learning and memory. Rodents that received the drug performed better than those that received a placebo. In one test, they quickly paddered down the correct arm of a radial maze to retrieve a food pellet, rarely if ever doubling back to paths they’d already explored.

Holguin’s tests suggest that the cocktail enhances the rodents’ ability to learn and remember. Under the staid surface of Wurtman’s lab, there is growing excitement that this cocktail could do the same in humans.

Even with the tantalizing possibilities of Wurtman’s drug, the three undergraduates do not relish the monthly Sac Days, which, like an ancient sacrifice, have their own rituals and rules. New lab assistants are exempt from their first sacrifice as they have inevitably become too attached to a particular batch of gerbils or rats. If someone has a favorite rodent, he or she can request not to operate on it. Was Sac Day somehow more difficult knowing that half of these rodents were highly intelligent, at least compared to their all-natural counterparts?

Intelligence, it seems, does make a difference in the way the lab assistants feel about the rodents. Camille, a sophomore neuroscience major, stole two gerbils from a
previous test group the day before they were scheduled to be sacrificed. As she biked home, they rode in a salad container balanced on handlebars. (Holguin gave Camille her blessing since the test group was uncommonly large and losing two gerbils would not affect the results.) “I hope they were given the drug and not in the control group,” Camille said, “because that would mean they’re smarter and might live longer,” a possible side effect of Wurtman’s drug.

After an hour of dissection, Camille removed a brain with a white, globular mass budding from a cerebral fold – an aneurysm, the likely result of a seizure. “Oh sweet,” she said sarcastically, “brain damage.” Then, noticing that this brain came from gerbil #27, Camille had a revelation. She remembered this gerbil as friendly and cooperative, never biting or trying to frantically escape her grasp. Now she suspected the root of its uncommon compliance. “That’s why he was so nice,” she said, “he wasn’t smart enough to be afraid.”

The lab assistant who had seen the most Sac Days was Joseph, a fifth-year senior who switched his major from chemistry to neuroscience. He was responsible for force-feeding this batch of rodents with DHA (the uridine and choline are administered in their diet). The process, called gavaging, required Joseph to grab the rodents by their nape, insert a syringe with a blunt end down their throat, and inject the liquid chemical compound directly into their stomach. The control rodents meanwhile get water.

The new drug is being developed with Alzheimer’s patients in mind. The degradation of synapses is a hallmark of Alzheimer’s disease. Wurtman’s cocktail is believed to help make more synapses, and perhaps delay the onset of symptoms such as memory loss. The drug is currently in human trials in Europe, where 10,000 Alzheimer’s
patients receive either a drink containing the three compounds or a taste-matched placebo. The drug could be on the market in five to ten years, according to Holguin.

Members of the lab are tight-lipped about the drug’s development. The reticence, they say, stems from legal concerns. Investors have been calling Holguin and her undergraduate assistants, attempting to sniff out the latest lab results and discover whether the cocktail is the real deal. Lab policy is to ignore such requests to avoid being charged with providing insider information.

But there may be something else at work. While feeding and weighing the rodents, Holguin and her lab assistants buzzed about the cocktail’s second, generally unspoken purpose. The same drug used to treat Alzheimer’s patients could be used to make ordinary people smarter.

A pill to turn average Joes into geniuses carries with it a range of ethical concerns. Would a smart drug be distributed equally, or doled out according to wealth and status? If you enhanced your intellect, would you be comfortable in your new brain? Would the drug alter your personality, your goals, your relationships? Would you be changed beyond recognition?

According to Holguin, the cocktail’s primary function as an Alzheimer’s treatment by and large absolves lab members from worrying about these ethical issues. But at some point, she says, “someone will have to deal with these questions.”

A drug like Wurtman’s cocktail could have the power to transform society, ushering in a new age in human history. But is this such a bright idea?

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As a science fiction staple, smart drugs and other means for augmenting human intelligence have been firmly ensconced in a far-away future. In the dystopia depicted in the film *Gattaca*, the genetic deck is stacked to produce children of physical perfection and intellectual brilliance. In *The Matrix*, characters can “plug in” to computers and instantly upload information to their brain, such as building blueprints or jujitsu know-how. Most examples of boosted brainpower in science fiction belong to a distant, foreign future in which man and society, eerily transformed by technology, are barely recognizable.

Yet over the past two decades, smart drugs, or rather their forerunners, have become a very real phenomenon. Ritalin, Adderall, modafinil and other brain boosters—prescription drugs that increase alertness and concentration—have become popular among students, businessmen, and other professionals looking for a competitive edge in a mentally strenuous environment.

Modafinil, generally prescribed to treat sleep disorders like narcolepsy, promotes wakefulness and improves focus without causing the jitteriness associated with amphetamines. The drug has been prescribed to aid workers coping with shift changes, allow businessmen to promptly recover from jetlag, and even help soldiers carry out exhausting covert operations. A 1999 U.S. Army study found that modafinil allowed pilots to stay awake and alert for 40 hours without suffering the ill-effects of sleep deprivation. Scientists are not exactly sure how the drug works, but studies suggest it inhibits the reuptake of dopamine and noradrenalin in the brain. Not surprisingly, modafinil has become popular among students pulling all-nighters before exams.
Still, the brain booster of choice for students is Ritalin, a stimulant with effects similar to caffeine, but far more potent. Ritalin amplifies the release of dopamine in the brain, thereby enhancing attention span and focus. With Ritalin commonly prescribed for attention deficit hyperactive disorder, students can often acquire the pill, and its promise of laser-like concentration, from a classmate with a legitimate prescription. According to the Partnership for a Drug-Free America’s 2006 study on drug use, approximately ten percent of middle school and high school students use stimulants such as Ritalin without a prescription. Like the cracked mirror image of the 1960’s counter-culture and its experimentation with “mind-expanding” drugs, this new form of drug abuse occurs in the name of overachievement.

The widespread appetite for brain boosters persists despite their limitations. The effect of these drugs is temporary, most often lasting a few hours, and their known side effects include loss of appetite and irritability (Ritalin), nausea and vertigo (modafinil), and insomnia and addiction (amphetamines). Yet the substantial underground market for brain boosters continues to grow, and their influence is beginning to spread.

Over the past eight years, the World Chess Federation has moved to implement mandatory drug testing in professional chess. Doctors now analyze the urine samples of grandmasters for traces of amphetamines, such as Adderall, and other drugs banned in physically demanding sports. Some in the chess community accept testing as a necessary concession if the game hopes to one day become an Olympic sport. However, many players bristle at the idea that drugs could improve something as rarefied as chess performance, which issues from irreducible genius, they would have it, rather than from a mix of chemicals in the brain.
This conceit, shaken by the emergence of brain boosters, may soon be hopelessly undermined by the next generation of smart drugs. While valued study tools, Ritalin and modafinil do not truly make people smarter. They permit greater focus and mental endurance by amplifying or prolonging the chemical interactions between pre-existing synapses in the brain. Neuroscientists racing to create a genuine smart drug are aiming to do nothing less than change the brain’s architecture, reshaping synapses in a long-lasting or even permanent way.

Over the past decade, small companies testing potential smart drugs have sprung up around star scientists in the field of learning and memory research. One such star is Nobel Prize-winning neuroscientist Eric Kandel, who joined forces with the German drug firm Bayer to found Memory Pharmaceuticals in 1998. Kandel began his career investigating the gill-withdrawal reflex in the Aplysia sea slug. The slug retracts its gill when squirted with water; yet after a repeated squirts, it stops reacting to the stimulus. The neural wiring behind this primitive form of memory, called habituation, helped Kandel understand how human memory functions at a molecular level.

One of the drugs being developed by Kandel’s company would raise the brain’s amount of CREB, a protein found to regulate the gene expression required for memory consolidation in fruit flies and mice. According to a developing consensus in the neuroscience community, memory results from structural changes in synaptic membranes that can increase or decrease the number and sensitivity of neuronal connections. Such synaptic modifications are tenuous, lasting only minutes or hours unless new proteins arrive to make the temporary changes permanent. CREB spurs the synthesis of these memory-preserving proteins.
In previous experiments, mutant flies, genetically altered to produce extra CREB, exhibited a “photographic” memory. According to some neuroscientists, CREB might explain the varying strength of memories. Why, for example, are some emotionally-charged experiences written permanently in our memory while quotidian details fade? Perhaps Kandel’s memory drug will burn the periodic table into students’ memories as vividly as their first kiss.

Like other neuroscientists developing cognitive enhancers, Kandel has stated that his express purpose is to treat those suffering from diseases. In the case of Memory Pharmaceuticals, the targets include dementia, schizophrenia, depression, and common age-related memory loss. Yet if the “secondary” market for brain boosters is any indication, many healthy people will clamor for access to a memory enhancer—and some will be willing to acquire it illegally. This latent demand for smart drugs has not been lost on investors: when Memory Pharmaceuticals went public in 2004, its initial offering garnered $35.4 million in investments.

With a commercial windfall at stake, a heated race is underway to see which company can clear the hurdles of the FDA’s phased trials and bring their drug to market first. Wurtman’s cocktail faces stiff competition in this regard: rivals include not only Kandel, but also Sention Inc. and Helicon Therapeutics, which also focuses on CREB. In More Than Human, computer scientist Ramez Naam reports, “In total, at least a dozen companies in the United States alone are pursuing some sort of memory-enhancing drug today. The motivation is a large and glittering market.”

So far, no drug has crossed the finish line; even those far along in the process still have years to go—that is, if they prove safe and effective in human trials. Perhaps
success in this race will depend less on the particular smart drug, and more on the person behind it.

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In his career as a neuropharmacologist, Dr. Richard Wurtman has been prolific and iconoclastic. His track record is impressive: over the past thirty years, he has generated patents for drugs treating mood disturbances, PMS, seasonal affective disorder, sleep disorders, and aging. He's also cultivated a reputation for being competitive and aggressive, if not bullish.

Wurtman makes a sport of exploding conventional wisdom. For example, his research has seemingly debunked the myth that Thanksgiving turkey, loaded with tryptophan, makes you tired. He places the blame on the carbohydrate-filled stuffing, gravy, butter, and pie, which elevate insulin levels and allow tryptophan to bring about its sleep-inducing effects on the brain. “But every Thanksgiving time, some idiot writes a story in the newspaper about how turkey makes you sleepy,” Wurtman says with characteristic pugnacity. Sugar high and runner’s high are other commonly held notions that he places in the same category as Bigfoot.

After graduating from Harvard Medical School in 1960, Wurtman undertook his clinical training at Massachusetts General Hospital. He went on to work at the National Institutes of Health in the laboratory of Julius Axelrod, who later won a Nobel Prize, and emerged to join the faculty at MIT where he is now the Cecil H. Green Distinguished Professor and director of the Clinical Research Center.
Along with the nutritionist Dr. Judith Wurtman, his collaborator and wife, he has undertaken a decades-long study of how diet can affect the brain. They have investigated how carbohydrates and proteins can cause fluctuations in neurotransmitter levels and discovered surprising applications to depression, blood pressure, and memory. Ordinary foods, besides drugs like caffeine and alcohol, were once thought to have no effect on the brain. The Wurtmans’ research was groundbreaking precisely because it contradicted this consensus view within the neuroscience community.

Their most highly publicized finding linked carbohydrates and the brain chemical serotonin. In the 1980’s, they proposed low-dose drugs to stimulate the release of serotonin, which their research suggested would reduce carbohydrate cravings and combat obesity. In the diet-crazy 90’s, Judith published a book based on their work, titled, The Serotonin Solution: The Potent Brain Chemical That Can Help You Stop Bingeing, Lose Weight, and Feel Great. Her husband, meanwhile, shared their findings with his MIT students, poking holes in their knowledge of the food-to-brain relationship, expounding the complex chemical cascade that results from consuming a cracker.

Wurtman seems to have brought the same against-the-grain spirit to his 30-year study of Alzheimer’s disease.

“Everyone talks about plaque,” he says, referring to the build-up of amyloid deposits on the surface of the Alzheimer’s ridden brain. Amyloid is an abnormal protein that causes neurites, the antennae of neurons, to wither and form toxic tangles. It is unclear what promotes the formation of amyloid, which cleaves from a larger protein that is produced naturally in all cells. Amyloid plaques have been the focus of scientists’ attention for years; according to Holguin, their physical prominence makes them easy to
study. Yet their role remains ambiguous. Do they cause the dementia of Alzheimer’s, or are they merely a symptom?

Wurtman believes his fellow researchers are missing the mark. He surmises that the mental deterioration associated with Alzheimer’s is caused not by amyloid but by the degradation of the brain’s synapses. Since synapses are the points at which neurons exchange information, a deficit would explain the accompanying impairment of memory and learning.

“Alzheimer’s patients lose synapses,” Wurtman says, pausing, as if daring anyone to challenge him. “How do I know? I went back into the literature and checked.”

Indeed, neuronal degeneration has long been associated with the progression of Alzheimer’s—though it has traditionally played second fiddle to amyloid plaques. In 1992, Wurtman and his colleagues examined brain tissue from deceased Alzheimer’s patients. They found a significant drop in the number of phospholipids, molecules that make up neuronal membranes. In the parietal and frontal cortex, for example, there was a 40-50% decrease in the amount of choline, as well as a 10-12% drop in major phospholipids. With fewer membrane components, neurons lacked the surface area to sustain the strong connections needed for normal brain function.

The same phospholipid drain was not evident in patients with Huntington’s disease, Parkinson’s disease, or Down syndrome. It was a phenomenon unique to Alzheimer’s. Wurtman set about creating a drug to restore these membrane components and save brain cells from shrinking into isolation. His undertaking has been encouraged by increasing evidence from other researchers that physical and behavioral dysfunction in Alzheimer’s patients occurs before the accumulation of amyloid plaques.
The uridine, choline, and DHA of Wurtman's cocktail serve as precursors for phospholipids. While the drug's rippling biochemical effects are complex, the strategy is relatively simple. The cocktail is believed to deliver the stimulus and raw materials needed for the growth of neuronal membranes. As these membranes elongate, the branching neurites will radiate farther afield, sprouting protrusions called dendritic spines that reach out to connect to other neurons. There's something vaguely vegetative about the process: the neuronal fibers, nourished by an enriching fertilizer, reach out like roots, grasping in extracellular space. More membrane, the thinking goes, means more neuronal encounters, more synapses, more relayed messages.

All three components, commonly found in a person's blood or diet, play a role in membrane formation. DHA, or docosahexaenoic acid, is an omega-3 fatty acid found in fish oil, eggs, flaxseed, and soybeans. As a building block for cell membranes, DHA increases sperm motility in men, preserves visual acuity by protecting retinal photoreceptors, and acts as the primary structural component of brain tissue.

Whether DHA, declared safe by the FDA in 2001, is beneficial as a dietary supplement has yet to be proven by long-term definitive studies. Yet that has not prevented manufacturers from making lofty claims about its effects. DHA supplements are advertised as a panacea to prevent or treat infertility, heart disease, mental decline, arthritis, depression, and ADHD. Americans spent $190 million on DHA pills in 2003 alone.

When I visited Vitamin World in Cambridge, Massachusetts, I asked for something to improve my memory. The clerk, a young man wearing a black tank top emblazoned with a skull and crossbones, led me past stacks of vitamins to the memory
wall. As I approached, the panoply of brain supplements looked like Warhol’s soup cans, except instead of Campbell’s labels there were brains—brains glowing, brains crackling with electricity, brains burning like sunrises. One ginkgo biloba package showed a twig inserted into the mouth of a silhouetted man, its leaves flourishing inside his otherwise empty cranium. Each supplement promised to deliver astonishing intellectual gains.

An ingredient in nearly half the supplements, DHA was ubiquitous. Printed small on the back of every label was the same message from the FDA: “These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.” This message acts as a disclaimer that allows companies to suggest scientific links that have not yet been proven. The same, it seems, applies to Vitamin World employees.

“This bad boy works wonders,” the clerk said, handing me Neuro-PS Gold With DHA, a pill bottle the size of a small coffee. The ingredients listed on the back included DHA and phosphatidylserine—a constituent of cell membranes and a “memory-supportive nutrient.” An asterisk floated above this last assertion, directing the consumer to the FDA’s qualification below.

The clerk gushed about Neuro-PS: “It boosts brain function. It sharpens mind, focus, memory, reaction time… everything. It could even help you live longer.”

People tend to buy Neuro-PS in bulk during sales, the clerk said. It’s easy to see why. One hundred and twenty soft gel pills go for $91.84. After a few minutes of comparison shopping, I noticed something strange. While the prices seemed roughly proportional across the board, the dosage fluctuated significantly. One DHA supplement advised consumers to take 100 mg once or twice daily. Another recommended 200 mg as
many as three times a day. Without a long-term study of DHA’s effect in humans, determining an appropriate dosage is still guess-work.

Yet as a commercial phenomenon, the supplements are thriving. Many now include antioxidants to eliminate the one known side effect of ingesting DHA: the unpleasant incidence of “fish burp.” Apparently, DHA purified from fish oil retains a certain essence of fish.

Not all supplemental DHA is sold in pill-form. Martek Biosciences, a DHA manufacturer, is trying to convince food makers to add DHA to their products, much as calcium is added to orange juice and cereal. Manufacturers of infant formula have embraced DHA—a natural ingredient of breast milk that is believed to aid brain development. One DHA-laced formula is Nestle Good Start Supreme. Recently, a Nestle representative contacted members of the Wurtman lab, expressing interest in the new drug. Perhaps they have visions of Crunch bars for the brain, memory-enhancing milk chocolate, or Kit-Kats that prevent infertility.

The chemical mechanism behind DHA has only recently been probed by scientists. A 2006 study at the MRC Laboratory of Molecular Biology (Cambridge University, UK) found that DHA activates a protein responsible for neurite outgrowth. Here’s where choline and uridine become essential ingredients in Wurtman’s cocktail. Choline, a nutrient found in meats, nuts and eggs, is a precursor to phosphatidylcholine (PC), a major constituent of cell membranes. Uridine, meanwhile, helps transform choline into PC. Holguin described choline and uridine’s role in the cocktail as “rate limiting”: without them, the DHA would be useless—a road builder without cement.
For the diseased brain, a city of collapsed bridges and crumbling highways, the cocktail could preserve memory and maintain brain function. Wurtman is quick to point out that his drug, if it works in humans, would be a temporary treatment for Alzheimer’s disease—not a cure. However, if the cocktail can help stave off the disease’s insidious effects for many years, it may be nearly as good. Many in the lab compare the drug to L-dopa, a chemical given to Parkinson’s patients to replenish low dopamine levels and reduce their characteristic rigidity and slowness.

“L-dopa is not a cure for Parkinson’s, but it can give patients a normal life,” Holguin says.

By replacing synapses snatched by the disease, Wurtman’s cocktail would offer a similar reprieve to Alzheimer’s patients.

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Over the years, Wurtman has gained a reputation for swiftly shepherding drugs through the FDA approval process. Raised in a family of lawyers, Wurtman seems to have inherited a legal shrewdness. According to Holguin, he hurries a drug from the research phase, in which it is tested on laboratory rodents, to human trials within five years—a lightning-fast pace, she says, that is rare in the field.

The way Wurtman sees it, his education makes him uniquely suited for this task. As an M.D., he has access to test patients that a researcher holding a PhD would lack. “I can hold my own as [both] a researcher and a clinician,” he says. “There’s a limited number of people who can do that in the world.”
When the time came to test his new drug on humans, Wurtman chose to conduct the trials in Europe, calling upon a network of researchers with whom he had previously collaborated. This transatlantic maneuver positioned Wurtman ahead of Kandel and many others, whose smart drugs are still in either Phase I or Phase II of FDA trials.

Phase I trials are small initial studies in which the blood samples and observation of around 20 to 80 healthy volunteers suggest whether a drug is safe and tolerable. The controlled clinical studies of Phase II evaluate a drug’s effectiveness and short-term side effects in a group that typically includes between 100 and 300 volunteers. Phase II is the bloodiest stretch of the FDA gauntlet: two-thirds of potential drugs in this stage are rejected as ineffective or plain dangerous.

For drug developers, Phases I and II suck up time and money, but are unavoidable—at least in the United States. In Europe, on the other hand, the FDA’s counterpart—the European Medicines Agency (EMEA)—has a “common sense” clause. If all the ingredients of a new drug have been approved as dietary supplements, a drug can leapfrog straight to a large-scale clinical trial equivalent to Phase III in the United States. Since DHA is sold in bulk at health stores and both choline and uridine are added to infant formula, Wurtman’s drug has immediately entered such a clinical trial. Ten thousand Alzheimer’s patients will soon be taking the cocktail at 21 facilities spread across 10 European countries. The results of this trial, together with information regarding rodent studies, manufacturing procedures, optimal dosage, and shelf life, will be submitted to the EMEA. If the drug is deemed safe and effective, the EMEA will grant a “positive opinion,” a recommendation that is sent to the European Commission, which ultimately approves a drug to be prescribed throughout the European Union. That, in turn,
would fulfill the requirements of the FDA, for whom the location of a clinical trial is considered irrelevant.

Wurtman is now working with an undisclosed pharmaceutical company that has taken out a patent on the drug’s specific concoction of supplements. The company is coordinating and presumably fronting the cost of the European trial, which may last between two and three years if no serious side effects surface.

Of course, as Holguin says, “Sometimes a drug that works well in animals turns out to be the worst thing for humans.” A recent example is TGN1412—an experimental antibody designed by a German pharmaceutical company to treat rheumatoid arthritis and other autoimmune disorders. When tested on monkeys and rats in the lab, the antibody caused no detectable side effects. On a Monday morning in March 2006, six men in a London hospital were injected with the drug in its first clinical trial. The dosage was 500 times lower than the dose found safe in animals. Within the hour, the men were convulsing in pain, tearing at their clothes and vomiting. In the next 48 hours, all six suffered multiple organ failure. The drug had triggered a devastating immune response—the opposite of the effect seen in animals. The men, who were paid around $4,000 for volunteering, survived, but were warned to expect an early death as a result of permanent damage to their immune system. The pharmaceutical company folded four months after the botched trial.

TGN1412 is an example of a drug that failed spectacularly and immediately in human trials. Some drugs, however, only reveal their side effects once they have passed the FDA trials. A Phase III trial with thousands of volunteers may not expose a side effect that occurs in a small percentage of cases. However, once millions of people are
taking the drug, thousands could experience a bad reaction. Five years after passing clinical trials, Vioxx was yanked from the market for possibly triggering what the FDA has estimated as between 88,000 and 139,000 heart attacks in the U.S.

In the aftermath of Vioxx, there has been a call for more rigorous post-approval surveillance, perhaps creating a kind of Phase IV trial when a drug becomes available to the public. Even if Wurtman’s cocktail satisfies the FDA requirements, a side effect could eventually emerge.

Still, many in Wurtman’s lab are convinced of the cocktail’s safety and efficacy. Nearly everyone—Wurtman included—has added a DHA supplement to their daily diet. Even Joseph, who is wary of who will truly benefit from the cocktail, pops fish oil capsules every morning. When asked if the pills make him smarter, Joseph shrugs, saying, “I hope so.”

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While clinical trials are prepared overseas, members of the Wurtman lab repeat their experiments, readying their data for publication in peer-reviewed journals.

Wurtman was wearing a festive pumpkin-colored shirt when they convened for a lab meeting on October 31, 2006. He had good reason to feel celebratory. Each of his graduate and postdoctoral students spearheads a different class of experiments, from behavioral to biochemical studies. Their work forms a constellation of knowledge about the cocktail and, at the end of October, the stars were aligning.
Two post-doctorate fellows, Mehmet Cansev from Turkey and Toshi Sakamoto from Japan, shared good news from the biochemical analysis front. While examining the rodent brains extracted by the undergraduate assistants, both Mehmet and Toshi found what they were looking for. In rodents that received the cocktail, the phospholipid count was up in the five brain regions that Mehmet studied, including the hippocampus and cortex—two areas vital to encoding memories. For example, the amount of phosphatidylcholine swelled 28% in the hippocampus—a statistically significant increase when compared to the control group. A similar effect was evident across the cerebellum and cerebrum, suggesting that Wurtman’s drug works equally throughout the brain.

Meanwhile, Toshi found that DHA generated 30% to 40% more dendritic spines in adult gerbils, the majority of which went on to form new synapses. As the DHA dosage increased from zero to 300 mg daily in gerbils, the density of their dendritic spines rose. A graph of this relationship formed what Wurtman deemed “a beautiful curve.”

Mehmet and Toshi’s data also demonstrated that the cocktail needs all three of its components to produce optimal results. Rodents that received choline, uridine and DHA were found to have a higher phospholipid spike and greater burst of dendritic spines than rodents that received only two of the three components.

Wurtman liked what he was hearing. Normally, he is not shy about critiquing his students’ science. But this time he could only reprimand his postdocs for not getting to the point fast enough: “Your presentation should start like Beethoven’s 8th symphony,” he said. “DAH DAH NAH NAH NAH … or you’ll lose your audience.”
Next to present was the soft-spoken Holguin, whose ream of statistics trumpeted successful findings in a series of rodent behavior tests—an ongoing project that has occupied her for over a year. The experiments are conducted in a small grey room, the walls bare except for a blue Egyptian hieroglyphic, a purple ying-yang, and the cartoon of a black cat. The rodents rely on these visual cues to navigate the polymorphic mazes that Holguin designs to test their ability to learn and remember. Lowering the rodents by their tails into the mazes, Holguin herself becomes a visual cue. As a result, she sits in the same corner during each experiment, sometimes for marathon stints of eight hours.

Holguin ran the latest batch of rodents through a radial arm maze. The gerbil or rat, dropped in the middle of an intersection of four radiating pathways, races to find a food pellet at the end of one arm. Denied food for almost twenty-four hours, the rodents are thus motivated to solve the maze as fast as possible. Some gnaw on their cage bars while waiting their turn in an adjacent room cluttered with unused equipment, a graveyard of past experiments.

To record each rodent's performance, Holguin notes how many trials are needed before it learns to quickly retrieve the food pellet by avoiding the arms that never contain food. Rodents fed Wurtman's drug mastered the radial arm maze in half the time of the control group.

No one in the lab meeting was surprised by these results—Holguin had run these tests before. But all were relieved. Animal behavior studies face intense scrutiny from the scientific community because behavior can be influenced by any number of subtle, unseen factors. Holguin repeats her experiments again and again, using both rats and gerbils to make sure, as Wurtman says, it wasn't a phase of the moon.
"The most difficult job in the lab is behavior," Wurtman says. "There's so many variables." For example, what if Wurtman's drug simply makes the rodents more coordinated and energetic, thus explaining their superior performance in the radial maze? So Holguin tests each rodent on the rotarod—a mechanical logroll that turns faster and faster until the rodents, slipping and clawing, fall into Holguin's open hands. In what might be the world's most peculiar work-out video, the rodent calisthenics are filmed to document that all test subjects are of equal physical dexterity.

The radial arm maze requires the rodents to memorize a straightforward spatial fact since the location of the food pellet is fixed. The results of this maze are directly applicable to Alzheimer's disease, which gradually erodes a patient's ability to remember facts or events.

Yet Holguin also put the rodents through a T-maze, in which they learned to turn left or right at the end of a long corridor depending on a visual cue. While the food pellet was randomly placed, Holguin always stood on the correct side of the maze. Their task, then, was to develop a memory reinforced by repetition—a habit, in other words.

A habit is less likely to be forgotten than a fact or event. While you may not recall the first time you rode a bike, you easily remember years later how to ride one. Studies have shown that procedural memory, which encodes skills and habits, tends to be largely spared by Alzheimer's, remaining intact until the very last stages of the disease. Other diseases, such as Parkinson's and Huntington's, are accompanied by a deterioration in habit-forming memory.

The T-maze, an odd choice for a drug meant to treat Alzheimer's, suggests Wurtman's wider hopes for the cocktail. At the lab meeting, Holguin submitted the T-
maze results, which proved just as significant as the radial arm maze. The cocktail, it seems, might treat a broad spectrum of diseases.

According to Holguin, Wurtman would rather not launch expensive and time-consuming clinical trials for each of the diseases the cocktail could treat. Instead, once the drug is approved for Alzheimer’s patients, a pharmaceutical company could make its versatility known to the medical community. At that point, doctors can prescribe the drug “off-label”—meaning for purposes that fall outside the drug’s specific indications as approved by the FDA. For a company to market its drug directly to doctors is illegal, Holguin says, but it is often the way things are done.

Wurtman’s cocktail could easily—and legally—be prescribed off-label. The FDA once required clinical trials to simply assess a new drug’s safety. In 1963, this policy was reformed to include effectiveness as well. To gauge a drug’s efficacy, drug companies had to stipulate which specific illnesses were to be tested. This was the beginning of the FDA-approved indications that now appear on drug labels.

Doctors are not held to these indications. Aside from certain controlled substances, like opiates, doctors are free to prescribe drugs as they see fit. According to a 2006 study by the Stanford Prevention Research Center, around 21 percent of all prescriptions are written off-label. For certain drugs, the percentage of off-label use is astronomically high. What keeps doctors from recklessly doling out drugs without solid scientific support is the threat of malpractice. Patients who have a bad reaction as a result of an off-label prescription have grounds to sue.
If Wurtman’s cocktail has no side effects—as many in the lab assert—nothing would prevent doctors from using it to treat a suite of diseases or complaints.

But the marketing scheme described by Holguin is still troubling, according to David Jones. An assistant professor in MIT’s Science, Technology and Society program, Jones also works as a staff psychiatrist at Cambridge Hospital. His office is lined with stacks of medical journals. The yellow vines of potted plants creep along the sill of a window that looks out over the Charles River.

Physicians can heed or ignore a drug’s indication, Jones told me, but the FDA prohibits drug companies from advertising their products for off-label use. Rising from behind his desk, Jones pulled from his bookcase a 2004 issue of The New England Journal of Medicine. After thumbing through the pages for a moment, he came upon an ad for Neurontin, a drug indicated to treat epilepsy and pain associated with shingles. The royal purple page depicted neurons on fire. The following two pages of the magazine were crawling with Neurontin’s fine print. This Neurontin ad was perfectly legal.

However, just a few years ago, Neurontin ran afoul of the FDA’s restrictions when its marketing company sent out a brochure touting at least 11 off-label uses. Psychiatric disorders, migraine headaches, pain management, a condition related to diabetes—all could be treated with Neurontin, the brochure claimed. Through such advertisements, Neurontin’s sales soared to $2.7 billion in 2003, and as much as 90% of its prescriptions were issued off-label. The drug company, Warner-Lambert, also tried to market Neurontin directly to doctors. For example, some doctors were paid to listen to pitches by Neurontin employees about potential off-label uses. Others were given free trips to conferences in luxurious destinations in Florida and Hawaii. In what Jones
describes as a landmark case, the FDA fined Pfizer, which had since acquired Warner-Lambert, $430 million for the unsupported claims about Neurontin.

If the pharmaceutical company that has partnered with Wurtman attempts to market the cocktail directly to doctors, it might be subject to similar fines by the FDA.

There are other methods, Jones says, that a company can use to promote the off-label use its drug. For example, some companies send employees undercover to talk to doctors. “I’ve been eating lunch in the cafeteria at [Massachusetts General Hospital] when a drug rep has sat down and raised suggestive questions about a drug,” Jones says. “It’s a very structured conversation. Ads can be easily regulated because they’re fixed, but conversations are harder to monitor.”

Other companies appeal directly to consumers. Cephalon Inc. recently applied for an “excessive daytime sleepiness” indication for their anti-narcolepsy drug Provigil. “The FDA said no because Provigil would be prescribed to 100% of the population and the insurance industry would go bankrupt,” Jones says. “Who doesn’t suffer from excessive daytime sleepiness? The FDA said there’s already a daytime sleepiness drug. Just drink coffee.”

But Cephalon, undeterred, has extended its message directly to consumers, meanwhile pushing the envelope of what’s legal. The Provigil website asks, “Do you feel tired even when you have had enough sleep? Do you often feel like you just don’t have the energy to do the things you need to do? If you think you may have excessive sleepiness, talk to your doctor.” Elsewhere on the site, a sleep questionnaire gives a list of situations, such as sitting and reading, and asks you to rate your chances of dozing off. If you answer a “slight chance of dozing” to all questions, you will have nearly earned a
diagnosis of potential excessive sleepiness. The website urges consumers to share the test results with their doctor. The company is careful to never explicitly claim that Provigil is a treatment for excessive sleepiness, but the insinuation is overwhelming.

“Wurtman will be walking the same fine line,” Jones says. “I can imagine their campaign. Have you ever misplaced your keys? Then you have a memory problem. This drug has been shown to improve memory in people with Alzheimer’s disease. Then they’ll let consumers infer the rest.”

At the Halloween lab meeting, Wurtman seemed without a care in the world.

“I wish I had champagne,” he said, urging all his lab members to write up their results for publication in Nutrition & Metabolism, Neuroscience, or “whatever has the biggest readership.” (Mehmet’s paper has since been submitted to Neuroscience, while Toshi’s paper was sent to Nature).

Although it was 11 o’clock in the morning, the urge to pop open a bottle of champagne seemed wholly appropriate. With the cocktail in human trials and the scientific groundwork all but laid, the end of their long collaborative project was suddenly in sight. Holguin will graduate within the year and seek a postdoc position at a lab researching the genetics of autism. And rumor has it that Wurtman will retire in the next few years.

“It’s been enormously frustrating to have so little to offer people that have Alzheimer’s disease,” Wurtman has said. His cocktail could bring hope to the estimated four-and-a-half million Alzheimer’s patients in America.
Yet that might be just the beginning of the story. More uses for the cocktail could be discovered: it could act as a treatment for Parkinson’s patients, a cure for senility, a helpful boost for the developing fetus. Perhaps long after Wurtman has retired, his drug, or one like it, will find an even wider market.

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No one knows exactly how biotechnology will transform humans and society in the years to come. Yet the most fervently argued versions of the future seem to pendulate between utopia and dystopia, nightmare and wish fulfillment.

Nick Bostrom, director of the Future of Humanity Institute at Oxford University, embraces 21st century technology with childlike wonder. In his 2006 essay, “Why I Want To Be Posthuman When I Grow Up,” the Oxford don muses about what life might be like after having your brain enhanced by technology. He writes:

You also discover a greater clarity of mind. You can concentrate on difficult material more easily and it begins making sense to you. You start to see connections that eluded you before... Your mind is able to recall facts, names, and concepts just when you need them. You are able to sprinkle your conversation with witty remarks and poignant anecdotes...Your experiences seem more vivid.... You begin to treasure almost every moment of life; you go about you business with zest; and you feel a deeper warmth and affection for those you love...

In 2003, the chairman of the President’s Council on Bioethics presented a much different vision of human enhancement. In “Ageless Bodies, Happy Souls:
Biotechnology and the Pursuit of Perfection,” Leon Kass rejects biotechnology as a path to dehumanizing perfection and a threat to human nature. Enhancement raises “the concern about ‘man playing God,’ or about the Brave New World,” he writes, and could be “a Faustian bargain that will cost us our full and flourishing humanity.”

For many bioethicists, a smart drug like Wurtman’s cocktail would be the first in a line of mind-expanding technologies just over the horizon. Through genetic engineering, our genes might be reined in and carefully selected for optimal intelligence. According to Ray Kurzweil, the prominent futurist and inventor, by 2030 nanobots will be nested in our brains, helping us to think faster, multitask, record and play back thoughts, and access full-immersion virtual reality. In his book Remaking Eden, Princeton biologist Lee Silver imagines a future where the prophesied limits of mental capacity are “swept aside” by technological advances.

Though many would consider these scenarios a technophile’s flight of fancy, an impassioned debate has ignited over science’s potential to transform our minds. It has generated activist manifestos, presidential commissions, and even a statement issued by the Vatican. Published in 2004, “Communion and Stewardship: Human Persons Created in the Image of God” warned that altering one’s intrinsic qualities is immoral. “The sovereignty we enjoy is not an unlimited one,” the document states. “Man is created in the image of God, but he is not God himself.”

As if in direct rebuttal, Natasha Vita-More’s “Transhuman Art Manifesto” champions our right to creatively transform ourselves using technology. “I am the architect of my existence,” she declares. Transhumanists, using their “unique ingenuity,” will “spread far out into the capillaries of our culture.” (The Vatican statement may have
reached a wider audience, but Vita-More was shooting for the stars. A copy of her manifesto, signed by hundreds of enthusiasts, is reportedly touring Saturn aboard the Cassini Huygens spacecraft.

With their acutely divergent attitudes, the Vatican and transhumanists represent the poles of the enhancement debate. In the newly emerging arena of biopolitics, critics of enhancement technology insist that there should be a limit to what people can do with their bodies. Proponents, on the other hand, dismiss the risks and argue for a free market when it comes to biotechnology. The divide resembles the culture war—but scrambled. Secular bioethicists and religious fundamentalists find common ground by professing the inherent hazards of enhancement. Libertarians and cyber-punks, meanwhile, crowd under the umbrella of unbridled technological progress. As in most debates, the voices at either extreme shout the loudest.

The problem with this intractable debate is the uncertainty of the future. How can we know the ethics of someone with superhuman intelligence when none yet exist? What, beyond wild speculation, can be said about a genius race that might rise from a primordial soup of silicon? Yet the tenor of the debate—whether shrilly catastrophic or zealously transcendent—is infused with an uncompromising finality, as if the answers had already been reached. There is little foundation from which to launch a fruitful discussion.

What is needed, it seems, is to find the right question. If the pill was set before you on a table, what should you ask yourself before pushing it away or downing it with a glass of water? An essential question that engages both sides could ground the debate, which so often diverges into imaginative theories about next-generation technology.
While many ponder the ethics of genetic engineering and nanotechnology, Wurtman’s cocktail—or a similar smart drug—could be our first real brush with biotechnological enhancement. The drug, touted as an Alzheimer’s treatment, seems to be advancing under the radar of those who fear such technologies. The possibility that a cognitive enhancer could arrive under the sheep’s wool of disease therapy is not lost on Leon Kass. At a meeting of the President’s Council on Bioethics in January 2003, Kass described how a dystopian future might take shape:

It bears emphasis that these powers and technologies have not been and are not being developed for the purpose of producing improved, never mind perfect or post-human, beings. They have been produced largely for the purposes of preventing and curing disease, reversing disabilities, and alleviating suffering... We must not be lulled to sleep by the fact that the originators of these powers were no friends to Brave New World. Once here, techniques and powers can produce desires where none existed before, and things often go where no one ever intended.

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“"The enhancement landscape has changed. People aren’t being so coy anymore,” says bioethicist Erik Parens. He points to Kandel’s Memory Pharmaceuticals, one of Wurtman’s most prominent rivals, as an example of the industry becoming more vocal about its intentions. “For the first time, Memory Pharmaceuticals has begun talking publicly and forthrightly about memory enhancement, rather than treatment for a disease,” says Parens. “Before you just assumed [the drugs] were for mild cognitive impairments and then, eventually, high school kids.”
Similarly, Sarah Holguin says that Wurtman’s cocktail will not be limited to diseased patients. “Our primary focus is Alzheimer’s disease,” she says, “but we can see the drug potentially heading to normal healthy adults.”

Critics are ready for a fight to suppress cognitive enhancers. According to George Annas, a lawyer and bioethicist at Boston University, the FDA could not ban Wurtman’s cocktail based on ethical qualms. “The FDA can only consider safety and efficacy in making a determination,” he says. “[A ban] would require a statutory amendment.” Whether a law would ever pass to prohibit smart drugs is unclear. But any legal blocks to cognitive enhancement could be flattened by an impatient public. In his *Reason* magazine essay, “The Battle for Your Brain,” Ronald Bailey gives an example from the 1960’s, when many states outlawed the birth control pill “on the grounds that it would be too disruptive to society. Yet Americans, eager to take control of their reproductive lives, managed to roll back those laws.”

The appeal of a smart drug will determine whether people clamor to make it legally available, and therefore could be critical to its success. Many futurists believe that the experience will be rapturous. Our brains, humming with newfound powers of pattern recognition, will see meaning where before there was chaos. We will deftly perceive a tree’s furled fractals, a symphony’s layered logic. According to Dr. Peter Whitehouse, a neurologist at Case Western Reserve School of Medicine, an upgraded brain would lend itself to “deeper reflection and enhanced wisdom.” He goes on: “Think Buddhist enlightenment also. Think intuition as an important enhancement.”

These predictions may be overstated when it comes to the memory boosters being developed by Wurtman and his rivals. Rather than spiritual illumination, they would offer
expanded memory and, Whitehouse says, an “ability to multitask better.” According to a
cognitive science rule of thumb, called the “magical number seven,” people can hold
seven chunks of information—such as numbers, words, or phrases—in their working
memory at one given time. If Holguin’s rodent tests are an accurate indication, the
cocktail could raise this number, allowing the mind to juggle many cognitive chunks
simultaneously. Nick Bostrom, the Oxford don, believes that a new appreciation for
complexity will entice people to swap gossip magazines for Proust and the latest issue of
Nature. Of course, the values he ascribes to the enhanced are suspiciously Oxfordian—
they might just as easily employ their remarkable working memory to play a demanding
and immersive video game. Whitehouse predicts that enhanced minds will crave more
intricate narratives—nonlinear plots that engage the intellect as well as emotions. He also
anticipates “expanded metaphor appreciation.” A one-to-one comparison will set off a
cascade of associations. Out of each metaphor, a Homeric simile will unravel.

But a sublime memory may not be the unalloyed good proponents claim.
According to Annas, there is value in both remembering and forgetting. “One would
think,” he says, “that people with so-called ‘photographic’ memories would have great
advantages in life, but they don’t.” He worries that an inability to prune memories could
increase incidence of post-traumatic stress. And who wants to vividly remember those
daily moments of embarrassment and disappointment that we normally brush off? An
enhanced working memory could precipitate a manic burn-out. Bernard Prusak, a
theology professor who has written extensively on cognitive enhancement, wonders
whether all the mental juggling will be overwhelming. “You don’t want to be constantly
remembering,” he says. “You want to be present.” A multivalent mind might be unable to
focus on a single task. If you’re busy spotting the Fibonacci sequence in a passing brick wall, for example, you might forget that you’re driving.

The effect of memory boosters like Wurtman’s cocktail will remain conjecture until clinical trials are undertaken. But one thing is certain: the lure of a profound intellect is potent and many will pay its costs. Especially if they feel compelled to keep up with others—whether colleagues, classmates, or family members—who have been enhanced.

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On a bitterly cold night this past February, I was making the rounds at a family party. When I came to my aunt Kerry and her six-week-old baby Kimmy, I noticed something strange. Kimmy’s eyes were locked on my face and her probing gaze followed me as I came closer.

“She’s so alert,” I said to my aunt.

“That’s what everyone tells me,” she said, shifting Kimmy to her other shoulder. “My doctor prescribed me a new prenatal vitamin while I was pregnant. It’s supposed to promote eye development and brain development. I think it worked.”

“What’s it called?” I asked.

“DHA,” she replied.

According to researchers in the Wurtman lab, DHA could dramatically boost a fetus’s still-developing faculties of memory and learning. Kerry’s obstetrician, excited about DHA’s potential benefits, recommended the supplement, insisting that it has no side effects.
“Kimmy was very active in the womb,” she recalls, “and now she’s by far my most alert baby. She was more awake earlier than my other three children. She follows people with her eyes and grabs things she wants—and she’s only a few months old.”

The DHA supplement was not cheap; it raised Kerry’s $10 monthly co-payment to $50. “I still went with it knowing it was the best thing for the baby,” she says. When Kerry recommended DHA to a friend who was also pregnant at the time, her friend balked at the price.

Many bioethicists worry that some children will be enhanced by a memory booster and others will not. If a drug like Wurtman’s cocktail becomes available to pregnant mothers, some simply will not be able to afford it while allergies or other health conditions could exclude others. A smart drug’s unequal distribution could be projected on the grand scale of the next generation’s intelligence. The arrival of such a drug, some fear, could send out ripples of deep social and economic stratification.

“If 10% of children get the drug, and their IQ is raised by 10 points, that gives them a huge advantage,” Holguin says. “Children who don’t get the drug might be naturally smart individuals, but now they’re on the low end of society. What happens to them?” Holguin also raises the issue of mothers who decide not to take the drug for ideological reasons, perhaps wanting their children to be “all-natural.” She asks, “Is it unfair to their children who face being left behind in society? Do we force mothers to take the drug? These are questions for people much wiser than me.”

And indeed bioethicists have long been fretting over the issue, wondering whether enhancement will amplify socioeconomic divisions or eventually split humanity into castes. This bio-Marxist vision is extreme, but Holguin’s scenario raises a plausible
opening through which divisions could creep into society. If some children are enhanced by Wurtman’s cocktail, a subtle hierarchy might develop within school systems, many of which already divide their students into levels based on intelligence and achievement. Will the gap between enhanced and unenhanced students widen so considerably that two segregated school systems are required? With IQ and education so closely correlated to socioeconomic status, do we really want to make some children smarter than others?

Theology professor Bernard Prusak foresees a culture even more consumed by competition. “You have to look at what would motivate parents to give their children better memories,” he says. “They want their kid to get into the best kindergarten, the best grade school, and then on to Harvard and MIT. It may not be in the children’s best interest to be thrust into a cutthroat society.” Smart drugs, which Prusak notes are tested on rats, would “intensify the rat race.”

“If you’re born with a better memory, you’re not going to complain,” Prusak says. However, if a memory booster’s ultimate effect is to transform society the way he predicts, who—no matter how brilliant—would want to live in it?

As a member of the President’s Council on Bioethics, political economist and prominent neo-conservative Francis Fukuyama advocated that biotechnology be limited to cases of legitimate sickness. “This general principle,” he wrote in Our Posthuman Future, “would allow us to use biotechnologies to, for example, cure genetic diseases like Huntington’s chorea or cystic fibrosis, but not to make our children more intelligent or taller.” To Fukuyama, a laissez-faire approach to biotechnology would radiate an unprecedented inequity, demolishing democracy and erecting an oppressive caste system.
in its place. Where transhumanists see opportunities for self-creation, Fukuyama sees intimations of master-race eugenics. Our only hope, he says, is to muster the self-control necessary and patently ban enhancement.

Yet the supposed line between therapy and enhancement is actually a fuzzy expanse of ambiguity. Cancer is certainly worthy of biotechnological treatment. But what about obesity, physical frailty, a below average IQ? Who, after all, will decide what requires therapy and what is “normal”?

Besides, one needn’t look to biotechnology to see inequality in action. As the college admissions game becomes more competitive, an industry has sprung up to help students get admitted to their schools of choice. This professional assistance, however, is pricey. Imagine a high school senior whose parents will spare no expense to see their child at Harvard. Besides the obvious monetary transactions—private school tuition, SAT prep courses, donations to the college itself—there are countless other advantages to be taken. For example, they could hire IvyWise, a New York-based consulting firm founded by Katherine Cohen. Cohen has a Ph.D in Literature from Yale, the good looks of an evening news anchor, and two books titled *The Truth About Getting In* and *Rock Hard Apps*. Her “platinum package” guarantees 24 advisory sessions and an hour of phone time per week—all of which is spent plotting how to get her clients into the country’s most selective schools. She helps her students craft pitch-perfect essays, places them in prestigious summer internships, and opens up her vast academic network for their use. Eighty percent of IvyWise students are admitted to their top choice. For Cohen’s services, parents shell out a one-time fee of $28,995.
Clearly, the playing field is already hopelessly tilted in favor of the wealthy. The IQ boost offered by a prenatal memory drug would be just one of the many advantages money can buy. And, as proponents of enhancement point out, new technology is often disseminated unevenly, bringing with it the potential to exacerbate social stratification. Cognitive enhancement may be no different in this regard.

So how will biotechnology be different from other technology, if not by its inequitable distribution? Fukuyama’s easy dichotomy obscures what is truly new about a smart drug. By rejecting an entire class of technology, he skirts the deeper issue of how a cognitive enhancer would affect the average person. According to ethicist Nicholas Agar, “the therapy/enhancement distinction shouldn’t serve as a shortcut to answers to questions about… what matters in human lives.”

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A sheep’s brain is about the size of an adult fist, but I remember it being much bigger. When I was in fourth grade, my parents drove me to a nearby school every Saturday morning so I could participate in classes like “Extreme Math” and “Blood and Guts.” The latter was a dissection-of-the-week class in which a group of ten-year-olds pulled on latex gloves and sank scalpels into cow eyes, among other anatomical curiosities. There was little guidance from the teacher; we were simply handed chicken legs and encouraged to “play.”

One Saturday, I cradled a sheep brain in my hands. The creased outer layer, the cortex, was tough and tan. It glistened with formaldehyde, the source of that alien aroma
filling the room. I raised my scalpel and hesitated. The deep fissure separating the
brain’s hemispheres suggested a natural place to cut. The brain opened like a sliced
orange and revealed the empty pockets of ventricles and a reef of white matter branching
within the cerebellum.

I took up the halves, one in each hand. The organ was fascinating, but I couldn’t
help feel the urge to juggle. They were just hunks of meat to me. How could this stuff be
the storehouse of memories, the fount of emotion, the slate on which our inner
monologues are written? To my ten-year-old self, the objects resting in my hands and the
thoughts swirling in my mind were irreconcilable. The idea that you could modify the
way a person learns or remembers by manipulating the brain would have seemed
laughable.

The same incredulity does not seem to apply to the innumerable other ways we
change and enhance our bodies. Cosmetic surgery, infertility treatments, organ
transplantation, diet pills, tanning salons—all are technologies that reshape us, and all
have been absorbed into the culture. So why does a drug that can sculpt the human mind
make many of us so ethically queasy?

Cognitive enhancers challenge some boundary that we intuitively recognize. The
molecular manipulations of a smart drug—what Francis Fukuyama calls “cosmetic
pharmacology”—could change qualities that are inextricable from who we are. A drug
that breaches the intimacy of our minds, compromising that seat of thought and memory,
may violate our sense of self.

This anxiety could stem from a resistance to seeing the mind as just another
organ. Since the Enlightenment, a bald materialism has steadily encroached on every part
of the cosmos—the brain, it appears, is the last frontier. Functional MRI machines are now being used to show in auroral vividness the blood-flow patterns in the brain. Scientists speculate that brain imaging techniques might one day be used to detect lies. As Fukuyama writes, “modern neuroscience has, in effect, lifted the hood and permitted us to peer, however tentatively, at the engine.”

Yet Fukuyama also points out what he sees as neuroscience’s limits. Material science, he writes, has thus far failed to explain subjective mental states—"the sensations, feelings, and emotions that you experience as part of everyday life." How after all does consciousness, and our experience of it, blossom from a knot of neurons? This enduring mystery has preserved the sense for many that our identity, and for some our soul, is separate from the body—a vestige of Cartesian dualism. The irreducible mind is a last bastion for human uniqueness, securing our position outside the world of matter.

Any drug that can infiltrate and rearrange our mind throws this distinction into question. A treatment somehow does not offend our sensibilities in the same way—perhaps because it seems to restore the mind to its natural state, its essence. But when an enhancement upgrades one’s learning and memory, the mind shakes off its inborn properties and is revealed, in the process, to be hardware—something physical, malleable. It is this possibility that sends shivers up the spines of many critics, spurring them to proclaim our minds off-limits to biotechnological meddling. They are not yet ready to give up the ghost in the machine.
With identity and enhancement so tightly bound, Wurtman’s cocktail confronts us with a difficult choice. It all boils down to authenticity—at least according to Erik Parens, a bioethicist at the Hastings Center in New York. Parens has written extensively about the ethical issues surrounding genetics, prenatal medicine, and enhancement. We are authentic, he writes, “when we exhibit or are in possession of what is most our own: our own way of flourishing or being fulfilled.” Faced with biotechnology, he says, staying authentic is our greatest imperative.

The “authentic self” is a murky concept, Parens admits. But it is also indispensable. Authenticity underpins the enhancement debate: both the knockers and boosters of enhancement believe that our inner self is sacrosanct. Our humanity, they insist, hinges on the freedom to be oneself. Whether biotechnology interferes with or facilitates this aspiration is the source of all the fuss.

The critics argue that “cosmetic pharmacology” detaches you from your true self. In Beyond Therapy, Leon Kass writes, “As the power to transform our native powers increases... so does the possibility for ‘self-alienation’—for losing, confounding, or abandoning our identity.” Proponents see the same technologies as a means for self-discovery and self-creation. Enhancement drugs would free the real person pent up inside us, confined by the arbitrary limits of our intellect.

The rhetoric of both sides may be overblown. “It’s like raising children,” Parens explains. “Sometimes you let them unfold in their own way and other times you shape them.” In public discourse, he goes on to say, passionate partisans make it seem like we must choose between the two—eschewing intervention or embracing the option of
creative transformation. In reality, he says, we operate in both frameworks, shuttling back and forth according to the situation.

Parens proposes Prozac as a test case. Does it hijack patients’ personalities, excising a vital albeit unpleasant part of them? Or does it liberate their true self from a cloud of depression? Parens predicts that the same questions will emerge if a smart drug like Wurtman’s cocktail appears. “If I am someone with a faulty memory,” he asks, “would a better memory somehow alienate me from myself?”

Some critics of psychotropic drugs argue that Prozac separates patients, however subtly, from reality. Would a smart drug do the same? Would an enhanced intellect act like a magnifying glass, bringing some things into intense focus, warping others, and ultimately robbing us of an essential wide-angle view of the world? Or, as many transhumanists allege, would a superior intelligence lay the world bare, revealing Nature’s interwoven harmonies in kaleidoscopic splendor?

A smart drug like Wurtman’s cocktail is unlikely to alter people’s view of reality, nor the unique way they interpret the world. Their new insights, associations and recollections might be background music that they willfully tune in or out. And while a memory booster could allow them to encode more vivid memories, the inner apparatus for managing and deploying those past experiences is all their own.

The mnemonic prodigies of the past offer an example. Truman Capote, with his knack for verbal retention, claims to have refrained from using a notepad and instead memorized entire interviews while researching *In Cold Blood*. But his eidetic memories, when recounted in the book, are colored by something distinctly Capotesque: a character’s brown eyes become "darkly translucent, like ale held to the light." Edgar
Degas would watch Parisian dancers rehearse for hours, then return to his studio to draw from memory. Would it be possible to mistake his dancers, realistically posed but awash in a pastel haze, for those of another artist?

A smart drug like Wurtman’s cocktail would almost certainly leave room for the self. The world may appear in higher resolution but one must still make authentic choices when interpreting and reacting to its varied landscapes. A piercing intelligence and prodigious memory—prized, sought after, and soon distilled in pill form—would not make the mind unfamiliar territory, but rather a deeper well in which to send thoughts echoing.

Future enhancements may cross these bounds. A network of nanobots could plant a virtual wedge between us and the world. Genetic engineering could squeeze our free will out of existence. Does it encroach on the authentic self? This should be our constant refrain, the question we put to each new marvel of biotechnology confronting us as we march into the future.

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On a dreary April morning, the twenty-five Alzheimer’s patients living at the Hearthstone at Choate care facility in Woburn, Massachusetts were gathered in a small common room. Members of the resident staff, many of them Haitian, sang Creole songs while setting breakfast. They stomped their feet, encouraging the elderly men and women to sing along. Rain drummed against the windows. A copy of the Boston Globe lay
folded on a table. The residents sat stiffly in their chairs, perched with heads bowed, faces hidden under shocks of white hair, all of them sleeping upright like owls.

Hearthstone at Choate is a home for Alzheimer’s patients who suffer from dementia and memory loss so severe that they require constant supervision. Life at Hearthstone provides a comforting structure and routine for the residents. Myra, the office coordinator, told me that each day has a regimen of activities—dancing, Bingo, gardening—with special holidays scattered throughout the month. “Last week we had a baseball cap day,” she said. “I was the only person who remembered to wear one.”

With its low ceiling and harvest colors, Hearthstone is designed to be cozy and, more importantly, easy to navigate. The private bedrooms and common room sprout from the stalk of a 150-foot hallway, which is trafficked by residents wishing to stretch their legs. The facility’s simple, linear arrangement makes it nearly impossible for residents to get lost. All exits are fitted with a keypad lock to make sure no one wanders off.

Prints of several famous paintings hang on the wall at one end of the hallway. The Museum of Modern Art sent a few dozen samples to Hearthstone and let the residents choose the ones that evoked memories and emotions. “We just asked them which they liked,” Myra said. The first two had obvious appeal: an exuberant, comic book-ish Lichtenstein and a Diego Rivera fresco with a coy-looking horse. But the third print came as a surprise. Andrew Wyeth’s haunting “Christina’s World” depicts a handicapped girl, paralyzed from the waste down. Marooned in a coarse field, she crawls toward a distant farmhouse.

Also lining the hallway are what the staff call “memory boxes.” A collection of personal mementos mounted in a glass box, a memory box hangs outside the door to each
resident’s bedroom. Most boxes exhibit a collage of photos: a sprawling family bunched together at a wedding, a row of children smiling on Christmas morning, the exterior of a snow-rimmed home. For many of the men, there is evidence of military service. Dog tags and medals dangle over browned photos of navy ships. One box displays a town government campaign flier. One woman’s high school valedictory essay is tacked up, still arguing after all these years that music is more potent than the spoken word.

I thought, at first, that the memory boxes helped residents, who can no longer read the name plaques, to find their way to the appropriate bedroom. But almost all are too sick to identify which mementos belong to them. At night, the staff must lead them to the correct bed.

Just ten miles south of Hearthstone is Dr. Wurtman’s Cambridge lab. His walls are adorned with photos of past students, impressionist paintings, a boat that he and his wife sail each summer from Boston Harbor to the tip of Cape Cod.

When reflecting on how he developed the cocktail, Wurtman claims to have worked backwards. “Most researchers start by asking what they can do for Alzheimer’s,” he explains. “I started by trying to discover a fundamental property in basic compounds. I saw how DHA, uridine and choline effect synaptic membranes. And I asked, now how can I use it.”

Alzheimer’s disease came to mind. The cocktail could help people with Parkinson’s, spinal cord injuries, and other maladies that involve a loss of neurons. The decision to target Alzheimer’s disease in particular was motivated, Wurtman says, by personal history. In the 1970’s, Wurtman met with colleagues in Zurich for the first
international meetings on Alzheimer’s disease. Dementia and memory loss had long been thought of as normal symptoms of old age; a diagnosis of Alzheimer’s was reserved for patients showing these symptoms before age 65. After Zurich, Alzheimer’s disease came to include people of all ages who exhibit the disease’s common pathology.

Wurtman’s early involvement with the disease fuels his sense of mission today. Since those initial meetings, plaque and tangles have been the bull’s eye for researchers—a strategy that Wurtman regards as a failure. “It’s been 25 years and [the study of plaques and tangles] hasn’t led anywhere,” he says. His hopes for the cocktail are high—both as a treatment and as a way to refocus the efforts of other researchers. “I can’t think of another strategy that increases the number of synapses per cell. If [the cocktail] works, attention will shift 180 degrees.”

An Alzheimer’s patient, like those at Hearthstone, would seem to have little in common with an ordinary person deciding whether to take a smart drug like Wurtman’s cocktail. Yet a kind of inverted kinship links their situation. For example, “enhanced” is a term also used at Hearthstone, though it has a very different meaning from people augmented by biotechnology. Following Myra on a tour, I passed a small dining room off the main hall. Inside, four old women sat giggling around a table as a resident staffer passed around shells and blocks. They were part of Hearthstone’s Enhanced Life Program for people in the latest stage of Alzheimer’s.

“‘Enhanced’ patients can no longer feed themselves or verbalize,” Myra said. Therapy focuses on sensory stimulation, such as hand massages, object handling, and exposure to pleasurable scents. I asked Myra if the scents were meant to act like smelling
salts. Not quite, she said. They do not rouse the enhanced patients to awareness, but rather engage what limited faculties they retain. A fleeting waft of grapefruit—an impression, a moment—is how the residents can experience the world. Without memory, they live almost entirely in the present. Without memory, the montage of the past—and what we call a sense of self—is lost.

If it works, Wurtman’s cocktail could preserve the identity of Alzheimer’s patients. It could rescue from the disease’s grasp the constellation of memories that make them who they are. But it also has the potential to throw into chaos the identity of ordinary people hoping for a brain boost. In both cases, a sense of self has to be protected. This is the difficult territory through which we must tread if Wurtman’s drug becomes available. Whether “enhanced” in either sense, we should always be able to walk down a hallway of memory boxes, recognize the collage of our life, and open the right door.
Acknowledgments

I would like to thank my thesis advisor, Robert Kanigel, whose thoughtful criticism and unrelenting support prodded this thesis into its present form.

A debt of gratitude to Dr. Richard Wurtman for welcoming me into his lab and to Sarah Holguin, a gracious guide and teacher.

Thanks also to my six classmates, who alone know the etymology of “curmur.” The answer may surprise you.
Selected Works


Cansev, M., Wurtman, R.J. “Chronic administration of docosahexaenoic acid or eicosapentaenoic acid, but not arachidonic acid, alone or in combination with uridine increases brain phosphatide and synaptic proteins levels in gerbils.” Neuroscience. submitted, 2007.


Sakomoto, T., Cansev, M., Wurtman, R.J. “Oral supplementation with docosahexanoic acid and uridine 5'-monophosphate increases dendritic spine density in adult gerbil hippocampus.” Submitted for publication, 2007.


Selected Websites

IvyWise: Empowering Students to Achieve their Academic and Personal Goals.  
<http://www.ivywise.com>


Provigil Home. <www.provigil.com>

Selected Interviews

Richard Wurtman, Cecil H. Green Distinguished Professor of Neuropharmacology at Massachusetts Institute of Technology

Sarah Holguin, graduate student in the Brain and Cognitive Sciences department at Massachusetts Institute of Technology

David S. Jones, staff psychiatrist in the Psychiatric Emergency Service at Cambridge Hospital, assistant professor in the History and Culture of Science and Technology at Massachusetts Institute of Technology

Erik Parens, adjunct associate professor in the Program in Science, Technology, and Society of Vassar College, associate for Philosophical Studies at The Hastings Center

George Annas, the Edward R. Utley Professor of Health Law and Chairman of Health Law Department at the Boston University School of Public Health

Peter Whitehouse, professor of neurology at Case Western Reserve School of Medicine, Staff Neurologist at the University Memory and Aging Center

Bernard Prusak, Lawrence C. Gallen Teaching Fellow in the Humanities at Villanova University

Mayra Alvalle, Executive Director of Hearthstone at Choate

Rebecca Dresser, JD, Daniel Noyes Kirby Professor of Law, Professor of Ethics in Medicine, Washington University Law School