Molecular Inference of Wisdom*

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Wisdom is a human trait upon which natural selection creates evolutionary pathways from the molecular biology of the gene, to the cellular organization of nervous system, to the physical functioning of the brain — and the transit is a two way street. Wellness is a selection advantage at every level. Molecular wellness is innate, though often compromised because selection is blind; intellectual or high level wellness is learned behavior fed back to the molecular level as a kind of vision. The wisdom of this is that lifelong wellness — to the point of dying healthy — is a goal for every person and every society because it precedes and influences all other achievements.

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Did you know that Fermilab, the world-renowned particle physics facility in Batavia, IL, outside of Chicago, has a bison herd on its campus? This seems curious for a place where work focuses on the discovery and measurement of subatomic particles. Their research has nothing to do with bison; rather the herd is there as a symbol of the frontier, just as it was for 25 years on the US nickel and still is today on the US \$50 gold coin. Fermilab sees itself on the frontier of high energy physics. But this is not a simple coincidence. The lab's first director, Robert Wilson, was born in the town of Frontier in southwestern Wyoming and arose in his career during the flush times for science during the presidency of John Kennedy which was known as "the New Frontier." But, there's an earlier link. In 1893, at the Columbian Exposition in Chicago, historian Frederick Jackson Turner presented a talk that had profound and long lasting influence on American intellectual life. Its title was "The Significance of the Frontier in American History."

Turner argued that pioneers moving into an undiscovered space created a new expression of democracy, with both good and ill characteristic, such as a strong desire for independence, along with a high degree of violence. He portrayed the frontier experience as a kind of evolution. Later generations modified but did not wholly supplant the theme that a

frontier, open for opportunity, is a desirable condition that becomes more complex over time. Today, we search for new frontiers and they exist among the stars, in the unexplored depths of Earth's oceans, and in ourselves. Self-knowledge may be the ultimate frontier. In this talk, I'll propose a frontier thesis of the brain as a way highlighting what earlier speakers on this program have "pioneered." First, though, let me explore with you the molecular inference of wisdom.

Wisdom is an observable human trait and always has been, or at least since Confucius, a half millennium before Christ. Confucius wrote "By three methods we may learn wisdom: first, by reflection, which is the noblest; second, by imitation, which is the easiest; and third, by experience, which is the bitterest." He also noted "Wisdom, compassion and courage are the three universally recognized moral qualities of men." By all accounts Confucius possessed and displayed great wisdom in his "day job" as an administrator of agricultural affairs. His recorded genealogy is the oldest of any person, coming to the present with a boy born in Taiwan in 2006. It would be interesting to know if wisdom has any measurable heritability through 80 generations.

Besides being observable, wisdom is highly distributed in nearly all people. Rene Descartes made a joke of this, pointing out that the most widely distributed trait in the world

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also means no one brain possess very much of it. While we know that wisdom is highly variable, it comes in two intellectual “flavors:” the individual, and the cultural. On the low end of individual wisdom is the folk expression, “common sense,” and one of the great purveyors of this form was Benjamin Franklin in the utilitarian pamphlets he printed annually between 1732 and 1758, known as “Poor Richard’s Almanack.” Among dozens of homely homilies he compiled were “Early to bed, early to rise, makes a man healthy, wealthy and wise,” and “Drink does not drown Care, but waters it, and makes it grow faster.” He once summarized these as “the Thirteen Virtues,” which, like “the Ten Commandments” offer wisdom for every day private life.

But individual wisdom also has a higher order in things like “inspiration,” “intuition,” and “insight.” It may be possible, as the 19th century phrenologists supposed, that some forms of thinking are localized in the brain, but that seem improbable. Higher orders likely involve the entire brain and for now remain as mysterious to us as the oldest light in the universe, though the latest finding about the oldest light was just announced last month. It comes from the flash within the first trillionth of a trillionth of a trillionth of a second after the “Big Bang,” and it has been traveling outward for about 13.8 billion years. An expanding rather than contracting universe is supposedly a good thing.

Scientific inquiry, of course, has been a great source of wisdom. Galileo’s observation about our sun-centered solar system produced the fundamental wisdom that, as much as some wanted to believe that the sun revolves around Earth, science proved otherwise. But science isn’t infallible, as we can see in a 1927 US Supreme Court case, “Buck vs. Bell.”

Carrie Buck was a young woman, whose mother had a criminal record for prostitution. Both lived in Augusta County, VA. When Carrie was known to the local authorities to have had a daughter out of wedlock, she was charged with “feeble-mindedness” under the 1924 Virginia eugenics law that prescribed compulsory sterilization for people deemed intellectually disabled. This law was the product of some of the most scientific advanced “wisdom” of its day. The term eugenics originated with Charles Darwin’s cousin, the biometrician Sir Francis Galton in 1883. It meant “well born.” Of course, it also implied that some were not so well born, and questions arose over how to detect and measure fitness and what to do about the “unfit.” Some of the early thinking about solutions were castration and spaying, just as farmers did with livestock. An American, zoologist Charles Davenport from the University of Chicago became a leading proponent of eugenics research and policy. In 1910, he established the Eugenics Record Office on the grounds of the biological research station at Cold Spring Harbor, NY (later becoming the Cold Spring Harbor Laboratory — one of the major hearths of the

A 19th century phrenology model.

genetics research world). Among his activities were sending out field study groups to gather data on curious and possibly unfit individuals and populations. He and his successor Harry Laughlin also promoted so-called “Fitter Families for Future Firesides” contests at state fairs, particularly in the Midwest, where there were lots of Northern European stock, considered to be the fittest. Generally speaking, this was a more advanced form of phrenology. Laughlin wrote the “Model Eugenic Sterilization law” in 1922, aimed at the insane, idiots, imbeciles, and epileptics, which became the Virginia law’s inspiration. Not stopping with that, the Virginia General Assembly also legislated its “Racial Integrity Act” which forbade interracial marriages until it was overturned in 1967. Under the sterilization law, Virginia performed “neutering” surgeries on 6,683 people (4,043 women; 2,640 men). Most were poor whites, including one, Carrie Buck. Her case had gone from county to state courts, and then up to the US Supreme Court, where Associate Justice Oliver Wendell Holmes, Jr. wrote the majority opinion that the state had an interest in the society’s “gene pool” which outweighed an individual’s body privacy. He thought compulsory sterilization was no different from compulsory vaccination. And, supposing that Carrie, her mother and daughter were probably all feeble-minded, he concluded with the memorable line “three generations of imbeciles are enough.”

The Eugenics Movement was not confined to Virginia or even the United States. Many countries including Canada,

the molecule that natural selection worked upon, was selfish about its own survival. He didn't mean this in an anthropomorphic way, but rather that units of DNA competed and the fittest for a particular environment prevailed and continued on to the next generation. Classic Darwinism. The less fit perished or at least remained dormant until the environment changed. Dawkins has been challenged and even vilified for his views since there is philosophical weight to the notion that the bedrock character of life is selfish, even though he explained how selfishness can lead to autism through complexity. In a sense, Dawkins implies that the thing genes are selfish about is their wellness, which is fundamentally an adaptation for survival. Ironically, this comes close to the well-born meaning of eugenics.

About a decade after *The Selfish Gene*, geneticist Christopher Wills at the University of California in San Diego published a book proposing that "the rapid evolution of our intellects has been facilitated by the ways in which the genes controlling development of our brains are organized. And, as with everything else in evolution, increases in intellectual ability have happened more than once." The title he chose was *The Wisdom of the Genes*. Like Dawkins he didn't imply an anthropomorphic "wisdom," but rather that the accumulated ability of genes to evolve in some cases and not evolve in others, represents a fundamental wisdom. This, of course, happens in the context of cells — neurons, for our purposes — and it's possible that the neurons of the autonomic nervous system are better at not evolving because they are always "on" for maintaining blood pressure, respiration, and other things, while the neurons of the frontal lobes are better at evolving for intellectual performance. Wise genes evolve into well genomes, which include well-wise neurons. I'm using wellness and wisdom as interchangeable terms, because that's the molecular inference.

In 1958, Francis Crick gave us what's called "the central dogma of molecular biology" which, simply put, is DNA makes RNA makes protein. We now know that this pathway is a two way street, and almost daily neuroscientists report congested traffic patterns. Earlier this spring, for example, the FANTOM consortium, headquartered in Japan reported how expression of the same gene differs according to its tissue location. What varies is the point in messenger RNA where protein synthesis begins. The gene for the dopamine active transporter protein, for example, is located on human chromosome 5, with 15 exons, spanning some 64,000 base pairs. Messenger RNA transcribes this gene, but the translation into protein can begin at different points depending on whether the expression is taking place in, say, the cerebral cortex, cerebellum or elsewhere. Mistranslations, polymorphisms and post translational modifications, such as methylation, are possible causes of or contributors to bipolar disorder, depression, and attention deficit-hyperactivity syndrome. These conditions may inhibit

wisdom, prevent it, direct it into a different pathway, or conceivably even promote it, as might have been the case with depressives like Abraham Lincoln, Charles Dickens and Leo Tolstoy, or biopolar sufferers such as Ludwig von Beethoven, Winston Churchill and Isaac Newton.

One more point about traffic patterns. Pyramidal neurons are cells found in the brain's cerebral cortex, hippocampus and amygdala, which are implicated in the cellular basis of wisdom. Santiago Ramon y Cajal, the Spanish pathologist called "the father of neuroscience" and winner of the Nobel Prize in 1906, discovered pyramidal cells and illustrated them as having a triangular shaped axon, with a long dendrite extending from its apex that branches as it moves out, and shorter base dendrites with branches. Both dendrites have spines which increase the impulse input from other cells while the axon serves output. Over the past several years, a group at Ludwig-Maximilians University in Munich has figured out how that input works. Microtubes run the length of the dendrites and axon, and function much as highways. Motor proteins called kinesin move molecular cargoes in one direction, toward the axon tip; while another, dynein, move them in the opposite direction. The cargoes are neuronal ribonucleoprotein granules which release their messenger RNA component at specific dendrite spines. These messenger molecules result in protein synthesis the reconfigure the shape of synapses. As the particles transit from one dendrite to another the sites of messenger RNA release become repeatedly activated in developing a memory for the delivery route. Even here, driving and texting don't happen simultaneously without dangerous consequences. In fact, the driving proteins repress the "texting" RNA from activating, which indicates that transport and translation are discrete processes. Otherwise, RNA-binding proteins might crash into what we call Alzheimer's and Parkinson's diseases. Over time, even without accidents, the delivery vehicles, their cargoes, and even the highways show wear and tear, which are part of natural aging. Environmental factors can alter this traffic pattern, but like highway safety, the wisdom of the genome has wellness as its original intent.

Researchers at Ludwig-Maximilians University who gave us insights into the ribonucleoprotein traffic patterns relied on antibodies to sort out the proteins of those granules. This technique built upon the work Gerald Edelman did at Rockefeller University in the 1960's and for which he and Oxford University biochemist Rodney Porter shared the 1972 Nobel Prize. In proving that antibodies are made of variable heavy and light chains of amino acids, Edelman and Porter explained how the immune system works. Further, with each cell division slight changes in the DNA coding generated further variation which natural selection worked upon to achieve in Edelman's words, not survival of the fittest, but survival on average of the fitter — that is, a more gradual rate of

evolution. He might well have spent the rest of his career in immunology, but the model of antibodies binding to cell surface antigens took him down another path to the discovery of adhesion molecules on cell surfaces which allow cells to form tissue. As subsequent studies showed there are four major families of cell adhesion molecules, the largest being the 765 members of the Immunoglobulin superfamily, which besides adhering cells to one another carry out signaling for growth and development including synapse formation. Here is another level of diversity for natural selection to act upon, and Edelman thought that neural evolution worked through three kinds of selection with one constraint. He saw “developmental selection” creating functional but heterogeneous neuronal groups, suggesting that no two people had exactly the same synapse construction; then, “experiential selection” from which memory develops involving multiple locations in the brain; and “reentry” where development and experience interact, resulting in a higher order of selection. Just as antibodies can react to antigens they have not encountered before, higher order selection produces the brain capability that transcends the molecular to the cellular level. He also added one more factor — value system which constrain selection processes by introducing biases, one of which may be the Dawkins’ “selfish” impulse. An important implication of Edelman’s interpretation of neural Darwinism is the molecular inference that wisdom is widely distributed within the brain — virtually a whole brain phenomenon, which isn’t surprising except that since the 19th century localization has been a main theme of neuroscience.

We are so sure that the brain is the seat of all mental processes that it’s hard to imagine that for most of history that wasn’t the case. Aristotle, contradicting both his teacher Plato and Hippocrates, proposed that the heart guided emotions and possibly the heart, liver, spleen and kidneys were responsible for all things biological. He thought the brain was simply a radiator that cooled the heart. Aristotle’s interpretation became what was known as “humoral theory” which held that a careful balance of four fluids — blood, phlegm, black bile and yellow bile — explained wellness and imbalance, illness. From this model comes the heart representing love, and sayings like “keep a cool head,” and “gut intuition.” Today, when we muse over melancholy as Robert Burton did in 1621 in the first book about the anatomy of melancholy, we are using a word that literally means black bile. Humoral theory gradually eroded from explorations of the nervous system, the brain’s topography and the mind’s “nature,” but it was a philosophical map from the individual to the cosmos for about 2,500 years.

In the 19th century, along with the scientific revolutions that arose from Darwin, Mendel, and Pasteur, we have a theory called “phrenology.” German physician Franz Joseph Gall was the first popularizer of the notion that bumps on the

skull, which resulted from bone protrusions into the brain, revealed specific functions of the mind. He concluded that the brain actually was not one organ, but rather 27, each with a specific location and mode of activity. With a slightly later proponent, Johann Spruzheim, phrenology spread in Europe and America, and with it localization interpretations of the brain and the mind’s moral concepts. This has an interesting history that leads into eugenics, but that’s a story for another day. Fast forwarding to the present, we have two California psychiatrists publishing in *The Archives of General Psychiatry* (2009) on the “Neurobiology of Wisdom?: A Literature Overview.” Actually, with fluorescent markers like GCaMP6, and functional neuroimaging, the literature traffic is getting heavy. PubMed has more than 26,000 full text journal articles under “wisdom,” though more than a few are by authors named Wisdom — Jennifer, Ronald, Amy and William, who often are neuroscientists of one kind or another. After their literature overview, Thomas Meeks and Dilip Jeste reached these conclusions which I’ll quote:

“The prefrontal cortex figures prominently in several wisdom subcomponents (e.g. emotional regulation, decision-making, value relativism, primarily via top-down regulation of limbic and striatal regions. The lateral prefrontal cortex facilitates calculated, reason-based decision-making, whereas the medial prefrontal cortex is implicated in emotional valance and prosocial attitudes/behaviors. Reward neurocircuitry (ventral striatum, nucleus accumbens) also appears important for promoting prosocial attitudes/behaviors. Monoaminergic activity (especially dopaminergic and serotonergic), influenced by several genetic polymorphisms, is critical to certain subcomponents of wisdom such as emotional regulation (including impulse control), decision-making, and prosocial behaviors. . . . Wisdom may involve optimal balance between functions of phylogenetically more primitive brain regions (limbic system) and newer ones (prefrontal cortex). Limitations of the putative model are stressed.”

It would be unfair to simply characterize these observations as old phrenology way-finding on the new sophisticated map of human brain science. But it does illustrate that from antiquity to our time philosophers and scientists have argued over whether or not the brain and the mind were one in the same or separate, whether mental processes are localized or distributed over the whole brain, and whether or not neurons alone explain consciousness and concepts like wisdom. These debates have lasted so long because the ultimate question is whether or not the concept of the soul is real. If the molecular inference of wisdom is selfish wellness, souls don’t need an explanation. Molecular actions explain everything. If it’s altruism, inference supports religious belief, which is a direction Meeks and Jeste move

A PET scan showing 97 regions of the brain recently discovered. Image courtesy of The Berkshire Eagle (<http://www.berkshireeagle.com/stories/updated-brain-map-identifies-nearly-100-new-regions,201373>).

in whether intentionally or not. Still, to give religion its due, it was Job's "Poem of Wisdom" in the Old Testament (Job, 27:12) which asked "But where shall wisdom be found? And where is the place of understanding?" Job, Ecclesiastes and Proverbs make up the Old Testament's so-called "wisdom literature." It's worth knowing these three books don't entirely agree on the means to wisdom.

Between Job's question and our understanding of neurobiology, the context of wisdom and wellness which interests us most is the individual, specifically personality, because it's closest to our desire for self-knowledge. Personality is what distinguished people from things. It's not a single quality, but an assemblage and often seen in negative terms. In the Oscar Pistorius murder trial, for instance, the prosecutor painted Pistorius as narcissistic, without empathy, paranoid and a liar — trying to establish guilt by personality.

It's safe to say that personality emerges from brain chemistry, in which neurotransmitters are the pace-setters. German-born pharmacologist Otto Loewi discovered the first neurotransmitter in 1921, but interest grew after World War II, in part due to genocide committed with nerve gas. Two neurotransmitters that seem crucial to presenting wisdom are serotonin and dopamine — the former first explained in the work of Betty Twarog at the Cleveland Clinic in 1953, and the latter, by Arvid Carlsson at Lund University in 1957. Before discussing these, we must again recognize the complexity involved. Multiple genes are involved in dopamine and serotonin expression, emitting, reception and control — as they are encoded on two chromosomes in each instance. Mutations, promoters, copy number variations and post translational modifications of the DNA induce variation from the start. Then there are generalizations about their action that are often vague or contradictory. So, we have to explore with caution.

Fifteen years of exploration followed Twarog's discovery which turned out to be a pathway to socialization. In the brain, serotonin influences mood, and plays a role in memory and learning. Too much of it has been linked to obsessive-compulsive disorder; too little, to depression. The antidepressant drugs Prozac and Zoloft work by retarding serotonin reabsorption in neurons which diminishes depression to the point of reversing it to a sense of well-being. That is the simple version of a protein which is generated in cells of the brain stem. It does its work through other proteins: the serotonin transporter which transits the extracellular space to at least seven different cell surface receptors, and monoamine oxidase-A which breaks down serotonin. In the case of the transporter, a gene on Chromosome 17, has a promoter sequence of 22 DNA bases, with either fourteen or sixteen repeats — the so-called "short," low expressing, and "long" high expressing versions. Studies have shown that the sixteen repeats result in what the ancients would have called a "sanguine" personality, coming from more serotonin circulating in the brain. The monoamine oxidase-A gene, on the X chromosome, has thirty bases in its promoter region which are repeated between two and six times. High expression levels have been linked to depression disorders, low expressions (resulting in greater amounts of serotonin, dopamine and noradrenaline) have been associated with impulsive aggression and violence.

Dopamine and serotonin are both monoamines — dopamine deriving from tyrosine; serotonin from tryptophan. Both are degraded by monoamine oxidase-A. And, as with serotonin, too much or too little dopamine has behavioral consequences. A deficiency can "freeze" personality; short of that, it causes indecisiveness. The best known deficiency is the absence of dopamine in the substantia nigra which causes Parkinson's disease. People with heightened dopamine levels are thought to be adventurous, thrill-seekers, and schizophrenic at hyper levels. The dopamine receptor gene, on Chromosome 11, has copy number repeats, where the greater the number the less effective the receptor is at capturing dopamine. Too much dopamine may explain what drives parachutists to jump off skyscrapers or people in barrels to go over Niagara Falls.

Autism, in some cases, derives from too much dopamine. Autistic symptoms can appear during infancy, when the baby won't hold eye contact with its mother or does not want to be held. A little older and they remain emotionless, except for fits of rage when their compulsive routines are disrupted. As adolescents they do not seek kindness from others, nor do they show compassion to others. They usually have difficulties with language — in learning to read, word use, and speech. "Autism" went unnamed until 1938, when Hans Asperger in Vienna coined the term, meaning self,

though Martin Luther may have encountered an autistic child whom he thought was Devil-possessed, and the Wild Boy of Aveyron fits the symptomatic description. This was a lost child of the French Revolution who lived alone for seven years in the wilderness. He was about twelve when of his own accord he came into a town. A young physician, Jean Itard, took him in, and named him Victor. Curiously, Victor became a kind of celebrity of the European Enlightenment, as natural philosophers speculated over qualities that distinguished people from animals. Itard specifically looked for language ability and empathy in Victor; he found some evidence, but not much of either. Carl Linnaeus speculated that Victor might belong to another species, “*Homo ferus*” (a feral human). Rousseau and Decartes dug for a deeper “nature” of humans, as in Decartes’s famous line “I think, therefore I am.” But in Victor’s case, the philosophers who found wisdom in nature did not take him as a reasoning human who could be civilized. He was a kind of sub-human, though above the animals. On a larger scale, the same interpretation supported empire-building with so-called “uncivilized” native peoples’ lives. Victor died in Paris at age 42.

It seems quite probable that Victor was autistic, but impossible to know why. Dopamine is implicated with some autistics, but so too is serotonin. Researchers at Kuopio University in Finland found autistic children who presented low amounts of the serotonin transporter. The term “autism spectrum disorder” includes both, but also implicates other neurotransmitters, monoamine oxidase-A, cortisol resulting from stress, gonadal hormones, and perhaps hundreds of other proteins in the brain’s traffic patterns. But, in addition, there are social factors.

Psychiatrists have observed that people who achieve a self-satisfying status — through their work or social achievements — have correspondingly high levels of serotonin. This has been found in animal studies too. A reversal in status, perhaps diminishing self-esteem, lowers serotonin. Similarly, nurturing autistic children can help ameliorate behavior by lowering their dopamine levels. A few years before Arvid Carlsson identified dopamine as a neurotransmitter, Johns Hopkins University psychiatrist Leo Kaner proposed that autism was rooted in a “genuine lack of maternal warmth.” This became known as the “refrigerator mother” theory which other psychiatrists fanned into thinking that autism was a parenting disorder. In some cases, it may have been. An abusive parent who humiliated, intimidated, or otherwise injured a child’s self-esteem — especially a child who was born somewhere on the natural spectrum of autism — would have switched genes off or on, driving to disorder. “Refrigerator” mothers and fathers could have been autistics themselves. By the 1980’s, however, research about neurotransmitters and the organizing of parents with autistic children into advocacy groups and foundations rebalanced

the interpretation to nature and nurture. Nature provides the genes; nurture affects their expression levels.

Earlier I mentioned Thomas Meeks and Dilip’s literature review, “the neurobiology of wisdom,” in which they defined wisdom as a composite of six components: 1) prosocial attitudes/behaviors; 2) social decision-making/pragmatic knowledge of life; 3) emotional homeostasis; 4) reflection/self-understanding; 5) value relativism/tolerance; and 6) acknowledgement of and dealing effectively with uncertainty. If this holds up we can define autism as the thief of wisdom. Severely autistic children show none of these traits; in fact, they show polar opposites.

You’ll also recall that Richard Dawkins proposed “the selfish gene,” where natural selection gave a survival advantage to selfish genes that were the best adapted to their environment. Christopher Wills wrote about “the wisdom of the genes,” which is close to Dawkins’ argument, their common ground being wellness abetting survival. Still, how could selfish genes end up supporting the kind of altruism (selflessness) Meeks and Dilip define as wisdom?

On the last page of his book, Dawkins backed off a little from a single, unrelenting selfishness by speculating about a possible difference between selfish genes’ short term interests and long term ones. A short term gain could inhibit a long term one, such as might arise between an illness and aging. Aging is not simply accumulated wear and tear on cells; illness and aging involve two distinct processes, though they are linked by a finite number of cell divisions. But in either case, cells function in a distributed, but highly connected network. Dawkins characterized this as a “conspiracy of doves,” where genes give up a bit of their innate short term selfishness for a long term advantage in wellness.

If, as I propose, wisdom and wellness are synonyms, let’s briefly consider what wellness has come to mean. Wellness definitions stretch from “an active process of becoming aware of and making choices toward a more successful existence” to a physio-psycho balancing act akin to homeostasis, but all who have addressed the subject agree that wellness is not the opposite of illness. Wellness is a higher state of health. In the simplest sense, it is a combination of health and happiness — neither of which are easier to define than wellness itself. The preamble of the World Health Organization’s Constitution (1946) reads that “health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” The meaning of “well-being,” however, remains vague, even while it has observable physical and psychological dimensions. Social wellness, for example, emphasizes human interactions, noting that isolated individuals are more susceptible to depression and weakened immune responses, leading to a greater premature death rate. Medical wellness recognizes that many actors play upon health and, consequently, there are multiple complementary

and alternative approaches to achieving a higher well-being. What all dimensions — social, physical, intellectual, emotional, mental, medical — have in common is self-motivation — an active pursuit where, in effect, every person strives toward self-reliance, even while depending on commercial products and services from others.

The former chief innovation officer for the US Centers for Disease Control and Prevention once pointed out the relative weight of factors contributing to premature death: genetics 30%, social 15%, environmental 5%, medical care 10%, and behavioral patterns 40%. All of these involve some degree of variability, but none more so than the choices we make in behavior. All people learn how to make good choices, which largely represent survival advantages. One of the hallmarks of developed countries is that the range of choices and the number of people who can make choices constantly expands — what Swedish historians Folke and Karin Dövring called “the optional society.” It may be that this widening range of choice contributes to the incidence of so many people making bad choices in their behavior, but perhaps that’s a fundamental question that remains on the molecular frontier.

Summing up the molecular inference of wisdom comes to this. Wisdom is a human trait upon which natural selection creates evolutionary pathways from the molecular biology of the gene, to the cellular organization of nervous system, to the physical functioning of the brain — and the transit is a two way street. Wellness is a selection advantage at every level. Molecular wellness is innate, though often compromised because selection is blind; intellectual or high level wellness is learned behavior fed back to the molecular level as a kind of vision. The wisdom of this is that lifelong wellness — to the point of dying healthy — is a goal for every person and every society because it precedes and influences all other achievements. This does not imply we should attempt to vastly expand human life expectancy. That would be quite unwise as it gives pathogens a standing target to attack; extinction becomes the price of immortality. But within our limited number of cell division spanning a maximum of about 120 years, advancing human wellness would be wise enough.

A frontier thesis of the brain could explore wisdom, but way finding poses three questions: what are the pathways to follow; what’s needed to carry out the exploration; and how will discovery change the pioneers and those who come afterward?

The pathways are really about what might be discovered, and in the complexity of the brain the possibilities approach the infinite, much like exploring the universe. I’ll only mention three:

- what is the pathway to personalized, predictive medicine? This arises from the “omics” revolution — genomics, proteomics, metabolomics, *et al.* — which shows the

uniqueness of each person (i.e. you are unique just like everyone else) and what is your “fate.” A gene expression study of medullablastomas in children illustrates this point.

- what is the pathway to redefining diseases in finer detail than what is obvious? Hippocrates described epilepsy and for three thousand years it has been understood as storms in the brain. Henry Molaison, patient “H.M.” to neuroscientists since 1953, was a 23 year old epileptic who the anterior two thirds of his hippocampus surgically removed to control his seizures. In a more radical procedure, a three-year old Maryland boy had a hemispherectomy for the same reason. The seizures were obvious; their cause was not, even leaving open the question of whether or not epilepsy is one disease or many under one name. The same might be applied to many, even all, brain and mind disorders — which might also extend to obesity, hypertension, and all kinds of addiction.
- what is the pathway to a more benevolent society? Every society is becoming more diverse which can strain the concept that civility depends on a disposition to do good. The “golden rule” — do unto others as you would have them do unto you — is the essence of benevolence. But diversity also introduces unfamiliar attitudes and values that often are seen as threatening, as we find in racism and ethnic discrimination. Could an innate xenophobia be the basis for this, and if so, how can it be managed? If not, what causes persecutions, from bullying to crime to mass murder? Eugenics attempted to answer this; so, we should expect this pathway to be a rough road.

Neuroscience will need new means to find its way on the frontier. Again, there are many and earlier speakers on this program have discussed one of most exciting discovery tools, optogenetics. I’ll mention three others: gene therapy, neural implants, and astute family doctors.

In March 1993, Kevin Klug from Cincinnati received gene therapy for a glioblastoma multiforma — one of the most serious forms of all cancers. He had surgery, chemotherapy and radiation therapy before, but the tumor grew back each time. Pioneering gene therapist at the US National Institutes of Health, Michael Blaese, drew up the protocol which relied on a recombinant retrovirus that incorporated the Thymidine kinase gene from Herpes simplex into the engineered Moloney Murine Leukemia Virus. After surgeons cleared the vascular bed, Dr. Blaese introduced the virus, which could only infect dividing cells as would have remained from the tumor, unseen. As you know, Herpes simplex causes cold sores, and anti-Herpes work by acting on the Thymidine kinase gene. So, in effect, gene therapy allowed this kind of brain cancer to be converted to a cold sore which was then treated with the

anti-viral, Thymidine kinase-targeting drug Gancyclovir. Kevin, who had a 30 day life expectancy when this was done, is now out 21 years. Gene therapy is a complicated technology that requires finding the best viral vectors, the proper producer cells to expand the virus, and careful delivery. Among the neurotropic vectors used today are HIV and rabies, and certainly gene therapy is on the frontier.

When George Orwell published “Nineteen Eighty Four” in 1949, neural implants were conceivable but impossible. In fact, they had been imaginable since H. G. Wells published “A Modern Utopia” in 1905, and conjured further in Aldous Huxley’s “Brave New World” in 1931. All three of these works of fiction figure in the social background of neural implants because they represent more than a century’s fear of such things. Their social acceptability is preconditioned by notions of psychological manipulation, mind control and brainwashing, all of which have non-fiction realities, perhaps most notably with “MKULTRA.” This is not the Chicago rock band by that name, but rather the US Central Intelligence Agency’s project, between 1953 and 1973 which experimented with human behavioral engineering, using drugs and various kinds of torture. It involved 149 subprojects which the CIA secretly contracted out to universities and private research foundations. Files that survived a burn order were declassified in 2001.

Now comes Cathy Hutchinson. In 1997, she was a 42 year old single mother of two, living in Attleboro, Massachusetts when she suffered a brain stem stroke that left her almost completely paralyzed in what’s known as “locked-in

syndrome.” She was unable to move, but was aware of events and conversations going on around her. She described losing her brain, but retaining her mind as being in a prison for a crime she didn’t commit. Massachusetts law prescribed that she be cared for in a nursing home, where in fact, she lived for 11 years. Because she felt deprived of both good care and privacy, she allowed her complaints to be bundled in a class action lawsuit, *Hutchinson v. Patrick*, in 2007 which prevailed and has since allowed nearly 1,200 institutionalized brain injured people to move out of nursing homes and into community residences where they can be closer to friends and family.

But that’s not the end of Ms. Hutchinson’s story. After winning the lawsuit, Ms. Hutchinson became a pioneering patient for neural implants. Dr. John Donoghue of Brown University and colleagues at Massachusetts General Hospital created a device called “BrainGate.” It is a tiny 100-electrode array of nanowires and silicon tips that interface with neurons of the motor cortex on the top of the brain. The implanted sensor detects the neurons’ electrical transmissions,

which normally control motions, and sends them to an external decoder where software translates thoughts into the mechanical movements of a robotic arm. A remarkable YouTube video for BrainGate shows Ms. Hutchinson thinking her way through drinking from a thermos of coffee for the first time in 15 years. Donoghue is now working on a wireless version for this technology.

BrainGate, along with cochlear and retinal implants and devices for deep brain stimulation to control Parkinson’s disease are enabling technologies for the impaired. Neural implants might also be developed for memory loss, drug addiction, or bipolar disorder. From there it’s not hard to imagine cyborg soldiers or athletes with performance-enhancing brain chips. Proceeding further to neural implants having a status akin to cosmetic surgery for those who could afford it, and government regulation that sees this technology as an acceptable competitive advantage, we could, indeed, have a “brave new world” for better or worse.

It is reasonable speculation that gene sequencing, optogenetics and neuron mapping, neural implants and “silent talk” brain imaging will allow neuroscientists to discover new pathways that capture headline news. But these technical wonders will wither on history’s vines if they do not reach the practices of astute primary care physicians who can scale big science into small science. Small sciences is where doctor and patient meet face to face in search of illness individuality. An example of such a place is the Clinic for Special Children in Strasburg, PA. It is the primary care facility for

the descendants of 16th century German-speaking Bohemian and Swiss Anabaptists who migrated to America and became known by the folk term “Pennsylvania Dutch.” They are the Amish and Old Order Mennonites. Because of the so-called “founder effect” and faith-based marriage traditions, today’s populations have high incidences of inherited metabolic errors that are rare in the general population. Maple Syrup Urine Disease, for example, is found in about 1 in 120,000 live births worldwide, but 1 in 271 live births among the Groffdale Conference of Old Order Mennonites in Lancaster County, PA. This disease floods the basal ganglia with the three branched chain amino acids, leucine, isoleucine and valine, and, in effect, starves the mitochondria of other essential amino acids, leading to basal ganglia death, if left untreated. Treatment involves an infant formula without the branch chain amino acid, and careful monitoring, especially during periods of typical childhood illnesses. (These slides show 71 such illnesses, of which 40 appear in Amish families, but not Mennonite, and 31 among Mennonites, but not Amish). Being able to detect these diseases before irreparable damage is done depends on having highly sophisticated genomic and proteomic equipment in the Clinic’s laboratory and having three physicians and a geneticist on staff who are familiar with population-specific molecular medicine and can practice it every day. Not many clinics have patients arriving by horse and buggy, but humanity has many genetic bottlenecks, and their relatively simple, if devastating, inherited illnesses are components, to some extent, in every other human disease. Like wisdom, between gene and cortex, big and small science represent a two way feedback mechanism.

Lastly in this frontier thesis of neurobiology, we have to consider how pioneering in the brain has changed us already and might do so further in the future.

Obviously, discovery has led to new drugs for brain diseases. Further research could produce medicines that are personalized to an individual’s metabolic rate, more targeted and with fewer side effects or adverse reactions. Beyond that, though, neuro-discovery could, and almost certainly will, re-define the nature of illness and wellness. In genetic and/or cellular pathways, it may turn out that some Parkinson’s sufferers have more in common with some autistics and some schizophrenics than they do with other Parkinson’s patients. Already, neurologists speak about “synaptopathies,” as for

example, “your form of Parkinson’s is a disfunction of glutamate transmission rather than dopamine, and is actually a rarer form of Fragile X syndrome.” Getting the diagnosis right in the first place is a big step in making health a more achievable and sustainable goal. Since it’s easy to see that most of what we call modern times would have been impossible without the discovery of germs, we can muse about previously unimaginable possibilities stemming from molecular brain theory.

In his book, “World Wide Mind,” science writer Michael Chorost raises a plausible, if not yet possible, interface between the human brain and the internet. Part of his inspiration comes from having two microcomputers in the form of cochlear implants connected to his auditory nerves; another part comes from his addiction, like millions of other people, to electronic “smart” devices that provide frequent stimulation, frequent distraction, and unconscious slipping away from direct personal contact — that is “real touch” as opposed to “touchscreen.” With self-assembling microrobots that could form wireless electrodes at specific functional zones on the brain’s cortex, it might become possible to put on a “thinking cap” as a wearable internet. This could avoid both real touch and touchscreen, resulting in an even greater isolation than we now see with a young couple, on a date, each paying more attention to their smart phones than to each other. Before that becomes a social pathology, however, people will have invented new forms of enchantment and intimacy, as Chorost says, that are necessary for survival of both individuals and societies. These new forms, which certainly should bring new values and behaviors, might be troubling or be fun, but either way they will be irreversible.

I’ll now turn the frontier thesis of the brain over to you. Think about the possibilities of brain function enhancement that could improve communications between people, or improve communications between the individual’s conscious and subconscious self. When your generation has mapped the brain, start mapping the mind. And when you reach these intersections, remember the last stanza of American poet Robert Frost’s “The Road Not Taken:”

Two roads diverged in a wood, and I —
I took the one less traveled by,
And that has made all the difference.