THE GENE IN THE BOTTLE

ROBERT GRAY PATTON
Chit-Chat Club

April 11, 2005

Advances in the natural sciences have often challenged conventional positions, both secular and religious, provoking intense and prolonged opposition. Such advances have, at times, had disturbing, and often unintended sociopolitical effects, or have seemed to some to threaten a dangerous intrusion into the natural order of life. Nowhere has this been more true in the last 150 years than in what has become known as genetics, the signal events being the Darwin-Wallace 1858 papers proposing an evolutionary process effected by natural selection, and the 1953 Watson-Crick paper on the chemical structure of DNA**.**

Charles Darwin was born February 12, 1809, into a prosperous Midlands family closely related to the Wedgwoods, titans of the ceramics industry. They were a family out of the pages of a Jane Austen novel. His grandfather was the famed corpulent polymath, poet, physician and scientist, Erasmus Darwin. Charles, from early boyhood was a keen naturalist and a prodigious collector of beetles, but it was assumed that he would go to the University of Edinburgh to learn medicine, his father's profession. Repelled by the horrors of human pain and suffering, he abandoned Edinburgh and went to Cambridge, with the intent of becoming a gentleman country parson, a position which would give him free time to pursue his biological and geological interests as an avocation.

As he was finishing his studies, however, through Cambridge connections, he was offered a position as companion to Captain Robert Fitzroy, who, in the HMS Beagle, was about to sail for a surveying voyage of both South American coasts, then to return to England across the Pacific and around the horn. The voyage was to last 5 years, during which time, on land as well as sea, Darwin saw and collected an immense variety of flora, fauna, and fossils and observed Homo Sapiens in its most primitive Fuegian form. He saw erupting volcanoes and earthquakes, evidence of the constant reshaping of the earth's crust.

He came home, soon married his cousin Emma Wedgwood, and became very involved in London scientific circles. Of special importance were his contact with Thomas Malthus author of the "Essay on the Principle of Population" and his close and lasting friendship with the geologist Charles Lyell. Lyell's theories of continuous geological change lent much to Darwin's developing ideas. Before long, the Darwins, with their increasing brood, moved to Downe, a small town in Kent. There Charles remained and worked for the rest of his life.

He wrote prolifically—several volumes on the findings of the Beagle voyages and many monographs on a wide variety of animal and plant species. In order to establish himself as a major figure among biologists, he completed a most exhaustive 3-volume work on barnacles. It won the Queen's prize of the Royal Society, but Darwin was later heard to say that the sight of another barnacle would make him ill. He studied the production of variations in domestic animals, especially domestic pigeons. Behind all these activities were the germination, development and fruition of his theory of natural selection. He was a committed evolutionist, at a time when the laity, of course the church, and <u>most</u> in the natural sciences still held firm belief in the immutability of all the existing forms of life, placed on the earth by

God at one time in a relatively recent era.

Darwin was by no means the first evolutionist. Many before him felt that there was progressive change in the flora and fauna, and in the surface of the earth itself—most notably Jean-Baptiste Lamarck and Charles's own grandfather Erasmus. But none had proposed a convincing theory of the mechanism. Darwin's idea was that of an almost imperceptibly gradual process, occurring over hundreds of millions of years, in which small variations occurred constantly in all forms of life. He applied the Malthusian principle—that there would be a geometric increase in population unless checked by starvation, predation, or disease—and that favorable variations would bestow success in the struggle for existence. He felt that life began with a very few primitive forms, perhaps only one, and developed as would a large tree, with limbs and twigs sprouting from the ancestral trunk. The successful branches would continue to grow and through successive successful variations would form new species. The unsuccessful would become extinct. Sexual selection would also contribute to evolutionary change, as any variations in males which gave them an edge in reproductive success would favor the survival of the lineage. The 19th century was still a male world and the participation of the female in sexual selection was not considered. Natural selection required no divine guidance or "intelligent design" and left no room in his mind for conventional religious beliefs. If not frankly atheistic, he certainly lost belief in a personal, hands-on God.

Darwin collected masses of data and scribbled reams of notes to support his ideas, but was reluctant to go public, fearful of the uproar it might provoke, and worried at the pain it would cause his deeply religious wife Emma. He discussed his work only with his allies and friends T. H. Huxley, Charles Lyell, and Joseph Hooker. He intended to go on collecting supporting data and perhaps publish at a later time when he would have amassed enough facts to overwhelm any opposition.

This plan was completely upset, however, on June 18, 1858, when Darwin received a package from Malaya. In it was a paper from a naturalist, Alfred Russell Wallace, with whom Darwin had corresponded but never actually discussed his ideas of natural selection. The paper "could not have made a better short abstract" of Darwin's own work! He offered to publish Wallace's letter immediately, but was persuaded rather easily by his friends to publish an abstract of his own work along with Wallace's at the Linnean society—coauthored and titled "On the Tendency of Species to Form Varieties, and on the Perpetuation of Varieties and Species by Natural Means of Selection." Wallace accepted this compromise with admirable charity and humility.

Darwin then moved quickly ahead to publish, on November 24, 1859, his famous 490-page book, <u>On the Origin of Species by Means of Natural Selection or the Preservation of Favored Races in the Struggle for Life.</u> It contained a wealth of factual detail in support of his argument. Evidence of physical adaptation in response to environment, the geographical distribution of like species which suggested common ancestry, fossil evidence of ancient precursors, morphological homologies, similarities in the embryos of widely different species, the presence of vestigial structures, and on and on. Darwin clearly felt that man was very much a part of the ongoing evolutionary scheme, with no divine exemptions from natural selection. Man's simian origins were implicit but not clearly stated in the "Origin," but in <u>The Descent of Man</u> (1871) he firmly concluded that man is descended from "a hairy, tailed quadruped, probably arboreal in its habitats."

The publication of <u>The Origin of Species was indeed sensational</u>. Reactions from press, clergy and scientists ranged from enthusiastic approval to indignant condemnation. The Rev. Baden Powell, Oxford mathematician, said that it "was a masterly volume, a work which must soon bring about an entire revolution of opinion in favor of the grand principle of the self-evolving powers of nature." Bishop Samuel Wilberforce of Oxford wrote a scathing review, which set the stage for the legendary debate with Huxley at a scientific convocation in the Oxford Museum of Natural History—a clash between theology and science. Wilberforce asked Huxley whether he was related on his grandmother's or his grandfather's side to an ape. Huxley replied, "If I would rather have a miserable ape for a grandfather or a man highly endowed by nature and possessed of great means and influence, and yet who employs those faculties for the mere purpose of introducing ridicule into a grave scientific discussion—I unhesitatingly affirm my preference for the ape!"

Darwin's theory was clearly not going to be vanquished, but there were some very difficult challenges. Scanty fossil evidence of intermediate forms was available—that would be answered by later progress in paleontology. Darwin's estimate of the age of the earth was challenged by Lord Kelvin although it too was later shown to be correct. There were, however, two more difficult problems—the lack of any clear explanation of how variations in living organisms occurred and of the mechanism by which inherited information was transmitted from one generation to another. Those questions would not be answered until the 20th century. More on that later.

Now I introduce Darwin's younger first cousin, Francis Galton, also a grandson of Erasmus—a brilliant but eccentric man whose work, though fairly benign in first intent, led to disastrous sociopolitical events. Curiosity about the world took him to Africa as a young man. Among his diverse interests, Galton was a compulsive quantifier. An example of his zeal occurred when, attempting to measure the buttocks of a steatopygic Hottentot woman who resisted his attempts to directly apply his tape, he used a surveyor's sextant to obtain her gluteal girth at a discrete distance. He was the first to explore Namibia, was a leader in the Royal Geographical Society, a meteorologist who discovered the high pressure center. He was the father of biostatistics—introducing correlation, regression to the mean and application of the bell shaped curve, and measured and tabulated the dimensions and form of thousands of arms, legs, and crania. He introduced fingerprinting, and attempted to measure human intelligence. He was certainly one of the earliest social scientists.

But above all he was profoundly influenced by the work of his cousin Charles, especially in human genetics and heredity. His first book was <u>Hereditary Genius,</u> in which he maintained that the fact that eminent men had eminent sons was clear evidence for the inheritance of ability. And he certainly thought himself to be among the eminent! He was the first scientist to use the phrase "Nature and Nurture"; nurture was clearly, to him, the less important. He was the first to do twin studies and to use pedigrees in the study of human inheritance. He was, late in his career, the leading British figure in the field of heredity.

Galton, who had already introduced the term "eugenics," meaning "good birth," and who had become interested in the perfection of the race, or at least the prevention of its decline, felt that "natural" selection should be modified by human intervention. "What nature does blindly, slowly and ruthlessly, man may do providently, quickly and kindly." He favored "positive eugenics" with augmentation of the favored stock by encouraging and rewarding superior couples in their reproductive successes. He was rather mild in his "negative eugenics" but did advocate discouraging population growth in the under classes. There was indeed in the temper of the time a growing concern among the more affluent and educated classes that lower birth rates among themselves and the increasing fecundity of the lower classes would lead to a disastrous dilution of the superior elements of society. Galton echoed the opinions of many when he said that “our enthusiasm to improve the race is so noble in its aim that it might give rise to a sense of religious obligation.”

The movement was adopted enthusiastically by the politically liberal as well as the conservative. G. B. Shaw spoke for his Fabian friends when he said “nothing but a eugenic religion can save our civilization.” A Eugenics Laboratory was established at the University of London, and a Eugenics Education Society, headed by Montague Quackenthorpe to publicize and encourage the cause. The movement quickly spread to Germany and the U.S. An eminent American geneticist, Charles Davenport, was named director of the Eugenics Record Office at Cold Spring Harbor, with the support of the Harrimans, the Carnegie Foundation and Alexander Graham Bell. Cold Spring Harbor is, of course, a current center of research in molecular genetics.

In 1912, the first International Congress of Eugenics convened in London. Representatives of the top levels of state, church, science and medicine were there. Winston Churchill was a vice president, as were Charles W. Elliott from Harvard and David Starr Jordan from Stanford. Darwin’s son Leonard was the chair and proclaimed that Western Civilization was endangered by natural selection, that the “human race was slipping into degeneracy, that the unfit were no longer killed off by hunger and disease but were cherished with care and allowed to reproduce.”

Though Arthur Balfour spoke eloquently in warning the audience against plunging into eugenic practices too hastily, he did little to dampen their enthusiasm. It should be pointed out that the most headstrong proponents were not genetic scientists, and that there was a sophomoric misapplication of Mendelian genetics to such conditions as “feeblemindedness,” epilepsy, criminality, alcohol and drug addiction, homosexuality, prostitution, pauperism, and even blindness and deafness—conditions now known rarely to be single gene Mendelian characteristics but rather multigenic and mostly with strong environmental causes. This error was not easily corrected in the social movement of eugenics, however.

The eugenics movement in England remained fairly benign, more talk than action, but it took a darker turn in the U.S. Eugenic sterilization became law in Indiana in 1907, and by 1930, 30 states had such laws to be applied to the “hereditarily unfit.” About 60,000 sterilizations were performed in the U.S., the majority in Virginia and California. Most sterilizations were performed on institutionalized people, and “informed consent” was certainly not required. Theodore Roosevelt wished that “the wrong people could be prevented entirely from breeding” and that “criminals should be sterilized and feeble-minded persons forbidden to leave offspring behind them.” In his opinion on the famous Carrie Buck sterilization case before the Supreme Court, Justice Holmes wrote that “It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes. Three generations of imbeciles are enough!” Later Carrie Buck and her daughter were found to be of normal intelligence.

Though the concept was not initially invented by the eugenicists, they gladly supported the idea of Nordic superiority. They feared that Western Civilization might “find itself becoming darker and shorter, lacking in initiative, less steadfast and persistent, and possibly more emotional.” Clearly many thought that darker complexion implied a fixed genetic inferiority, just as Prospero described the dark Caliban as one “on whose nature, nurture can never stick.” The rapid increase in immigration from eastern and southern Europe was regarded as a grave threat to the character of the country, a view proclaimed by Harry Laughlin, the director of the Eugenics Record Office. Good housekeeping necessitated a genetically pure and wholesome home, and the magazine of that name contained the following from President Calvin Coolidge. “There are race considerations too grave to be brushed aside for sentimental reasons. Biological laws tell us that certain divergent people will not mix or blend. The Nordics propagate themselves successfully. With other races the outcome shows deterioration on both sides.”

The very restrictive Immigration Restriction Act of 1924, though not without opposition, passed with a large majority and was hailed as showing great “biological wisdom.” It was thought that without the “drastic inhibition upon a world migration to our shores, what we know as the American people and its institutions would have been submerged in chaos,” ideas not entirely foreign to some in our country today.

Because of its abuse and misapplication of genetic science and its increasingly racist tone, most genetic scientists in the U.S. abandoned eugenics during the ‘20s and ‘30s, and as a sociopolitical movement it had lost much of its energy by the Second World War. But Germany was quite ready for the eugenics movement, especially during its socioeconomic collapse after Versailles. Then came to power the Nazi party in 1932, with it race-hygiene policies, and we need say no more. What had begun as a relatively innocent attempt to intervene and direct natural selection for the improvement of mankind, eugenics, as it deviated more and more from its scientific roots, became sinister and eventually a catastrophe. Have more recent scientific developments introduced eugenics in a new form?

Returning to the main flow of pure genetic science, we find around 1900 the rediscovery of the Moravian monk, Gregor Mendel, who, in his monastery garden 30 years earlier, had carried out his famous breeding experiments on the garden pea, showing that there was a particulate form of inheritance from each parent plant, expressed in the offspring as either a dominant or recessive character. Cell structure, the nucleus, and cell division were observed microscopically in the latter part of the 19th century, as was the penetration of the sea urchin ovum by the sperm, and fusion of the two to form one nucleus. Walter Fleming in 1884 saw thread-like structures in the nucleus which he called chromosomes, and noted that they were duplicated and shared between daughter cells at the time of cell division**;** and August Weismann in 1888 declared the chromosomes to be the carriers of inherited information. Initially skeptical, Thomas Hunt Morgan of Columbia, working with the fruit fly, Drosophila, did map the location of genes on the chromosome, and also revealed the existence of X-linkage. Miescher, in the 1880s, had identified a substance in the nucleus called nuclein, which was shown to contain a sugar called desoxyribose, and was thence called desoxyribose nucleic acid, or DNA. Oswald Avery in the 1940s showed that non-lethal bacteria, grown in a broth containing DNA from a lethal strain, were transformed into the lethal strain.

DNA was then surely the substance of heredity, but its structure remained an amorphous puzzle until 1953 when an elated Francis Crick rushed into a Cambridge pub and exclaimed “we have found the secret of life.” He and James Watson, with an assist from Rosalind Franklin, had found DNA to be two very long, linear, sequences of four elements, A, T, C and G—one chain from each parent, wound in an embrace with each other in a double helix, strands which unwind and separate at the time of cell division. The DNA sequence of each gene forms a template which is translated into proteins. All structural and functional parts of every living organism are produced in accordance with this gene map.

Paralleling this discovery was the defining of the structure of chromosomes, the little packages of genes which reside in the cell nucleus in pairs, one from each parent. Our species was finally found to have 46 chromosomes—22 pairs of autosomal and two sex-determining chromosomes, the X and the Y. Males have an X and a Y and females two

Xs. It has been thought that the second X chromosome in females was inactive, but it's now known that this X does have many active genes. As Maureen Dowd has recently pointed out in her New York Times column, it is now known that a woman's 2^{nd} X chromosome has many more genes than the puny male Y, which seems to be losing its genes at a steady evolutionary rate. Thus the gene gap is increasing in favor of the female, suggesting that there may soon be parity even in mechanical engineering genes! The exceptions in chromosome number are the sperm and ovum, which are reduced to 23 chromosomes by a special form of cell division, meiosis. During meiosis, the paternal and maternal chromosomes may exchange little bits of genetic material, a process which contributes to the variation predicted by Darwin. Today the chromosomes of the fetus can be examined by cell culture from amniotic fluid in early pregnancy for abnormalities in number or structure, many of which may cause serious fetal maldevelopment.

The discovery of DNA structure and function has shifted research to the <u>contents</u> of the chromosomes, the genes themselves. By the 1960s, we were beginning to locate a number of genes on their chromosomes, and to determine their molecular sequences**.** By the '70s, using enzymes, Stanley Cohen and Herbert Boyer, the founders of Genentec, were able to snip genes from one species and insert them into the genome of another, creating "transgenic" plants or animals. By so doing scientists were able to "farm" recombinant bacteria for hormones and vaccines such as insulin, and to genetically engineer plants to produce better yields. Despite its promise, there was so much anxiety about genetic modification, with fears of a world overrun by chimeric microbial monsters, that a conference of scientists from around the world was held at Asilomar in 1975. Intense antagonism developed between those who wanted to stop this research completely and the fully libertarian side, but eventually a compromise was reached, with a brief moratorium followed by relatively mild NIH guidelines.

Gene mapping and cloning research continued apace. A technique for producing massive amounts of DNA from very small samples, called PCR, was invented by a Bay Area surfing scientist, Kary Mullis, an advance which won him the Nobel Prize. Then came the race between Francis Collins of the NIH and the competitive Craig Venter of the private company Celera to sequence the entire human genome, which, in June 2000, ended in a tie. The human genome, our blueprint for life, has been found to contain three billion molecular units, or base pairs, less than 5% of which comprise our 25-35,000 genes. The rest is "junk" DNA with no known function, possibly evolutionary garbage. Each of our one hundred trillion cells contains, tightly coiled in little chromosomal packets, an amount of DNA, which, if stretched to linear form, would measure 2 meters. The Chimpanzee genome is 98% identical to the human, and among all races of Homo Sapiens, there is 99.9% identity.

We are working rapidly to identify the location and function of all the 25-35,000 genes in the human genome, to understand how they interact, and to determine what turns them on and off. All the details of our body structure, metabolism, and, to a great extent, behavior have genetic determinants. Some are simple Mendelian, some polygenic and many involve interaction between genes and environment. The same is true of our susceptibility to disease. More than 1,000 genes whose mutations cause disease are now known, and for many conditions detecting the abnormal gene provides the most accurate diagnosis. Prenatal detection of many mutations is now possible, allowing for early diagnosis and intervention. Cystic fibrosis and hemophilia are among the simple Mendelian disorders, diabetes is polygenic with an environmental component, and atherosclerosis may involve a genetic defect in cholesterol metabolism but may be accelerated by adverse modes of life style. There are many genes whose function is not fully understood, but which nevertheless are identifying markers for increased susceptibility to such illnesses as breast and ovarian cancer, Parkinson's and Alzheimer's.

Extrapolating from the rate of progress in the last 30 years, is it not likely that in another generation one's entire genomic map will be at hand, and that our life history may be foretold not long after conception? Even now, the embryonic product of in vitro fertilization can be tested before implantation for a limited number of genetic disorders. One day in the not too distant future a computer printout of the embryo's entire three billion bit genome might be available instead. Certainly this information may be immensely valuable in making medical and reproductive decisions, but the use of it may also lead to entanglement in an immense thicket of ethical issues.

The other major thrust of genetics in the next generation will be the repair or replacement of defects in the genome—introducing healthy genes into people with illnesses, especially single gene conditions like cystic fibrosis. Such a process requires finding a transporting vector, most likely viral, which can be genetically modified to carry the healthy gene into the sick cell—a very challenging problem, but once solved it opens a floodgate of treatment options. And stem cell research, while not directly related to evolution and genetics, holds promise of solving further mysteries of gene action within the cell.

Once the problems of somatic gene therapy have been solved, the next step might be germ line gene replacement—genetic engineering of the sperm or ovum. This would cure not only the affected patient but his or her descendants as well, but obviously comes with great risks. Beyond this step lies the possibility of using synthetic genes, or genes from other species--plant or animal, thus creating a true transgenic man. Such a development may be wild science fiction, and introduces the dangers of what Francis Fukuyama calls "our post-human future," but we should not deny the eventual technical potential.

The old eugenics may have dimmed, but the new molecular form has brought us to a critical intersection of science and ethics. Man has moved beyond the "red in tooth and claw" form of natural selection, as he has become able to manipulate his own genetic future. Is this a dangerous Promethean challenge to the order of nature, or is engineering of the human genome just a new brilliant and inventive kind of adaptation quite consistent with Darwinian natural selection?

Does the growing distrust of evolution in our country reflect a fear that Darwinian concepts have led us into perilous waters? Even though Pope John Paul II himself has said that "fresh knowledge leads us to recognition of the theory of evolution as more than just a hypothesis," our president claims that "the jury is still out on evolution"!

I conclude with a question—Are we slipping into the disturbing "brave new world" of Aldous Huxley, or are we poised on the threshold of the wondrous and promising "brave new world" of Shakespeare's Miranda?

AN ABBREVIATED BIBLIOGRAPHY

Browne, Janet. Two-volume biography of Charles Darwin, Voyaging and The Power of Place.

-

Darwin, Charles. The Origin of Species and The Descent of Man.

Gillham, Nicholas. Sir Francis Galton.

Gould, Stephen J. The Flamingo's Smile

Henig, Robin Marantz. The Monk in the Garden.

Ludmerer M.D., Kenneth. Genetics and American Society.

The New York Times, March 23, 2005.

Ross M.D., Dennis W. Introduction to Molecular Medicine.

Watson, James. DNA.