NOTES FROM THE FRONT –Evolution on the Move

June 12, 2006 John A. MacLeod

While doing my usual ruminating as I prepared to read the paper this evening, it came to me that I might have some understanding of Larry Summers' experience and how he came to resign as President of Harvard as of the end of the current academic term. From all reports, he had brilliant ideas and a rough style that increasingly rubbed his faculties the wrong way, especially the faculty of Arts and Sciences – earning him a vote of no confidence a year or so ago, and another one seemingly on the way. An element in his aggressive curricular planning was what President Summers believed to be an overdue strengthening of the Science programs and faculties and all of this without timely faculty consultation.

So – in my meanderings it comes to me that I intend to read you a paper possibly larded with science – or at least notably seasoned with it – and that without so much as a "by your leave".

Therefore, wanting a different fate from that of Larry the Leader, I am giving you some notice – also designed to sharpen your alertness, and also having the good advice in mind that science, presented without formulae and equations, becomes the tastier fare. And do not overlook that all of this is very much for the good of the order – as our old friend, Bob Hilton, was fond of saying – and for your own good no less.

The inspiration for this evening's paper comes from a number of sources, as you will hear, but the title "Notes from the Front" comes from a headline in AAAS Matters, the periodical of the American Association for the Advancement of Science, in the autumn issue for 2005. The headline was "Evolution on the Front Line", reporting on the many developments and controversies connected with the teaching and reporting about evolution recently. My concentration this evening will not be on the controversies generating so much public interest but rather on the outpouring of new discoveries, approaches, methods and applications to everyday life. The volume of this material is so extensive that I have adopted something of a snapshot method for selecting topics, limiting my camera to an approximately six-month period, from near

the end of 2005 to early 2006, and utilizing a method of scanning headlines but then discovering myself, at times, immersed in the details of the news stories and articles.

All of you have been exposed to a similar flood of information including cover stories in our major news magazines, the essentially simultaneous publication of two collections of Darwin's four major books in November 2005 – edited by two equally eminent scientists – numerous reports of relevant discoveries in the daily news media and scientific papers – almost beyond count, and in juried professional journals. A relatively recent paper of mine, read here at the Literary Club, carried the title, "Cycling for Science", the story of riding an exercycle while reading science journals in a futile effort to keep pace with developments. I am thinking now that a more contemporary method might be "scanning for science" – some automatic method for storing the flood of information in one's brain and categorizing the outpouring in one's brain and memory.

Far from incidental is the exhibit touted as the most in-depth presentation on Darwin, on display in the American Museum of Natural History, opening this past January 2006 and continuing there until Memorial Day when the exhibit will go on the road to Boston, Chicago, Toronto, and finally London in time for the 2009 Bicentennial of Darwin's birth.

In some measure, I'll be modeling my paper's organization after the style of Norm Levy though I'll be surprised if I come through in his poetic voice elaborating on headlines from around the world. My approach to this will not be one of comprehensive coverage, but rather focusing on the headlines from the past five to six months and giving more detail to three or four breakthroughs, which have special relevance for the membership.

It has occurred to me that at the outset I need to share a definition of evolution with you as a wide range of understandings exists and even the dictionary definitions leave much confusion. So I am going to offer Edward Wilson's thinking as the foundation for my approach. I take his remarks from one of his essays introducing Darwin's "Four Great Books".

"Evolution by natural selection is perhaps the only one true law unique to biological systems, as opposed to non-living physical systems, and in recent decades it has taken on the solidity of a mathematical theorem. It states simply that if a population of organisms contains multiple hereditary variants in some trait (say, red versus blue eyes in a bird population), and if one of these variants succeeds in contributing more offspring to the next generation than the other variant, the overall composition of the population changes and evolution has occurred.

Further, if new genetic variants appear regularly in the population (by mutation or immigration), evolution never ends. Evolution in a pure Darwinian world has no goal or purpose, "the exclusive driving force is random mutations sorted out by natural selection from one generation to the next".

First a few comments about the recently published collections of Darwin.

In a review of the two editions of Darwin's four principle books, Jonathan Weiner, a science writer, in the March 2006 issue of Scientific American, calls the simultaneous publication of the two collections "A publishing coincidence". Two of the world's best known biologists since Darwin, Edward O. Wilson and James D. Watson, each issue a volume containing Darwin's "Voyage of the Beagle", "On the Origin of Species", "Descent of Man", and "Expression of the Emotions in Man and Animals". To Weiner, the most interesting thing about this little publishing coincidence is the larger coincidence that these three biologists, Wilson, Watson and Darwin, who have succeeded in opening up new views of life, have been brilliantly successful popular writers also. An observation I had not been aware of is that Darwin's books were outstanding bestsellers in their day including an additional book of Darwin's, "A Study of Earthworms" – surely an earthshaking contribution – which he published in 1881, the year before he died. Darwin is quoted as saying, "My book has been received with almost laughable enthusiasm." Watson's book, "The Double Helix", a memoir of his Nobel winning discovery, was a best seller too. As for Wilson, his skills as a writer won him two Pulitzer prizes and an audience as wide as Watson's. What I had not realized is that the two men, Watson and Wilson, were on the Harvard faculty together for a good number of years during the 1950's and 1960's as young biology professors. Wilson is quoted in his remarks regarding Watson, "I found him the most unpleasant human being I had ever met". In my mind, such feelings might relate to intense competitive struggles possibly reflected in their concurrent publishing of Darwin's collected works. Wilson's collection ended up being some four to five hundred pages longer than Watson's because he included a large number of footnotes and an index for each volume and a general index. The editions stand on their own as significant contributions. "Great discoveries are like sunrises," says E.O. Wilson. "First they touch just the tips of a few peaks and steeples; then they illuminate the whole world." "The greatest

discoveries change everything for us," says James D. Watson: "Not only our feelings about science, but about existence". Weiner's point about good writing is that developments in biology have been a powerful story to tell and all three science writers Darwin, Watson and Wilson, have told the story well and understandably to a very wide reading audience indeed.

The Evolution of Charles Darwin

Just a brief primer on Charles Darwin. In a very rich article in the December issue of the Smithsonian magazine, Frank J. Sulloway gives important background material on Darwin. I was surprised by how early the voyage of the Beagle began – it was on a December night in 1831 – the mission of the voyage was to chart the coast of South America and on board was the twenty-two-year old amateur naturalist, Charles Darwin, who was recruited for the voyage largely to provide company for the Beagle's aloof and moody captain, Robert FitzRoy. The little ship was just 90 feet long and eight yards wide and sailed up and down Argentina, through the strenuous Straits of Magellan and into the Pacific, before returning home by way of Australia and Cape Town, a voyage of five years. The Beagle spent five weeks at the remote Galapagos Islands and here Darwin began to formulate some of the ideas about evolution that would appear – a quarter of a century later in the "Origin of Species".

Darwin introduced the notion of evolution: that lineages of living things change, diverge and go extinct over time, rather than appear suddenly in immutable form, as Genesis would have it. A corollary is that most of the species alive now are descended from one or at most a few original forms. By itself, this was not a wholly radical idea, but Charles Darwin was the first to muster convincing evidence for it. He had the advantage that by that time geologists had concluded that the earth was millions of years old (today we know it is about 4.5 billion years). Darwin had his notebooks and the trunk loads of specimens shipped back to England.

What is remarkable is the amount of careful classification Darwin and his colleagues were able to accomplish and the theoretical thinking that emerged from those labors. The pace was slow and deliberate and the technology – for example, the importance of a handheld magnifying glass – was quite primitive. This very gradual pace of the 1800's has now been succeeded by the accelerating flood of new technology and discovery.

Breakthrough of the year – Evolution in action.

At the end of each year, Science magazine rates the 10 outstanding developments in science for the previous 12 months. For the year 2005, its breakthrough was "Evolution in Action". Each year researchers worldwide discover enough extraordinary findings tied to evolutionary thinking to fill a book many times as thick as all of Darwin's works put together. Amid this outpouring of results, 2005 stands out as a banner year for uncovering the intricacies of how evolution actually proceeds. Concrete genome data allowed researchers to start pinning down the molecular modifications that drive evolutionary change in organisms from viruses to primates. (A genome is a single set of chromosomes.) Painstaking field observations shed new light on how populations diverge to form new species. One of the most dramatic results came in September 2005 when an international team published the genome of our closest relative, the chimpanzee. With the human genome already in hand, researchers could begin to line up chimp and human DNA and examine one by one the forty million evolutionary events that separate them from us. (DNA – any of the class of nucleic acids that contain deoxyribose found chiefly in the nucleus of cells – and that function in the transference of genetic characteristics and in the synthesis of proteins.)

The genome data confirm our close kinship with chimps: we differ by only about 1% in the nucleotide bases that can be aligned between our two species and the total difference in DNA between the two species comes to about 4%.

Such evolutionary breakthroughs are not just ivory tower exercises; they hold huge promise for improving human well being. Humans are highly susceptible to AIDS, coronary heart disease, chronic viral hepatitis and malignant malarial infections; chimps aren't. Studying the differences between our species will help pin down the genetic aspects of many such diseases. Researchers have already used such techniques to home in on a gene for age related macular degeneration.

Another brief report.

More diseases are able to mutate and jump to infecting humans. Bird flu is but the latest in a growing number of diseases humans risk being overrun by. Researchers have documented

38 illnesses that have made that jump over the last 25 years. That is not good news for the spread of bird flu, which experts fear could mutate and be transmitted easily among people. One explanation for the increased number of pathogens that infect humans, says Mark Woolhouse, of the University of Edinboro is that because of recent and wide scale changes in how people interact with the environment in the populated world, we cannot insure that pathogens stay restricted to animals. Examples from recent human history include: HIV, Marburg, SARS, and other viruses.

New methods yield mammoth samples: shades of Jurassic Park.

Ancient DNA has always held the promise of a visit to a long-vanished world of extinct animals, plants, and even humans. But although researchers have sequenced short bits of ancient DNA, most samples have been too damaged or contaminated for meaningful results. Now in a paper published by Science in December 2005, an international team reports using new technology to sequence a staggering proportion of DNA from a 27,000-year-old Siberian mammoth. "The next generation" sequencer that was used will revolutionize the field of ancient DNA.

A Dinosaur Shocker – a late breaking story – a look inside Tyrannosaurus rex.

A 68,000,000 year-old Tyrannosaurus rex has been found in the Hell Creek Formation in Montana and using the tools of modern cell biology, Mary Schweitzer, a paleontologist, has upended conventional wisdom by showing that some rock-hard fossils, tens of millions of years old may have remnants of soft tissue, such as blood vessels and muscle, hidden away in their fossilized bone interiors. The observations could shed new light on how dinosaurs evolved, how their blood vessels and muscles worked and settled the long-running debate about whether dinosaurs were warm-blooded, cold-blooded or both. The work is reported in the May 2006 issue of Smithsonian magazine. (Most paleontologists now agree that birds are the dinosaur's closest living relatives.)

Climate change in human evolution – an ancient story.

In a rich summary article, "Climate Change in Human Evolution in a January 2006 issue of Science, Anna Behrensmeyer comments on the increasingly profuse data on climate variations during the seven million years now thought to cover the development of hominid species – that is species similar to and preceding homo sapiens – that's us – with exciting revelations about the prolonged tensions between local ecosystems and global climate change – a strikingly relevant theme also for the future of our world.

How much can we rely on these time estimates of ancient periods? Improved techniques and experience lead to improved confidence, though I am mindful of Harry Horwitz's uncertainty principles.

The influence of pregnancy on the development of the mammalian brain.

A report reviewing significant steps in evolution gives evidence that - pregnancy and motherhood change the physical structure of the female mammal's brain, making mothers attentive to their young and better at caring for them. New research, reported in Scientific American early this year, suggests that hormone-induced alterations of the female brain may make mothers more vigilant, nurturing and attuned to the needs of their young, as well as improve their spatial memory and learning. In fact, some researchers are suggesting that the development of maternal behavior has been one of the main drivers for the evolution of the mammalian brain. As mammals arose from their reptile forbearers, their reproductive strategy shifted from drop-the-eggs-and-flee to defend-the-nest, and the selective advantages of the latter approach may have favored the emergence of hormonal brain changes and the resulting beneficial behaviors. The hand-or-paw that rocks the cradle indeed rules the world.

This does not mean that mothers are better than their virgin counterparts are at every task; in all likelihood, only the behaviors affecting the survival of their offspring would be enhanced. Still many benefits seem to emerge from motherhood as the maternal brain rises to the reproductive challenge placed before it. In other words, when the going gets tough, the brain gets going – its structure changes.

What leads to change and the creation of new species?

Regarding the origins of novelty and variation in the recently published, "The Plausibility of Life", an account intended for general readership, Kirschner and Gerhart, argue that the Darwinian explanation is incomplete and that the results of recent discoveries in cell and developmental biology can be used to remedy this defect. Unlike some of their predecessors, they are not hostile to the view that evolutionary change is the product of natural selection acting on variation that arises ultimately from mutation. Rather, they argue that the basic properties of cells and their interactions during development have profound consequences for the properties of the variability available for use by selection. These properties and interactions both constrain the possible types of alterations to the organism structures and offer opportunities for the rapid evolution of novel structures. The authors call this, "facilitated variation" which they offer as "an explanation of the organism's generation of complex change from a small number of random changes of the genotype".

Genomes for Everyone – a time for thoughtful appraisal.

Next generation technologies make reading DNA fast, cheap and widely accessible and are coming in less than a decade. Their potential to revolutionize research and bring about an era of truly personalized medicine means the time to start preparing is now. In an article in the January issue of Scientific American, the Human Genome Project (HGP) development is reviewed – the project's goal was to produce one individual complete human genome sequence for $3 billion between 1990 and 2005. The easiest 93% of the work was accomplished in the early years and the ongoing refinement of the technologies and methods has brought the street price of a human genome sequenced enough to be useful down to about $20 million each today. Still that rate means large-scale genetic sequencing is mostly confined to dedicated sequencing centers and reserved for big, expensive research projects. The "$1,000 genome" – that means your personalized complete sequence – has become shorthand for the promise of DNA – sequencing capability made so affordable that individuals might think the once in a lifetime expenditure is worthwhile – to have a few personal genome sequences read to a disc for doctors to reference. Many people attend to daily weather maps; perhaps we might one day benefit from

daily pathogen and allergen maps. The barrier to these applications and many more, including those we have yet to imagine, remains cost. Two NIH funding programs challenge scientists to achieve a $100,000 human genome by 2009 and a $1,000 human genome by 2014. A survey of the new approaches in development for reading genomes illustrates the potential for breakthroughs that could produce a $20,000 human genome as soon as four years from now.

What kind of numbers are we considering?

The human genome is made up of three billion pairs of nucleotide molecules. You can imagine the possibilities for variation and error, and the inevitability of mutations. Our three billion base-long genome is broken into twenty-three chromosomes. Recent improvements in sequencing analysis techniques have resulted in a nine-fold reduction in costs. Analytic imaging devices can now collect raw data at rates of one billion bytes (a gigabyte) per minute and computers can process the information at a speed of several billion operations a second.

Beyond developing new sequencing technologies, much work remains to be done to get ready for the advent of low-cost genome reading. Software will be needed to process sequence information so that it is manageable by doctors, for example. They will need a method to derive and individualize priority lists for each patient of the top ten or so genetic variations likely to be important. Equally essential will be assessing the effects of widespread access to this technology on people. This area needs priority, I believe, for early and focused attention.

More on genomes – Genes and Family – What science can tell you about your history and your health.

Our blood holds the secrets to who we are, and increasingly, individuals, families and research scientists are using genetic testing to tell us what we don't now know. Human genomes are 99.9% identical; we are far more similar than diverse. And that tiny 0.1% difference holds clues to our ancestries, the roots of all human migration and even our propensity for disease. Tens of thousands of Americans have swabbed their cheeks and mailed in their DNA to companies nationwide for testing.

As individuals track down their personal family narratives, population geneticists are seeking to tell the larger story of humankind. Our most recent common ancestors – a genetic "Adam" and "Eve" – have been traced to Africa and other intriguing forbearers are being discovered all over the map. Last month, one group of scientists found that 40% of the world's Ashkenazi Jews descended from just four women.

The more we learn about our families, the more we learn about our beginnings, using DNA markers and mathematical time clock calculations. Scientists say that by using Y and mitochondrial DNA, they can date the earliest female to 150,000 to 250,000 years ago and the earliest male to 60,000 to 100,000 years ago.

The most ambitious effort by far is the National Geographic society's $40 million Genographic Project which aims to collect 100,000 DNA samples from indigenous populations around the world over the next five years. The goal: to trace human roots from the present day back to the origin of our species.

Not everybody supports the Genographic Project. Indigenous populations have had their share of colonialists pillaging and many, still distrustful of dominant cultures, are wary of handing over their blood and the information it contains.

Genetic markers expand, so does debate over use.

As the use of genetic markers expand, so does the debate regarding limits and dangers of so-called personalized medicine. The gene variance is an indication of risk, not guarantees of disease, that evolved as humans moved around the globe. Even as such discoveries paved the way for targeted medicine, they raise concerns about cost, access, and genetic discrimination. "What do you do with the information when it's not guaranteed that someone will get the condition?"

Notes on unlocking the secrets of longevity genes – some remarkable possibilities.

In an article entitled, "Unlocking the Secrets of Longevity Genes" in a recent issue of Scientific American, Sinclair and Guarente report that researchers have found that a family of genes involved in an organism's ability to withstand a stressful environment, such as excessive

heat or scarcity of food or water, have the power to keep the body's natural defense and repair activities going strong regardless of age. By optimizing the body's functioning for survival, these genes maximize the individual's chances of getting through the crisis. And if they remain activated long enough, they can also enhance the organism's health and extend its lifespan dramatically. In essence, they represent the opposite of aging genes – longevity genes.

As one of the first longevity genes to have been identified, SIR 2 is the best characterized and will be the focus of this "Note". Much of the early work on this gene involves the study of yeast cells. When an extra copy of this SIR2 gene was added to the yeast cell, the cell's lifespan was extended by thirty percent. Amazingly, it was soon discovered that extra copies of the SIR2 gene also expanded the lifespan of roundworms by as much as fifty percent. It has now been established that in organisms as complex as fruit flies, the longevity gene is required to extend lifespan. And because the body of an adult fruit fly contains numerous tissues that are analogous to mammalian organs, we suspect that extending life in mammals is also likely to require the longevity gene.

A striking example of the longevity gene's ability to foster survival in mammalian cells can be seen in the Wallerian mutant strain of mouse. In these mice, a single gene is duplicated, and the mutation gives their neurons higher resistance to stress, which protects them against stroke, chemotherapy-induced toxicity and neurodegenerative diseases. Intervening pharmacologically in the longevity gene pathway might therefore forestall not only aging, but also specific ailments.

Because people have sought to slow aging for tens of thousands of years without success, some may find it hard to accept that human aging might be controlled by tweaking a handful of genes; but without actually knowing the precise, and potentially myriad causes of aging, we have already demonstrated in a variety of life forms that it can be delayed by manipulating a few regulators and letting them take care of the organism's health.

We also know that this family of genes evolved far back in time because today they are found in organisms ranging from baker's yeast, parasites and round worms, to flies and humans. In all these organisms but the last, which has not yet been tested, sirtuins – the name of the class of gene – dictate length of life. This fact alone convinces the investigators that sirtuin genes probably hold the key to human health and longevity as well.

We will not know definitely how sirtuin genes affect human longevity for decades. Those who are hoping to pop a pill and live to 130 may therefore have been born a bit too early. Nevertheless, those of us already alive could live to see medications that modulate the activity of sirtuin enzymes employed to treat specific conditions such as Alzheimer's, cancer, diabetes, and heart disease. In fact, several such drugs have begun clinical trials for treatment of diabetes, herpes, and neurodegenerative disease.

It may seem hard to imagine what life will be like when people are able to feel youthful and live relatively free of today's diseases well into their nineties. Some of you may even wonder whether tinkering with human lifespan is even a good idea. But at the beginning of the 20th century, life expectancy at birth was around forty-five years. It has risen to about seventy-eight, thanks to the advent of antibiotics and public health measures that allow people to survive or avoid infectious disease. Society adapted to that dramatic change in average longevity, and few people would want to return to life without those advances. No doubt future generations accustomed to living past a hundred will also look back at our current approaches to improving health as relics of a bygone era.

We have covered the waterfront, sufficiently to impart a sense of the range of forward movement. The influence of technical developments is profound, both on our understanding of the evolution of man and his early history and increasingly on applications influencing our health and lives generally. And the pace of advancement is quickening. But as much as I'm fascinated by the new discoveries, I am greatly concerned that the need for ethical guidelines may not be met in a timely way. If we know in greater detail possibilities of disease or developmental difficulties, possibilities not actualities, how should that information be shared, or protected, or employed. These will not be easy questions to answer.

And I must say that the concept of extending healthy human lives by 30% in the next few decades boggles my mind. The impact on the Literary Club alone leaves me speechless – and may require another paper to consider – but that will be on another occasion.