

P/272.2 The Human Organism

(2)

This was 80 minutes
after removal of
genus!
60 → 70 minutes

In this lecture, I will be confining my focus to the human organism, in the here and now, but as the product of organic evolution. I am reminded of the prophetic scene in Arthur Clarke's "2001" - the apeman's bone weapon, vaulted in the air is suddenly transformed into a rocket ship; and I will be asking you to use your own imagination to fill in, better than I could tell the story, about the evolutionary process in the interval.

Before I leap to the present, please allow me a remark, how the Darwinian model of the accumulation of information by selection of random variation has met every experimental test that can be devised in the laboratory. Processes as diverse as the development of drug resistance in bacteria and the development of specific antibodies in immunity have been amply explained in this way. Even directed assembly is (to stretch the concept beyond its lawful limit) a selective one: the units diffuse at random and those are selected which make the best fit. At a microscopic level, it may be difficult to distinguish what goes on in the black box of information transfer. Who knows how much of our own creative imagination is an ex post facto selection from a random combinatoric?

Nevertheless, however plausible is the Darwinian interpretation, the more we learn of biological adaptations, the more we are in awe of their intricacy; and there is still a leap of faith in insisting that is the whole story. The only alternative is a (Philip Henry) Gossean "special creation", the universe having been made (perhaps just one microsecond ago) exactly as we see it, with all of its fabricated evidence of fossil history, not to mention our own private memories. By its very terms, this is logically unassailable; and I would not waste much time arguing against it. We can proceed together to study the universe we see and try to make whatever sense we can of it; let those who will describe it, and our own consciousness, as a divine fiction.

My last interruption concerns "sex", and that needs no apology.

Before the work of the 1940's on bacteria and viruses, sex was thought to be an advanced evolutionary specialization. Now we observe it at the most primitive level.

How should we think about its origins? I take a more elementary view.

My own model of the ^{entire} biosphere ^{from its beginning to the present} is that of genetic systems all in some mutual interaction,

Some have even proposed that sex was ~~invented~~ invented by viruses to facilitate their more rapid dissemination.

remote or intimate.

be it cooperation or competition, Every animal, including the human, is immediately dependent on the genetic systems of plants, their functional systems of photosynthesis and of biosynthesis of amino acids and vitamins. A few animals have incorporated algae as intracellular symbionts. All of us have mitochondria likely to be of similar origin; the same for the chloroplasts of higher plants. The expression "plasmid" was coined to embrace the entire panoply of intracellular symbioses, including DNA or RNA fragments no longer capable of independent existence, like the viruses. It is a secondary, sometimes contradictory attribute whether the relationship is advantageous for the host. *Sax is one pole of that continuum of interrelationship.*

Even if life had a single monophyletic origin, it would soon have diversified, and given many similar opportunities for chemical symbiosis, as soon as specific catalytic potencies had emerged. Obviously, molecules or molecular complexes that were predisposed to easy aggregation of complementary capabilities would have had an evolutionary advantage.

Perhaps this is already built in to template directed assembly through template switching (copy choice recombination). This model goes beyond that of the potential for evolutionary adaptability, the usual argument for sex, to the use of recombination to meet a pressing exigency through cooperation of specialized genome parts.

So we should look for sex at the most primitive molecular level.

SLIDE -- copy choice assembly

not used.

In fungi today, it is easy to demonstrate several levels of integration:

- (1) cross-feeding of complementary mycelia, exchanging nutrients through the medium (syntrophism);
- (2) heterokaryosis - diverse nuclei sharing a common cytoplasm, sometimes even as between a parasite and its host;
- (3) heterozygosis - the more definitive exchange of chromosomes, and along with that,
- (4) crossing-over, the exchange of chromosome parts. These interactions can be regarded as a continuum, relying on progressively more elaborate, evolved functions.

This concept of hierarchies of genetic organization has long been thought of as what we mean by a (multicellular) organism, perhaps even of a society.

MECHANISM

Central to the biologists' model of the human is mechanism.

How easy for the lay person to assume that the scientist -- or the physician, is lacking in empathy -- not understanding that the very discussion of the matter imposes an eschatological dilemma.

I want to take up the phrase
" Man as "mere machine". "

Some people are horrified, others take delight in this kind of attribution. For example, Dr. D.E. Wooldridge, a physicist perhaps known as a founder of TRW (Thompson-Ramo-Wooldridge) Inc. --wrote a work ^{some time ago} entitled "Mechanical Man -- the Physical Basis of Intelligent Life," ^{with the faulty conclusion} concluding "that a single body of natural laws operating on a single set of material particles completely accounts for the origin and properties of living organisms. Accordingly, man is essentially no more than a complex machine." *He and I use ~~it~~ in its epicure sense, males & females alike.*

A few eccentrics aside, the whole community of contemporary science shares the view that the same laws of nature apply to nonliving and living matter alike. All of us who investigate the chemistry and physics of living organisms pursue our work as if organisms were complex machines, and we find man to exhibit no tissues or functions that would except him from this way of analyzing human nature.

Nevertheless, we are or should be careful to state just what we mean before we assert that "man is a machine," and much more so before using the phrase "merely a machine." The statement that man is "a mere machine," or a mere anything, is a needless irritant to precise communication between scientists and laymen. (We might better proclaim that "man is merely the most complex product of organic evolution on earth, the only organism whose intelligence has evolved to the point that his culture ~~far~~ ^{far} *transcends* his biological endowment.")

The "mere machine" phrase is usually a retort to the claim that there are mysteries of human nature that are, in principle, beyond the reach of scientific investigation. Scientists would do better to save their breath quarreling about what they can analyze in principle; in their own work, they are mercilessly pragmatic about confining their conclusions to what they can examine in practice.

There are, in fact, theoretical limits to scientific analysis that may justify men in repudiating ~~by~~ Wooldridge's assertion that "the concept of the machine-like nature of

man is incompatible with a long-cherished belief in human uniqueness." There is nothing "mere" about a machine as complex as a man; the word "machine" is just a manner of speaking about the scientist's faith in a universe ordered by natural law. That faith was expressed most eloquently by the French philosopher the Marquis de Laplace, who averred that, given complete knowledge of the universe at one instant, the scientist could in principle compute all of its future states in infinite detail.

In practice, we must now remind ourselves, the scientist and his computers are machines that occupy space and consume energy. The process of calculation itself soon reaches fundamental limits. If the whole visible universe were one gigantic computer, made of components at the theoretical lower limit of size and energy consumption, it would still be insufficient for some problems that are soluble "in principle." In fact, a priori calculations of the folding of a single protein molecule would be one of these. So calculability in principle is a long way from assurance that we can use mechanical laws in practice for precise prediction of the ~~the~~ behavior, even of the simplest organism: not that any non-mechanical principle is involved, but sheerly from complexity.

To deny mechanism is simply to shirk from the task of analysis. Secrets like the mechanism of gene replication were once thought to be beyond the bounds of imaginable understanding. Until we try, we do not know how complexity will yield to our abstractions. We have the reassurance that natural selection could not have operated on the unpredictable, ^{its substrate must} ~~unless this tended to~~ be inherited from one generation to the next. Development, e.g. that humans generally emerge from human eggs, must also depend on conserved outcomes. That enhances the odds that the complexities will be amenable to our analysis.

EVOLUTION AND THE NATURAL Evolution and the concept of the natural Fallacies of the "wisdom of nature." Man as a man-made species -- Hesiodic myth: Prometheus' justification, not so different from the biblical (Legend of the Garden) -- subject to Nature alone, we would have been destroyed or displaced by further evolutionary progress. Culture / Technology has stayed that. We are left relying on our own imperfect wit to manage a global economy, unwilling to pay the price of natural selection, of a free market; and to match in a few centuries a pace of change that would be hundreds of millions of years by nature's own devices.

Imperfections of organic adaptation: e.g. Hb-S. Time scale dissynchronous with

human change; and ethically blind. The dark side of "nature" -- the evolutionary law of marginal advantage. Proportionately as many "deaths" from homozygous sickle cell disease as were saved from malaria. This is merely the best known case of balanced polymorphism by heterozygous advantage; whole panoply of MHC related disease, e.g. immune system, diabetes must have similar foundations.

Abortion

Disappointment at shallowness of debate. Life a continuum
 Implications of accepting fertilized egg == human. When a
 conscious person? (A chick embryo is alive; so are tissue cells.
 Theologically arbitrary. Augustine: No man can tell

Genetic variability and genetic fatalism. Tabu subject.

Poverty of current methodologies, e.g. in genetic determination of I.Q. Political abuse has overshadowed the undeniable foundation of much individual variability in human attributes; but I hasten to add this is unlikely to be dominated by racial categories. Shortcoming of twin studies (despite Cyril Burt, worth commenting on.) Domain of application is the environmental spread of the studied population. And what do you do with a result that claims, e.g. that 65% of the variance to due to genetic diversity in that population? Differentiated remedial efforts most likely; we often don't know enough. Illegitimate to transfer any such conclusion to racial categories when environmental differences are rampant; and culture of poverty, of 1 parent families, of teenage pregnancy, is so hard to alter.

In due course, like next year, we will see the RFLP technology applied to an ever increasing number of behavioral traits. IQ is certainly polygenic, but if fruit yield in tomatoes can be dissected that way, surely IQ can be as well. Need large segregating kindreds; again problems in transferring to other groups, but at least specific tags can be looked for. Remediability (contra fatalism) of focalized problems is the socially constructive motive to pursue such research. Just as we have learned much from the genetics of heart disease that is being used today as the basis of prevention and pharmacology, the genetics of IQ will give us our clearest paths to the enhancement of intellect for everyone. Meanwhile, we have yet to make full use of the obvious, that prenatal infection and malnutrition account for a substantial toll of mental retardation.

Race as sexual selection. Discrimination has left such deep scars that politically and legally we have taken the path of emphasizing racial classification in the name of redress. Obviously untenable as biological categories; but we may have passed the point of no return in decision to establish the US as a multi- rather than a non-racial community. In the long run, the propensity of humans to mix will create such admixture that the multi-racial system will collapse, except with some historical sentiment of ancestral traditions, often mixed within a given family. Multi-racial divisions are likely to continue, no matter how flawed the biological basis, as long as many people are discriminated against or feel they are the legatees of historic injustices.

NEW REPRODUCTIVE TECHNOLOGIES

Having been among the first biologists to bring up the "implications" -- ca. 1962 -- and discovering that it seemed to function more as a diversion from the REAL ethical problems, like the needless deaths of millions of children, I've been loath to spend much time discussing the "new reproductive technologies". But there have been remarkable technical strides just within the last few years, and we are facing some pragmatic issues of ethical and legal perspective -- ~~surrogate maternity (not really new technology); transovulation (done in cattle); -- which in these examples do not involve novel genetic techniques -- and a number that do, where ideas of Gene therapy and cloning are paramount.~~ Be clear where I stand: I dis-advocate; I would discourage; I am concerned about commercial exploitation; I hesitate to forbid -- I don't relish the policemen in the bedroom or the delivery room.

Before we condense we should be having a more serious debate about the values we are trying to protect. Center the system about being innovative in this field area.

Every day in "normal" parenting we have monstrosities that do far more human damage than any technology is likely to concoct. ~~We see that~~ ^{In their capricious sphere,} social workers impose severe standards for adoption that we would not think of imposing on biological parenthood. *Why is one more a matter of protected privilege than the other?*

I would forbid the enforcement of contracts, the profit motive. And I am pleased to see a number of states moving towards legislation that put limits on "renting a womb" for a few, in keeping with ~~new legal standards against the marketing of human organs for transplant.~~

I don't plan to go into exhaustive speculation about all the contingent possibilities of genetic engineering. They will be developed in a social and technological milieu notably

reproductive technologies and

SLIDE

different from our own. No fear they will arise without close scrutiny and public attention!

In today's headlines: *(AID is incidental)*. *Innovation* / *use in medicine* coming. *Surgeon*. *legal action* ~ *sale of organs*. ~ *human dignity*. [*Fees to mediators* / *surgeon see below vs.*]
IVF - jumped into practise s/ extensive animal or clinical trials as far as reported, mainly problem is low success rate.
Don't push it: odds of malformation.

separate
biop. from social
affiliation

Genetic screening and prediction -- earliest reality of all
The RFLP markers.

Zygote selection far more robust. Prenatal diagnosis, applied to IVF moving along; may become feasible to diagnose genetic disease before implantation.

Dysgenic implications of rescuing faulted genotypes.
Gene frequency change takes a long time.

With respect to genetic interventions generally, I would prefer what I call the "euphenic" approach, a term I coined about 25 years ago to stress we had an alternative to "eugenics" ...

Somatic "gene" therapy. Don't confuse with eugenics!
alternative is tissue grafting

Germline gene therapy -- problematics of need for perfect targeting. What problem does it solve.

Parthenogenesis - radical feminists' dream
Spurway story. Turkeys.

Cloning -- essentially achieved in mice. To what end?

THE HUMAN GENOME PROJECT.

As we have seen, explanation in biology is largely reduced to an expression in the

ARE THESE REALLY THE IMPORTANT ISSUES?
We fiddle about 1 frozen embryo - and we let AIDS happen

come back to that.

language of DNA-sequences. To a degree unprecedented in biological history, we can describe the agenda for much of the programmable research for several decades to come.

It is undeniable that a full catalog of a human DNA sequence would be a great convenience in the solution of problems pertaining to particular segments. You have all heard of the proposal to mount a coordinated project to achieve the total map of the human DNA within this century.

There is great merit in the prospect, and I would share the excitement of achievement in a host of steps toward that goal. Nevertheless, I have many concerns about some of the marketing for the project, going on round the world; though I am reassured that much of the US leadership involved in planning the project shares my concerns. I am not sure that a Manhattan project is the best way to achieve the scientific aims of understanding the genome.

a) The Project is overwhelmingly a technological rather than a scientific one. To be sure, on the way to the map, many anomalies and enigmas will be discovered -- these phenomena will demand scientific inquiry; but they are not part of the project budgets. If they were, The Project would be no more than a restatement of the current broad efforts at understanding the genome, i.e., molecular genetics.

b) It may be a highly centralized effort, with large funds flowing to a few centers. This is perhaps why it may be so attractive to certain entrepreneurial spirits; but I do not believe this is the best way to encourage scientific creativity and a critical elan. It has already attracted political constituencies who smell "pork", and initiated turf battles among government agencies. Are we likely to get good science out of such processes?

c) It runs great risk of crowding out a host of other diversified research efforts. d) Many of the premises about "the genome" still need to be met head on. It is certain that information about the polymorphism of particular genes within the human population will be at least as important as getting all 3 billion characters of one sample onto a computer memory. We have more subtle methods for looking at polymorphism than the brute force of total sequencing. Furthermore, it is far from certain that the genome remains constant within a given individual, apart from the germ line of cells. We know it is variable in cells of the immune system, and it may well be in others in relation to

development and aging.

e) The Project is being sold ^{by some} on false premises. Were we to have the entire map given to us by a *deus ex machina*, say by an extra-terrestrial, we would be just at the start of the enterprise to understand how those sequences relate to all the gene products that are the substance of the cell. About 100,000 of them have to be accounted for. We have by now profound information concerning a score or so human proteins; each of them is at least a life's work. At a modest \$10 million each, that would amount to a trillion dollars for the full set. Will there not be a backlash of distrust of those who marketed The Project as the last word in biomedicine?

~~My own~~ ^{The} recipe ^{I hope will be adopted} is that we make more discriminating selections of targets before committing to the task. A few hundred human proteins are now discernable as agents of important biological activity; that number will soon grow to perhaps a thousand, that percentile should be the priority list for further inquiry. For these, we will look in detail into regulation, three-dimensional structure, genetic variability within and between species, physiological interrelationships and therapeutic applications. To pursue such enquiries will take much more than the engineering mentality that would apply a single methodology for a single sweep. It will need a sense of the organism, and a focussed expertise on, even fascination for the parts under scrutiny.

How far will reductionism take us in the long run? 100,000 genes and gene products interact in the developmental pathways: and we have great challenges in understanding the structure and function of the components one by one! We can foresee great advances in explaining an epigenetic or pathogenetic pathway once observed -- that clinical or natural historical observation will help isolate the pertinent variables. Much more difficult will be the prediction of, say, the details of disease issuing from nucleotide changes in an arbitrarily marked gene. The enormous complexity of these interactions of genes with one another, and with environmental experience may, to be sure, be made more tractable with the development of mathematical formalisms and computer models: indeed these are rapidly becoming indispensable even for narrowly focussed research. In practice, for the foreseeable future, explanation in biology will still resemble that in history more than it does in nuclear physics. Practical applications will emerge from accumulated knowledge looking for uses to a much greater degree than in past decades, but most of all from the convergence of theory with the observation of the world as it has actually evolved.

The ideology of the Human Genome Project is a fruit of the most important revolution in

biological science of the 20th Century. Let it not be so institutionalized that it submerges the next generation of unprogrammable innovation.

No matter how titillating these algenical dreams, main biological intervention is prolongation of life-span!

We have seen, in this decade, the completion of two cycles of medical science and practice; with the DNA revolution we are well into the third.

The first cycle rested on the scientific foundations of medical microbiology laid just a century ago. The recognition of germs as living organisms and as specific agents opened the era of scientific medicine. With the looming "conquest" of bacterial infection, the next major challenge to medical science was the more formidable one of the human constitution: heart disease, cancer, psychiatric disorder overtook scarlet fever, tuberculosis and polio as the central objects of public health concern. But physiology, flowering from 1922 on (the milestone is the discovery of insulin) was crudely empirical. The inherent intricacy human pathology, rooted so deeply in molecular and cellular structure, outreached the existing base of applicable scientific knowledge. This ignorance delayed the building of a theoretical program for the control of these killers comparable with the advances in the golden age of bacteriology. Basic science, during that second stage, owed more to insights from clinical practice than vice versa: note, e.g. the effectiveness of phenothiazines in schizophrenia. Just in the last few years have we seen many new drugs that have been designed on rational principles, and rest on a robust foundation of prior knowledge of DNA and protein structure.

These medical advances are burgeoning, doubling the average life span in the century, with enormous consequences for the structure of our population. Much to do about health costs, and blamed on technology. Others argue that only technology can drive costs down; but we must take account of our insatiable appetite for long life (and good health when that can also be had.) Yes, health costs will continue to go up immeasurably with ever more effective technology, and esp. with abrogation of mortality, the only cost saver.

The end result is that the nursing care of many individuals between their tenth and fifteenth decades is going to be the largest cost connected with the elaboration of health technology. When an artificial heart is perfected, it will be a costly intervention, and of course it would be

far preferable to prevent heart disease than to use a machine replacement. The person who is in heart failure will not take kindly to that admonition. The real cost of that technology, a large multiple of the implant itself, will be the innumerable tableau of further surgical procedures that will be enabled: a) from the mere survivorship of aging candidates, and b) from the fact that the fragility of cardiac function is one of the principal deterrents to aggressive surgery in elderly patients.

Yes, we can hope for improvements in the quality of living as well as in the prolongation of life, but that is a more difficult thing to do. To keep the overall organism going in some patchwork, makeshift fashion is technically far easier, whether we are talking about today's medical care or about new patterns in medical advances.

Health is a good to which we all aspire, to which there will always be some margin at which we are willing to make some investment. It is our own decision about the point at which we are willing to forego further costs, for ourselves and for others, that might be applied to the next marginal hour of longevity, to add some marginal hope that a remedy can be found for our ill.

Need better planning re savings during productive life. Intergenerational responsibility

SPECIES CENTERED IDEALS

Concern that these bioethical controversies have distracted attention from population pressure, hunger, disease in the world. One frozen embryo ... more attention than 3 million avoidable deaths from diarrheal disease.

PANDEMIC AS NATURAL EVOLUTIONARY EVENT.

I referred earlier to the wisdom of nature; that should not be confused with human advantage. The evolutionary paradigm is blind to the moral superiority of the human species. Nowhere is this more poignantly thrust on us than in the human species' continued vulnerability to large scale infection. We fail to acknowledge our relationship to microbes as a *continued* evolutionary process. This is far from equilibrium, and we cannot take for granted near term outcomes that would be optimal from either our, or our parasites', perspective, We have a reasonable lead on bacterial intruders; we grossly neglect the protozoan parasites that mainly afflict the third world; we are dangerously ignorant about how to cope with viruses. Some

mitigation is built into the evolution of the virus: it is a pyrrhic victory for a virus to eradicate its host! This may have happened historically, but then both that vanquished host and the victorious parasite will have disappeared. Even the death of the single infected individual is relatively disadvantageous, in the long run, to the virus -- compared to a sustained infection leaving a carrier free to spread the virus to as many contacts as possible. From the virus' perspective, its ideal would be a nearly symptomless infection, in which the host is oblivious of providing shelter and nourishment for the indefinite propagation of the virus' genes. Our own genome probably carries hundreds or thousands of such stowaways. The boundary between them and the "normal genome" is quite blurred; intrinsic to our own ancestry and nature are not only Adam and Eve, but any number of invisible germs that have crept into our chromosomes. Some confer incidental and mutual benefit. Others of these symbiotic viruses (or "plasmids") have reemerged as cancer genes.

At evolutionary equilibrium, we would continue to share the planet with our parasites, paying some tribute, but even deriving from them some protection against more violent aggression. Such an equilibrium is unlikely on terms we would voluntarily welcome: at the margin, the comfort and precariousness of life would be evenly shared between the parasites and ourselves.

In fact, innumerable perturbations remind us that we cannot rely on "equilibrium" -- each individual death of an infected person is a counter-example. Our defense mechanisms do not always work. Viruses are not always as benign as would be if they had the intelligence to serve their long term advantage. We must now face the even greater absurdity of the intentional dissemination of pathogens in warfare. This is indeed the subject of the 1972 Biological Warfare Disarmament treaty; and for a time we had hope of breathing easier. The recent breakdown of enforcement of the 1925 Geneva Protocol, on chemical warfare, warns us of the need to establish a stronger international regime, particularly with respect to proliferation to smaller and more irresponsible countries and splinter groups. This is a subject on which the US and USSR finally see eye to eye, and the more serious problem is the regulation of chemical exports from countries whose governments have a talent for looking the other way. They will rue it; but so will we, and unhappily perhaps not before the BW treaty is flouted as outrageously as the CW has been.

As one species, we share a common vulnerability to these scourges. No matter how selfish our motives, we can no longer be indifferent to the suffering of others. The microbe that felled one child in a distant continent yesterday can reach yours today and seed a global

pandemic tomorrow. How can we procrastinate any further, or have any reservations, about a common cause -- one that responds to every outbreak of disease anywhere as a challenge to all of us. "Send not to know for whom the bell tolls ... it tolls for thee."