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THE BIOLOGICAL MODERN

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The Biological Modern.

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> *"The mode of existence peculiar to such entities [epistemic objects] derives precisely from their resistance, resilience and recalcitrance rather than from their malleability in the framework of our constructive purposive ends."* [1]

Although one could identify many possible starting points for the modern discipline of biology, a convenient choice is 1802 when the term "biology" was coined in two separate places in Europe, ***logos*** was joined to ***bios***. The act of nomination of a nascent science of living beings qua living beings indicated an awareness that the eighteenth century categories and practices of natural philosophy were increasingly obsolete more than the announcement of a mature replacement. [2] As I showed in French Modern: Norms and Forms of the Social Environment, diverse lines of knowledge and action in multiple domains during the nineteenth century can be characterized by a gradual, temporally and spatially extended, process of disarticulation of previously embedded elements. [3] Previously inter-related elements came to be seen as losing their natural (cosmic, theological, moral) locations and connections and hence their inherent meaning. As this process spread, constitutive elements, each in their own distinctive fashion, were coming to be seen as independent, or quasi-independent, of previous contexts and attachments. One instance of this process was the incremental dissolution of the authority of claims for the inherent moral and political import of architectural styles, or, to take an example of an ascendant response to such dissolution, the rise of the "social" as an object of intervention meant to remedy the erosion of moral bonds, traditional or otherwise.

What had seemed natural or necessary was under attack, or simply mocked, or appeared antiquated, in the light of new forms of thought, action, and passion. Or, at the very least, in anticipation of the emergence of such forms. [4] By the end of the century, reformers and revolutionaries were reshaping multiple domains into one or another form of technological modernism: that is to say, object domains constructed in such a manner that knowledge produced about them takes the form of a normatively impelled intervention for reform. The problem was: how to establish a relationship in which norms and forms would be mutually re-enforcing?

There was broad agreement that progress, or social amelioration, or pubic health, or urban spaces, or the psyche, would have to pass through the dynamic mediation of knowledge claims and technical practices. The process of disaggregation of previously articulated elements contributed to rendering the domains they constituted as epistemologically and ontologically occupied by objects susceptible to intervention, available to be reshaped according to norms subject to specification and debate among and between citizens, scientists, and experts. By the end of the century thinkers concurred on the need to consolidate an analytic vocabulary adequate to understanding these changes and the problems they posed; in this light one thinks of the work and reception of Emile Durkheim, Max Weber or (slightly later) Aby Warburg or

Ludwig Wittgenstein, among many others. With this broad disruption of tacitness came a sense of a crisis of human life forms that only gained momentum and urgency as the processes of internal rationalization, standardization, and loss of aura, proceeded; a process that subsequently has been thoroughly described and theorized by generations of professors.

In retrospect, a prime diacritic of these changes was the emergence of categories of analysis and self understanding such as "culture" and "society." This emergence was a correlative of an awareness of a state of crisis in "*Lebensfuhrung*." Whether the crisis was cast as one of economy and society, or as one of the disconnection between culture, society, and psyche, the path to understanding was seen to be found in a nascent twentieth century social or human or cultural or psychoanalytic science. And their associated techniques of reform.

Although the turn of the century generation of social thinkers tended to see these processes as indicators of crisis and dissolution, the same processes could be -- and were -- interpreted in other ways, including as a vast freeing up of new possibilities, a sudden lightening of the load of tradition, a new dawn. Whatever else it has been, the twentieth century has been a century during which vast forces, creative and destructive, have been unleashed. If the social sciences diagnosed a sea change in forms of human life, and if a century of unprecedented death and destruction followed, there were also myriad creative efforts of new forms in literature, music, dance, architecture, painting, theater, social organization, kinship relations, property systems, and, of course, myriad knowledges. In retrospect, from a vantage point at the beginning of the twentieth first century, few of these changes appear to be as revolutionary as they pronounced themselves to be; in fact many are better characterized as partial continuations of aspects of previous practices but severed from a mangle of historical connections and accretions; or as swerves or "secessions" from previously taken-for-granted norms and forms. [5]

In vitro.

Recently, historians have begun to identify and document homologous processes in the sciences of living things during the twentieth century. It was early in the century that a move away from the holism of the living organism and its milieu as a privileged and distinctive site of bio-science initiated a century long process that the historian Philip Pauly has aptly called "biological modernism." [6] Pauly identifies a key aspect of this process as the entry into the life sciences of what he calls the American engineering ideal of "just do it," and figure out later what it means or why it works. One example of this approach can be found in what historian Lawrence Kohler has nicely dubbed the "Lords of the Flies" at Columbia University who through their technical tinkering with the fruit fly, *Drosophilia Melangonaster*, chosen in part for is adaptability to the academic calendar (rapid breeding, easy upkeep, large numbers, consistent observable phenotypes) ushered in the modern science of experimental genetics. [7] The Columbia example underscores both that there is no single way of writing this history, one can easily identify precursors to such developments (such as Mendel) even while candidate precursors exhibit distinct differences as well (individual rather than team work, timing and institutional placement of the work, explanations of the phenomena, retrospective plausibility of the results, etc.) and subsequent developments in *Drosophila* genetics that eventually led investigators back to the wilds to do population studies. What Mendel and Thomas Hunt Morgan shared, however, was a living organism as their object of study. In that regard, their break with the older biology was not total. While Mendel's peas were observed and described in the monk's carefully cultivated garden – living beings in a controlled milieu – Morgan's multitudinous swarms thrived in glass tubes, set on racks at least when the tubes were not being held up to the light and observed. In retrospect, today we can see the Columbia group taking a half step forward in the momentous change from biology working *in vitro* rather than *in vivo*. Or more emphatically, we can see a step toward controlled experiment, under laboratory conditions, i.e. science.

Anthropologist-historian, Hannah Landecker, in her book, Culturing Life: How Cells Became Technologies, poses and answers the following question: "How is it that life, once firmly in the interior of bodies of animals and plants, came to be located in the laboratory?" How did living matter get extracted from and stripped of the individual forms of organisms? [8] She describes a move away from the nineteenth century techniques of removal of tissue from the body and its dissection and histological analysis to one in which the primacy of the *in vivo* is gradually replaced by controlled experiments *in vitro*. Landecker documents the series of technical procedures starting early in the century that were eventually gathered together first under the name of "tissue culture" (1907) and later "cell fusion" (1960s). Iconoclast innovators such as Jacques Loeb and Alexis Carrel audaciously proposed a biological modernist agenda and imagined an experimental program that would test its viability: the engineering ideal in biology took shape.

Loeb continued to work on inducing changes in whole organisms (sea urchins). The French-American transplant surgeon and Nobel Prize winner Carrel, working at and being funded by the Rockefeller University in New York, sought to go beyond the organism with its unmanageable complexity and to devise techniques for tissues to be made available for observation and experimentation removed from any body or natural milieu – yet still alive. Furthermore, Carrel saw that for long term experiments on process to be possible, it would be necessary to keep them alive in such a controlled milieu - indefinitely. While the popular coding of this program presented it as a version of the dream of immortality, scientifically it was taken up as a technical necessity, a problem to be solved. Carrel's solution was the technique of ”subculturing,” of using fragments of the old culture and providing “fresh nutrient media, and thus starting a new culture continuous with the old. This approach eliminated the necessity of going back to the organism for more tissue: “in principle, once a culture was established, it became the source of ongoing life.” [9] The successful creation of such a controlled milieu would enable Carrel to “do physiology at the cellular scale,” to intervene or interrupt “life processes to see how they worked, as they worked.” [10] These steps –- technical, scientific, visionary, affective -- were instrumental in ultimately establishing the cell *in vitro* as a fundamental (if not unique) site of experimentation on fundamental biological processes.

The fact that (tissues) cells could live and thrive outside the organism once certain basic conditions (reagents, nutrient milieu, sterile and standardized glassware, refrigeration, steady sources of electricity, etc.) for their survival and thriving were mastered came as a shock to the scientific establishment as well as for the public and the media. The affect of holism both underpinned previous physiological understanding “life” and obscured (what proved to be) scientifically superfluous beliefs, assumptions, and meanings. Carrel, Loeb, Harrison and others, modernists all, contributed to a critical disaggregation of this superfluidity. Typically, those who held previously simply unexamined or scientifically indefensible positions and suffered consequent dis-orientation either re-examined their positions or anathamized the blasphemers with the slings and arrows of diatribe, polemic, and character assassination, the weapons of ressentiment and fading power.

Thus, tissue culture technology freed biological experimentation from its reliance on organisms and their natural milieus. It successfully substituted an *in vitro* milieu that was gradually improved through long practical trial and error with reagents, materials, standardization of procedures, exchange of know how, re-organization of laboratory spaces and supplies. The tissue culture technique provided a means to render the internal processes of the cell visible, it permitted an extraordinarily precise visibility of previously hidden structures and functions. Additionally and most importantly, this isolation and visibility provided a platform through which and upon which the temporal dimensions of these processes could be observed, studied, and altered.

If tissue culture permitted an unexpected autonomy and plasticity to fundamental vital processes to be revealed, its later prolongations in the techniques of cell fusion and cell hybridization showed that many more assumptions about what was taken to be the fundamental givens of nature would have to be re-examined in the light of scientific demonstrations to the contrary. Cell fusion – bringing the contents of cells of different species or different organisms into a common cellular envelope – demonstrated that, at least within cells, not only were species barriers not universally operative but what the nascent science of immunology had taken to be the organism's basic defense systems could be bypassed as well at the cellular level. Thus, species barriers and individual immune defense proved to be of lesser significance – that is to say they applied within specific domains of biological activity but not everywhere -- than biologists and theologians had taken them to be. Nature, once again, proved to be more plastic and more complexly structured than poets and scientists had dreamed of, or allowed for.

After the Second World War, new waves of technological innovation made it possible to cultivate viruses in cell culture. A further step was the subsequent inclusion of living human materials fully into the domain of the reconstructed milieu, the famous cell lines that have played such an important role in medical and molecular biological research. These developments were spurred by the (ultimately successful) attempts of the virologist John Enders at Harvard to define the conditions necessary for an artificial medium to grow viruses. In the 1940s Enders succeeded in infecting cells with a virus and keeping them alive long enough to have the virus produce more of itself. This achievement allowed scientists to observe the process of growth and infection with its concomitant changes in the infected cell. Cytopathology was born; it was now feasible to conduct experiments on human tissue overcoming the practical constraints that parallel experiments on human organisms confronted. The formal elaboration of the ethics of such research would only take place decades later.

The whole enterprise of *in vitro* experimentation was improved and accelerated with the appearance of new funding sources as well as a new scale of demand calling for a different order of materials and coordination. The National Foundation for Infantile Paralysis, supported by the March of Dimes charity, adroitly and aggressively using the new media (radio, television, movies, advertising) and calling for and achieving mass participation in the funding and direction of scientific research provided unprecedented resources for individual researchers as well as a national infrastructure of research and dissemination. "It was through this association with polio that human cells in culture became subjected for the first time to manipulation directed toward their mass production and wide distribution as a semi-standardized research tool." [11] The Polio campaigns also required and achieved an ethic of large scale exchange of cell culture materials between individual scientists, moving beyond (although not eliminating) the personal exchange networks previously in place. Trust and personal knowledge of others' motives and research agendas continued to play their role but the heroic days of hand delivery of cell lines from one scientist to another was passing into history and folklore. The success of the polio vaccine campaigns, the growth of the National Institutes of Health, the massive funding of the War on Cancer, the challenge of Sputnik, all contributed to a change of scale and pace in American scientific culture.

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Landecker summarizes these changes thusly: "Tissue culture was in many ways the expression of a strong, century-long desire to fit complex beings into the same easily manipulable experimental spaces as their simpler single-celled counter-parts, bacteria. Not so much to use bacteria as model organisms for more complex animals, but literally to make complex animals more like their model organisms by making their constitutive biological matter conform to the shape, time and technical forms of their simpler experimental models." [12] Variants of this program not only continue today but have been amplified beyond imagination. Subsequent decades (1970-2005) witnessed the understanding of the genetic code, the rise of recombinant DNA technology, sequencing methods, oligonucleotide construction, the polymerase chain reaction that yielded nearly unlimited quantities of DNA upon specification, powerful cloning vectors, the mapping and sequencing of genomes, the vast powers of computing, the internet, the rise of the biotechnology industry at a global scale, the rise of the bioethics establishment, transgenic animals and plants, and many more less heralded if significant technological tools. Analytic manipulation – amplification, reduction, activation, deactivation, arrangement, rearrangement, substitution, elimination, proliferation, variation, -- continues apace.

Although the normativity of much of this activity remains in the line Landecker has described – making constitutive biological matter conform to the shape, time, and technical forms of [ ] simpler experimental models – recently the equally hoary impulse to engineer living beings per se has re-emerged. Its current avatar is called "synthetic biology" or "synthetic genomics." This time around it may well be a plausible project.

What Synthetic Biology was in 2004.

Synthetic biology began its existence as a visionary but minimally defined project. At the outset, the name was a basically a place-holder or as some of its critics hold, a hoped for brand. From our perspective, Synthetic Biology is another development within the (at least) century old tradition of the "Engineering Ideal in American Culture." [13] At the beginning of the twenty-first century, after at least two decades of massive sequencing projects (and their associated apparatus), twenty-first century synthetic biology represents a return of the organism (and both the internal and external milieu) as an object of reformation. Or, perhaps more accurately, as we shall see shortly, remediation. Of course, Loeb's organism and that of synthetic biology are quite disparate. Today, that organism is "the simplest one known" or better "the simplest one possible." (Tom Knight). Nonetheless, these engineers clearly have a feeling for the organism. And that feeling is palpable excitement about making living beings function differently. Synthetic biology aims at nothing less than the (eventual) regulation of living organisms in a precise fashion according to instrumental goals set by the engineer.

In 2005, not only are genomes sequenced with regularity and a steady flow of genes inventoried and annotated but an array of other active biological parts and functions is being identified and catalogued. All of this science and technology proceed on the basis of a tacit faith in a principle of an economy of nature. That is to say that nature must consist in isolatable and describable units and functions. Things appear to be complex in part because we don't yet posses the capacity to analyze them, to break them down into parts. And the skill to reconstruct them other than what they had been. Living beings are also complex, it is held, because of their history; they evolved under specific selective pressure in particular environments. The products of such natural selection demonstrate fitness but do not necessarily yield the only way that the organism can function; quite the contrary. Evolutionary history contains lessons about functionality but for contemporary biologists there is nothing scientifically sacred about the paths followed to arrive at the functionality. Furthermore, the specific functions themselves are neither inviolable nor immutable. For a scientist, there is no ontological or theological reason why specific functions – whatever their history -- can not be redesigned.

Today, the engineering project of building parts that either embody or produce specific biological functions and inserting them in living organisms is at the stage of moving from idea to concept. The concept is being synergistically linked to an ever-expanding set of technologies and to increasingly sophisticated experimental systems. There is agreement within the synthetic biology community (and beyond) that a necessary if not sufficient initial step required to further this project is to conceive of, experiment with, organize, and reach broad consensus on, standardized measures and processes. These standards are recognized to be initially crude, and will certainly have to be redone, but the important step is to begin to create them and to instill an awareness and sensitivity among practitioners as to their importance.

The recent history leading to the present conjuncture is well-known ranging from several decades of demonstrating how DNA could be manipulated without altering its fundamental qualities. DNA is remarkably pliable; longer and longer oligonucleotide sequences have been constructed (hence they are no longer oligos anymore). Precise sequences have been inserted with increasingly precision and forethought into other organisms; it is archaic and misleading to speak of "strawberry" or "flounder" genes. Such archaisms lead to metaphysical or theological debates about what mixing species does, when what is really being discussed are sequences of DNA inserted into other sequences of DNA. No laws of nature are being violated –

quite the contrary. DNA itself is universal; if there are questions to be posed about qualitative distinctiveness of living beings such questions must be posed at a different level. The specificity of species does not lie at the molecular level. The vision of the molecularization of life is, as they say, "so 90s."

The massive sequencing power put into practice during the 1990s produced complete DNA sequences for a new biological unit called the "genome." The genomes of multiple organisms have now been sequenced and the process of cataloguing and annotating those genomes is proceeding apace. Biologists can now be sure that they can have the complete inventory of an organism's genes, if by genes one means coding and regulatory functions as dictated by DNA sequences. Of course, such an inventory does not equal the organism nor does it determine its behavior or physiology although it does contribute to these functions in ways that are only beginning to be understood. A simple but powerful example of this insight is found in the work of the Roger Brent lab on yeast where they demonstrate that genetically identical yeast behave differently, have different physiological dynamics. Sequence information, however, unquestionably does provide a foundational source of information that can be relied on for its completeness at its own level. From that starting point other functional domains can be approached.

The organisms, however, are not objects of contemplation but are being worked over to improve their utility as tools (to improve the environment, to produce specific materials such as hydrogen). The goal is to invent and implement design principles that will alter living forms to increase their ability to perform specific tasks chosen by the engineers. Here the conditions of living things are broken down analytically into functional parts and those parts standardized and mass produced but their functionality is available for alteration. It should go without saying that once again they are available for improvement.

June 2004.

The First international conference on Synthetic Biology was held at MIT in June 2004. The host group at MIT had been engaging in a project to produce, stockpile, and distribute a growing inventory of standard functional parts, for cells. A group of undergrads had met for an intensive training session in January 2004; five universities participated in a series of summer workshops and competitions; and more activities of this sort were planned.

> "What is synthetic biology? Natural biological systems process information, materials, and energy. Our understanding of these systems is rapidly advancing. Unfortunately our ability to use biology as a technology to process information, materials, and energy, as we desire is limited by our understanding. To circumvent these limits, a field of study is emerging based on intentional engineering of biological systems.
>
> Synthetic Biology is focused on the intentional design of artificial biological systems, rather than on the understanding of natural biology. It builds on our current understanding while simplifying some of the complex interactions characteristic of natural biology." "Those working to (i) design and build biological parts, devices and integrated biological systems, (ii) develop technologies that enable such work, and (iii) place the scientific and engineering research within its current and future social context." [14]

Relevant Research areas: biochemical or genetic network design, energy sources, parts fabrication, characterization, assembly, network analysis, bio-materials, bio-mimetics, computation using biological components, design principles of systems and networks, device physics, directed evolution and evolutionary optimization strategies, information processing and control theory, micro-fluidics, molecular machines, modeling of synthetic systems, noise in systems and components, organism engineering, programmable organisms or systems, protein engineering, quantitative measurement techniques, reporters, sensors and actuators, single molecule manipulation, and or measurement methods.

As of June 2004, the results were limited. The range of initial projects includes:

- getting a bacteria to turn and off a phosphorescent signal (Endy, MIT). Description.
- to a project to reduce the cost of a natural occurring molecule used with great efficacy to combat malaria by a million fold so that the drug can be used at a global scale for minimal cost (Keasling, UC Berkeley. Description.
- In April (2004) Ron Weiss and collaborators at Princeton described E coli cells equipped with population-control modules, so that the cells committed suicide if their population density rose above a certain level. The synthetic module includes genes that can make the bacteria emit a chemical, so that they can 'smell' how many other cells are in their vicinity. If this 'smell' gets too strong, a killer gene is activated that causes the cell to die. Programmed behaviour like this could be exploited to turn bacteria into environmental sensors that spot an dsignal the presence of toxic chemicals. [15]

At the conference there was talk of design and fabrication, elements and modules, stochastic processes, noise, evolution and experiment, and the like. The papers presented varied in scope and ambition. At one pole there were a series of basic "engineering exercises" undertaken with the strictest sense of prudence as concerns both the organisms worked on and the functions altered, amplified, or suppressed. At another pole one project presented a formal schema for "genome shuffling" in which all possible combinations of genomic arrangements could be generated on a simple genome within a test tube. The presenter argued that only a small fraction of possible arrangements and re-arrangements had ever been seen in nature and that there was no reason not to see what the rest of the possible variations would look like. They could then be screened for specific functions. There were a wider range of projects somewhere in between in which a specific function of cell physiology of interest to medical or agricultural practitioners was "improved." The key function was identified, isolated, and a replaceable part designed. The part could be a gene, a pathway, a protein, a signal, a switch, etc. Having identified this function, and having separated design from fabrication, the papers were mainly concerned with strategies of fabrication and problems encountered.

Regulation.

There was a keen awareness, clearly articulated as a central issue by the organizers, that the risks of synthetic biology had to be thought about, framed and addressed as far as possible from the outset. Otherwise, one inflammatory press report, one botched experiment, and the like could spawn a major "alert" and controversy. One did not have to be a conspiracy theorist or paranoid to see that if the project of synthetic biology were to be even minimally successful – and the over three hundred attendees were committed to exploring its potentialities – then issues of "risk" (the coverall term to include considerations of safety, security, danger, preparedness) had to be confronted in a pro-active manner.

- a range of possible topics that fell in the "improving nature" slot. While Craig Venter is already engaged in building a whole organism the participants at the conference were identifying and altering functions so as to engineer them; that is to say to produce standard parts that would produce standard outcomes and a metric to evaluate those outcomes.
- The fact that it would not be especially difficult to engineer a virus (or bacteria) for "more virulence" was taken as a given. Set against the SARS

outbreak or the ever escalating emergence of the spread of the avian flu virus jumping species lines, the prospect of both amplification of specific genes or the recombination of genes (as is typical in nature) was ominous.

- Public perceptions and fears. Including politicians. And security people.

Proposed Regulatory Responses.

- Using the model of the Asilomar conference and subsequent NIH RAC, there was talk of establishing an international committee who would monitor and approve all experiments.
- Using the model of the hacker communities in the world of computers, there was focused discussion of how to avoid a similar outcome in synthetic biology where it could well spell either the end of the practice or extremely nefarious consequences. Perhaps one could say this was a model of morals and ethics that amounted to a politics of synthetic biology. The morals were that such behavior was bad in an of itself as it violated the ethos of the community and the most minimal vocational strictures of science. The ethics came in because the way to stop or stem such a trend of biological hacking would have to rely on the training and internalization of limits by biologists. The politics enters in so far as a community (even a virtual one) governs itself than it will be in a stronger position to resist being governed by others.
- Using the model of the standard cell repository, arguments were presented as to the feasibility of tracking specific "parts." These would include some form of contractual agreements with penalties and sanctions for those who violated the agreements.

There was a strong sense in which none of these measures were likely to be instituted in the short run short of a major incident in which case they would be imposed in one form or another. Roger Brent has named such a situation as the "crossing the valley of death" moment before anything like a set of regulations, surveillance mechanisms, standard practices, community control mechanisms, and policing can be established. The years to come therefore are likely to be full of danger. The task then becomes establishing a risk terrain so as to begin the process of turning amorphous and fear producing dangers into risks that are least somewhat calculable and predictable.

NOTES

[1] Landecker, p. 19. Rheinberger, 2000a, 272).
[2] Michel Foucault, Les Mots et les choses, Francois Jacob, La Logique du vivant .
[3] French Modern: Norms and Forms of the Social Environment, Chicago: University of Chicago Press, 1989.
[4] Technical practices and knowledge claims themselves were brought into an ever-tighter mutual dependency resulting in cycles of an accelerative productivity.
[5] The 'swerve" is discussed in my Making PCR: A Story of Biotechnology, Chicago: University of Chicago Press; "secession" in Anthropos Today: Reflections on Modern Equipment, Princeton: Princeton University Press.
[6] Philip Pauly,
[7] Lawrence Kohler, Lords of the Flies,
[8] Hannah Landecker, in her book, Culturing Life: How Cells Became Technologies, (p. 16.) Cambridge: Harvard University Press, 2006.
[9] Landecker, p. 27.
[10] Landecker, p.26.
[11] Landecker, p. 142.
[12] Landecker, p. 198.
[13] The phrase is from Phillip Pauly, The Engineering Ideal in American Culture.
[14] [http://conference.syntheticbiology.org/
[15] What is life? Can we make it? , Philip Ball, August 2004, Prospect-magazine (UK) .