THE DREAM OF SYNTHETIC LIFE GENERATES RECOMBINANT ORGANISMS ENDOWED WITH UNPREDICTABLE RISKS (*"EL SUEÑO DE LA RAZÓN PRODUCE MONSTRUOS"*)

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INTRODUCTION

On May 20, 2010, Craig Venter and his team of researchers of the John Craig Venter Institute published in *Science* on line, a paper entitled "Creation of a bacterial cell controlled by a chemically synthesized genome" (Gibson 2010). The title and the summary of the paper explicitly stated that the important point was the chemical synthesis of a complete and functional bacterial genome, that of the bacterium *Mycoplasma mycoides*. After the introduction of the engineered DNA into a different recipient bacterium, *Mycoplasma capricolum*, the progeny of the resulting transitory genetic chimera, after a few generations consisted of the sole components of the "synthetic" genome, those of the recipient bacterium having been destroyed by restriction enzymes. Actually, Craig Venter did not mention the production of "synthetic life," in contrast to what many news media excessively reported. The paper stuck to the description of the conditions of the production of a new genetically engineered organism, whose complete genes differed from those of the recipient bacterium. From a scientist viewpoint, the experiment did not add up significant information to fundamental biology, yet it was an extraordinary biotechnological achievement, rich for future developments in the scientific and industrial fields, thus explaining why the MIT considered it as one of the ten most significant technological achievements of the year 2010.

However, the words of the title have obviously not been associated at random: their association is dictated by the intention(s) of the authors.

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This text answer the question, posted by the editor, on the philosophical, scientific and social problems followed from the synthetic ensemble of the modified genome of the bacteria *M. Mycoides,* announced in May 2010 by the J. Craig Venter Institute.

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Both the intriguing title and the content of the paper confront historians of sciences and of environment with serious questions. Firstly, since the emphasis is placed on "synthetic," to what extent is proper or improper to use such word?, and how are Venter's experiments related to research and questioning on synthetic and artificial life as they developed during the first half of the twentieth century and, in a profoundly different manner, during the last twenty years? Secondly, what if such genuinely new organisms whose DNA has been entirely constructed in the laboratory are likely to be released in nature either deliberately or by accident? These novel organisms have never been exposed to natural ecosystems, thus have never been selected or co-evolved with other organisms. Their precise impact on ecosystems cannot easily be predicted. Anyhow, the introduction of a living organism in a new medium has repeatedly been observed in the past and sounds familiar to historians of the environment. These two facets of Venter's experiment will briefly be discussed in the following sections.

AN EVOCATIVE SEMANTIC PLAY

Actually, the title of the paper contains three highly significant words: "*creation*" and "*synthetic genome.*" In addition to its religious meaning, *creation* conveys the idea of a completely new object, of something invented. *Synthetic* genome tells the manner in which the *genome* has been constructed. The association of the three words strongly evocates the idea of a new life, *de novo* created in the laboratory due to human chemistry.

Does such a conclusion fits the experimental data or, on the contrary, is merely an elaborate semantic construction aimed at suggesting a message without being assertive about it? By examining the protocols used by Craig Venter's group, it comes out that they do not differ from the experimental logic that prevails for more than half a century in studies in physiological genetics and in molecular biology. Since 1944, we know that DNA is the physical support of heredity; since 1953 we know that DNA folds in a double helix and, since that decade, we all know that the genes aligned along chromosomal DNA are, materially speaking, sequences of DNA issued from the defined assembly of the four nucleotides. The order of appearance of the nucleotides in the sequence of a gene dictates the properties of the molecule encoded by that very gene. From its beginning, molecular biology has dominantly been analytical and has attempted to describe, down to the atomic level, the structure and functioning of the molecules involved in the transmission of genetic information from generation to generation. Thus, the determination of the DNA sequence of a genome, which finally ends as writing down the gigantic chemical formula of a linear macromolecule, has long been perceived as the ultimate goal in the

analysis of a living organism. Genomic DNA of an organism was assumed to be the material support of the whole of the codes which define an organism. Its construction, namely the synthesis of a complete genome, is the precisely opposite operation. Actually, the two complementary approaches to heredity, deconstruction and construction, have the same age: they can be dated to the beginning of the 1960s and have developed more or less at the same pace since then. Keeping solely to the synthesis of nucleic acids, the deciphering of the genetic code in the 1960s already had involved the use of short synthetic nucleotides. Since those heroic times, numerous longer and longer genes have been produced by properly assembling shorter fragments of "genuinely" synthetic DNA. Those artificial genes, when inserted in the proper expression cassette, proved to be functional. Thus, the chemical synthesis of a bacterial chromosome could theoretically be seen as the mere extension of *in vitro* gene production; the principle is the same, namely the association, in a precise order, of all the nucleotides of a complete bacterial chromosomal DNA. However, the order of magnitude is obviously quite different: millions of nucleotides in a genome vs. thousands of nucleotides in a gene. Such difference questions the notion of chemical synthesis in Craig Venter's adventure. For, are we faced with a genuine synthetic bacterial genome? Are we arguing about classical complementarities of the "analysis-synthesis" couple in which the functionality of the chemically synthesized product validates the results of the analytical approach?

The chemical synthesis of a DNA molecule one million *bp* long is not directly feasible yet in the laboratory. In contrast, the synthesis of shorter DNA fragments can be carried out through the sequential addition of nucleotides on an initial one, immobilized on a solid support. The main difficulties of DNA chemistry reside in the proper succession of chemical reactions (coupling and protection of reactive groups) and washings, which requires reagents to be introduced at precise steps within each reaction cycle, to finally obtain a reasonable yield of the desired product. The building up of fragments of DNA is carried out by automatic DNA synthesizers. Fragments 25-30 nucleotides long were easily obtained in the middle of the 1990s. DNA fragments 250 nucleotides long are nowadays routinely prepared and several fragments can be linked together to make longer DNA molecules. Nonetheless, the chemical synthesis is unable to go further than one thousand nucleotides and must be relayed by biological processes or using biological tools, largely due to physical difficulties in the handling of long DNA molecules. What then could be the meaning of claiming the chemical synthesis of a unique, one million *bp* long, DNA sequence?

The researchers had for long chosen to work on mycoplasmas, a family of bacteria whose genome is small, slightly larger than the one of megaviruses. Their genome harbors the smallest number of genes found in the

bacterial world, a number close to that of simplified bacteria obtained after *in vitro* evolution experiments aimed at limiting a genome only to the handful of genes required for the cell multiplication. The genome of *Mycoplasma mycoides* is 1 078 million bp long. In a first run, the sequence of the genome has been digitalized, i.e., the sequence initially in the form of ...ATCG... was converted into a series of 0 and 1. Then, the resulting series was split into 1 078 numerical cassettes each coding for a 1 080 nucleotide long DNA fragment. The fragments, synthesized by Blue Heron Technology Inc., were properly assembled ten by ten using the ligase enzyme system, a biological tool. The resulting fragments, each now 10 000 nucleotide long, were similarly assembled. The long fragments were then assembled into a unique DNA sequence long of 1'078 000 nucleotides inserted in an artificial yeast chromosome (YAC), according to a technique mastered since the middle of the 1990s. That artificial chromosome was amplified in yeast to recover enough genomic DNA. The complete genome of *Mycoplasma mycoides* thus issued of a complex, but *in fine* classical, tinkering of DNA was extracted from the YAC and introduced as a bacterial chromosome into a recipient *Mycoplasma capricolum* whose restriction enzymes had been inactivated, i.e., the DNA of the recipient bacterium will be destroyed by the restriction enzymes of the donor *Mycoplasma mycoides*. After a period of transient genetic chimerism, all of the initial components of the recipient cells are replaced by the components derived from the *in vivo* deciphering of the "artificial" chromosome genes: the final bacteria thus present all characteristics of *Mycoplasma mycoides*. The artificial chromosome is proven to be fully functional. It only differs from its model DNA by identification tags aimed to show it is an artificial chromosome, by the names of the authors, some quotations from literature and, perhaps more importantly, by the suppression of genes encoding pathogenic substances. The newborn bacterium species (or quasi-species?) was baptized JCVI-Syn.1, standing for *John Craig Venter Institute* and *Synthetic*.

The techniques used have been discussed in detail since it helps to understanding the title of Venter's article. It is evident that Craig Venter has succeeded in constructing, for the first time in history, a complete and functional bacterial genome. Anyhow, such construction has been far from being done with chemistry alone. Chemical synthesis was restricted to the production of the initial 1 000 blocks. For the following steps, the construction required the action of enzymes and basically the resort to yeast in order to harbor and amplify the YAKs, particularly the final bacterial chromosome. That chromosome is, not unexpectedly, an inert sequence of DNA: i) The machinery for its replication has first to be provided by yeasts, a living organism; ii) the machinery needed for the expression of the genes has initially to be provided by the recipient bacteria. The artificial DNA primarily behaves as a large virus, as a kind of parasite able to subvert

and transform an infected cell. We are thus faced with the best present combination of chemical synthesis and biological resources, as in other functional constructs prepared in many other laboratories, less ambitious but similar in nature. It is worth noting that we are discussing the present status of biotechnological research. As for organic chemistry during the nineteenth century, things are likely to evolve and one cannot exclude the future genuine chemical synthesis of a complete chromosome by some, to be conceived, automatic machine.

Since the interplay between bioinformatics, chemistry and biotechnology had functioned that well, the construction of other complete pro- or eukaryotic chromosomes can be envisaged. Then organisms, endowed with new properties or even entirely new organisms with genes coding for proteins that do not exist in nature, can be produced. Whatever those organisms may be, a conclusion is that they will require for existing a first passage through a recipient living organism. Moreover, they will use the same codes, the same metabolic machinery as in the present case. Therefore, it can clearly be proposed that the resulting organisms do lie apart from the general concept of genetically modified organisms, whatever their novelty is. At that point, the present construction is not the result of a synthesis, except if one names "synthesis" the assembly of their various components into a car or an airplane. Distant as it is from chemical synthesis, it might well be one of the genuine meanings of "synthesis" in present biology.

Why then was it the bearing of "chemical synthesis" that Craig Venter has put forward, when reality appears so different and when the biotechnological achievement is in itself impressive enough? One could simply estimate that the communication policy of Craig Venter rests on the psycho-social representations associated to the creation of life by human skills, in other words, in the laboratory. Indeed, the very same results would have been reached by using PCR and the genomic DNA of *M. mycoides* as template. The copy would have been as exact as the constructed chromosome. Nevertheless, the recourse to chemistry would have been much smaller; actually it would have been slimmed down to the synthesis of primers. All that would have made irrelevant the idea to shape large genomes through chemistry. It would have been impossible to conceive new forms of living organisms before life itself is created in the laboratory. That might largely appear weird, but the important point resides there: in-depth manipulation of living organisms is now accessible. In that sense, Craig Venter adds to fantasies by saying that he is now able to construct a human chromosome, but, he adds, that would be of no interest. For the moment, JCVI-syn1 is not the *Golem* and Craig Venter is not Rabbi Loeb, Maharal of Prague.

Even though chemical synthesis of a chromosome was far from being complete, the hemi-synthesis used to construct a functional genetic memory is equivalent to saying that human skillfulness has succeeded in the passage from the lifeless world of individual small molecules to the "genetic soul" of a living organism, its DNA. Functional viral DNA had previously been constructed, but viruses are not considered (at least their status is questionable) as living organisms. Bacteria are. The biotechnological success of Craig Venter should them be replaced in the frame of the numerous studies on artificial and synthetic life, which proliferated during the first half of the twentieth century, and have been resumed, although in a markedly different manner, over the last ten years.

It has never been possible to give a positive definition of life: life is the resultant of numerous natural phenomena all associated with manifestations of living organisms. In other words, life is the feature common to all living organisms, which means life is opposed to death and vice-versa, an unsatisfactory definition indeed. It thus comes out that life cannot be studied by itself but rather can be approached by the study of its multiple and diverse manifestations. Actually, the question "what is life?" acquired a genuine meaning only with the analytical capacities developed by science during the nineteenth century. The multiple facets of a living cell or a living organism could then be separately studied and described. The debate became even more active when scientists began to study heredity, the nature of genetic characters and the mechanisms of genetic transmission: the propagation of characters was given the same physical dimension as the propagation of life. The debate on synthetic or artificial life significantly developed at the moment the scientific questioning of genetics was addressed.

Actually, most of the researchers studying artificial and synthetic life were primarily involved in the production of material forms mimicking the morphology of living organisms and some of their manifestations, such as growth and cell division. It was assumed that morphogenesis should be driven solely by physical and chemical parameters. According to the survey of artificial morphogenesis researches made by Evelyn Fox Keller (2004), D'Arcy Wentworth Thomson certainly was one of the most inventive authors in that field. He developed correlations between mathematics, forms and growth (*On Growth and Form*, 1917). His work was largely based on earlier studies carried out between 1900 and 1915 by a much less known researcher, Stéphane Leduc. Leduc succeeded in mimicking morphological changes of living organisms by creating "osmotic figures" and he even mimicked the main steps of cell division, including the movements of chromosomes, by using precipitates of iron salts. Leduc

explicitly linked artificial morphogenesis to spontaneous generation: the creation a synthetic and an artificial life followed morphogenesis. Leduc was constrained to introduce spontaneous generation, much in the way Lamarck had to at the beginning of the nineteenth century. He first wrote in his *Philosophie zoologique* that "*La nature n'a pas besoin de lois particulières : celles qui régissent généralement tous les corps lui suffisent parfaitement pour cet objet*". He then had to solve the contradiction existing between the general features of inert matter and the properties of living organisms. Physical laws were acting on both, but the additional property of living organisms, life itself, required as *primum movens* of life some elusive, vital force, permitting spontaneous generation. Faced to the successes of genetics and physiological genetics, the dominance of morphogenesis declined after the 1930s to regain some strength with the work of mathematicians such as René Thom in the 70s and his theory of catastrophes. That dominance is also implicit in hypotheses claiming for a primary importance of self-assembly and self-organization in biology, often displayed as a strange combination of thermodynamics of irreversible processes with a kind of spiritualism. We suggest that all these attempts to first create forms, and then admit the emergence of a transformation of the form into living cells, correspond to a research of artificial life largely based on excluding the recourse of genetics and heredity.

Indeed, a definition of life as the "catastrophic" event following morphogenesis does not fit well with modern genetics, according to which biological forms are for a very large part determined by the unrolling of a genetic program, which defines the sequential appearance of molecules whose associations determines the form of the cells and ultimately that of organs and organism. The steps initiated with physiological genetics and developed in a more general way by molecular biology thus placed information as the axis of the transmission of biological features, and therefore of the multiple facets of life manifestations. As pointed out by Fox Keller, the dispute among biologists stopped concerning the definition of life to deal with the place information occupies in the organization needed for the manifestations of life. Genetics was obviously placed in the center of the discussion, although Andre Lwoff recalled with some cruelty, in 1990, that the genetic continuity of organelles was part of the transmission of the biological information and was inscribed in the shape of the organelles.

With the primacy attributed to the informative content of genetic material, of molecules and of organelles, science progressively addressed the nature of the frontier separating the inorganic from the living, instead of the frontier separating life from death. As a scientific problem, the latter had been introduced more by human sciences than by biology. François Jacob (1970) ascertained that before the Age of Enlightenment, the concept of life did not exist. For Michel Foucault, the concept of a limit separating

the inorganic from the living was the product of human history, rather than the product of an evolutionary process (Foucault 1966, quoted by Fox Keller 2004). History of biology confirms Foucault's abrupt conclusion: Considering that organisms and cells are primarily structures where flows of information converge and where they are analyzed and integrated, then the difference between inorganic and living becomes so thin it may not anymore exist. Indeed, a large part of the present biology has broken free from any reference to life.

It seems obvious that the notion of "synthesis" used by Craig Venter participates in such way of thinking, one that has experienced a remarkable development over the past ten years and is characterized by the permeability of the frontiers between experimenting on living organisms and experimenting with entirely artificial, computational, model systems. Craig Venter does not owe anything to the dreams of synthetic life of D'Arcy Thomson or René Thom. He owes nearly everything to a theoretical thinking that abolishes the limits and even the contents of all earlier theories of life. In that context, it is far from absurd to speak of synthetic life.

PANDORA'S TEMPTATION

Notably Craig Venter did not pay any attention to environmental constraints of life in a given ecosystem. At the precise opposite of the scientific and epistemological discussions on Craig Venter's experiments, lies the sentence by Goya placed as subtitle to the present paper. Indeed, scientific and theoretical discussions on what life is or may be do not abolish the material reality, the possible generation of genetic monsters by developing Venter's procedures on genetic engineering. The reference to Goya illustrates the denial of some of the consequences of that kind of scientific investigation: the novelty introduced by Craig Venter, which far exceeds the usual production of recombinant organisms, can be summarized as the ability to construct organisms (bacteria so far, but no other organism is excluded) endowed with totally new features that had never previously been selected under natural conditions. One could even imagine those organisms equipped with genes encoding novel proteins generated either through tinkering of domains or through our knowledge at the molecular level of binding sites and the action mechanisms of enzymes. Taken together, such possibilities offer a rich field for scientific investigation. It can even be said that after transgenesis and homologous recombination in vertebrates, large scale genome tinkering appears as the third way of transforming genetics into an experimental science, perhaps introducing the probing of evolution theories under natural conditions.

This being said, the authors of the paper have made it clear that they intend to penetrate industry, particularly oil production and degradation, as well as mass production of raw material for the food industry. The

nature of the envisaged productions will not be addressed here. For us, the problem lies far beyond. All starts from the evidence that, either deliberately of by accident, such new organisms will leak out of the laboratory. Experience says that confinements are never as absolute as wished. Thus, if new organisms escape the reactors they are confined in, and slip out into natural ecosystems, if the latter is favorable, the organisms will proliferate.

The point is that these new organisms have not co-evolved with the other organisms that would likely control their proliferation and contribute to a new biological equilibrium in nature. The answers, death or proliferation, may also depend on the nature of the ecosystems themselves. To the best, one can hope new organisms will be faced to predators-regulators. They may as well get killed and disappear. To the worst, they may expand in a preoccupying way. Concerning the latter point, the history of environment is particularly rich in examples of organisms which have settled far from their natural, original, ecosystem, and profoundly altered their new habitat.

Let us start with the deliberate introduction of an upper species, a vertebrate. In a comment concerning rabbits introduced in Australia, a reader of a Victoria news paper gives the following evidence in 1868: "But about the beginning of this year they appear to have suddenly multiplied to a wonderful extent [...] they scattered themselves over the whole country within ten miles of the original burrows." Devastation was such that "thousands of acres of perhaps the richest pasturage in Victoria are eaten as bare as an overstocked sheep run, and the damage they have done is very great," becoming a source of anguish: "when the pocket was so severely touched there was no more heard of sporting delights, but the question stared us broadly in the face, how were we to destroy them." Rabbits had been introduced only nine years earlier in 1859, to meet with the preferences of hunters and to transplant a taste of their native Great Britain. Damages were rapidly extensive and required important financial resources for several generations. Of course, people thought of combating rabbits by introducing some of their natural European predators (cats, stone martens, ferrets and polecats) with no more result than the decline of autochthonous marsupials and birds. Twenty years later, in 1888, that edifying example was used in calls for carefulness in whatever concerns the action of man on environment: "*En aidant à la destruction ou à l'accroissement d'une espèce nous ne savons jamais ce que nous faisons, ni quel retentissement l'action de l'homme peut avoir dans les harmonies de la nature. Le moindre coup de baguette dans cette eau limpide peut la troubler profondément de proche en proche et à l'infini.*" After the organization of the systematic killing of rabbits, the laying of traps, the erection of fences (the rabbit-proof fence constructed between 1901 and 1907 was 3 253 km long), one conceived in

1919 the idea of using a myxoma virus responsible of lethal myxomatosis in rabbits. The virus was introduced in Australia in 1950, with immediate and impressive effects since about 99.8 per cent of the rabbits died of the disease. Albeit, in a few years, resistance to the virus was selected in rabbit populations, which started expanding again. Moreover, since the propagation of the virus depends on mosquitoes, that need water, the virus did not diffuse well in arid lands. Thus, in 1995 a new pathogen agent causing a hemorrhagic fever (the rabbit hemorrhagic fever virus) was introduced. It significantly reduced the size of rabbit populations, particularly in arid zones. When are resistances to appear? That is expected; the emergence of resistance is a constant biological phenomenon in the interplay between pathogenic agents and their hosts. It is only a matter of time. The fight against rabbits in Australia might well be endless.

The calls for carefulness have proven useless. Invariably, the same scheme is reproduced in biological struggles against an invading species undertaken by introducing other exogenous organisms supposed to limit expansion of the invader. One could mention butterflies (*Lymantria dispar* in the USA, 1869), giant terrestrial snails (*Achatina achatina* Hawaïen, 1936), plants *Elodea nuttallii* in Belgium around 1939, or *Fallopia japonica* introduced in Europe during the nineteenth century and which became an invading species during the twentieth. Since the end of the twentieth century, the consequences of the introduction of exogenous species are well known. The first monographs concerning the phenomenon, like those by Theodore Sherman Palmer (1868-1955), a zoologist of the American Agriculture Ministry, are significant in that respect. The paper written by Palmer is a historical landmark on that very point since it underlines the importance of the damages caused by introductions (Palmer 1894). Even so, one has to wait until 1958 for the first in-depth ecological study to be published (Elton 1958, last edition 2000).

Of course, the reader knows well that JCVI-syn1 is neither a rabbit nor a plant. Let his mind be at ease. Numerous examples concern viruses and bacteria, at least viruses and bacteria revealed by the occurrence of a disease. Emerging diseases are invariably associated to the unexpected contact of men with an environment containing pathogens new to human species. Forest leishmaniasis and Chagas' diseases are classical examples in Central and South America (*Parassitologia*, special issues, 2005 and 2008). This important issue has been much debated elsewhere. Keeping to a few recent examples, the west Nile virus, first isolated in 1937, has been introduced in the United States in 1999 most probably by a bird or an *Aedes*. Since then, it has spread all over North and Central America and in Caribbean islands. The 2002 epidemics in the United States caused numerous human cases of encephalitis with about 300 fatal issues, whereas numerous horses were affected. The blue tongue virus, after mutation and

changing its vectors, has invaded Europe particularly in the 2000s after having devastated herds in Africa. The distribution of parasites and other pathogens depends on the insect vectors. In the case of avian malaria in Hawaii, the simultaneous introduction of the parasite (*Plasmodium relictum)* and its mosquito vector (*Culex quinquefasciatus*) resulted in the disappearance of about one half of the bird species in the archipelago (van Riper III, et al., 1986; Derraik, et al. 2008). Although the impact on biodiversity of the recently introduced micro-organisms pathogen for wild animals has been only recently studied, the consequences on agriculture in general are better known. The bacterial fire, caused by the bacterium *Erwinia amylovora* attacks a diversity of fruit trees such as apple, pear and others. It now affects most European countries after its introduction in Great Britain in 1950 (Wittenberg, et al. 2006). The knock of the bacterium is such that pear production has nearly been abandoned in the United States. The list of the consequences of introduction of exogenous species is quite long. They are not limited to the proliferation of rabbits in Australia.

Of course, dissemination of organisms is a natural process which accounts in part for the distribution on earth of all living species. It is however limited by numerous factors, being a good example the natural frontiers. Anyhow, men, due to the very fast colonization of earth, the circulation of goods and persons, has entirely changed the initial natural conditions of the dissemination of organisms. In order to limit the introduction of exogenous plants and animals, quarantine procedures have been designed, such as the Lacey Act in 1900 or the Quarantine Act of the United States in 1912. These laws did not significantly slow down the man-driven process of dissemination. Even more, introductions have often been deliberately made and most of the invasive vertebrates, with the exception of mice and rats, have been inserted with intention, for fun, for economic reasons, and scientists themselves have often put forward such initiatives. Of course, not all introduced species survive forced migrations and even if they do, most do not become noxious organisms. Even so, the proportion of species which have been launched from elsewhere is rather impressive: 20 per cent of vascular plants found in Germany are of foreign origin; 30 per cent in New England; 47 in Hawaii and New Zealand, (Vitousek, et al. 1996), Their impact on autochthonous biodiversity is not known yet. By contrast, their economical impact has been quantified and is rather formidable, about 12 billions dollars for a single year in Europe (McGeoch, et al. 2010). The struggle to contain the invasion by *Erwinia amylovora* amounted, for Swiss alone, to 12 millions Swiss francs between 1989 and 2000. It is worth noticing that the success of an introduction is facilitated by the previous degradation of the environment caused by human activities, and on their side, the introduced species speed up that very degradation. Even worse, attempts to counteract

damages by introducing an antagonist organism are more likely to aggravate the situation. That conclusion is known since the end of the nineteenth century: "*Mais, lorsque l'équilibre est rompu, rien n'est moins facile que de le rétablir. Tous les efforts tentés dans ce but ne font qu'accroître la perturbation*" (Confévron 1888).Thus, there is no particular reason to admit that Venter's new organisms will have no impact on environment and ecosystems, except if they are rapidly destroyed.

Sure, the worst is not always to occur. After all, the fraction of introduced organisms which become invasive is small, probably less than one per cent. Also, it is not easy to predict which organism is to become invasive in a given ecosystem. There is often a large delay between the introduction of an organism and the moment it becomes invasive, assuming it is genetically unchanged, a point far from being established. Faced with the uncertainty of predictions, it appears difficult to take decisions concerning the risks of introducing an organism in a natural environment, except if those decisions are *a priori*, very restrictive. In that very particular case, in a recent book (Bensaude and Benoit-Broewers 2011) it is pointed out that Venter's construction has not been thought in terms of its relation with a given ecosystem, a surprising evidence at a moment when living organisms progressively have ceased to be considered from only the genetic view point, to be regarded as interacting entities. One cannot predict the ecological success or failure of the biotechnological monsters that Craig Venter wishes to produce for the industry and most probably not for the good of complex ecosystems (GG and CV personal opinion). There is however no difference in principle between the expected impacts of those new constructs and that of any historical transplanted bacterium or virus. We can thus anticipate the occurrence of problems. As an example taken out of Venter's projects: what could be the impact on water of oil producing bacteria? It is tempting to admit that creation of new organisms will be one more example of human stubbornness to maltreat nature while invoking a progress, the meaning and the benefit of which are far from being obvious.

History of sciences cannot predict the future, but it helps to distinguish events, attitudes and actions. When those are repeated in time, they betray an obstinate scheme of thinking specific to humans, sustained by our relative inability to escape from repetitions. Psychiatrists have much to say about logically motivated compulsion to repetition... In the present case, novelty should not cloud the worrying evidence that the expected future will operate along lines so far unknown to us. Historical experience can only remind of the already known risks associated to the introduction of new species. It is not a minor issue.

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