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Les liaisons dangereuses: genome-edited cattle, antibiotic resistance and cancer

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1. The generation of life

In his epistolary novel (Choderlos de Laclos , 1782) Pierre Choderlos de Laclos depicts the alternating fortunes of the decadent French aristocracy before the Revolution of the late 18th century. Something similar happened during the history of science, marked by periods of decline followed by periods of great success in human creativity. For example, until the beginning of the nineteenth century, life was thought to emerge spontaneously from inanimate matter. In other words, it was enough to leave a dirty garment and a few ears of corn in a stable to generate a crowd of worms, insects and rodents in a few days. It took the empirical insight of scientists like Francesco Redi and Lazzaro Spallanzani to reveal the deception of the spontaneous generation of life. Today we actually know that life originates exclusively from life and that the rules that underlie the biological continuity of living beings have been written by evolution, not by modern engineers.

2. Primum non nocere

The selective breeding of plants and animals began a few millennia ago to satisfy basic human needs, and we still have a debt of gratitude to nature that allowed us to domesticate cereals, vegetables, goats and cattle for food production and others primary goods. Nowadays, the so-called genetic improvement of plants and animals obtained through technological manipulations is not designed to satisfy human needs, but to produce varieties with traits suitable for the commodities market while developing new agro-industrial patents and new commercial products. In the last half century, there have been many clear confirmations of this trend. A multitude of researchers have trafficked with organisms or parts of them (genomes, cells, tissues, and so on) based on both the illusion of being able to successfully force the deep nature of biological systems and the presumption of not making mistakes. However, lacking a "true" good reason (basic needs?), common sense suggests that invasive manipulations of the natural world should be carefully avoided, particularly when the reliability of the results and assessment of possible risks have not been clarified. The injunction "Primum non nocere" (First do no harm), which is the founding principle of Hippocratic oath and of medical practice, means to always seek solutions that cause the least possible damage, if any, in planning our actions.

3. Biotechnological failures

One of the most popular attempts to force biology (sexual reproduction) of domestic mammals was made in 1996 (the famous Dolly case), when a sheep was cloned at the Rosling Institute (Scotland) to produce "photocopied" sheep by using a controversial technique known as SCNT (Somatic Cell Nuclear Transfer). (Please note: Dolly was cloned from a cell taken from the mammary gland of a six-year-old Finn Dorset sheep and an egg cell taken from a Scottish Blackface sheep). The results of the experiments, however, proved to be incompatible with the optimistic predictions of biotechnologists. The use SCNT technique to artificially "reproduce" mammals with identical phenotypic traits failed, showing a tremendously low efficiency: indeed, most of the embryos died before they were born, while those who arrived at birth died shortly thereafter.

Recently, the story has repeated itself by adding a new entry to the list of human failures to force the nature of complex biological systems such as mammals. Last August, the FDA (Food and Drug Administration) documented an interesting case of animal genetic manipulation that showed serious problems. The Agency found that the genetic material of animals belonging to a dairy breed modified to inhibit the growth of horns contained bacterial genes for antibiotic resistance (neomycin/kanamycin and ampicillin). The genome of these animals had been previously altered through gene-editing, a molecular protocol based on enzyme systems (nucleases) able to cut the genetic material in a precise way and increase the control over molecular changes. Furthermore, in the genome of genetically modified animals, additional genetic sequences of bacterial origin were detected, along with a duplication of manipulated DNA sequences to obtain the hornless (polled) phenotype. The work of the FDA researchers aimed to detect whole-genome sequencing data from calves that were germline genome-edited, while the screening method was able to detect unintended off-target events. The foreign DNA sequences discovered by the FDA came from the bacterial plasmid used in 2016 by the biotechnologists of Recombinetics Inc. (a Company based in Minnesota) to introduce the "polled" gene in the dairy cattle genome. It is worth noting that, being a germline molecular manipulation, every cell of the GM cattle contained antibiotic resistance genes, facilitating the transfer of antibiotic resistance to non-resistant bacteria.

4. Animal machines and biological systems

Currently there is only one GM animal species authorized (in the US) for human consumption (the AquAdvantage Salmon). Biotechnological manipulations to produce food of animal origin for human consumption should be strictly regulated to counteract products not sufficiently tested for their safety. The case in point must be taken very seriously. The presence of antibiotic resistance genes had never been detected in engineered farm animals, particularly in dairy breeds, which raises serious and legitimate concerns over the alleged safety of the so-called NBTs (New Breeding Techniques). Worldwide there is a strong pressure on public health Agencies to strengthen efforts and tools needed to prevent and reduce the spread of genes that confer resistance to antimicrobial drugs[a]. It is widely recognized that in the United States, traditionally, there is no substantial objection to the use of molecular techniques to modify plants and animals. Yet a very critical problem – leaving aside for a moment the ethical implications on the use of animals as "machines" – is that the genome-editing technique applied to dairy cattle can interfere with human food chain, leading to a number of potential risks that should not be underestimated. Indeed, the acquisition of antibiotic resistance from dairy products cannot be excluded. The genome-editing procedure has been promoted by biotechnology industry as absolutely safe, since its molecular precision would exclude the occurrence of undesired alterations. However, current biological knowledge shows that molecular manipulations of multicellular organisms fail to evade the uncertainty due to the non-linear dynamics that regulate morphogenetic and physiological processes. Furthermore, each screening approach is based on hypotheses and possible biases that could lead to not detecting many unintended alterations. Examples of unpredictable molecular events are well documented, such as the complex genomic rearrangements observed at or near the target site in many experiments involving the manipulation of mammalian genomes. It is worth noting that, in 2016, the results produced by Recombinetics researchers were published in the prestigious *Nature*

[a] https://www.who.int/antimicrobial-resistance/en/; https://www.cdc.gov/drugresistance/about.html; https://www.ecdc.europa.eu/en/antimicrobial-resistance/facts/factsheets/general-public

Biotechnology (Carlson et al., 2016). In their report, the Authors stated that the genome control for possible off-target events had given negative results: a statement that in the light of the current evidence sounds like a mockery. It should be emphasized that, among the numerous and critical health problems linked to the widespread resistance to antibiotics, bacterial infections affect anyone, particularly the elderly, young and sick, that is to say the most vulnerable individuals. The emergence of antibiotic-resistant bacteria is a real threat to these people, as antibiotics are the main line of defense when the immune system weakens. Antibiotic resistance threatens the effective prevention and treatment of an ever-increasing range of infections caused not only by bacteria but also by parasites and viruses. In 2016, around 500,000 people worldwide have developed multi-drug resistance to tuberculosis, and drug resistance is now starting to complicate the fight against HIV and malaria. The WHO believes that this is an urgent dilemma, as both resistant and multi-resistant infections are increasingly frequent and difficult to treat, as well as very costly to sustain. The health care for patients with resistant infections is much more expensive than assistance for patients with non-resistant infections, due to the longer duration of the disease, additional tests and the use of more expensive drugs. The problem foreshadows serious implications for global public health and requires action in all sectors of society and government[b]. At the state of the art, antimicrobial compounds based on new mechanisms of action are still few and, among these, most of them have not yet completed the pharmacological testing process. A further critical problem depends on findings emerging from studies on large populations of pathogenic bacteria that show a positive correlation between the ability to develop biological resistance to a drug and the ability to develop biological resistance to more drugs. This phenomenon generates simultaneously an enigma both for biomedical research and clinical treatment. In general, it is believed that the biological mechanisms that determinate the resistance to antibiotics are different in different bacterial strains. According to a hypothesis currently being tested, different strains of pathogens can reciprocally exchange molecular “tools” to develop resistance to different antimicrobial molecules, thus accumulating a shared multiple resistance (Rayamajhi et al., 2010).

[b] https://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance

5. Antibiotic resistance and cancer

The supporters of the absolute power of science, who in the past proclaimed that progress would have definitively made man free from infectious diseases, had naively underestimated the impressive evolutionary properties of bacteria. Thanks to their peculiarities, these microscopic creatures have done the job that perhaps no one can do better than they have, bypassing the toxicity of a large amount of antimicrobial compounds and reducing almost completely the effectiveness of their use in medical treatments. This global problem will have a great impact in particular on oncological medicine, involving over 30 million people worldwide: a huge group of patients that is destined to continue to grow. Bacterial infections are responsible for common complications among cancer patients, who often become much more sensitive for several reasons. Any type of cancer is a major cause of body stress and, as such, has the effect of lowering biological defenses. Additionally, it should be noted that white blood cell tumors, such as leukemia and lymphoma, have a great impact on cancer patients resilience by directly influencing their immune system (Pfeil et al, 2015; Leibovici et al, 2006;). After surgery, many patients require antibiotics to treat infected wounds. Moreover, conventional anti-cancer therapies performed to kill cancer cells kill also cells of our immune system. This means that patients who receive radiation or chemotherapy often develop infections that require treatment with antibiotics. Transplantations and other treatments are also impossible to perform without using effective antibiotics. Antibiotic-resistant bacteria are currently expected to make cancer treatments increasingly difficult, while the incidence of cancer cases will continue to increase in the years to come. This can result in higher mortality from cancer, more difficult and more expensive treatments and many side effects. Antibiotic resistance will have important consequences in the hospital environment, due to patient management and interactions with healthcare professionals. For example, it will be necessary to increase isolated hospitalization spaces to limit the circulation of drug-resistant infections (Teillant et al., 2015).

6. Different intelligences

The scenario reported above is not what we would have expected after the advances in well-being, biomedicine and science of the last century. Bacteria have lived on our planet for about 3.5 billion years and are the most common life form in the biosphere. Their ancient "knowledge" of the rules necessary to survive environmental adversities seems to be much more sophisticated than the human technologies presented today as the most advanced frontier of the so-called "nature control". Although it may seem an inappropriate reflection, bacteria have developed an unquestionable intelligence, which explains why, after more than three billion years, they still have unparalleled biological success on Earth. Their extraordinary ability to renew themselves, despite the numerous survival problems they face every minute, currently puts human life to the test. Perhaps, aware of this, they are sending warning messages to our strange intelligence that, instead, is now driven almost exclusively by business and has lost the ability to place itself at the service of mankind.

Conflict of interest

The Author declares no competing interests.

References

Pierre Choderlos de Laclos, Les Liaisons dangereuses. 1782, Durand Neveu.

Norris AL, Lee SS, Greenlees KJ, Tadesse DA, et al, 2019. Template plasmid integration in germline genome-edited cattle. Biorxiv Preprint; https://www.biorxiv.org/content/10.1101/570739v1

Carlson DF, Lancto CA, Zang B, Kim ES, et al, 2016. Production of hornless dairy cattle from genome-edited cell lines. Nat Biotechnol; 34, 479-481.

Rayamajhi N, Bin Cha S, Sang Yoo H, 2010. Antibiotics Resistances: Past, Present and Future. *Journal Biomed Research*; 11(2) : 65-80.

Leibovici L, Paul M, Cullen M, Bucaneve G, et al, 2006. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer; 15;107(8):1743-51.

Pfeil AM, Allcott K, Pettengell R, Minckwitz G, et al, 2015. Efficacy, effectiveness and safety of long-acting granulocyte colony-stimulating factors for prophylaxis of chemotherapy-induced neutropenia in patients with cancer: a systematic review. Support Care Cancer; 23(2):525-45.

Teillant A, Gandra S, Barter D, Morgan DJ, et al, 2015. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. Lancet Infect Dis;15(12):1429-37.