Organoids Research: What are the ethical issues?

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In our Memo entitled "Research on Embryos and Embryonic Models for Scientific Use (EMSUs)", we examined the question of the moral and legal status of these new artifacts that, in many ways, resemble human embryos, created by researchers in order to better understand the development of the early embryo because they recapitulate certain aspects of it in terms of their organization and development.[1] These EMSUs, also referred to as "gastruloids", are part of what are now called "organoids". This Memo is devoted only to the ethical issues raised by research on entities created in the laboratory from post-natal cells; it will not revisit those raised by EMSUs as entities resembling human embryos.These organoids, developed from cell cultures, have become innovative tools for research in biology, as they enable a better understanding of the normal or pathological functioning of the organs they mimic. They are therefore a source of multiple therapeutic promises that need to be evaluated, not just medically, but also ethically. This is one of the reasons that led us to examine the ethical issues raised by research on organoids, issues which, as we shall see, are multiple.

What is an organoid?

First of all, it is necessary to clarify what is meant by "organoid". There are many definitions in the literature, two of which we found to be particularly relevant. Here is the first:

> "The term *organoid* means 'resembling an organ'. Organoids are defined by three characteristics. The cells arrange themselves in vitro into three-dimensional organisation that is characteristic for the organ in vivo, the resulting structure consists of multiple cells found in that particular organ and the cells execute at least some of the functions that they normally carry out in that organ. [...] Gastruloids constitute a certain type of organoids that are cultured out of human pluripotent stem cells and that recapitulate early stages of embryonic development."[2]And the second:

1 Memo published in 2019, p. 5-6, available at: https://www.inserm.fr/sites/default/files/media/entity_documents/Inserm_Note_ComiteEthique_GroupeEmbryon_Janvier2019.pdf.

2. S. Boers & al., "Organoids as Hybrids: Ethical Implications for the Exchange of Human Tissues", *Journal of Medical Ethics*, 2018, vol. 45/2, p. 2.

> "Stem cell-derived or progenitor cell-derived 3D structures that, on much smaller scales, re-create important aspects of the 3D anatomy and multicellular repertoire of their physiological counterparts and that can recapitulate basic tissue-level functions." [3]The second definition clarifies the origin of organoids, which is either from stem cells or progenitor cells – to which primary cells must also be added. However, this remains somewhat restrictive because of the existence of certain structures comprised of adult differentiated stem cells that are also sometimes called "organoids". It is also important to emphasize that the use of stem cells (embryonic or increasingly often induced to pluripotency from adult somatic cells) makes it possible to obtain a quantity of human organ models that has been impossible to achieve so far.

Many types of organoids have been developed, particularly for the pancreas, kidney, liver, thyroid gland, retina, ovary, and brain. These 3D structures present some of the functions[4] of the whole organ *in vivo,* structures that nevertheless only quite remotely reflect the organ that they mimic, in terms of its architecture, the cell diversity of the tissue reproduced, and its functions. Some authors use the term "mini-organs", which we shall see is misleading, although rhetorically striking. Tumor organoids, called "tumoroids", have also been created in order to study certain types of cancer and to test novel therapeutic approaches – even though it is not cancer that has benefited the most from this approach so far.[5]In the literature, the term "organoid" is often used in a general and somewhat vague sense: for a decade it has been employed to designate an entire series of cell cultures that can sometimes be quite different.[6] We feel it is important to characterize more thoroughly their use and therefore introduce the following distinctions and clarifications:[7]Organoids are not simple 3D cell cultures, because in the latter the function of the organ is not present. What characterizes an organoid is that it performs certain *functions* specific to the organ concerned.

- Organoids self-organize, spontaneously, which is not the case of bioengineering products that use a biocompatible synthetic matrix (scaffold), which can be natural or artificial. However, the two approaches have been known to be used simultaneously.[8] Self-organization is often stimulated by forces setting the organoid in motion and by air-media interface or culture media conditions. 3D

3. G. Rossi & al., "Progress and Potential in Organoid Research", *Nature Reviews*, 2018, vol. 19, p. 671.

4 We shall see in the last section of this Memo that referring to "function" is not, strictly speaking, correct and that it is preferable to use "functioning" or "activity".

5 Rossi & al., *Ibid.,* p. 680 and J. Akst, "Tumor Organoids Hold Promise for Personalizing Cancer Therapy", *The Scientist,* June 15, 2019, https://www.the-scientist.com/notebook/tumor-organoids-hold-promise-for-personalizing-cancer-therapy-66093.

6 M. Simian and M. Bissell, "Organoids: A Historical Perspective of Thinking in Three Dimensions", *Journal of Cell Biology,* 2016, vol. 216/1, p. 31.

7 See also the document by the "Organoids" Research Group of Aviesan's Health Technologies Multi-Organization Thematic Institute, which presents an ontology of organoids.

8 Rossi & al., "Progress and Potential", p. 683.

printing is a technological tool used to create biological models and nothing more. It can also be used to create organoids.

- The part does not have the same properties and functions as the whole; thus an organoid does not have the same properties and functions as the organ as a whole, a cell does not have the same properties and functions as the tissue or the organ of which it is a part. It is therefore incorrect to refer to organoids as mini-organs. In particular, it is inappropriate to refer to organoids derived from brain cells as "mini-brains"; we will avoid this expression in favor of "cerebroids".

- Some authors consider that organoids fall within the scope of synthetic biology because they manifest spontaneous organization.I It does not seem judicious to us to consider them thus, synthetic biology being often associated with attempts to create artificial living organisms, like Craig Venter's *Mycoplasma.*[9]The project to develop human quasi-organs *in vitro* is nothing new. Since the beginning of the 20th century, researchers have sought to imitate organogenesis in culture[10] and it is generally believed that the history of organoids dates back to the 1970s when Howard Greene and his colleagues demonstrated that it was possible to cultivate epidermis-like associations of human keratinocytes and fibroblasts *in vitro*.[11]According to some authors, the organoid construction technique is even older. Jamie Davis considers it contemporary with the work of Wilson who, as early as 1910, showed that sponge cells could be dissociated and randomly reaggregated to rebuild a viable organism.[12] This experiment is important because it shows that cells isolated from an adult organism contain sufficient information to specify a multicellular structure, unaided by external instructions or anatomical structures related to their embryological history, even though we cannot extend it to organs isolated from vertebrates, such as the liver or the brain. This hypothesis and basic method of disaggregation and reaggregation have been used by researchers since the 1950s.

- What characterizes an organoid is that it performs certain *functions* specific to the organ concerned.
- Organoids self-organize, spontaneously.
- An organoid does not have the same properties and functions as the organ. It is therefore incorrect to refer to organoids as mini-organs.

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9 R. Kwok, "DNA's master craftsmen", *Nature, 2010, vol.* 468, p.22–25. See also B. Baertschi, *La vie artificielle*, 2009, ECNH, Bern, available at: https://www.ekah.admin.ch/inhalte/ekah-dateien/dokumentation/publikationen/f-Beitrag-artificielle-2009.pdf.

10 Simian and Bissell, "A Historical Perspective", p. 33.

11 Rossi & al., "Progress and Potential", p. 671.

12 J. Davies, "Organoids and Mini-Organs: Introduction, History, and Potential", in J. Davis et M. Lawrence, dir., *Organoids and Mini-Organs*, Academic Press, 2018, chap. 1.

The state of research on organoids

Organoids are research tools; they do not as yet have a therapeutic application, although some are envisaged for the future. We will illustrate their role by presenting some examples of projects conducted by Inserm researchers who were interviewed by the Working Group.

Olivier Goureau's team (U968, Vision Institute, Paris) is interested in the production of retinal cells from human pluripotent stem cells for transplantation strategies and to model certain degenerative retinal diseases. Retinal organoids are very useful here because rodents do not present all the characteristics of a human eye. These experiments on organoids should minimize the use of animal models for testing purposes. It is important to stress that while organoids are useful for studying diseases of genetic origin - which they can mimic - they are not always useful for analyzing phenotypic phenomena, making them of limited value in understanding the mechanisms of a multifactorial disease such as age-related macular degeneration (AMD). The case of the retina is interesting for another reason: in order to treat blindness, three promising and alternative technologies are likely to be available: gene therapy, microchip implants and organoid cell transplantation. How will we choose?

The project coordinated by Jean-Charles Duclos-Vallée (U1193 *Inserm* Paris-Saclay University) is aimed at bioconstructing a transplantable liver from human induced pluripotent stem (iPS) cells. The liver is constructed in blocks, which involves producing organoids and connecting them to the biliary and vascular trees. The potential utility of organoids is primarily clinical, to avoid transplantation from donors and thus compensate for the shortage of grafts. It is also envisaged to develop a functional extracorporeal purification system with a bioreactor that includes liver cells, which will make it possible to temporarily take over a patient's liver functions - as is already the case with the kidneys[13] - as well as construct a liver on-a-chip to study predictive toxicology.Isabelle Sermet-Gaudelus' team (*Inserm* U1151 - Institut Necker-Enfants Malades (INEM)) deals with respiratory diseases, including cystic fibrosis. They have become interested in the use of organoids to evaluate innovative therapies for this disease. Indeed, the CFTR protein implicated in this pathology is also present in the intestinal epithelium, and changes in the

13 Unlike the kidney, the liver performs enzymatic activities essential for the assimilation of nutrients and the detoxification of xenobiotics, as well as synthesis functions (albumin, coagulation factors, enzymes, etc.) essential for the body to function properly.

protein's activity can be detected in this tissue. Using biopsies, intestinal spheroids - simple 3D cultures that are inaccurately referred to as "organoids" - have been created in the Netherlands to test correction of the CFTR protein function, which should make it possible to avoid prescribing ineffective molecules with potentially serious side effects. However, it has not yet been well established whether these "organoids" are a good model for diagnosis and the evaluation of therapies despite current enthusiasm. Other models derived from respiratory cells can be envisaged.

These three examples therefore concern the *in vitro* production of structures that mimic certain organ functionalities. Also, the teams all emphasize that the lack of vascularization and/or innervation of these *in vitro*-produced models is a limitation that can present serious problems. That is why there have been implantation attempts in animal organs[14] or other biological media, such as lymph nodes;[15] some teams are still working on how to generate vascular networks *in vitro* (real vessels or artificial oxygenation network by microfluidic system). This illustrates the fact that organoids do not contain all the cell types or certain structures (blood vessels, in particular) necessary for the functioning of an organ observable *in situ*, but only some of them.

- Organoids are research tools that do not yet have a therapeutic application.
- It has not yet been well established that organoids are a good model for all diagnosis and the evaluation of therapies.
- The absence of vascularization and/or innervation is a limitation of these *in vitro*-produced models.

Ethical issues raised by the use of organoids

A review of the state of research has already raised certain ethical issues: the shortage of grafts for transplantation, the use of animals in research, the allocation of resources in terms of both individual treatment - which therapy to choose in case of blindness? – and the direction of research: not to invest the limited financial resources available in unpromising avenues, even if they are "fashionable". But there are many others. Most of them are not new, however they are an opportunity to bring back to the profession questions that are not only related to the use of organoids but remain open and require ongoing reflection. Here are the main ones which can be seen to concern many fields, such as clinical ethics, institutional ethics and even anthropology:

14. M. Munsie & al., "Ethical Issues in Human Organoids and Gastruloid Research", *The Company of Biologists*, 2017, vol. 144, p. 942.
15. M. Francipane and E. Lagasse, "Maturation of Embryonic Tissues in a Lymph Node: a New Approach for Bioengineering Complex Organs", *Organogenesis*, 2014, vol. 10/3, p. 323-331.

1. **The evaluation of risks, benefits, and safety**. The most frequently mentioned benefits of organoids research are: a better understanding of human diseases thanks to the use of human tissue, the possibility to test drugs on a model close to the human organism in real life and, eventually, the ability to repair defective organs[16] - including in the case of brain lesions. Toxicology, pharmacology, and cell therapy are therefore also concerned.Since organoids are often derived from iPS cells, **the consent of the donors of the original cells must be obtained** - this is also a regulatory requirement. The production of certain organoids could raise some reticence (genital tract, brain) and raises the question of the degree of consent and information given to the donors. It also raises the question of the ownership of the resulting organoids, which can also be sources of profit, as well as their patentability;[17] in short, the question of *who* will benefit from the use of organoids must be asked, as well as the *nature* of these benefits (financial, therapeutic, etc.).[18] The genetic analysis of organoids also raises a major issue of health data protection, particularly genetic data, which must be taken into account at the consent stage, although it is not easy to say how.**The ideology of promise**: organoids are presented as the source of multiple therapeutic advances. But is this actually the case? Indeed, there seems to be little ethical justification for holding out the prospect of speculative and random benefits. The question here is to ensure the biological and then medical relevance, in order to avoid building an ideology of promise from *in vitro* findings that have been extrapolated too quickly.

2. **The moral status of organoids**.[19] This status concerns organoids either in the sense that they could be regarded as individuals (which could concern gastruloids), or to the extent that they possess properties relevant to the attribution of moral status, such as sentience (which could concern cerebroids). This question of status also arises in the relationship between organoids and their donors, whose cells are the source of organisms with a certain degree of autonomy. However, there have been no studies so far on the value that donors attribute to "their" organoids[20] and we must ask ourselves, especially with regard to brain organoids and gastruloids, how cell donors will perceive the fate of these isolated cells that lead, so to speak, a

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16 We often talk about "regenerative medicine", but this expression is erroneous in that it is about repairing defective organs, not regenerating them like a salamander would regrow a limb.

17 A. Bredenoord & al., "Human Tissues in a Dish: The Research and Ethical Implications of Organoid Technology", *Science*, 2017, vol. 355, p. 3.

18 S. Boers & al., "Organoids as Hybrids: Ethical Implications for the Exchange of Human Tissues", *Journal of Medical Ethics*, 2019, vol. 45/2, p. 131-139.

19 Munsie & al., "Ethical Issues", p. 943.

20 Bredenoord & al., "Human Tissues in a Dish", p. 3. We could even ask ourselves whether donors are always aware of the existence of these organoids.

life of their own - this should also be taken into account when collecting consent. **The nature of consciousness and sentience**: brain organoids are constructed; could such entities feel pain, or even possess some form of consciousness? If so, their moral status should be assessed accordingly.

3. Insofar as organoids could be obtained by 3D printing, the process would imply a certain artificialization of the living; however, for some people, the distinction between natural and artificial has a moral value. **What does "creating living entities" mean in this context**? This question is a striking illustration of the paradigm shift that has taken place since living entities have been conceived as a set of parts to be assembled.

4. **The creation of chimeras by xenotransplantation**: to ensure the vascularization and innervation of organoids, the latter can be transplanted into animals - including human cerebroids into the brains of adult animals.[21] Chimeric organoids can also be created, but this is not necessarily relevant to understanding biological mechanisms in humans. It will no doubt also be possible to pair organoids with computers or robots,[22] just like what has already been done with neurons or in the project to build an artificial retina. **Animal ethics.** Organoids enable the development of alternative methods that are used upstream of or in parallel to animal testing. This represents a potentially substantial contribution to the 3Rs.[23] Fewer animals will be used, for example, to test the efficacy of new drugs, since some of this testing can be done on organoids. This is also valid for toxicology - especially since many drugs on the market reveal hepatotoxicity that does not show up in animals, as André Guillouzo points out. Insofar as organoids can be used in organ transplantation, animals will also benefit, since the project to breed genetically modified animals for the purpose of transplanting their organs into humans (the project to develop xenotransplantation) could be abandoned.[24] While official terminology refers to the killing of animals following a research protocol, it is

21 A. Lavazza and M. Massimini, "Cerebral Organoids: Ethical Issues and Consciousness Assessment", *Journal of Medical Ethics*, 2018, vol. 44/9, p. 608 and A. Yeager, "As Brain Organoids Mature, Ethical Questions Arise", *The Scientist*, August 1, 2018, https://www.the-scientist.com/features/brain-organoids-mature--raise-ethical-questions-64533.

22 A. Lavazza, "What (or Sometimes Who) Are Organoids? And Whose Are They? ", *Journal of Medical Ethics*, 2019, vol. 45/2, p. 144.

23 Bredenoord & al., "Human Tissues in a Dish", p. 2. The 3Rs are: refine, reduce and replace. This means that animal research must strive to reduce the stress on the animals (refine), reduce the number of animals used and, if possible, replace the use of animals with other methods.

24 J. Loike and R. Pollack, "Develop Organoids, not Chimeras, for Transplantation", *The Scientist,* August 23, 2019, https://www.the-scientist.com/news-opinion/opinion--develop-organoids--not-chimeras--for-transplantation-66339 .

interesting to note that the term "sacrifice" is sometimes used for organoids after they have been used in an experiment, just as it is for animals.

As can be seen from this list, the ethical issues can be grouped under the following two headings:

A. What norms and rules should be applied when researchers work on organoids?

B. What is the moral status of organoids?

The first directly concerns our behavior as *moral agents*, while the second relates to the nature of *moral patients*. A moral patient is a being towards which moral agents have moral obligations;[25] the question then is whether or not organoids are moral patients (organs are not moral patients, but just objects or things). This issue is raised for cerebroids, as we have just seen, and gastruloids.These questions relating to the ethical rules and statuses applicable to organoids could be usefully clarified and supplemented by the legal questions that accompany them. At this stage, there are no legal norms governing them and it may be difficult to determine with certainty who is the owner or custodian of this biological element obtained from a culture of human body products and to which legal category they belong: that of tissues and cells, that of organs, that of gametes in the case of ovarian organoids, etc.? This exercise, which is necessary in order to identify the rules applicable to the sample (from a living or deceased person), to the consent of the initial donor, and to the use that can be made of it, is all the more difficult since our norms do not precisely define the concepts that already exist. There is, for example, no legal definition of the organ.

The elements collected within this Memo will make it possible to enrich these legal reflections, which will undoubtedly emerge.

In this Memo, we are essentially limiting our reflection to the issue of consciousness, which specifically concerns the cerebral organoids, on which one of our interviewees, Frank Yates, a teacher-researcher at Sup'Biotech, is working with the aim of better understanding degenerative diseases (ethical issue no. 4). But first, we would like to say a few words about the paradigm shift mentioned above (ethical issue no. 6) and the ideology of promise (ethical issue no. 3), which concerns all research conducted on organoids - and even well beyond that - as it is linked to the transition to the clinical setting.

25 T. Regan, "The Case for Animal Rights", London, Routledge, 1983, p. 151-156.

A paradigm shift

Life, or more precisely being living, this property that characterizes certain natural beings manifesting self-organization, autonomy, ability to react, reproduction, evolution, and metabolism,[26] has long been considered as something given. Biotechnology has made it a construction, even a creation. As regards the embryo, for example, "this was commodified at the early stages of development and has become a quasi-object to be manufactured, tested, deconstructed into biobricks from which to derive the totipotent cells that have changed not just reproductive biology but the relationship to the individual body".[27] We observe the transition from a natural order to an artificial one, namely an engineering of the living state, which is morally problematic for some in that it denotes an inappropriate attitude on our part. Thus, says Jürgen Habermas: "My particular concern is with the question of how the biotechnological dedifferentiation of the habitual distinction between the 'grown' and the 'made', the subjective and the objective, may change our ethical self-understanding as members of the species"[28] and Mark Hunyadi specifies: "The frontier between the natural and the artificial […] offered a solid grammar to our spontaneous understanding of the world. But if life itself becomes an artifact [...] then a frontier hitherto taken to be fixed is crossed, producing instability, creating uncertainty".[29] Beyond the ethics, biotechnologies and philosophy of life that they convey[30] raise anthropological questions: what conception of ourselves and humanity do they raise and imply?[31]

- What moral value should be given to living entities conceived as sets of parts to be assembled?
- We observe the transition from a natural order to an artificial one, namely an engineering of the living state, which is morally problematic for some in that it denotes an inappropriate attitude on our part.
- Currently, there are no legal norms governing organoids that would allow, among other things, to determine with certainty who is the "owner" or "custodian" of this biological element.

26 Debates on the exact list of properties characteristic of the living state, namely on the question of the nature of life, continue. See M. Bedau, "The Nature of Life", in M. Boden, *The Philosophy of Artificial Life*, Oxford, OUP, 1996.
27 M. Botbol-Baum, "Biologie synthétique et renouvellement de l'éthique de la recherche", *Scienza et Filosofia*, December 15, 2019. "Commodified" means: reduced to the status of merchandise.
28 *The Future of Human Nature,* Cambridge, Polity, 2003, p. 23.
29 *Je est un clone*, Paris, Seuil, 2004, p. 21.
30 See B. Baertschi, *La vie artificielle*, Bern, ECNH, 2009.
31 Being transgressive is not unique to biotechnology: the dissection of cadavers in order to know and understand human anatomy was also transgressive in the beginning.

The ideology of promise

We have seen that although organoids are essentially a research tool at present, certain therapeutic applications are envisaged. For example, the bioconstruction of liver tissue for liver purification, the restoration of retinal function, the provision of rapid tests for cystic fibrosis treatment and, more generally, the repair of various types of organs and the availability of large numbers of histocompatible grafts. What should we think of the therapeutic prospects related to organoids, as well as the promises and hopes they raise? How can we move from an ideology of promise to an ethic of promise?

The language used by scientific research, for structural reasons of funding, is unfortunately becoming increasingly narrative and utopian, contrary to its epistemological and hypothetical approach that must be prudent. Science must guarantee a critical approach with the exercise of vigilant control over its own prospective advances, pledging not to promise anything that cannot be confirmed. For this, a broader approach is needed, which encompasses the human and social sciences, and promotes an open dialogue between science and civil society.

The ideology of promise is also fueled by patients: their demand is very strong, and even if it concerns research for the time being, it is not always easy to convey this when communicating with the public. Likewise, clinical trial subjects, when they suffer from the disease to which the research relates, tend to harbor hopes that are not justified by the trial methodology: this is referred to as therapeutic misconception.[32]

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Cerebroids and consciousness

A cerebroid is a 4 mm-diameter globule of which some of the developmental aspects, the electrical activity of neural networks in particular, appear similar to those of the brain of a 19 to 24-week-old fetus.[33] It is very useful for studying

32 P. McConville, "Presuming Patient Autonomy in the Face of Therapeutic Misconception", *Bioethics*, 2017, vol. 31, p. 711.

33 Lavazza and Massimini, "Cerebral Organoids", p. 607. See also S. Reardon, "Mini-Brains Show Human-Like Activity", *Nature*, 2018, vol. 563, p. 453 and A. Olena, "Human Cortical Organoids Model Neuronal Networks", *The Scientist*, August 28, 2019, https://www.the-scientist.com/news-

neurodevelopmental diseases such as autism, epilepsy, trisomy 21 or Fragile X syndrome,[34] as well as some types of cancer.[35] It is also used to evaluate the toxicity and pharmacological effect of new drugs. The idea that cerebroids, or at least those among them that mimic to some extent the functioning of the brain as an organ, might experience pain or possess some form of consciousness is often raised in the literature. Certainly, the use of the term "mini-brains" contributes to this; however, correcting our vocabulary is not enough for the query to disappear.If this possibility makes us stop and think, it is because the possession of characteristics, such as sentience (the ability to feel pleasure and pain) and consciousness are decisive for the question of moral status: a sentient or conscious being is a *moral patient* and not a *thing*. As far as humans are concerned, pain is defined by the International Association for the Study of Pain (IASP) as an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". It is notoriously difficult to say whether or not a non-human organism possesses sentience and consciousness. In the case of the former, this has long been known, especially in debates on the status of animals. Sentience is in fact a private phenomenon, which cannot be observed from the outside: all that we see and can see are physiological behaviors and reactions, which is sometimes possible to correlate with anatomical particularities, but they do not tell us anything certain about the psychological states that accompany them, or even if they are accompanied by mental phenomena.

Anatomically, we know that many animals possess nociceptors,[36] but we do not know the nature of the relationship between nociception and feeling - except in humans, for whom we have a decisive element of aid to understanding: language. However, since animals have a set of physical manifestations typical of pain in humans (frozen posture, cries, raised hairs, sweating, etc.), while we do not know their feelings, we can by analogy detect their suffering.

opinion/human-cortical-organoids-make-brain-waves-66368.

34 Recently, Ali Brivanlou's team has created neuruloids, i.e. constructions that recapitulate neurulation and could be useful for studying Huntington's disease (T. Haremaki & al., "Self-organizing Neuruloids Model Developmental Aspects of Huntington's Disease in the Ectodermal Compartment", *Nature Biotechnology*, 2019, https://doi.org/10.1038/s41587-019-0237-5.

35 F. Jacob & al., "A Patient-Derived Glioblastoma Organoid Model and Biobank Recapitulates Inter- and Intra-tumoral Heterogeneity", *Cell*, 2020, vol. 180, p. 1-17.

36 Animals and humans have nociceptors, which allow them to detect and respond to any stimulation that could be dangerous for them. Nociception does not need the brain (the spinal cord reflexes are sufficient) and can exist without pain (pain can also exist without nociception, as in fibromyalgia).

In the case of consciousness, we encounter the same difficulty. There is also a semantic obstacle: "consciousness" has many meanings. In particular, its use by psychologists and physicians is not at all the same. Among the former, it is generally the clarifications proposed by Ned Block that are referred to. This author distinguishes four meanings of the word: phenomenal consciousness, access consciousness, self-consciousness, and monitoring consciousness.[37] Phenomenal consciousness consists in the subjective experience of what happens to us and of what we do, in short, in feeling - it is therefore present in the experience of pain -; access consciousness includes all the representations we have, such as our thoughts or desires, representations that can be used by our executive system (decisions, actions, etc.); self-consciousness designates the representation we make of ourselves and monitoring consciousness is the reflexive consciousness, i.e. this second order-capacity of being able to examine what is happening in our mind.

Neurologists use a different classification when talking about states of consciousness in coma patients. As Éric Racine points out:

> It is important to understand that the clinical approach to consciousness as a neurological concept is different. [...] Clinical approaches to consciousness typically consider it a two-fold concept defined by wakefulness and awareness. First, wakefulness is basically equated to arousal; wakefulness consists of mechanisms that keep 'the patient awake and which relates to the physical manifestations of awakening from sleep'. Second, awareness refers to 'the content of consciousness or the awareness of self and environment', including psychological functions such as emotions, thoughts and sensory experience."[38]

Another tradition, also prevalent among neuroscientists, is inspired by William James. The taxonomy of consciousness thus remains a complex and debated subject;[39] therefore, the question of whether organoids are conscious presents as vague and, in the end, poorly-formulated. Hervé Chneiweiss pertinently states that: "The fundamental question actually lies in our vocabulary. What do we mean by the terms 'emotion' and 'consciousness'?"[40] Some neuroscientists work with Ned Block's distinctions when they have ethical questions,[41] but they remain the

37 N. Block, "Some Concepts of Consciousness", in D. Chalmers, ed., *Philosophy of Mind: Classical and Contemporary Readings*, 2002, Oxford, OUP (revised version, available online: epa.psy.ntu.edu.tw).
38 *Pragmatic Neuroethics*, 2010, Cambridge MA, MIT Press, p. 141-142.
39 See S. Dehaene & al., "Conscious, Preconscious, and Subliminal Processing", *TRENDS in Cognitive Science*, 2006, vol. 10/5, p. 204-211.
40 *Neurosciences et neuroéthique. Des cerveaux libres et heureux*, Paris, Alvik, 2006, p. 174.
41 T. Sawai & al., "The Ethics of Cerebral Organoids Research: Being Conscious of Consciousness", *Stem Cell Reports*, 2019, vol. 13, p. 440-447.

exception. Perhaps we should not use this expression and refer to "mental states" instead? It is not obvious that the discussion is becoming clearer, because on this point too, the debates are not closed: what is a mental state and what are its properties? For example, since Sigmund Freud at least - he echoes this in his book *Metapsychology* – there has been a dispute as to whether unconscious mental states exist or whether they are by definition conscious, thus to be distinguished from most cerebral states.[42]

The part and the whole

What then of the assertion that cerebroids could possess some form of consciousness or sentience, in short, something like a mental life? Many authors consider the question seriously and mention the study that revealed electrical activity in cerebroids similar to that seen in the brains of fetuses at 19-24 weeks.[43]

On a very general level, it cannot be ruled out that an entity made up of neurons possesses mental states, given the existence of relationships of correlation and even causality between the mind and the brain. During the course of evolution, consciousness gradually emerged, when there was a nervous system capable of supporting it. The same is true in the history of each of us: an embryo does not think, a child does.[44] Whatever metaphysical position we adopt, monistic or dualistic, materialistic or spiritualist, we must agree on the existence of these causal relationships, which also mean that a brain that is too damaged becomes incapable of thought and consciousness.[45] Thus, the hypothesis that cerebroids might experience pain is a thought experiment, based on the idea of the emergence of consciousness: if pain is a brain activity, future and complex organoids could hypothetically experience it (function emerges from structure).

However, we cannot draw any major conclusions from this general observation, for we must be careful to bear in mind that electrical activity as such cannot be equivalent to consciousness or sentience. More fundamentally, it seems very problematic to attribute the properties of a whole to its parts. This is already the case of the organs themselves: if we want to be precise, we must say that an

42 S. Freud, *Métapsychologie*, Paris, Gallimard, 1940.
43 The analogy was revealed by an algorithm, the reliability of which has however been called into question by some authors (H. I. Chen & al., "Transplantation of Human Brain Organoids: Revisiting the Science and Ethics of Brain Chimeras", *Cell Stem Cell*, 2019, vol. 25, p. 464).
44 This is a banal observation and not the assertion that ontogeny recapitulates phylogeny.
45 A causal relationship between two events does not imply that they are of different or the same nature; thus the fact that the mind and the brain interact causally is compatible with their identity. See J. Searle, *Minds, Brains and Science*, British Broadcasting Corporation, 1984, chap. 1.

isolated organ, outside the body, has no function. It is certainly possible to detect functioning in such an organ and study its mechanisms but this does not constitute a true function. For example, the beats of an isolated perfused heart are produced by the electrical and mechanical activity of the cardiac muscle, but this organ only functions as a pump ensuring blood circulation when in relation with the rest of the body. The same is true at the other levels of organization of this organism. At the biochemical level, the oxidation of hemoglobin into oxyhemoglobin by means of the iron present in the molecule ensures the oxygenation function of the tissues only when it takes place in the organism in relation to the other organs. Thus, if we maintain the same rigor, we would say that a brain cannot think, because thinking is a function of the organism as such, when it is situated in an environment that provides it with stimuli through receptors. A brain cannot be conscious of anything, nor can it have the slightest sentience that can be translated at the psychic level.

The same is especially true of cerebroids, particularly since many of them only replicate a particular region of the brain, and not the brain in its entirety;[46] for instance, only two types of cells are found: neurons and astrocytes. But even with regard to whole brain organoids, it should be pointed out that it is not just because their volume is only 1/1'000 of a mouse brain and 1/1'000'000 of that of a human being, or that they have no mature neural networks and so are unable to interact with their environment[47] that they do not possess consciousness, but because they are not functioning organs within an organism. Thus, if it is true that "no one knows how many neurons it would take for a distinctively human thought to emerge",[48] it is because the question does not make sense.

Consequently and more precisely, it is very important, in the case of cerebroids, to distinguish between *organization*, *activity* and *function*. Current data show that cerebroids acquire an activity and it is not impossible that, as we gain knowledge, we would be able to create more complex organizations, such as a circuit between two organoids - some teams are currently developing fused organoids, also referred to as "assembloids".[49] This should not be enough to create a function. This observation is enlightening when we draw a parallel with the brain activity of people in a state of coma or minimal consciousness. These patients maintain brain activity (otherwise they would be declared dead) and yet certain

46 Chen & al., "Transplantation of Human Brain Organoids", p. 463.
47 Munsie & al., "Ethical Issues", p. 943.
48 W. Cheshire, "Miniature Human Brains: An Ethical Analysis", *Ethics and Medicine*, 2014, vol. 31/1, p. 9.
49 Sawai & al, "The Ethics of Cerebral Organoids Research", p. 444 and Chen & al., "Transplantation of Human Brain Organoids", p. 464.

lesions mean that they can never regain consciousness, understood here as the ability of an awake person to say "I".

The search for reliable markers indicating the presence or absence of consciousness is an open problem, as is the reliability of the detection mechanisms used.[50] A recent contribution by Lionel Naccache and his colleagues at Pitié-Salpêtrière Hospital sheds particular light on this question and by analogy on the issue of "conscious cerebroids", suggesting that there are not two states of our brain, conscious and unconscious, but different degrees of consciousness - in the sense that neurologists understand this term.[51] This research is based on analysis of the functional activity that allows us to associate different regions of our brain. According to their hypothesis, in contrast to static descriptions of brain function, consciousness relates to a dynamic process: a "consciousness network". They compared healthy individuals and patients suffering from disorders of consciousness (coma, vegetative state, minimally conscious state). They looked for a pattern in which they could recognize brain regions that activate together and those that function in opposition, one activating when the other switches off. They then observed that the brains of patients in an altered state of consciousness showed a pattern of low coherence between the different brain regions: those that should have activated together no longer did so and those that should have activated when others switched off did not do so either. The alteration of consciousness thus seems to be marked not by inactivity of brain regions but by the loss of ability to be active together. These findings show that consciousness is based on the brain's ability to maintain coherent dynamics and that it is the coherence of the interactions between the regions of our brain that supports our presence in the world, their specific synchronization enabling us to be conscious. It would take time before researchers are able to reconstruct a brain that is capable of all this, but success is not inconceivable.

The situation may be different when cerebroids are transplanted into the brains of animals, such as rats or pigs, which have mental states.[52] Their chimeric brain is then an organ functioning within an organism. It has already been observed that this transplantation normalizes the expression of the genes of neurons, which is

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50 Sawai & al, "The Ethics of Cerebral Organoids Research", p. 441.

51 A. Demertzi, & al., "Human consciousness is supported by dynamic complex patterns of brain signal coordination", Science Advances, vol. 5, no. 2, February 6, 2019, https://doi.org/10.1126/sciadv.aat7603. See also H. Chneiweiss, *Notre cerveau*, Paris, L'Iconoclaste, 2019, p. 85-86.

52 Yeager, "As Brain Organoids Mature".

altered in *in vitro* cerebral organoids.[53] What will be the moral status of these "humanized" animals, i.e. these chimeras? At first glance, there are no answers to this question. Here we are confronted with a problem that we had raised in the Memo on EMSUs: these chimeras will have to be human enough to be used as a research model and then, if all goes well, in therapy, but not human enough to fall under the protection that belongs to human beings.[54]

Nevertheless, we can already propose some elements of an answer. As Isaac Chen and his colleagues have shown, it is not plausible to think that a rat brain, which has a number of cells equivalent to just 0.5% of the human brain, can replicate human brain architecture, even if most of its cells were of human origin. For larger animals, such as pigs and primates, the same authors suggest the use of behavioral tests such as the mirror test.[55] Even if the relevance of this test as a measure of self-awareness is disputed, we can see that we will not be without means to approach the question of the moral status of animals with a chimeric brain when the question arises concretely.

- The possession of characteristics such as sentience or consciousness is decisive in defining the moral status of cerebroids as that of any individual.
- The meaning given to the terms "emotion" and "consciousness" is essential for understanding the moral status of cerebroids.
- While electrical activity in itself cannot be equivalent to consciousness or sentience, it cannot be ruled out that an entity made up of neurons has mental states since there are correlation and even causal relationships between the mind and the brain.
- Consciousness relates to a "network of consciousness" that is thought to be based on the brain's ability to maintain coherent dynamics. Thus it is the synchronization and coherence of the interactions between brain regions, a condition not currently met by in vitro cerebroids, which allows us to be conscious.
- The identification of the means available making it possible to approach the question of the moral status of animals into which human cerebroids will be transplanted must be considered in concrete terms.

53 D. Kwon, "Organoids Don't Accurately Model Human Brain Development", *The Scientist*, October 23, 2019, https://www.the-scientist.com/news-opinion/organoids-dont-accurately-model- human-brain-development-66629.

54 U. Lee McFarling, "Near the Campus Cow Pasture, a Scientist Works to Grow Human Organs – in Pigs", *Stat*, October 20, 2017, https://www.statnews.com/2017/10/20/human-pig.

55 Chen & al., "Transplantation of Human Brain Organoids", pp. 468-469.

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