Review of: "Bioethical Assessment of Research with Humanoid or Humanized Biological Entities with Uncertain Moral Status"

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The authors have provided a nicely organized and well-referenced catalog of the many ways in which human tissue, cells and genetic material can be developed *in vitro* or combined with animals *in vivo*. Unfortunately, their emphasis on contents rather than functions leads to recommendations and conclusions that seem inappropriate for the future and even in conflict with currently accepted practices. *Ex cathedra* moral declarations about the humanness of embryos derived from various processes provide little basis for ethical discourse.

The percentage content of human vs. non-human material is easy to assess but useless for an ethical assessment of “humanness.” There is a long history of xenotransplantation (https://en.wikipedia.org/wiki/Xenotransplantation) in which xenografts from animals are implanted into humans to treat diseases with little concern that the recipients might be less human according to the percentage weight of the transplanted tissues. Conversely, if we genetically engineered all cells of an adult monkey to add in the 2-3% of human DNA that it is missing, would it suddenly become human?

Even being 100% human doesn’t automatically come with much ethical imperative. Most Western cultures do not consider a fertilized egg, embryo or unviable fetus that is 100% human to be entitled to human status (but perhaps the US Supreme Court will soon). Most modern societies accept the concept of brain death, in which a 100% human becomes no longer entitled to most legal and ethical protections of personhood. The electroencephalographic criteria for brain death require only a loss of organized activity in the cerebral cortex. The rest of that human brain and body may be and likely is functioning almost normally; at least some isolated cells and circuits of the cerebral cortex may also be alive and functional.

We are human not because of our contents but because of how those contents are organized. There is nothing unique about human neurons per se; it is the circuits that they develop over a lifetime that endow us with the capabilities that make us human, hence able to propose and debate abstract concepts such as those in the subject essay. Those few genes that make us human presumably govern the developmental processes and learning algorithms that cause the neurons to self-organize in ways that do not occur in nonhuman species. A human clonote that survived embryonic and fetal development would be no less human than a human developed by in vitro fertilization, a technology once deemed unethical and now common (particularly in Scandinavia, a region with high ethical standards). A societal decision to ban human cloning should be based on the potential for defective results (currently high) and socioeconomics, not the moral

opinion that appears to underlie the authors' Best Practices on this topic.

To be sure, there must have been intermediate species, resulting from intermediate bits of genetic code, that were sufficiently human to warrant ethical and legal debate if extant today. The recent paleoanthropological discovery of many individuals from a hominid species (Homo naledi) that ceremoniously buried their dead 200,000 years before Homo sapiens may constitute such an intermediate species (https://en.wikipedia.org/wiki/Homo_naledi). It is entirely possible that transgenic "monkeying around" with human and primate genes could result in a modern version of such an intermediate, but only if those genes had the opportunity to express themselves as an individual's brain developed. That is certainly something to be avoided on ethical grounds, as the authors clearly discuss in their section on Transgenesis but then undermine in their Best Practices ("human-animal transgenesis…should only be done…from human to animal").

The ethical questions raised here might be illuminated by the recent discussion in*Qeios* of the essay "Not quite like us? – Can cyborgs and intelligent machines be natural persons as a matter of law" (https://www.qeios.com/read/9WPMG4). This is a more difficult argument because it deals with functionality rather than contents, and the functionality of artificial intelligence has no known bound. Daniel Gervais, the author of the essay, had to resort to having a "biological embodiment" rather than transistors to avoid granting legal personhood to a sufficiently large and well-programmed computer. In my review, I proposed an alternative based on a hierarchy of creation – a machine created by man is not manlike in the same way that a man made by God is not godlike (https://www.qeios.com/read/F6QSNL). When man creates an independently developing brain from a mix of natural (if you will, god-created) species that includes man, is the result man? Given such an adult, we would be in the unfortunate situation of needing to assess its level of mental function, a dangerous exercise given the wide range of intelligence of normal humans and our long history of dehumanizing those whose cultures were simply different from ours. That is the moral and ethical dilemma that we need to avoid as scientists and citizens.