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From mythology to technology and back

Human-animal combinations in the era of digital recombinability

Who does not know the wonderful human-animal combinations in Greek mythology?[1] The Centaur, the creature with the upper body of a human and the lower body and legs of a horse; Medusa, the woman with eyes of stone, from whose head snakes grow instead of hair; Chimaera, the monster with the head of a lion, the body of a goat and a snake for a tail? They sowed death and destruction. Quite comforting that they don't exist.

Or should we say: did not yet exist? Because human-animal combinations are among us again, and this time not as creations of mythological imagination, but as products of contemporary biotechnology, such as cybrids and chimeras. Think of mice with sizable pieces of genetic code that originated from the human genome, used in cancer and pharmaceutical research, or pigs with a human heart, that are grown for medical applications.

Such biotechnological creations evoke a lot of resistance in public debates. This resistance is partly based on rational arguments, such as health risks, but often strong emotions, like feelings of disgust, play a major role as well. Why would that be the case? All things considered, contemporary biological insights inform us that human beings, like all species, actually are already polygenomic organisms, and for that reason, fundamental biological concepts such as 'individual' and 'species' deserve considerable nuance. On closer inspection, the mythological human-animal combinations appear to contain more truth on this point than nineteenth-century biology, which was strongly driven by a separative cosmology, which still haunts common sense conceptions of life today.

In this essay I will discuss recent developments in postgenomic molecular biology from the perspective of the interconnective cosmology of Greek mythology. Not in order to claim the 'eternal truth' of this ancient cosmology, but to show that it contains insights that help us to better understand contemporary postgenomic biology and philosophical anthropology and to situate them in a broader world-historical context.

1 This article is adapted from the lecture 'Open-source evolution? Human-animal combinations in the era of digital recombinability' that was given at the symposium *Human-animal combinations. From mythology to technology*, Amsterdam, 12 February 2019. The symposium was organized by the Royal Netherlands Academy of Arts and Sciences on the occasion of the publication of a scientific fact sheet on cybrids and chimera, written at the request of the Health Council of the Netherlands, which, at the request of the Dutch government, had to issue an advice with regard to the amendment of Article 25 of the Embryo Act, which sets limits for biotechnological activities involving human-animal combinations. See: https://www.knaw.nl/nl/actueel/agenda/mens-diercombinaties-van-mythologie-naar- technology

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1 From gray to green technology

When we look back at the technological developments of the twentieth century, we immediately notice the enormous impact of the sciences of inanimate nature, such as physics and inorganic chemistry, and the technologies based on them. New means of transport such as cars and airplanes, nuclear energy with its peaceful and military applications, the introduction of plastics and last but not least the electronic computer and various information and communication technologies have defined the appearance of the twentieth century.

However, especially since the first adequate description of DNA in the mid-twentieth century by Francis Crick and James Watson, the life sciences have started an impressive advance. With the iconic Human Genome Project (1990–2003) – characterized by scientific director Francis Collins as "the most important and the most significant project that humankind has ever mounted" (Kolata 1993) – the primacy seems to have shifted definitively to the life sciences, both in terms of funding and possible impact. Although Collins' talent for understatement seems to be somewhat underdeveloped, it probably is not too bold to predict that the twenty-first century is going to be the century of the life sciences and biotechnology (Dyson 2007).

Of course, I do not mean to say that there will be a full change of the guard. Without doubt, 20th-century technologies will continue to develop, and disciplines like robotics, artificial intelligence, nanotechnology and quantum computers will undoubtedly continue to confront us with all kinds of welcome and less welcome surprises. Moreover, the impressive development of the life sciences and biotechnology to a large extent has become possible thanks to the computer. In the era of converging technologies, biology and information technology have become as closely intertwined as the strands in the double helix of the DNA molecule (De Mul 2013).

This can be easily read from the Human Genome Project and the development of postgenomics (Richardson and Stevens 2015). The sequencing and storage of roughly three billion nucleotides and the analysis of the interaction of the approximately 23,000[2] genes encoded therein and operating in complex networks with the environ-

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2 The number of genes in the human genome has been continuously downgraded since the start of the human genome project. Based on the 'one gene one function' paradigm and the fact that the human body is made up of about 100,000 different proteins, the initial expectation was that the human genome would contain about the same number of genes. The fact that there are only about 23,000 – while some rice varieties have more than 60,000 – seems at first a serious offense to human pride. However, we must realize that genes not only vary in size (in the human genome from just a few thousand pairs of nucleotides or 'base pairs' to over two million), but that most genes function in multiple, often very complex networks, whereby they can fulfill different functions per network. In addition, many of the three billion nucleotides in the cell nucleus that are not part of the genes (and initially wrongly referred to as junk DNA), appear to fulfill important regulatory functions, often epigenetically driven by the environment. Just as not only the number of neurons in the brain, but even more so the number of connections between them, determines the complexity of the behavior of ment would not be possible without powerful computers and algorithms, advanced databases and sophisticated methods of data mining and profiling. An important part of biology has moved from living nature (*in vivo*) and the laboratory (*in vitro*) to the computer and has become *in silico*.

Many of the current techniques in life sciences are based on information technologies, with striking similarities between the natural sciences and the humanities. After genetics had become proficient in reading the genetic code, techniques such as CRISPR-CAS9 – also referred to as programmable scissors[3] – have entered the era of genetic writing and editing. While results today are impressive, it seems likely that cutting and pasting in the life sciences are still at kindergarten level. However, we are dealing with a very promising student!

2 Database ontology

As is often the case with new technologies, they function not only as a tool for the scientist, but also as a metaphor for understanding the object of research. For example, the advent of machine technology in the sixteenth and seventeenth centuries inspired the idea that the human body is a complicated machine. The HUMANS ARE MACHINES metaphor not only created a new image of life, but also opened a new space for action (cf. Lakoff and Johnson 1980). Every ontology entails a deontology. Not only was the heart now understood as a pump, but this image also invited a defective heart to be repaired or replaced, as in the case of a broken machine. The epistemic and practical power of metaphors can hardly be overestimated. The machine metaphor has

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a species, so does not only the number and size of the genes are important for organic complexity, but also, and even more, the total number of their connections, functions and interaction with the environment. In that respect, the genes are more like a natural language, in which not only the number of different words determines the richness of the language, but also the number of combinations and the different meanings the words can have in various combinations and life contexts (cf. Borgstein 1998).

3 "CRISPR, which is an acronym for clustered regularly interspaced short palindromic repeats, is a family of DNA sequences found in the genomes of prokaryotic organisms such as bacteria and archaea. These sequences are derived from DNA fragments of bacteriophages that had previously infected the prokaryote. They are used to detect and destroy DNA from similar bacteriophages during subsequent infections. Hence these sequences play a key role in the antiviral (i.e. anti-phage) defense system of prokaryotes and provide a form of acquired immunity. CRISPR are found in approximately 50% of sequenced bacterial genomes and nearly 90% of sequenced archaea. Cas9 (or „CRISPR-associated protein 9") is an enzyme that uses CRISPR sequences as a guide to recognize and cleave specific strands of DNA that are complementary to the CRISPR sequence. Cas9 enzymes together with CRISPR sequences form the basis of a technology known as CRISPR-Cas9 that can be used to edit genes within organisms. This editing process has a wide variety of applications including basic biological research, development of biotechnology products, and treatment of diseases. The CRISPR-Cas9 genome editing technique was a significant contributor to the Nobel Prize in Chemistry in 2020 being awarded to Emmanuelle Charpentier and Jennifer Doudna" (N.N. 2021, Wu and Peltier 2020) given wings to modern medicine. Of course, the metaphor also implies the dangerous possibility of taking it for reality itself, leading to a reductionist mechanicism, as happened, for example, with Richard Dawkins in *The Selfish Gene* when he reduced organisms to mere survival machines of the genes (Dawkins 1976).

With the rise of the computer, new metaphors have appeared, such as that of the database. Databases are an integral part of almost all computer programs; they form the heart of the computer, as it were. They are characterized by four basic operations, the ABCD of information processing: Add, Browse, Change and Delete (the commands Insert, Select, Update and Delete of the Structured Query Language (SQL) commonly used for the design and use of relational databases). These four basic operations constitute the database ontology of the information age (De Mul 2009). However, the database is not only an indispensable tool for researching and analyzing the genome, but it also functions as a conceptual metaphor. The evolution of life on Earth is no longer understood solely, or even primarily, as a nearly four-billion-year long history, but rather as a contingent path through the database of life, also known as 'the global gene pool'.

A comparison with the development from the traditional story to the computer game may illustrate this point. Where the classic story has a linear – chronological or not – plot, a computer game can also be understood as a multilinear story space, a database that discloses many different paths. The number of possible (re) combinations is unimaginably large. Queneau's *Cent mille milliard du poèmes* is a good example of this (Queneau 1961). It is a small collection of 10 (by definition 14-line) sonnets. However, each page is cut into 14 strips, each with one line. The reader can thus combine any line of any sonnet with each of the lines of all other sonnets, yielding 10^{14} – 'Cent mille milliard' (one hundred trillion in American English) different sonnets! Various digital versions can be found on the Internet, where we can randomly recall one of the one hundred trillion poems with a single mouse click.[4] Incidentally, this idea of such a non-linear hypertext is not completely new. We already find it in the at least two and a half thousand-year-old Chinese *I Ching* (易經), also known as *The Book of Changes*), an oracle book composed of 64 hexagrams of whole and broken lines (Redmond 2017). These hexagrams inspired the binary number system of philosopher and mathematician Leibniz (Leibniz 1705), which in turn has made possible the countless digital versions of this oracle book on the Internet.[5]

An even more dizzying, but merely imaginary expression of the database ontology is the Library of Babel in the 1941 eponymous story by the Argentinian writer Jorge Luis Borges (Borges 1999, 112–118). This quite unique library encompasses all possible books, created by the recombination of the 25 orthographic signs of the Spanish

4 See for example http://www.bevrowe.info/Internet/Queneau/Queneau.html
5 See for example: https://www.ichingonline.net/. Various editions of the original text and English translations of the *I Ching* can also be found on the internet, e.g. at the website of the Chinese Text Project: https://ctext.org/book-of-changes/yi-jing

alphabet (22 letters, period, comma and space). In Borges' story, each book consists of 410 pages, each containing 40 lines of 80 characters, yielding $25^{1,312,000}$ books. Compared to this literally hyper-astronomic number, the number of particles estimated by cosmologists in our universe – 10^{80} ($\approx 25^{57}$) – is negligible. Just as the inhabitants of the Library of Babel search for meaningful books (after all, most books consist largely of meaningless strings of letters), so the geneticists in the 'Library of Mendel' (global gene pool) are looking for the meaningful sequences in the sea of 'junk DNA' that surrounds them.[6]

Contemporary geneticists, unlike the inhabitants of Borges' Library of Babel, are not only interested in finding meaningful sequences in the 'Library of Mendel', but, in addition, they want to design new meaningful sequences. Expressed in the language of the database, they are not only interested in the already existing paths through the database of life, but want to design new, alternative paths as well. In so-called 'alien genetics', for example, researchers have extended the familiar terrestrial DNA by adding new bases to it, increasing the already vast number of possible recombinations tremendously (Benner, Hutter, and Sismour 2003, De Mul 2013),

Thanks to the programmable scissors CRISPR-Cas9, genetic editing can not only fix errors in genes (caused by unwanted mutations), but in principle also design all kinds of new recombinations. Obviously, as we shall see, this is not as easy as cutting and pasting in the digital world with programs like Photoshop. But the number of possible combinations here too – just like in the Database of Babel – is hyper-astronomically vast. Now, of course, the number of possible viable recombinations is not equal to the logically possible number. There are numerous physical, chemical, biological, historical, and factual limits to genetic recombinations (Dennett 1995, 104–107). A winged horse such as the mythical Pegasus is logically conceivable and does not seem physically and chemically impossible. However, biologically it is impossible that a herbivore could gather enough energy to take to the skies, and because the equines once took the path of the herbivores, they are unlikely to ever develop into carnivores. In addition, the probability that through creative cutting and pasting using CRISPR-Cas9 we will ever create a chimera like the mythical Centaur is highly unlikely because of the evolutionary distance between horse and human.

6 Unlike the non-coding DNA in the human genome, which has a regulatory function and for that reason is erroneously called junk-DNA (see note 2), most recombinations in the Library of Babel are actually 'junk' because the majority of the hyper-astronomical number of books are (almost) completely meaningless. See about the fascinating mathematics in 'The Library of Babel' William Goldbloom's *The Unimaginable Mathematics of Borges' Library of Babel*` (Bloch 2008) and about the 'Library of Mendel' the chapter 'The possible and the actual' in Daniel Dennett's *Darwin's Dangerous Idea* (Dennett 1995, 107ff.).

3 Natural and artificial human-animal combinations

This brings me back to the main topic of this essay: human-animal combinations. Although spectacular chimeras from Greek mythology will probably always remain mythical creatures, the artificial construction of chimeras and related human-animal combinations such as cybrids is now one of the biotechnological possibilities.

Instruments like CRISPR-Cas9 do not only enable geneticists to cut and paste in the genome of a single individual and to exchange the genetic material between the individuals of one and the same species, but also make it possible to create recombinations of genes taken from genomes of different species.

Such recombinations are not entirely new. In nature, spontaneous human-animal combinations also occur, for example in the form of hybrids, in which the mature egg cell of one animal species is fertilized with a sperm from another species. A well-known example is the mule, a hybrid of horse and donkey. The same phenomenon has occurred in humans in the past. In recent years, geneticists have shown that archaic and modern *Homo sapiens* also interbred with other simultaneously living hominids, such as the Neanderthals, the Denisovans and unspecified African hominids, over the past 300,000 years (Wolf and Akey 2018).

Of much more recent date are artificial human-animal combinations such as transgenic animals, in which one or more human genes are added to the genome of an animal using genome editing techniques such as CRISPR-Cas9.[7] This is done in part to study the function of various genes, in order to produce human-specific proteins, or to 'humanize' animal tissue intended for xenotransplantation in order to prevent rejection, or to facilitate the growth of human tissue in animals. Although these transgenic animals can be called human-animal combinations, to a large extent they retain their species-specific properties.

In this respect, cybrids and chimeras are different. *Cybrids* come into being when the cell nucleus (diploid, i.e. containing two copies of each chromosome) and the cytoplast (all other parts of the cell, such as the cytoplasm, mitochondria and other organelles in a cell) originate from different cells. When the nucleus comes from the same species, we speak of cloning. In that case, the embryo can grow into a viable organism (for instance, Dolly the sheep), but there is no combination of species, since both cells come from the same species. However, cybrid techniques are also used to 'retrieve' extinct animal species through nuclear transfer into the zygote (single-celled embryo) of a related species. In this case we speak of interspecies cybrids (Fatira et al. 2019).

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7 The following explanation of these artificial human-animal combinations is largely derived from the *Factsheet Human-Animal Combinations* of the Royal Netherlands Academy of Arts and Sciences (KNAW 2019). See note 1.

When a human nucleus is placed in the cytoplast of another animal, or an animal nucleus in a human cytoplast, it is a human-animal cybrid.[8] The chance that human-animal cybrids are viable is extremely small due to incompatibility of the DNA in the nucleus and that in the mitochondria. There are also no direct clinical applications for this type of human-animal combinations, although – in principle – we are confronted here with interesting ontological (i.e. philosophical-anthropological) and ethical questions. However, in cases in which the human cell nucleus is surrounded by animal mitochondria, the resulting organism can still be called human , because the share of mitochondrial DNA is low in both quantity and quality (the latter because it is mainly involved in metabolic functions). And given the limited viability of cybrids, it is also questionable whether we can call them embryos at all, since – as happens in the current Dutch Embryo Act, for example – "the ability to grow into a human" is considered a defining characteristic of embryos.

Chimeras are not a combination of genetic material of two species in a cell. Rather, they are composite organisms, which already *before* birth consist from cell populations that originate from fertilized eggs of different species.[9] In addition, a distinction can be made between primary chimerism, in which the combination of cells of the different species take place immediately after fertilization, and secondary chimerism, where the combination takes place after organogenesis (formation of organs) has started. In mammals this is after implementation in the uterus. Successful chimera formation depends to a large extent on the evolutionary relationship of the combined organisms. Since the 1980s, for example, it has been possible to make chimeras from different mouse species, or by combining genetic material from mice and rats, goats and sheep (sometimes called 'geeps' in popular media), and the European bovine and Zebu. Chimerism can come in several variations. This is partly due to the type of cells that are used (Summers, Shelton, and Bell 1983).

If the cells used are totipotent or pluripotent (i.e. stem cells that in principle can still form all the different cells that make up the organism), or – by reprogramming differentiated cells – have been made pluriform (so-called induced pluripotent cells), then the chimerism can be scattered all over the animal. Also important is the location to which the donor cells are transplanted and the time at which this occurs. If

8 It is also possible, instead of the nucleus, to transfer the mitochondria in the cytoplast, which have their own DNA, from one cell to another. Although a related technique, the result judged by definition is not a cybrid, and the impact of mitochondrial DNA on the embryo is small, as the proportion of mitochondrial DNA is small in quantitative terms, and it mainly affects the metabolic rate functions (metabolism). However, when one of the two cells is a human cell, it is still a human-animal combination. Yet another construct related to cybrids is the bi-nuclear cell, obtained by the fusion of nucleated cells of two different species and the above-mentioned hybrids, which are the result of a fusion of the egg cell of one animal species with the sperm cell of another animal species (KNAW 2019, 19).

9 Organisms in which cells from another organism are introduced *after* birth are therefore not counted as chimeras but are regarded as examples of xenotransplantation.

the donor cells are transplanted at the time and place at which they also arise in vivo, they are most likely to contribute to natural organogenesis (KNAW 2019, 10ff.).

Injecting induced or uninduced mouse and rat pluripotent cells into a pig embryo showed that the contribution of the introduced pluripotent cells in embryonic development was very small. Similar findings resulted from the experiment in which induced human stem cells were introduced into pig blastocysts (i.e. embryos in early development, before implantation in the uterus), produced in vivo. Apparently a form of "genetic xenophobia" or – to put it more neutrally – "xeno barrier" occurs here: when the evolutionary distance and therefore the genetic difference are too great, chimeric formation appears impossible. This is a good example of the previously mentioned limits on genetic recombinability (see section 2).

However, in principle it seems possible to grow an organ with only human cells in animals in relatively close evolutionary proximity, such as pigs or apes. To this end, before pluripotent cells are introduced into a blastocyst or embryo of the host animal, the genes responsible for the formation of a particular type of tissue are switched off in the host by means of genetic modification. The cultured organ can then be xeno-transplanted postnatally (after the birth of the donor animal) into a human. When the pluripotent cells come from the same human ("patient-derived xenograft"), the risk of rejection is lowest.

The creation of human-animal chimeras is generally motivated and justified by the increase in knowledge it enables and its clinical application. The latter could be the testing of drugs or therapeutic applications of stem cells with a view to developing partial regeneration or complete replacement of organs damaged by disease or accidents.

4 Technical risks and ethical questions

The creation of human-animal combinations raises many questions. In part, these relate to the *risks* associated with experimenting with and clinical use of cybrids and chimeras. Not only does the human immune system appear to be very violent against animal organs, but animal tissues often contain potentially dangerous genetic elements. For example, the DNA of the pig (a favorite donor animal, because of its evolutionary proximity), is full of copies of the pig virus (PERV), which can come along with the organ like a Trojan horse and infect humans. CRISPR-Cas9 now makes it possible to disable such viruses; renowned synthetic biologist George Church succeeded in eliminating all 62 PERVs in pig DNA in 2015. However, studies published in *Nature Medicine* and *Nature Biotechnology* have shown that genome editing using CRISPR-Cas9 can inadvertently result in deletion and displacement of entire sequences in the host's DNA. In the cases studied, this caused serious damage to the DNA, as up to 20% of cells lose their anti-cancer functions and become potentially pathogenic

(Kosicki, Tomberg, and Bradley 2018). Because errors often occur in locations far from the modified parts, they are difficult to detect with standard genotyping methods used to see if a CRISPR-Cas9 edit is successful.

These effects are hardly surprising when we recall the dizzying complexity of genetic networks, in which one and the same gene can fulfill various functions. This not only provides material for interesting science fictions films like *Annihilation* (2018), in which genetic experiments lead to an explosion of animal-human-plant combinations, but also recalls real tragedies that are the result of unpredicted and often unpredictable side effects of technical intervention in nature (De Mul 2014). In itself, this is not a reason to stop or prohibit research into and use of cybrids and chimeras, but it makes clear that the use of these biotechnologies require great caution.

A 2009 comparison of UK and international studies of the social acceptance of chimeras showed that between 60–67% of the population is against making chimeras (Kantor 2017). In polls that explicitly point to existing or anticipated medical applications (for example in Parkinson's disease and Alzheimer's disease), the number of opponents fell to 30% and the number of advocates increased to 50%. It is striking, however, that the resistance to making chimeras for research purposes is significantly bigger than to using and making human embryos.

This suggests that in the case of chimeras, more is at stake than practical concerns about safety, and ethical concerns about the instrumental use of human and animal embryos. Opponents of chimera often express their dislike in emotional terms, reporting disgust in particular as a ground for their rejection. Sometimes this happens on religious grounds, for example when reference is made to the sanctity of the Divine Creation, on the basis of which man is not allowed to intervene in the order of nature.[10] The secular side often refers to human dignity and the integrity of the species. In either case, there seems to be a taboo on disturbing an order of nature (divine or otherwise), especially when it consists in mixing what is separate by polluting genetic purity.

In the essay 'Menselijke organen kweken in dieren: een ethische discussie' [Growing human organs in animals: an ethical discussion], written on request of the Dutch Ministry of Health, Welfare and Sport, the authors mention three forms of the humanization of the animals that they regard as ethically problematic:

> 1) changes in the animal brain that could theoretically lead to human cognitive abilities or human forms of consciousness, 2) the also theoretical, but not impossible development of functional human reproductive cells, which could be can lead to the growth of a human embryo in an animal, and 3) the development of human body characteristics in the animals / chimeras such

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10 Graig Venter, the desperado of genetics and synthetic biology, well-known for his provoking signature hubris, once answered the question of a journalist whether he was not playing God, with an indignant 'I'm not playing!' See for an analysis of the ethical and theological implications of Venter's claim to have created creating living beings in the laboratory: ''Are You Playing God?': Synthetic Biology and the Chemical Ambition to Create Artificial Life'(Schummer 2016).

as the skin type, (part of) the limbs, or the facial structure (Jochemsen, Dondorp, and Wert 2017, p.12, translation from Dutch JdM).

Because of the aforementioned xeno barrier, the authors underline that the contribution of human cells outside the target organ probably will be very small, i.e., no more than 1%. Nevertheless, they seem to endorse further precautions to prevent chimeras from developing beyond the embryonic stage.

What is striking about reflections like this is that ontological and ethical considerations are almost as closely intertwined as the genetic material in chimeras. From an ethical perspective, there seems to be nothing wrong with making animals smarter. Especially if this would also result in granting animals more rights than we usually do. Moreover, it fits within the emancipatory aim that has characterized our thinking and acting since the Enlightenment. And don't we enjoy fables in which animals display all kinds of human forms of cleverness and cunning?[11] And we do not have much trouble with taking over body characteristics such as skin type – witness the existence of fur coats and tiger prints. The ethical problem rather seems to be connected with the blurring of the ontological distinction between humans and animals.

11 An opposite interpretation of the pointe of animal fables is given by Chris Danta in his book *Animal fables after Darwin. Literature, Speciesism, and Metaphor*: "This book is an argument against the logic of animal uplifting, which tries to imagine a post-biological future for human and nonhuman creatures alike. To argue against the notion of uplifting I turn to what may seem a surprising source: the literary form of the fable. For many, the fable is a moribund genre of literature that belongs to the lost hours and forgotten pedagogy of childhood. Few would consider it as an aesthetic form that can help us to think through the grownup and contemporary issue of biopolitics. But the fable acquires new significance, I suggest, in the era of uplifting in which humans prove capable of literally anthropomorphizing animals by scientifically enhancing nonhuman cognition. Synthesizing contemporary genetic science, theology and fable, the discourse on animal uplifting imagines a future in which humans realize their stewardship of the earth by transforming nonhuman animals into truly fabulous subjects: sapient creatures that talk and reason like us. Uplifting is the utopian thought that we might somehow reproduce Aesop's talking animals in the laboratory. So, along these lines, Dvorsky proposes the 'idea of a United Nations in which there is a table for the dolphin delegate'. In this book, I present the fable and, particularly, the post-Darwinian fable as an antidote to the species utopianism of animal uplifting. The fable is an ancient literary cognate of animal uplifting. In fables, animals acquire the power of speech and reason by literary rather than scientific magic. As in uplifting, the purpose of elevating nonhuman animals to the status of humans in the fable is to play with the vertical order of things. But the essential vertical movement here is down not up. Animals are anthropomorphized in fables to expose human foibles and to lower our estimation of the human. Rather than lifting the human up out of the realm of biology, fables cast the human down by casting the human as an animal. The act of animal uplifting on the part of the fabulist thus serves an ironic purpose – and the fable challenges all modes of thought that seek to transcend the limits of biology or species. While the discourse of animal uplifting sanctifies the human as a quasi-theological agent able to transcend biology in the name of planetary stewardship, the fable de-sanctifies the human by reminding it of its biological destiny" (Danta 2018, 2–3).

5 Ontological pollution and ethical ambiguity

This ontological ambiguity and the intertwining of the ontological and ethical, which problematizes the modern separation of 'is' and 'ought', is reminiscent of the interconnected worldview of the pre-Socratic Greeks, as expressed in mythological stories about Chimaera and in Greek tragedies.

Every culture is based on a number of fundamental distinctions, for instance, those between nature and culture, between human and divine, life and death, and male and female (Oudemans and Lardinois 1987, 31). However, our modern, separative cosmology is different from the ancient Greek one because in the latter the distinctions remain ambiguous—because they contain numerous implicit connections—while these distinctions are made absolute in the former. Whereas in a separative cosmology the natural phenomenon and the divine being belong to radically separate domains, in an interconnective cosmology lightning is not just a natural phenomenon, but also the action of a divine being. It is impossible to separate 'is' and 'ought', *Sein* and *Sollen*. That's why the goddess Dikè in Greek mythology stands for both the factual and the moral order of nature.

However, in cultures with interconnected cosmologies like the ancient Greek culture, ambiguities – pollutions of the natural order – are as problematic as in cultures with a separative cosmology. What cannot be separated is uncanny (*unheimlich*), it evokes disgust and is considered (potentially) dangerous. The Greek mythology chimera with its lion head, goat body and snake tail pollutes the dividing line between the species and is therefore a threat. That is the reason that these creatures, according to the myths, sow death and destruction.

This theme of pollution is the recurring motive in Greek tragedy (De Mul 2014, 85–90). In the tragedy of Sophocles of the same name, when Oedipus kills his father and marries his mother, he pollutes the ontological and moral order at the same time (Sophocles 1972). As a result, plague breaks out in Thebes. Given our modern, separative cosmology, this sounds strange or superstitious, but we have to remember that remains of interconnective, mythical thinking are still there in our modern world. In some (religious or spiritual) circles, diseases like AIDS and COVID19 are considered a *punishment* for violating the divine or natural order through homosexual acts or disrespect for nature.

In pre-Socratic Greek culture, this mythical thinking was dominant In Sophocles' *Antigone*, the sequel to the Oedipus myth, the two sons of Oedipus kill each other in the battle for succession (Sophocles 1972). Oedipus' brother-in-law Kreon takes his responsibility and tries to reinstall order in the divided city by giving one brother a hero's burial and giving the body of the other brother to the vultures and wolves as punishment for his betrayal. However, their sister Antigone thinks it is her sacred duty to bury her brother. After all, dead people belong underground. Kreon has violated the natural and moral order. As punishment, Kreon locks her up alive in a cave.

This causes a second pollution: after all, the living should be above the ground and not buried. As usual in tragedies, things end very badly.

All cultures try to ward off pollution and they develop different strategies to this end. According to Chimaera myth, the misery only comes to an end when Bellerophon – curiously himself seated on another chimera – the winged horse Pegasus – kills the Chimaera with his lance. The Greeks anticipated the idea of inoculation: sometimes you have to fight large pollutions with smaller pollutions. In Greek tragedies, the pollution of the natural and moral order is usually reversed by the sacrifice or self-sacrifice of the tragic hero. When Oedipus finds out that the man he killed is his father and the woman he married his mother, he gouges out his eyes and exiles himself from the city. Kreon also leaves the city completely distraught after his son (NB Antigone's fiancée!) and his wife commit suicide as a result of his actions. And Antigone, too, is sacrificed in order to reinstall the natural and moral order.

In modern cultures we try to ward off pollution by making distinctions absolute. Where in the mythical, interconnective worldview the natural and moral order are constantly intertwined – the mythical chimeras and the Greek tragedies both show the presocratic obsession with pollutions and ambiguities – in modern, separative thinking, is and ought, and good and evil, are strictly separated. And whereas the tragic heroes are destroyed by fate, we, moderns, try to ward off fate by taking control of our destiny with the help of impressive technological means (De Mul 2014).

The question, however, is whether that will really work. The tragic irony is that modern technologies constantly cause a variety of pollutions. Today, the uncanny Antigone, floating between life and death, can be found in a comatose state in intensive care[12], and thanks to advanced biotechnologies we are constantly creating cybrids, chimeras and other 'pollutions'.

6 Organic (in) purity

The point is not just that biotechnology produces chimeras, postgenomic research also leads to a de-purification and – more specifically – chimerification of our image of living nature. Let me illustrate this by the "central dogma" of Neo-Darwinism, as formulated by Francis Crick in 1956 (Crick 1956).

This "central dogma", which has dominated mainstream genetics for some fifty years. It teaches that genetic information can only be transferred from DNA to RNA and the proteins, but never the other way around. Neo-Darwinism assumes that only the genes present in the cell nucleus are carriers of hereditary properties, that the genome unique to each organism can be found in every cell of the body and that it hardly changes during the life of an individual (except small deviations that are the result

12 See my (Dutch) essay 'Antigone op de intensive care' [Antigone in intensive care] (De Mul 2018)

of mutations, copy errors that arise under the influence of radiation). The genome (genotype) would thus determine the development of the organism (the phenotype) in a deterministic, pre-programmed manner.

This gene-centrism led to the expectation that mapping the precise sequence of the base pairs in the human genome – as was done in the Human Genome Project between 1990 and 2003 – would not only allow us to distinguish the human genome from genomes from other species, but also human individuals and groups of individuals can be distinguished on the basis of the small mutual differences in their DNA. Forensic genetics is largely based on this when it identifies a specific individual or group of related individuals by examining genetic traces.

However, post-genomic research has made it clear that the central dogma is incorrect in some respects and in others a rather simplified abstraction of biological reality at best (Noble 2015, Richardson and Stevens 2015, De Mul 2017). Let me explain this with reference to three research areas.

In *epigenetic research*, for example, it has become clear that the role of chemical substances in the cytoplasm, of the environment and of the behavior of the organism on the expression of the genes is much greater than previously thought, and these influences are also hereditary. A spectacular example is the experiment that Sun has conducted with his colleagues in Wuhan (Sun et al. 2005). The nucleus of a germ cell of a carp was placed in the fertilized egg of a goldfish, which had been stripped of its nucleus (and thus of its genome). Where, on the basis of the central dogma, the result could be expected to be a carp, the experiment turned out to yield a hybrid, which was more closely related to goldfish than to carp in terms of the number of vertebrae (Sun et al. 2005). Various epigenetic effects have also been demonstrated in humans. For example, a longitudinal study conducted in Sweden shows that men who were malnourished during their pre-adolescence had grandsons who died less often of cardiovascular disease (Pembrey et al. 2006).

An example of epigenetic inheritance through behavior is Ian Weaver's study of the effect of the licking and caressing of young rats by their mothers, which showed that later in life these youngsters began to exhibit the same behavior towards their offspring as the parents (Weaver 2009). The explanation for this is that care behavior leads to specific chemical groups attaching to relevant genes in the hippocampus, the part of the brain that plays an important role in memory function.

Now it could be said that in these forms of genetic inheritance the DNA in spite of the attachment of an extra chemical group – by methylation, for example, this happens by a methyl group attaching itself to one of the nucleotides (cytosine), converting it into 5 (methylcytosine) – remains the same, but in reality there is a change in molecular structure. The two molecular structures can only be called the same on the basis of a Platonic abstraction – purification, if you like – of chemical reality, by equating DNA with a four-letter code (Dupré 2015).

A second undermining of the central dogma takes place in the research on *horizontal inheritance*. The central dogma assumes that hereditary material is only passed on vertically, within each species from one generation to the next. According to microbiologist Carl Woese, that picture needs to be adjusted. According to Woese, in the early phase of the evolution of life on Earth, there were no separate species at all, but there was a continuous free horizontal transfer of genetic material between prokaryotes (cells without a nucleus), whereby all cells benefited from each other (Woese and Goldenfeld 2009). A rather early form of 'open source biology"! The first eukaryotes (cells with nucleus, such as bacteria) that refused to divide – 'anticipating Bill Gates by three million years' – ended this 'biological communitarianism' and marked the beginning of Darwinian evolution in which the different individuals and species are constantly battling each other.

It could now be argued that this "open source biology" is a thing of the past, but current biotechnology seems to be restoring it through genetic modification and the creation of cybrids and chimeras, whereby genetic material is exchanged between species. The physicist Freeman Dyson in his essay "Our biotech future" even calls the vertical inheritance with an impressive sense of understatement a short-lived "Darwinian interlude" of the horizontal inheritance (Dyson 2007). In the coming post-Darwinian era, distinct species will no longer exist and the rules of open-source sharing will have expanded from the exchange of software to the exchange of genes.

This may be hyperbolic, but post-genomic research has also revealed that horizontal gene transfer has not been limited to prokaryotes but has often occurred in the animal kingdom in evolution. The fact that the mitochondria in the human cell possess DNA deviating from the cell nucleus, as mentioned earlier, is due to the fact that they were originally free-living bacteria, which started to live intracellularly in symbiosis with their host at an early stage in evolution. In that sense we are by nature human-animal combinations. Moreover, horizontal gene transfer appears to occur not only between bacteria and humans and viruses and humans (a process that occurs regularly due to globalization and the accompanying ongoing worldwide exchange of organisms, but also between different animals. In an article published in 2017, Huang show and colleagues, by randomly comparing the human genome with the genome of 53 other vertebrates, showed that at least 642 genes – mainly genes related to metabolism – are derived from other vertebrates by horizontal transfer, the majority even from non-mammals (Huang et al. 2017).

While epigenetics and horizontal genetic gene transfer may question the genomic purity of individual species, there is a third reason to question the genetic purity of species, which is in a way even more radical, as it calls into question the species concept as such: the *polygenomic character of organisms*. This is related, as John Dupré argues, to the fact that our body contains trillions of bacterial cells, which together make up about 90% of all cells in our body. And given their wide variety of DNA, these bacteria make up 99% of the total DNA that is in our bodies. Moreover, an even greater number of viruses are part of our bodies. About 5% of our DNA originated from viruses, Arthur Rimbaud's famous oneliner "Je est un autre" should not only be taken as a poetic image, but as well as a factual statement about our existence as a multitude (Yong 2016)!

Now, of course, one could conceive of these bacteria and viruses – as also happens in discussions about the mass emigration of foreigners to Europe – as parasites, which for opportunistic reasons reside in certain regions where they do the dirty work – in the case of the bacteria mainly in the intestines – and that better should leave as soon as possible, so that we can finally be ourselves, in each other's familiar company. Own genes first! However, in the case of both bacteria, viruses and immigrants, this ignores the fact that the health and well-being of the receiving party is highly dependent on the visitors.

Perhaps it is better to conceive of the human and bacterial cells as symbionts that simply cannot live without each other (Dupré 2015). For example, it appears that bacteria not only play an indispensable role in digestion, but also play an important epigenetic role, because they activate certain genes as part of the immune system, for example, and that, conversely, certain genes in the human genome play a role in the regulation of the bacteria populations in the human body. Viruses, too, maintain a dual relationship with the human body. They not only need the human reproductive system in order to survive, but they also execute important functions in our body: bacteriophages (also known as bacterial viruses) play an important role in our immune system battling harmful bacteria, and retroviruses play a role in the development of organs like the placenta and the brain (long before the viral memes that are being distributed via the internet nowadays). It is not without irony that the original invaders now help keep out potential new invaders.

The insight into the importance of the co–evolution of humans and their bacterial inhabitants has resulted in an extensive Human Microbiome Project, which is seen as a necessary successor and perhaps even an integral part of the Human Genome Project. What is particularly fascinating here is that bacteria, due to their wide variety of genetic material, which is the result of the aforementioned horizontal gene transfer, contribute greatly to the uniqueness of human individuals. The very question is whether the word "individual" – which literally means "indivisible" is still useful at all, given the symbiotic nature of man and microbe. Dupré and O'Malley argue that we might better understand living things as temporary things at the intersection of genetic lineages and metabolic processes (Dupré and O'Malley 2009).

Clearly, the assumption of genomic purity of individuals and species through the study of epigenesis, horizontal gene transfer, and the polygenomic nature of organisms has been seriously problematized, as is the meaning of the terms "individual" and "species". The idea of individuals and species competing with each other also deserves at least a considerable nuance. In the evolution of complex systems, as we saw, there is also an important role for cooperation, in and between individuals and species. It should be noted, however, that co–evolution – for example in the case of humans and pathogenic bacteria – does not always end well. Tragedies and sacrifices are not only cultural phenomena but take place on the biological level as well!

Perhaps emphasis on individualism, struggle for life, and survival of the fittest in classical Darwinism and Neo-Darwinism was motivated more by the rise of nineteenth-century liberalism and capitalism than by biological reality.[13] Social circumstances often function as a metaphor in scientific theories.

7 Moral confusion and ethical paradoxes

Finally, let me briefly return to the ethical assessment of making, experimenting with, and clinically applying chimeras. Whatever reasons there may be for exercising restraint (the practical risks I have pointed out above could offer a good reason), I also hope to have made clear that invoking or calling for respect for the integrity of individual organisms and biological species cannot constitute a reason because it lacks any factual basis. It is quite problematic to plea for the preservation of biological integrity if in reality it never existed.

But perhaps another ethical objection is conceivable. Dietmar Hübner argues that the creation of chimeras and hybrids creates moral confusion because they create an unsolvable ethical dilemma (Hübner 2018). When we try to survey the ethical discussions about chimeras and related human-animal combinations, it is striking that the moral intuitions travel in opposite directions. While on the one hand – as I already pointed out above – the creation of such combinations provokes disgust, because they disrupt the supposed sacred or natural order and seem to undermine the integrity of individuals and species and human dignity, on the other hand there is the intuition that such organisms deserve special protection precisely because they possess human qualities or have the potential to develop them. Both intuitions are often held simultaneously in a person at the same time. This ambiguity, argues Hübner, manifests itself in an uncomfortable oscillation of pity and disgust, fascination, and disgust.

The ethical dilemma arises from the fact that the intuition that the human-animal combinations deserve compassion and protection is based on the supposed moral status of the *individual organism*, while the rejection of these human-animal combinations is based on the supposed moral integrity of *groups or species*. While the integrity of the human species is the basis for the integrity of the chimeric individual, since it partially or potentially participates in the human domain (for example, by having the ability to develops (self)consciousness), the same chimeric individual undermines the distinction between the species on which the very notion of the integ-

13 In section 349 of (the second, expanded edition of) *Die fröhliche Wissenschaft* (published in1887) Nietzsche develops a somewhat similar social explanation of the emphasis on Darwinism: “Um den ganzen englischen Darwinismus herum haucht Etwas wie englische Uebervölkerungs–Stickluft, wie Kleiner–Leute–Geruch von Noth und Enge. Aber man sollte, als Naturforscher, aus seinem menschlichen Winkel herauskommen: und in der Natur herrscht nicht die Nothlage, sondern der Ueberfluss, die Verschwendung, sogar bis in‘s Unsinnige“ (Nietzsche 1980, Band 3, 585).

rity of the species rests. This blurring of the distinction leads to the impossible choices faced by the tragic characters who are confronted with contradictory principles, as in Sophocles' 'Ode to Man,' in which man is ironically advised to respect both the laws of the state and the conflicting divine laws (De Mul 2014, 121–137).

The fact that chimeras and other animal-human combinations bring us into such ethical dilemmas is, according to Hübner (2018, p.202), a subtle reason not to start making them, in order to avoid such tragic dilemmas. The problem, however, is that post-genomic research shows that diverse human-animal combinations populate nature even without biotechnologies. Seen in this way, the chimeras are not mere figures from a mythical past that has been closed for good, but they still haunt us today and will haunt is even more in the coming Age of Biotechnology. That is why there is no simple one-way development from mythology to technology. Inevitably, the road leads from mythology to technology *and back*.

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