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ISIS Report -- May 2, 2001

First GM Humans Already Created

While debate on germline gene therapy is still going on worldwide, geneticists have gone ahead. **Prof. Joe Cummins** and **Dr. Mae-Wan Ho** report on how scientists have sidestepped regulators and created the first GM human beings, despite fierce public opposition.

"Researchers have announced "the first case of human germline genetic modification resulting in normal healthy children." Specifically, the researchers transplanted ooplasm from donor eggs into the eggs of women whose infertility was due to ooplasmic defects. One side effect of those transplants was the transfer of mitochondria, introducing new mitochondrial DNA (mtDNA) into the eggs. This news should gladden all who welcome new children into the world. And it should trouble those committed to transparent public conversation about the prospect of using "reprogenetic" technologies to shape future children." So began an editorial in the April 20 issue of *Science* magazine [1].

Germline gene therapy amounts to changing the gene pool of the human species by genetic modification of the gametes produced by individuals. While the pros and cons of GM crops and GM animals are still being debated, genetic modification of human beings has met with almost universal condemnation. The prospect of maniacal dictators trying to produce super races is none too theoretical for those who have lived under the Nazi regime. And all the more abhorrent that academic science should be perverted to such ends. Human germline therapy has been shelved, if not rejected, by most advanced countries, and copious volumes have been generated by ethicists, philosophers and geneticists from ivy league universities, telling us why rushing into human germline therapy is not prudent.

In spite of those academic reservations and widespread public concern, a form of germline therapy has already been performed in New Jersey with little fanfare and no opportunity for

public input. A university laboratory completed an experiment that led to the birth of fifteen apparently healthy babies as the result of germline gene therapy [2]. But worldwide, there have already been 30 babies born that have been created in this way.

In the US, the Recombinant DNA Advisory Committee (RAC) was created to oversee and publicly discuss federally funded gene transfer research. RAC's guidelines say that it "will not at present entertain proposals" for germline interventions. "Given RAC's *de facto* ban on germline intervention, what reasons might have moved highly respected researchers to announce that they had achieved just that?" *Science* magazine asks [1].

The experiment was justified on the specious claim that egg cytoplasm (ooplasm) alone was transferred to the defective eggs of infertile women which would not allow normal development. In fact the researchers had assumed mitochondrial defects in the eggs and corrected them by injecting egg cytoplasm containing presumed normal mitochondria.

The RAC dicta were sidestepped on the basis that the research intervention did not use recombinant DNA (rDNA) technology. However, a recent American Association for the Advancement of Science (AAAS) report [3] already pointed out that RAC's purview is unduly restricted to techniques (rDNA) that now are more than two decades old. The AAAS working group argued that if new techniques raise the same ethical concerns as those raised by "traditional" germline gene therapy, then either RAC's purview should be expanded to encompass them, or a new, RAC-like body should be created to oversee them. More importantly, they should be subject to the same public scrutiny if they raise the same ethical questions as the traditional germline interventions. Examples of new techniques considered in the report include the introduction of artificial chromosomes, the use of oligonucleotides to repair genes *in situ* -- and the transfer of mtDNA.

Another caveat is that federal funds were not used in the ooplasmic transfer experiment, and RAC guidelines are binding only on those who receive federal funding. However, other privately funded researchers whose work raises novel issues have consulted with RAC. Given that the researchers recognized they were engaged in "germline modification", *Science* magazine considers it "unfortunate -- though perfectly legitimate -- that they did not bring their protocol before RAC" [1].

Frankly, that narrow view reeks of academic sleaze. Genetic recombination involves both gene exchange on a chromosome and re-assortment of chromosomes. When new mitochondrial DNA was introduced in ooplasm, the eggs produced were, strictly speaking, made recombinant as the result of an artificial recombinant DNA technology. The claim that the experiment falls outside RAC purview is therefore spurious.

The apparent cure of infertility by creating heteroplasmic individuals (those with a mixture of cytoplasm and hence mtDNA) may also give rise inadvertently to individuals who have the extreme diseases associated with mitochondrial heteroplasmy, most frequently expressed beyond puberty, or much later in life.

Each mtDNA molecule contains 13 protein-encoding genes and 24 RNA genes that allow protein synthesis to take place inside the mitochondria. Transcription and translation of mtDNA is controlled by the nucleus through the only non-coding region of the

mitochondrial genome (the 1 kb D-loop). The proteins synthesised from the 13 mtDNA genes interact with more than 60 nuclear-encoded proteins to form the mitochondrial respiratory chain. The respiratory chain is responsible for extracting energy from metabolic products of glucose that powers all living activities.

Mitochondrial function is, therefore, dependent on the interaction of many nuclear and mitochondrial genes, and abnormalities of either nuclear or mitochondrial genome may give rise to mitochondrial disease. Human cells contain at least 1000 copies of mtDNA. In normal individuals, all copies of the mtDNA are identical within the coding region. Individuals with mtDNA disease often exhibit heteroplasmy, ie, they harbour a mixture of mutated and wild-type (normal) mtDNA. Within single cells, the proportion of mutated mtDNA must exceed a critical threshold before the cell expresses a mitochondrial respiratory-chain defect, but the relation between the proportion of mutated mtDNA and the clinical phenotype of the whole organism is less clear [4].

After fertilisation, sperm mtDNA is degraded. As a consequence, mtDNA is transmitted exclusively through the mother. Thus, affected men do not transmit the genetic defect. By contrast, a woman with a heteroplasmic mtDNA mutation, may transmit a variable amount of mutated mtDNA to her children. Early in the development of the female germ-line, the number of mtDNA molecules within each oocyte (developing egg) is reduced before being subsequently amplified to reach a final number of about 100 000 in each mature oocyte. This restriction followed by amplification of mtDNA accounts for the variability between individual oocytes, and the different proportions of mutant mtDNA seen in the children of a woman [4].

Mitochondrial DNA mutations have been linked to seizures, strokes, optic atrophy, neuropathy, myopathy, cardiomyopathy, sensorineural hearing loss, diabetes mellitus, and other syndromes. Mitochondrial DNA mutations may also play an important role in aging, as well as in common age-related neurodegenerative disorders such as Parkinson’s disease [5]. Typically, mitochondrial diseases arise by single base pair changes in the coding regions for proteins or transfer RNA but some arise by short deletions. More often than not, the disease symptoms are delayed until puberty or midlife.

So, what exactly was the genetic defect corrected in the GM babies produced [2]? It turns out to be highly ambiguous. The researchers state, "The basis for this work is the supposition that embryonic failure may be related to hitherto unknown cytoplasmic pathology." *In other words, the experiments were not based on any scientific finding* . The inheritance of mitochondria was studied after the ooplasmic transplant. The report focuses on two one-year old children.

Significant differences were found in the hypervariable (D-loop) region of the mitochondrial chromosomes between donor and recipient in both children using DNA fingerprinting technique to identify single base changes. No other mtDNA region was investigated. It was assumed that the D-loop mutations were useful as markers, but did not relate to the dysfunctional ooplasm. In other words, those mutations are assumed to have no relevance for mitochondrial disease. However, the D-loop mutations observed in the human recipient eggs were never given a clean bill of health for the fetus resulting from the eggs. It is clear that the D-loop region regulates replication, transcription and translation. Moreover, those D-loop

mutations in the recipient eggs are flanked by genes, mutations in which are known to be associated with mitochondrial diseases involving severe neurodegeneration that appear after the onset of puberty. Barritt and coworkers [2] hypothesize that the defective eggs may be deficient in ATP content, but assumed that the D-loop mutations were unrelated to the presumed ATP deficiency.

The researchers appear to have been prepared to risk the health and long term prospects of infants created in their experiments even though the oocyte defect was undefined. Were the parents informed of the lack of fundamental knowledge when they gave their consent?

Finally, it seems bizarre that RAC should allow 'recombinant' to be redefined to exclude the traditionally accepted definition. Certainly, ooplasm grafting is a rDNA technology; it produces a recombinant mtDNA genotype differing from either parent. In normal reproduction, mtDNA inheritance is exclusively maternal.

Now is not the time to bring human germline therapy in through the back door and to promote it through claims of "success" which may be premature and announced *after* the experiments. Genetic engineering may be proceeding along the lines taken in the development of nuclear weapons. The scientific "elite" may have convinced the political "elite" that the masses need to be led like cattle to the brave new world.

References

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