Topical Seminar
Lewes Library
Friday, January 5 at 1:30 pm

DESIGNER BABIES
Ray O'Neill, Seminar Leader

Think about the following questions as you read through the materials.

1. JUST BECAUSE WE CAN, SHOULD WE?
2. WHO GETS TO DECIDE?
3. HOW SHOULD THE DECISIONS BE ENFORCED?

Purpose of the seminar: To have an informed discussion among laypersons of the **Bioethics** involved in future attempts at **human genetic modifications**. (https://en.wikipedia.org/wiki/Bioethics)

Bulleted Background Information:

1. Rather than rewrite what already has been extensively vetted, this short document contains embedded links to the web page urls of Wikipedia, the Washington Post, and other "open access" sources. A summary article and cover page picture of a baby graced the July 4, 2016 issue of Time Magazine, titled "The Gene Machine: What the CRISPR experiments mean for humanity" (http://time.com/4379535/in-the-latest-issue-75/).
   However, doubt exists, see "Five Myths about Gene Editing (https://www.washingtonpost.com/outlook/five-myths/five-myths-about-gene-editing/2017/08/24/f524b484-86a6-11e7-a94f-3139abce39f5_story.html?utm_term=.ed198f8f931d).
   Other articles discuss designer babies in an evolutionary perspective (https://www.nationalgeographic.com/magazine/2017/04/evolution-genetics-medicine-brain-technology-cyborg/).

2. As you read and discuss this topic, please keep in mind the fundamental crucial distinction between S**omatic cell versus Germ cell gene modification**. Sperm and eggs are germline cells that create the next generations, and can't under **present US regulations** be genetically modified to produce a living baby. Somatic cells are bone, muscle, liver etc cells that can't create a new generation (with a few technical exceptions e.g., https://en.wikipedia.org/wiki/Dolly_(sheep) or https://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell). Somatic cells have been legally genetically modified via gene therapy since the 1980s (see thousands of ongoing studies at https://clinicaltrials.gov/). Special cases get attention, for example, a recent genetic modification experiment in **embryonic** cells was terminated before a fetus developed (https://www.washingtonpost.com/news/to-your-health/wp/2017/08/02/first-human-embryo-editing-experiment-in-u-s-corrects-gene-for-heart-condition/?utm_term=.6733b2b94b41).

3. For human babies, the three part procedure of In Vitro Fertilization (IVF of harvested semen with harvested eggs https://en.wikipedia.org/wiki/In_vitro_fertilisation) and then Genetic Testing

(https://en.wikipedia.org/wiki/Genetic_testing) with selection of an acceptable embryo(s), has been routinely used successfully since the 1980s to create healthy "test tube" babies. These three procedures comprise a subset of Assisted Reproductive Technologies (ART https://en.wikipedia.org/wiki/Assisted_reproductive_technology). This procedure allows parents that carry deleterious single gene disorders (Mendelian genes https://en.wikipedia.org/wiki/Mendelian_inheritance) to choose an implantation in the mother of only a non-defective embryo of a selected sex (if desired), but only if the parents can afford $20,000 or more for a three-part procedure. It is not uncommon for more than one attempt be made at the same high cost.

4. For living human patients, the US Food and Drug administration (FDA) approves or disapproves the commercial marketing of Somatic Cell gene therapies that often correct genes in **cultured In Vitro cells** (aka Ex Vivo) from that patient before re-implantation into that single patient. In recent years, the FDA has approved gene editing directly in **living patients (In Vivo)** rather than first in cultured cells (https://www.washingtonpost.com/news/to-your-health/wp/2017/12/06/a-cut-could-have-killed-him-then-HYPERLINK "https://www.washingtonpost.com/news/to-your-health/wp/2017/12/06/a-cut-could-have-killed-him-then-he-got-experimental-gene-therapy-for-hemophilia/?utm_term=.25b056ae7dfe" he-got-experimental-gene-therapy-for-hemophilia/?utm_term=.25b056ae7dfe).

   Since the 1980s, gene additions for Genetic Therapy (https://en.wikipedia.org/wiki/Gene_therapy) has usually been attempted using genetically engineered viral backbones of many types that for safety are typically impaired in replicative ability (https://en.wikipedia.org/wiki/Viral_vector#Gene_therapy). Since 2014, there is great excitement that a revolutionary new non-viral tool called **CRISPR** (https://en.wikipedia.org/wiki/CRISPR) will allow not only additions but deletions and substitutions to more efficiently, accurately and cost-effectively provide gene therapy. Previous research tools such as Homologous Recombination, Zinc Finger Nucleases, and TALENS have a head start toward FDA regulatory approval but are vastly more inefficient and costly and won't spread to international third tier biomedical laboratories (or terrorists? P13 in https://www.dni.gov/files/documents/SASC_Unclassified_2016_ATA_SFR_FINAL.pdf) the way the revolutionary CRISPR tool has. Experiments on living patients officially require many levels of regulatory approval, including the FDA for several increasing risk levels or phases of experimental use. Usually a company does **premarketing** experiments in human subjects to show sufficient Safety and Effectiveness to achieve the expensive approval for commercial marketing (https://en.wikipedia.org/wiki/Food_and_Drug_Administration). **Post-marketing** studies are sometimes ordered by FDA in special cases. The underlying laws at FDA for Drugs, Biologics, and Devices differ; thus different policies and vocabularies apply.

5. The CRISPR tool is being used so extensively and successfully that it is widely expected to revolutionize many areas of science, analogously to DNA sequencing, molecular cloning, and the PCR tool (https://en.wikipedia.org/wiki/Polymerase_chain_reaction) developed over the last 50 years. It is now trivial in any country's research lab to make designer mice, and probably agriculturally important animals such as low-fat quick-growing pigs and mega-milk cows, with any desired phenotype at the single gene (Mendelian) level. Theoretically any trait (Phenotype https://en.wikipedia.org/wiki/Phenotype) with sufficient Heritability

(https://en.wikipedia.org/wiki/Heritability). For a complex review on estimated heritability for many diseases and normal traits see: https://pdfs.semanticscholar.org/05d5/0e059ac28ea421fa3f35f09e5330ca7286e4.pdf) Many traits can be controlled, but at present many Complex Multi- or Polygenic phenotypes (such as height or blood pressure) require much basic additional identification and characterization to achieve more than just partial control. This is because multi-genic traits result from the Interaction of 2-100 genes with each other and with many factors (termed Epistasis https://en.wikipedia.org/wiki/Epistasis) and each gene's expression depends on which one of many Alleles (one of hundreds of 'flavors' of a gene, https://en.wikipedia.org/wiki/Allele) that collectively affect a Multi-genic or Polygenic phenotype

THREE QUESTIONS FOR DISCUSSION: First, JUST BECAUSE WE CAN, SHOULD WE? How far are you specifically willing to travel down the following 6-step slippery slope?

Morally, do you oppose the **ongoing** genetic **correction** of **Somatic cells (non-sex cells)** for **diseases and disorders** such as: (The following examples are provided for illustrative purposes. You don't need to understand every one of the examples for the purposes of discussion.)

ADA "bubble boy" disease, Tay Sachs, hemophilia, another 8,000 Mendelian diseases, cancers (populations of wildly aberrant somatic cells), eliminate HIV endogenous proviruses or add CCR5 delta32 co-receptor resistance gene (despite enhanced susceptibility to West Nile Virus), remove sensitivity to Cystic Fibrosis despite enhanced susceptibility to tuberculosis.

Morally, do you oppose genetic correction of Somatic cells (non-sex cells) for **conditions of debatable medical significance** such as; soldiers and/or special populations made immune to potential bio-warfare agents, deafness, aging reversal such as muscle wasting or facial wrinkles in the elderly, lower 'bad' cholesterol PCSK9 versus diet.

Morally, do you oppose genetic **enhancements** of Somatic cells (non-sex cells) such as; athletic performance factors such as erythropoietin 'Lance Armstrong' doping (EPOR), anabolic steroid 'Barry Bonds' doping, muscle size MSTN gene, left handedness, perfect eyesight for baseball outfielders, **IQ** (multi-genic, probably neuronal interconnections), requiring less sleep DEC2.

Morally, do you oppose **future** genetic **correction** of G**ermline cells (sex cells such as sperm and eggs)** for **diseases and disorders** such as; ADA bubble boy disease, Tay Sachs, hemophilia, 8,000 Mendelian diseases, susceptibility to alcoholism and other addictive behaviors, obesity is ~60% heritable through ~30 genes, susceptibility to breast BRCA or lung cancers p.53 etc. related to smoking, susceptibility to Alzheimer's APOE for factors that could be subverted to enhance memory in average people {poll at 50%, i.e., 50% of polled people oppose future germline **correction** of Mendelian genetic mutations}.

Morally, do you oppose **future** genetic correction of Germline cells (sex cells such as sperm and eggs) for **conditions of debatable medical significance** such as; male or female (technically possible now in mice), eye-skin-hair color (multi-genic), deafness (sometimes Mendelian), soldiers and/or special populations made immune to potential bio-warfare agents, a displeasing gratitude or happiness set point, religiosity (~40% heritable), aging reversal, height (multi-genic), "savior siblings."

Morally, do you oppose **future** genetic **enhancements** of Germline cells (sex cells such as sperm and eggs) such as; athletic performance factors including muscle size, left handedness, perfect eyesight for baseball outfielders, narrow hips in women for avoiding ACL knee injuries and speedy running.

Second Question, WHO GETS TO DECIDE? The over-arching question is whose rights take precedence: either two parents and their team of doctors, or society at large? Who should pay for this? Both the initial procedure and in those few cases it goes wrong? Must every parent have equal access despite unequal abilities to co-fund it (possibly except in France, Israel and Sweden where many Assisted Reproductive Technologies are typically covered?)

In the **US**, for **experiments** the FDA and the hospital IRB (https://en.wikipedia.org/wiki/Institutional_review_board), and possibly a NIH committee such as the RAC (https://en.wikipedia.org/wiki/National_Institutes_of_Health_Office_of_Science_Policy) needs to approve each specific protocol before starting. Once given FDA marketing approval, typical medical standards from state to state apply. If harm is caused, the hospital, doctors and sponsoring company can and will be sued possibly to bankruptcy by the parents and possibly the harmed child when they reach legal age.

Should the patient's (baby's) sperm or egg carry the deleterious gene or the new corrected gene? Who can give Informed Consent (https://en.wikipedia.org/wiki/Informed_consent) for alterations that are genetically permanent across multiple generations?

How will LONG-TERM Safety and Effectiveness be monitored? (e.g., for possible off-target mutations, cancer due to insertional mutagenesis, acute and chronic immune reactions). Note that there is an underlying 1-2% genetic problem rate even for natural human births, so what additional risk likelihood for genetic correction/enhancement is acceptable? (Equal, 1/10th, 1/100th?)

What about hundreds of **foreign countries**? China, India, and several European countries participated in the 2015 National Academy of Science "International Summit on Gene Editing" that drafted early voluntary standards (https://www.nap.edu/read/21913/chapter/1). Mexico and a few other countries are briefly covered in Jennifer Doudna et al's book, "A Crack at Creation: Gene Editing and the Power to Control Evolution." China could be or become a major player, as could any third world country that can attract the immigration of (guessing) ~20 foreign biomedical research staff and <$100 million in 5-year funding.

Third Question, HOW SHOULD THE DECISIONS BE ENFORCED? How many types of Stakeholders will want/deserve a place at the debate?

New laws, regulations, FDA Guidelines, FDA Guidance (State and local laws).Civil suits, Criminal charges, Physician licensing and societies. Other ideas?

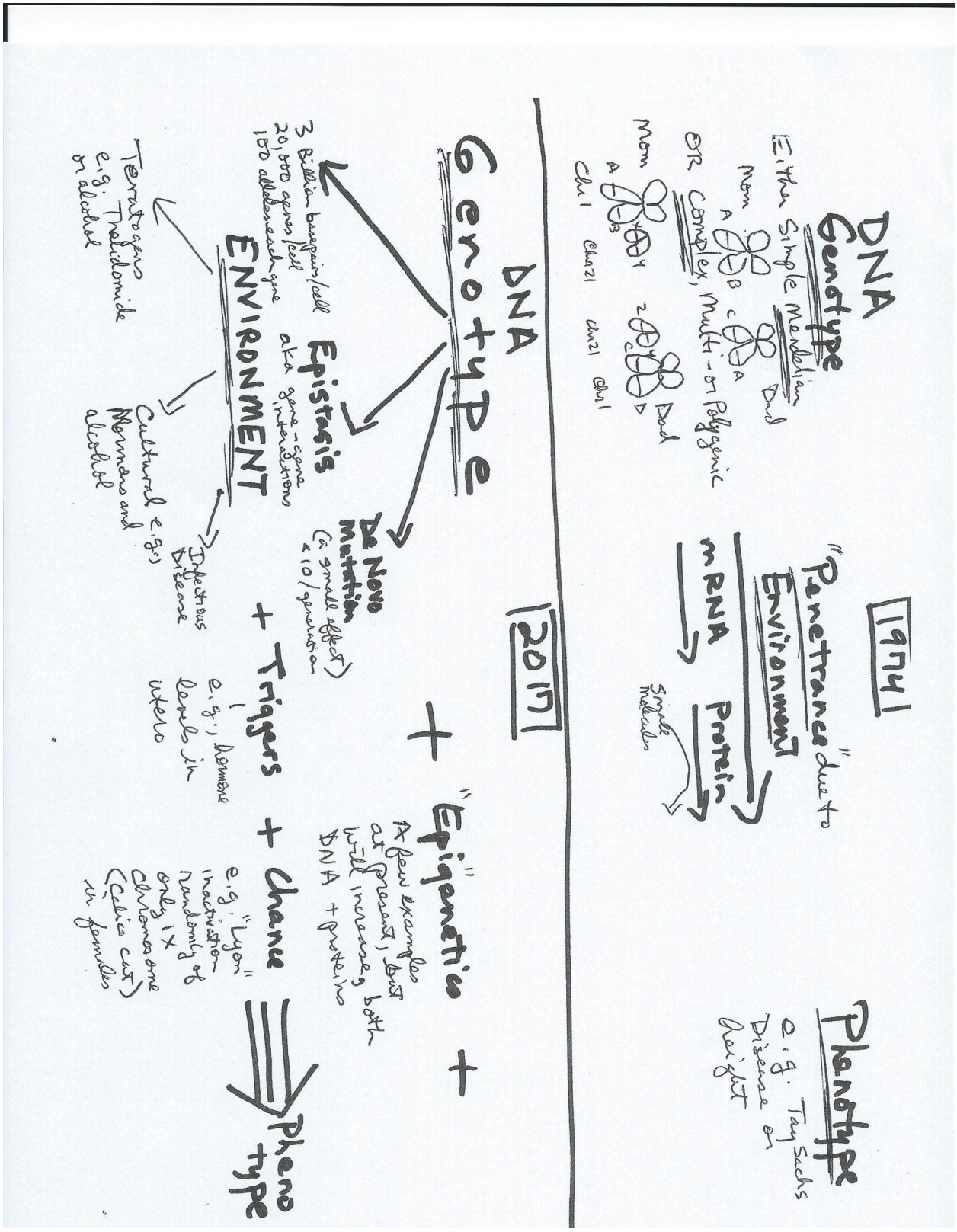

Figure 1. Contrast between a view in 1974 and 2017 of how Nature (aka Genotype) and Nurture (aka Environment) affect Phenotype (e.g., appearance or blood chemistry)

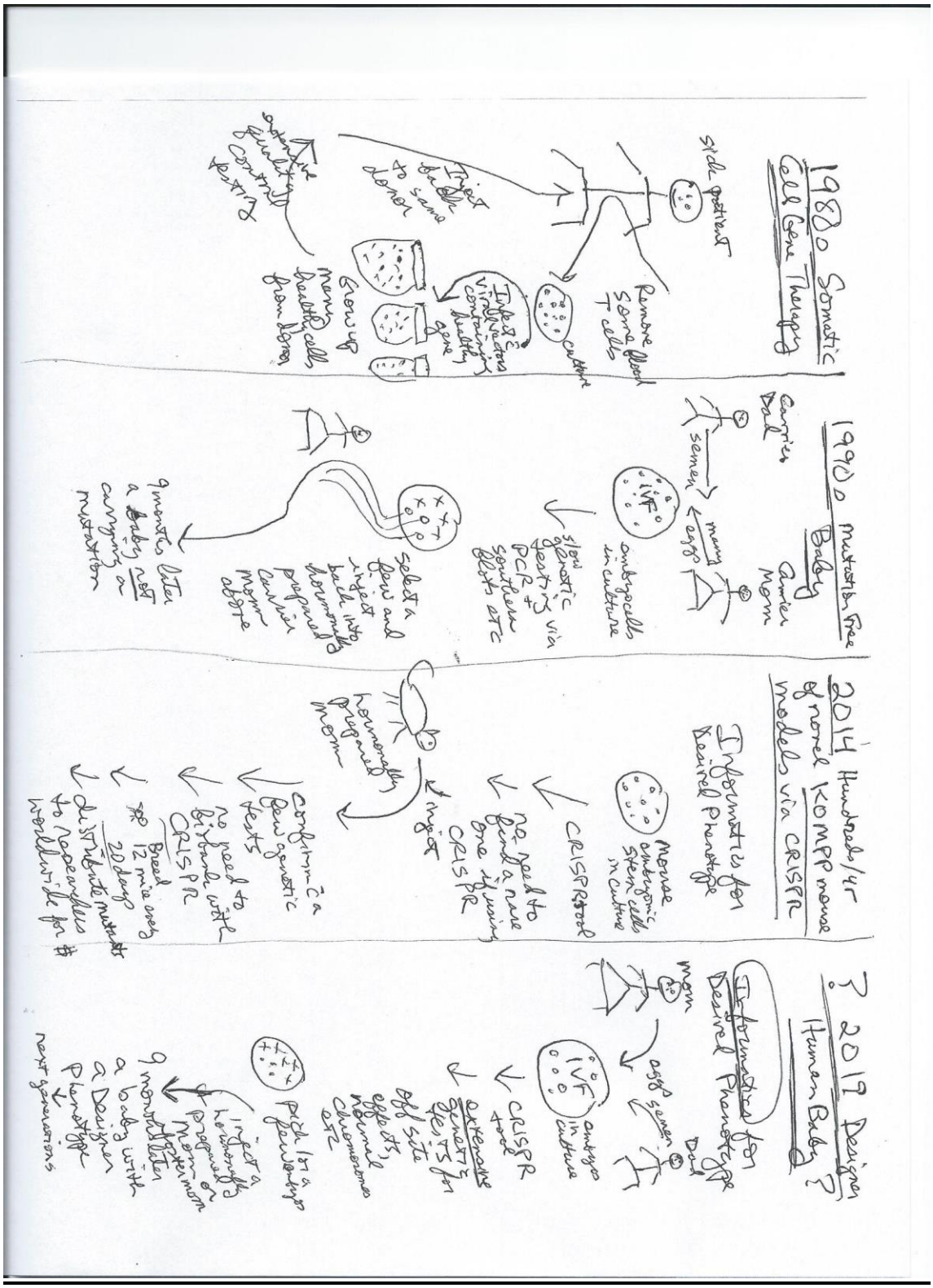

Figure 2. A visual explanation of the major steps involved in four biomedical/clinical procedures

Brief biographical sketch: The presenter spent 40 years at NIH and FDA in varied positions until 2014. In 1985, his small group was first to clone a xenotropic MuLV retrovirus of potential use as a gene vector for gene therapy, knew French Anderson of NIH who was a major pioneer in early somatic cell gene therapy, was part of small team first to clone mouse glucocerebrosidase deficient in the human Mendelian Gaucher Disease, was part of the first team to clone NPC-1 deficient in Mendelian Niemann-Pick disease, spent 5 years in NIH Review and 15 years in NIH Extramural Program, including his last professional years co-managing the International Knockout Mouse Phenotyping Project (KOMPP) (https://commonfund.nih.gov/komp2) that has generated thousands of mouse models of Mendelian human diseases that are used both as basic genomic research information for Multigenic Diseases and to inform human gene therapy.