The Gene Revolution: Changing Human Nature (Storyville)

https://learningonscreen.ac.uk/ondemand/index.php/clip/163119
also available at https://www.bbc.co.uk/programmes/m000dt7d (until end of 2020)

Once in a while a truly exceptional documentary comes along; *The Gene Revolution: Changing Human Nature* is one such programme. The combination of interviews with leading players in the story of genome modification and some very clear graphics make this an excellent introduction to genome editing. It is an outstanding introduction to the science of the CRISPR/Cas9 genome editing tool, and the ethical challenges posed by some of the current and future applications of this technology.

The programme is quite long: 90 minutes in total. However after a short introduction it is divided into six chapters, which offers the opportunity to watch it in chunks rather than in one sitting if you prefer. The following guide is written to help you get the most out of watching the documentary. A set of structured questions are offered to prompt your reflections. Feel free to use these as you work through the episode.

Introductory sequence

The programme starts with Prof Robert Sinsheimer addressing the California Institute of Technology in October 1966. He puts genetic research in the context of the history of the planet, before stating *"We will surely come to the time when men will have the power to alter, specifically and consciously, his very genes"*.

Question 1: What common mistake does Prof Sinsheimer make during this opening speech? (*Hint: think about what Watson and Crick actually discovered in 1953*)

Chapter 1: Needle in a haystack (starts at 02:30)

In the first chapter of the documentary we are introduced to the basis of genetic illness (through the example of sickle cell anaemia) and walked through a brief history of gene therapy up to the point where CRISPR radically altered the rules.

Question 2: What genetic mutation is the underlying cause of sickle-cell disease?

Question 3: One of the interviewees says, somewhat inaccurately, that the mutation [in *HBB*, the gene for the beta-subunit of haemoglobin] "causes a kink in the protein that

prevents it from folding properly". What actually are the molecular consequences of the change in the gene? (If you want to check online sources for this, you could usefully start with https://www.uptodate.com/contents/sickle-hemoglobin-polymer-structure-and-functional-properties or http://www.sicklecellinfo.net/fiber_formation.htm).

Several of the contributors then first attempts at "gene therapy", which Hank Greely summarises as "Add[ing] in a copy of the gene that works". This approach has turned out, in almost all cases, to be unsuccessful.

Question 4: Describe, in your own words, the problem(s) that hampered the original approach to gene therapy.

Fyodor Urnov then discusses development of methods aiming to exploit a cell's natural systems for "homology-directed repair"

Question 5: What is "homology-directed repair"? What did scientists (e.g. Sangamo Biosciences) try to do to switch this to a method for correcting a genetic error (rather than adding an extra copy of that gene)?

Chapter 2: CRISPR (starts at 15:00)

The next section of the documentary moves on to the discovery of "Clustered Regularly Interspaced Short Palindromic Repeats" (CRISPR) and the associated protein Cas9, elucidation of their original purpose in bacteria, through to the realisation that this might be adaptable for genome editing.

Question 6: Once you've watched the whole of this chapter, describe in your own words the role that the naturally-occurring CRISPR system plays in bacterial cells, and outline how it works.

Chapter 3: The gene machine (starts at 29:20)

The focus in Chapter 3 moves to applications of CRISPR. Genetic modification of humans will be covered in more detail later in the programme, so this section mostly picks up on its use for xenotransplantation, the use of animal organs for transplantation into human patients. Rather like gene therapy (mentioned earlier in the episode) xenotransplantation is an exciting potential development in medicine which failed to live up to the initial optimism.

Question 7: What were the practical difficulties that researchers encountered when they first tried xenotransplantation? How should using CRISPR help with this problem?

Chapter 4: Brave New World (starts at 38:45)

From Chapter 4 onwards, the focus moves more from "Could we genetically modify humans?" to "Should we?". The film touches on two sorts of changes "somatic" and "germ-line". The former would be a changes to the individual, the latter would be inherited.

Question 8: Before watching this section (or after, if you've already watched it!), draw up a grid with two columns labelled "arguments <u>for</u> genetic modification of humans" and "arguments <u>against</u>". As you watch through this chapter, makes notes of the arguments

made. (you might want to put an "S" alongside if it is just an argument about somatic changes, and a "G" if it is just relevant for germ-line).

Chapter 5: Good genes (starts at 52:10)

Chapter 5 is a continuation of the thread started in the previous section, but with the emphasis now squarely on *germ-line* modification.

Question 9: Continue adding any fresh points to the grid you started during Chapter 4. When you have finished this section, ask yourself "would I be in favour of germ-line genome editing of humans, or not?" When you have decided what you think, try to construct a reasoned argument from the opposite perspective.

Chapter 6: Playing God (starts at 69:20)

In the final section, a comparison is made between the emerging tools for genome editing and centuries of work in agriculture where farmers have picked characteristics they liked in crops and livestock, even carrying out selective breeding. This implies that humans "Playing God" is nothing new.

Question 10: In what ways is it fair to compare genome editing to farming? And in what ways is it different.

Along the way, they also discuss the ongoing prevalence of sickle cell within the population. Since (as pointed out by Matt Porteus in Chapter 1, most children with sickle cell disease would die between the ages of five and eight, without the intervention of modern medicine, i.e. before the age when they could reproduce, how is it that sickle cell has persisted?

Question 11: In terms of basic genetics and inheritance, how can a disease like sickle cell continue down the generations? What are the specific features of "sickle cell trait" that are believed to feed into the ongoing prevalence of this specific disorder?

Right at the end, Jennifer Doudna (one of the co-inventors of using CRISPR for genome editing) poses the question "What do we value about human society?" Hopefully watching this programme (and working through these notes) has helped you formulate a view on that.