**Biology 446 October 3, 2016** Physics & Cytology of Atherosclerosis

**1)** What do you conclude from the fact (assuming it is a fact) that veins never develop atherosclerotic "plaque"? However, after "bypass operations", plaque soon develops in the grafted veins.

**2)** What do you conclude from that change about the cause of plaque formation?

**3)** Conversely, what could you have concluded if plaque never formed in grafted arteries? Imagine if some species of mammal never gets atherosclerosis:

**4)** Would that prove or suggest any important conclusions, that you wouldn't otherwise have known?

**5)** Would you expect that sizes of animals would affect whether atherosclerosis occurs? (Hint: Would a larger or taller animal to have higher blood pressure, at least in some parts?)

A very powerful research strategy is to produce and select mutant strains of mice, rats, or other model organisms which are abnormal in some property of interest.

**6)** Could you use this genetic approach to find out more about the molecular and physiological causes of atherosclerosis?

To find those animals that have a certain abnormality, you need what is called a "**genetic screen**";

That means a systematic criterion for detecting which animals have a certain abnormality (and sometimes methods for weeding out all the animals that don't have the altered property that you are interested in).

**7)** Figure out some methods or criteria by which you might be able to find mutant animals that have either more or less atherosclerosis; Or mutants which develop atherosclerosis sooner, more rapidly? Or conversely mutants which develop atherosclerosis more slowly.

**8)** What might be the normal functions of proteins whose amino acid sequences can be changed in such a way as to increase atherosclerosis?

Hint: Suppose such a protein were an enzyme? Suppose it were an extracellular fiber? Suppose it served to transmit some signal, from certain cells to others? Suppose it were the receptor for a signal protein?

Suppose that it were a phosphate kinase? What else might it be?

**9)** By what experiments or other observations could you distinguish which of these alternative kinds of proteins affect atherosclerosis?

**10)** Could the CRISPR method help you answer such questions?

**11)** How could such genetic screens and genetic mutations lead to improved treatments for curing or reducing atherosclerosis.

**12)** When performing arterial "bypass" surgery, suppose that small pieces of atherosclerotic plaque could safely be dissected out of a patient's arteries, and then put in tissue culture, what abnormalities would you look for? (Abnormalities that could tell you more about causes and possible future cures for atherosclerosis?)

**13)** What hypotheses could be tested by grafting small pieces of atherosclerotic arteries, either to veins or to parts of arteries that have not yet developed atherosclerotic plaques?

**14)** What one fact or experimental result would (perhaps) be the most helpful for advancing understanding of atherosclerosis, and how to cure or reduce it.

**15)** Imagine an experimental "reverse bypass" operation, consisting of grafting a short length of atherosclerotic artery in place of an equal length of vein. What might you reasonably hope to discover from such an operation.

**16)** If you look carefully at the cross sections of human arms and legs in ***Gray's Anatomy*** or equivalent books, you can see that most of the larger arteries have a vein and a bundle of nerve fibers right next to them. Please discuss possible functions, and possible causes, of this anatomical pattern of adjacent and parallel arteries and brains.

**17)** At least five processes "go wrong" in atherosclerosis: **(A)** Smooth muscle cells grow and divide abnormally much; **(B)** Smooth muscle cells become more separated and less aligned than the had been when that artery was normal; **(C)** Very large numbers of macrophages invade outward through the endothelium and accumulate among the arterial smooth muscle cells; **(D)** These macrophages become "foam cells", full of spherical vesicles; **(E)** Large amounts of cholesterol accumulate in the extracellular spaces between smooth muscle cells and the foam cells. Guess which of these five changes cause each other, and in what order of cause and effect. For example, are growth and rearrangements of smooth muscle cells caused by stimuli from the foam cells, or the reverse?

**18)** What experiments or other observations could test alternative cause and effect sequences among these five abnormalities? For example, if certain changes consistently occur sooner than others, what does that suggest, or prove? If you had a drug that directly caused, or prevented, a particular one of these abnormalities, then what could you learn from resulting changes in the other four abnormalities? (If anything?)

**19)** Argue pro or con whether all five of the changes listed above are separate effects of some one fundamental cause.

**20)** Would you guess (and argue in a debate) whether the normal structure of arteries is actively rebuilt by the same original embryological mechanisms that build arteries in the first place? (e.g. some combination of negative and positive feed-back cycles?) Or do you tend to assume that arterial structure is static, with no turnover and replacement of parts?

**21)** In regard to discovery of new or improved medical treatments for atherosclerosis, how much is it likely to matter whether components of arteries are dynamically being continually being rearranged and/or rebuilt and/or replaced? (As opposed to statically resisting change, purely by passive physical strength).

**22)** If tissue culture cells attach to the surface of thin glass rods, guess whether they elongate in any particular direction (e.g. Circumferential? Longitudinal? Different directions depending on the diameter of the glass rod? Different directions depending on whether the cells are smooth muscle cells, fiber secreting cells, nerve cells?

**23)** Would it help invent better treatments for atherosclerosis to have a better understanding of whether there are changes in the directional orientation or the contractile strength of the smooth muscle cells which are the major component of artery walls?

**24)** Why do you suppose that artery walls bulge inward as they thicken in atherosclerosis, instead of bending outward? Can you imagine some change that would cause the outer surface to bulge outward, with the inner surface (the endothelium) continuing to be cylindrical with its diameter unchanged? Could answers to this preceding question be the basis of new kinds of treatment for curing, preventing or minimizing atherosclerosis?

**25)**  When an anatomical structure consists of particular geometric arrangements of several different materials (e.g. collagen fibers, contractile cells, extracellular materials that swell) then changes in shape probably result from changes in whichever component is stronger? Weaker? Both? Neither? Sometimes whichever is stronger, but other times whichever is weaker?

**26)** Imagine if you discovered that a relatively harmless drug (used for other purposes) also has the (previously not realized) effect of causing most cell types to double their contractile strength, for a period of several hours. For what new medical treatments might you reasonably hope to use this cell-strengthening drug?

**27)** Suppose another drug caused local weakening of cell contractility; For what medical functions might it be most useful?

**28)** What if a focused beam of X-rays of a certain frequency could cause long-term or permanent weakening of smooth muscle contractile strength?

How might you use that to treat atherosclerosis? To treat "slipped discs", in the spinal chord?