Cholesterol is an essential component of the plasma membrane, but people who have very high levels of cholesterol in their blood tend to have heart attacks. Cholesterol in the blood is carried in the form of cholesterol esters in low-density lipoprotein (LDL) particles. LDL binds to a high-affinity receptor on the cell surface, enters the cell via a coated pit, and ends up in lysosomes. There, its protein coat is degraded and cholesterol esters are released and hydrolyzed to cholesterol. The released cholesterol enters the cytosol and inhibits the enzyme HMG CoA reductase, which controls the committed step in cholesterol biosynthesis. Patients with severe hypercholesterolemia cannot remove LDL from the blood. As a result, their cells do not turn off normal cholesterol synthesis, which makes the problem worse.

LDL metabolism can be conveniently divided into three stages experimentally; binding of LDL to the cell surface, internalization of LDL, and regulation of cellular synthesis by LDL. Skin cells from a normal person and two patients suffering from severe familial hypercholesterolemia were grown in culture and tested for LDL binding, LDL internalization and LDL regulation of cholesterol synthesis. The results are shown in the figure.

Figure 1: LDL metabolism in normal cells (● ●) and in cells from patients FK and JD with severe familial hypercholesterolemia. (▲ ▼) A. High affinity surface binding of LDL. B. Internalization of LDL. C. Regulation of cholesterol synthesis by LDL. Binding and uptake of LDL can be followed by labeling LDL either with ferritin particles, which can be visualized by electron microscopy or with radioactive iodine, which can be measured in a gamma counter. Surface binding can be reversed by washing with negatively charged polymers, but internalized label cannot be washed away.
A. In Figure 1A the surface binding of LDL by normal cells is compared with LDL binding by cells from patients FK and JD. Why does binding by normal cells and by JD's cell reach a plateau? What explanation can you suggest for the lack of LDL binding by FK's cells?

B. In Figure 1B, internalization of LDL by normal cells increases as the external LDL concentration is increased, reaching a plateau fivefold higher than the amount of externally bound LDL. Why does LDL not enter cells from patients FK and JD?

C. In figure 1C, the regulation of cholesterol synthesis by LDL in normal cells is compared with cells from FK and JD. Why does increasing the external LDL concentration inhibit cholesterol synthesis in normal cells by not affect it in cells from FK or JD?

D. How would you expect the rate of cholesterol synthesis to be affected if normal cells and cells from FK or JD were incubated with cholesterol itself? (Free cholesterol crosses the plasma membrane by diffusion)