

Outline:

Bacteria => Enzyme reaction. This will be the first great hurdle; to try to understand that what happens in a biological system is actually caused by chemical catalysts.

Specific attack. The enzyme has specifically attacked the organic part of bone. It has also had some effect on the skin.

What is the organic part of bone? While they will not have come across bone calcification they should be able to reason a few things (with or without prompting):

1. Bone must have an organic component to give it structure. Otherwise calcium salts would just crystallise randomly.
2. Calcium is a positively charged ion. Therefore the organic component should be negatively charged (or contain multiple H-bonding sites) to bind the calcium.
3. It should be a polymeric material in order to maintain structural integrity.
4. Therefore it is likely to be a biopolymer. Biopolymers they have come across are lignin (poly phenolic compounds), proteins/peptides (poly amides), carbohydrates (poly sugars – acetal linkages) and DNA/RNA (combination of sugars and organic bases and phosphates).
5. They should be able to reason that the biopolymer in question is protein. This is not crucial to the exercise, as development of the **postulated** pharmacophore is independent (after all, this is only historical TV, who's really to know what happened, especially after all the relevant documents have been lost).

The reasons it's protein?

DNA/RNA is not usually a *structural* biopolymer – though it does consist of many negatively charged phosphates that would bind calcium ions well in a matrix.

Sugars might be likely – lots of hydrogen bonds and a good structural matrix. The reason to exclude these is that skin lesions were also formed. Skin is mainly protein – eg keratin and suchlike. This is a general knowledge thing that they might not figure, however.

Lignins are found mostly in plants. People aren't plants. Also, poly phenolics would be much harder to break up through simple chemistry. Sounds tricky.

Proteins are likely. What's more, they are likely to be poly glutamic or poly aspartic acids. This would be a bonus if they make this leap, but they have been introduced to amino acid functionalities (in this case carboxylic acids) in lectures. Proteins being in skin (as mentioned above) are also a major clue.

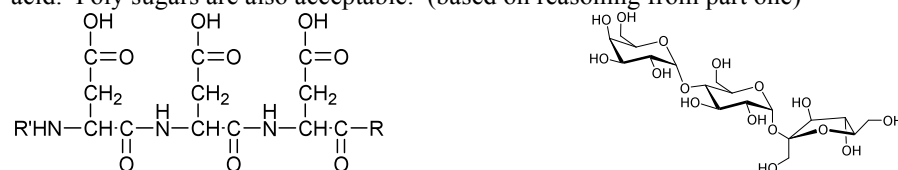
Postulation of a novel pharmacophore.

1. Whats a pharmacophore?

It's a drug. Pharma (from the latin) meaning drug and can be related to words like pharmacology (the study of drugs).

2. How do we design one?

The best possible pharmacophore will be one that bears structural similarity to poly glutamic/aspartic acid. Poly sugars are also acceptable. (based on reasoning from part one)



The easiest way to break these down (hydrolysis) will be a good assumption for mode of action of the enzyme. Other postulates can be presented, but should make sound chemical sense. This can be discussed amongst the group when each presentation of story content is made.

If, for instance, hydrolysis is chosen as the mode of action of the polymer, a drug should be designed that prevents hydrolysis. The chemistry must be different at the reactive centre. This should be a key point.

Specificity should be built in. If you have a non-specific target for enzyme binding, it may block other enzymes in the body. This should be a (serious) consideration. This is why a poly-peptide, rather than a single amino acid analogue is the best choice as it will fit better to a binding pocket. (*Principle of specificity in molecular recognition*)

Synthetic scheme for the pharmacophore.

This should be short and based on compounds that look like they would be easily obtained. Reagents need not be specified in complete detail – eg "strong base" is ok – 'what sort of strong base might you use' is a question that should be asked if this crops up. These sorts of questions should be discussed amongst the group. The chemistry should be critically assessed in the presentation by the other teams, but need not be spot on. It should be simple also – Chris Ewans didn't have much time to prepare his cure. Something along the lines of a simple peptide coupling (Matthew's part of the course – they may not have come across it yet, but they should know how to synthesise amides! – key points being leaving groups, and making sure things are protected to prevent cross coupling) – then some sort of unusual amino acid that will not hydrolyse – maybe a reduced derivative (will there be elimination or spontaneous hydrolysis? Beware) or a carbon replacing the NH of the amide or a F replacing the carbonyl (will this work or eliminate?) or a combination of the two to prevent elimination. Any ideas, so long as the principle is sound. (the more ideas the better – do not be overly critical of the chemistry (their peers are there for that – and the people watching the TV show (just like where they analyse things by GC in X-files and show a mass spec as the result!)), encourage creativity but point out potential flaws and get them to think up workarounds). (maybe one will reinvent penicillin)

Things like modern apparatus (NMR (is it small enough to take on an exploration?), GC, Mass Spec, IR), reflux apparatus, whatever - all these things should be described. Why? So that they can practice explaining the stuff they do and the 2163 audience will not have seen such archaic things – all the chemistry then will be done by robots in a combinatorial fashion. If a student comes up with the idea of combinatorial chemistry CHEER! and encourage all the other students to think about this idea – it is becoming much more prevalent in pharmaceutical companies today and is a brilliant way of generating many drugs to test against these plague bugs.

Testing of the compound

This should not be too detailed – but think up kinetic ways to test – would Chris have had access to pure enzyme? Maybe a chemical type of test, maybe he just fed it to all his crew and hoped. Maybe something much more dramatic to capture the interest of the TV viewer.