

**THE POTENTIAL OF NANOTECHNOLOGY IN THE  
DESTRUCTION OF LESIONS FORMED IN CORONARY  
ATHEROSCLEROSIS**

BY

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PASS WITH DISTINCTION

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## Abstract

Nanotechnology is essentially the manipulation and manufacture of materials on the atomic scale, encompassing physics, chemistry, biology and engineering into a single field of technology<sup>1</sup>. It has already found its place in the commercial world, but it is hoped that in the future nanotechnology will feature far more extensively in the field of medicine than at present.

Atherosclerosis is the thickening of an artery due to atheromatous plaque<sup>2</sup>. If the coronary arteries are affected (as they are in almost all adults working in the industrial community) atherosclerosis can cause heart attacks, ischemic heart disease, peripheral vascular disease or aneurysms of the aorta. Thus far the formation of atheromatous lesions on the walls of the artery has been found to be an ongoing process, developing early in the affected individual's life and progressing over the years. This paper is a compilation of my research and ideas into how nanoparticles could be used to destroy the lesions formed in atherosclerosis.

## Introduction

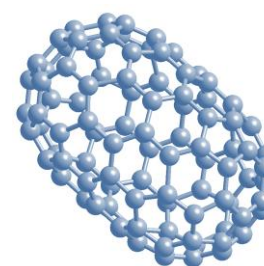
During his 1959 lecture, 'There's Plenty of Room at the Bottom<sup>3</sup>,' American scientist Richard P. Feynman asked his audience the following question: "Why cannot we write the entire 24 volumes of the *Encyclopaedia Britannica* on the head of a pin?" Through nanotechnology, working at the scale which Feynman is describing has become a possibility.

For billions of years, nanotechnology has been applied to many different aspects of nature; the reactions involved in DNA replication, the absorption of solar energy by plants, and the conversion of minerals and water into cells all occur at a scale of nanometres (nm). However, although nature can work so effortlessly at the nanoscale, there are various difficulties involved in manually creating reactions of this scale: for example, learning how to "manipulate and characterise individual atoms and small groups of atoms reliably<sup>4</sup>." Already a daunting task, working on such a small scale is made still more difficult when considering the effect of the altered surface-to-volume ratio of the structures; the enlargement of the surface-to-volume ratio of an element significantly increases the reactivity of the atoms involved.

### Carbon Nanotubes

Despite such difficulties, working at the nanoscale has not only been proved to be possible, but also carries with it the possibility of revolutionising the medical field; the formation of carbon nanotubes brought with it huge potential for targeted drug delivery systems<sup>5</sup> in the human body.

A carbon nanotube (CNT) is essentially a sheet of graphene rolled into a tube - graphene is a single layer of graphite. As in graphite,



each carbon atom is attached to three others (see figure 1), but the CNT has the strength-to-weight ratio of

**Figure 1-model of carbon nanotube (C<sub>69</sub>)<sup>6</sup>**

diamond. In this way, what has essentially been created is a hollow nanocontainer. With this protective shield, drugs or other such externally manufactured structures could be transported around the body without the risk of releasing toxic chemicals into the blood.

### Coronary atherosclerosis

In certain cases of coronary atherosclerosis, thickened areas called atheromatous lesions forming on the walls of the coronary artery reduce the size of the lumen<sup>7</sup> - the central cavity within the artery, thus lessening the blood flow to the myocardium. Once the growth of the lesions has reached a point where the blood flow to the myocardium has reached a critically low level, the symptoms of coronary artery disease will begin to show in the affected individual.

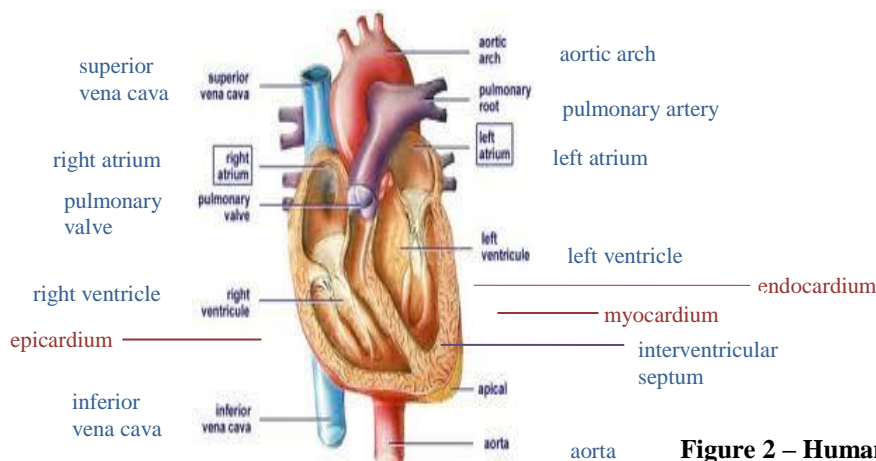
Due to the spontaneous nature of the changes in the lesions, the degree to which the lesions can be reduced (in terms of their obstruction of the lumen) is yet to be known. The key to preventing coronary heart disease may be in somehow preventing the accumulated materials within the lesions from reaching this critical level, thus preventing further impediment of the lumen. I believe that by targeting sodium hydrosulphide-filled CNTs towards the lesions and destroying the atherogenic materials within the lesions, both the level of obstruction of the lumen and the risk of subsequent plaque build-up would be significantly reduced, thus lessening the chances of the affected individual suffering from coronary artery disease as a result of the rupture of atherosclerotic lesions.

## Discussion

### Anatomy of the Heart

To understand the major implications of atherosclerosis and coronary artery disease, it is necessary to be familiar with the basic structure and function of the human cardiovascular system. As the muscular pump which drives blood through the blood vessels to and from all parts of the body, the heart is an essential structure within the human body.

The heart is divided into right and left halves by septa or partitions, and these halves are in turn subdivided into two chambers – the atria and the ventricles - thus giving it four individual chambers (see figure 2).



**Figure 2 – Human cardiovascular system<sup>9</sup>**

The right atrium receives deoxygenated blood from all the tissues in the body except the lungs - this deoxygenated blood flows from the right atrium into the right ventricle, from where the pulmonary artery carries the blood to the lungs. The left atrium, upon receiving oxygenated blood from the lungs, delivers this blood to the left ventricle which, as can clearly be seen from figure 3, has a very thick muscular wall. This muscular wall constantly contracts and retracts, forcing oxygenated blood from this chamber through the aorta, through the arteries (hepatic, mesenteric, etc.) and eventually to all tissues in the body except from the lungs. In this way, oxygen and nutrients which are carried in the blood can be delivered throughout the body. So it is clear that the heart is a vital structure within the human body, providing the organs with oxygen and nourishment, but the heart itself also needs a constant flow of oxygen and nutrients to keep beating. The next section looks at the heart's method of obtaining oxygenated blood.

## Coronary Arterial System

The wall of the heart is made up of three distinct layers (see figure 2): the epicardium, myocardium, and the endocardium – respectively the outer, middle, and inner layers<sup>10</sup>. Due to the thickness of the myocardium (the muscular layer that causes the heart to contract) and the ‘waterproof’ properties of the endocardium (the lining of the heart), the heart cannot obtain the required oxygen and nutrients from the blood within its chambers. To resolve this problem the heart has its own vascular system– the coronary arterial system (see figure 3).

The coronary arterial system consists of two major coronary arteries – the right and left. As seen in figure 3, the left coronary artery divides into two branches; the left anterior descending and the circumflex coronary artery, both of which have multiple branches. It is at these branch points (arterial bifurcations<sup>12</sup>) that atherosclerotic plaques tend to form, making the treatment of coronary atherosclerosis especially difficult to treat.

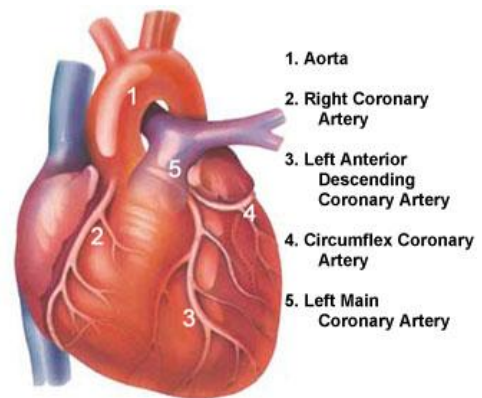


Figure 3 – Human coronary arterial system<sup>11</sup>

## Structure of the Artery

As previously mentioned, the arteries transport oxygenated blood to all the tissues in the body. The continuous pumping action of the heart causes the blood to flow very rapidly through the arteries, thus exerting a high pressure on the walls of the artery. In order to withstand this pressure, the arteries have strong, yet elastic walls.

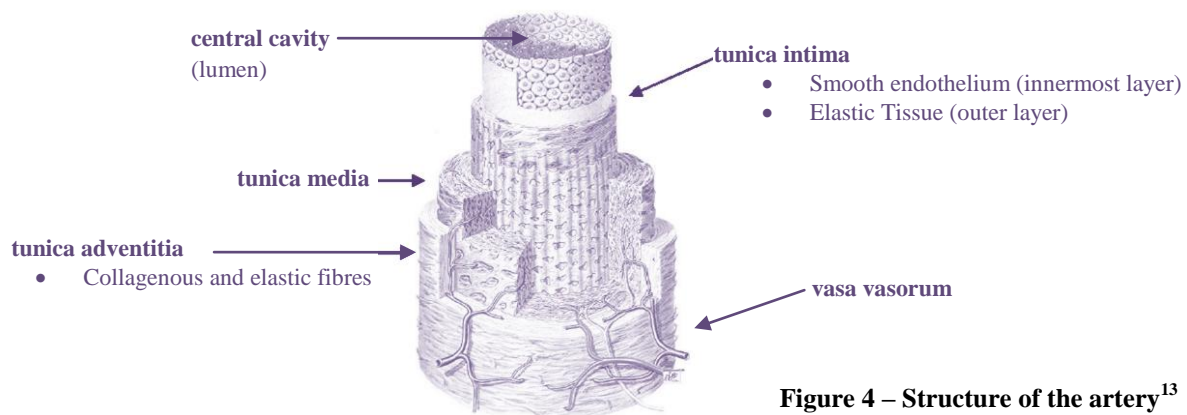


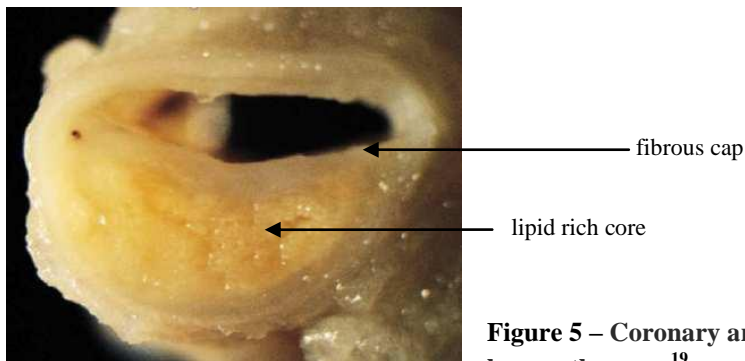
Figure 4 – Structure of the artery<sup>13</sup>

The wall of the artery consists of three layers (see figure 4) – the tunica intima, media and adventitia<sup>14</sup>. The innermost layer – the tunica intima – is made up of a smooth endothelium covered by a surface of elastic tissue. The middle layer – the tunica media – is the thickest layer, consisting of muscle cells and elastic fibres. Both the tunica intima and tunica adventitia are supplied with nutrients by diffusion (from the blood flowing through the central cavity.) The outermost layer – the tunica adventitia – consists of both collagenous and elastic fibres. As the strongest of the three layers, the tunica adventitia creates a limiting barrier, preventing the artery from over-expanding as blood is pumped through it. As seen in figure 4, small blood vessels called the vasa vasorum supply the tunica adventitia with the necessary nutrients.

## Formation of Atheromatous Lesions in the Artery

Atherosclerosis is a disease which affects medium and large-sized arteries; the artery is thickened by atheromatous lesions or atheromas which develop early in the affected individual's life, and progress over a period of many years. The development and growth of an atheromatous lesion is thought to be dependant mainly on two factors: the first is the accumulation of cholesterol at the sites of the thickening, and the second is the formation of thrombi<sup>15</sup> – blood clots – in the endothelial surface of the artery (see figure 4.) I will be focusing primarily on the development due to the build up of cholesterol. The following theory on the growth of atherosclerotic lesions due to lipid accumulation is from a paper written on coronary artery disease by Prof. John McPherson<sup>16</sup>.

Upon being ingested by the individual and entering the bloodstream, low density lipoprotein (LDL) cholesterol is modified by the artery's endothelium; an LDL receptor in the endothelium binds the LDL, alters it through a process of low-level oxidation, and then transports it through the endothelium. As this process continues, the LDLs begin to accumulate in the subendothelial space (below the endothelial layer.) This accumulation stimulates the vascular cells into producing cytokines, which in turn generate monocytes, causing further oxidation of the LDLs. Cytokines are substances that are secreted by specific cells of the immune system<sup>17</sup>. They are glycoproteins, peptides or proteins, and are essentially 'signalling' molecules: they carry signals locally between cells. Significantly oxidised LDL (oxLDLs) are recognised as foreign or injurious by the body, hence the secretion of cytokines, and are therefore absorbed by scavenger receptors on macrophages<sup>18</sup> which then turn into foam cells (so called because the macrophages take on a 'foamy' appearance.) The formation of groups of these foam cells is the first visible indication of an atherosclerotic plaque developing in the artery; oxLDL appears to be the main component of atheromas (figure 5).



**Figure 5 – Coronary artery with significant luminal obstruction by an atheroma<sup>19</sup>**

## Histopathology of atherosclerotic lesions

Classification according to the Stary system:

- **Stary I lesion:** Endothelium expresses E-selectin and P-selectin – cell adhesion molecules<sup>20</sup> – which attract more polymorphonuclear cells (also known as granulocytes) and monocytes into the subendothelial space. Granulocytes are a type of white blood cells characterised by microscopic sacs of enzymes, or granules, in the cytoplasm<sup>21</sup>.
- **Stary II lesion:** Scavenger receptors on macrophages begin to take up large amounts of oxLDLs, causing a fatty streak to be formed in the artery. This fatty streak is essentially the accumulation of LDLs within the intima of the arterial wall (see figure 4).
- **Stary III lesion:** As the process continues, the macrophages become foam cells.

- **Stary IV lesion:** Lipids accumulate in the extracellular space, coalescing to form part of the lipid core (see figure 5). The lipid core is made up of foam cells, extracellular lipids, calcium and necrotic cellular debris<sup>22</sup> – foam cells that have died.
- **Stary V lesion:** Smooth muscle cells (SMCs) and fibroblasts (connective tissue cells) move in, forming fibroatheromas with soft, lipid cores and outer fibrous caps made of SMCs and collagen. Similar to the adventitia, atherosclerotic plaques in the development stage can acquire their own vascular network called vasa vasorum<sup>23</sup> (see figure 4)
- **Stary VI lesion:** Rupture of the lesion due to weakening of the fibrous cap with resultant thrombosis (the lipid core is highly thrombogenic) causes acute coronary syndrome. (ACS is the range of problems directly affecting the heart.) Thrombosis is the formation of a blood clot inside a blood vessel which obstructs the flow of blood through the circulatory system<sup>24</sup>. The thrombi (blood clots) can either obstruct the lumen itself, or, upon detachment, will move into the coronary arterial system and eventually block smaller branches further along the system<sup>25</sup>. Atherosclerotic plaques with higher lipid content in the core and thinner fibrous caps are very prone to rupture; these plaques are said to be vulnerable plaques.
- **Stary VII lesion:** As the lesions stabilise, they become fibrocalcific.
- **Stary VIII lesions:** Stabilised lesions are fibrotic with extensive collagen content.

As previously mentioned, atherosclerosis is a progressive disease; to reach the stage defined by the Stary VIII lesion, atherosclerotic plaques require 10-15 years of development.

### Breakdown of lipid hydroperoxides in oxLDLs

Recent research suggests that hydrogen sulphide (H<sub>2</sub>S) could be used to destroy lipid hydroperoxides (LOOHs) - the compounds within oxLDLs which 'make' them atherogenic<sup>26</sup>. H<sub>2</sub>S is already known to destroy hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>),



so it is possible that H<sub>2</sub>S may also be able to destroy LOOHs in oxLDL, thus significantly reducing LDL activity. The destruction of hydroperoxides could significantly limit the atherogenic potential of oxLDLs; hydroperoxides can break down into lipid alkoxyl (LO<sup>•</sup>) and peroxy radicals (LOO<sup>•</sup>), both of which can attack and alter other biological molecules. The following section looks at the evidence collected by Muellner [*et al* 2009] which indicates that “H<sub>2</sub>S can reduce LOOHs to the less reactive LOHs.”

### H<sub>2</sub>S treatment decreases ability of oxLDLs to induce HO-1

LOOH has the ability to stimulate the release of HO-1 in vascular cells, or more specifically, endothelial cells. (Haem oxygenase (HO) is an enzyme that catalyses the degradation of haem; haem, an iron-containing compound, forms the non-protein part of haemoglobin<sup>27</sup>.) The experiment carried out by Muellner [*et al* 2009] shows that the presence of oxLDLs in isolated and cultured human umbilical-vein endothelial cells (HUVEC) results in a five-fold induction of HO-1 (see figure 6)

Following 1mmol l<sup>-1</sup> H<sub>2</sub>S treatment for 30mins at 37°C, HO-1 in HUVEC is almost completely eradicated. These results show that H<sub>2</sub>S treatment eliminates the ability of the oxLDL to induce HO-1, indicating that the LOOHs in the LDL have been destroyed.

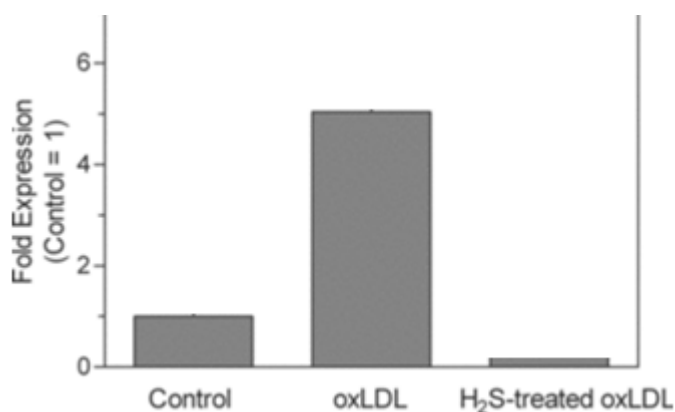


Figure 6-Graph showing the effect of H<sub>2</sub>S on the induction of HO-1 in HUVEC<sup>28</sup>

### Reduction of 9-HPODE to 9-HODE by H<sub>2</sub>S treatment

High Performance Liquid Chromatography (HPLC) analysis shows that 9-HPODE (9S-hydroperoxyoctadecadienoic acid) is a compound found in oxLDLs. Upon its incubation with H<sub>2</sub>S for 30mins at 37°C, 50% of the 9-HPODE is reduced to 9-HODE (9S-hydroxyoctadecadienoic acid). The reduction of 9-HPODE suggests that H<sub>2</sub>S reduces LOOH to LOH – a less atherogenic compound - and my method for the treatment of coronary atherosclerosis with CNTs is built around this basis.

### Method

Alongside carbon monoxide and nitric oxide, H<sub>2</sub>S was recently discovered to be a third endogenous gasotransmitter in the circulatory system. Endogenous substances are those that “originate from within an organism, tissue, or cell<sup>29</sup>.” Gasotransmitters are a family of “endogenous signalling gaseous molecules”<sup>30</sup>. However, free H<sub>2</sub>S does not exist in sufficiently high quantities *in vivo* to directly affect LOOHs in the lesions. If H<sub>2</sub>S could be stored and transported within or on the surface of a CNT, it could be used to directly attack and thus reduce the LOOHs in the oxLDLs.

### Targeted CNTs

In order for nanoparticles to be used in the transport of H<sub>2</sub>S, targeting of the CNTs must be considered; the H<sub>2</sub>S must be released at the correct site - the release of an acidic gas in the human body at the wrong location is highly undesirable. In order to ensure the H<sub>2</sub>S is released at the correct site, the nanoparticles must somehow be targeted towards the lesions. The ability to target atherosclerotic plaques may lie in the presence of CD36 – an adhesion molecule expressed by macrophages which plays a key role in the binding and internalisation of oxLDLs<sup>31</sup>. CD36 plays a major role in the uptake of oxLDL by macrophages and the subsequent formation of foam cells. As previously explained, the uptake of oxLDLs by macrophages is a fundamental step, both in the initiation and the development of atherosclerotic lesions, so the ability to target the CNTs towards this particular site is essential. A study carried out investigating the terminal six amino-acids of the cytoplasmic tail of CD36 shows that a specific site on the tail is critical in the binding and internalisation of oxLDL. Essentially, the study shows that the truncation (deletion) of the last six amino-acids in the tail (construct R467STOP) significantly reduces the ability of the molecule to bind and internalise oxLDLs. Through determining the DNA sequence of this small chain of amino acids using the Sanger method<sup>32</sup>, the corresponding DNA molecule could then be sequenced. The DNA molecule could then be ‘wrapped’ around the CNT, as seen in figure 7. The nanoparticle should, upon reaching a sufficient proximity to the atherosclerotic lesion, target the lesion. A radioactive ‘tag’ should also be attached to the surface of the nanoparticle to allow its position within the body to be constantly monitored (see figure 9)

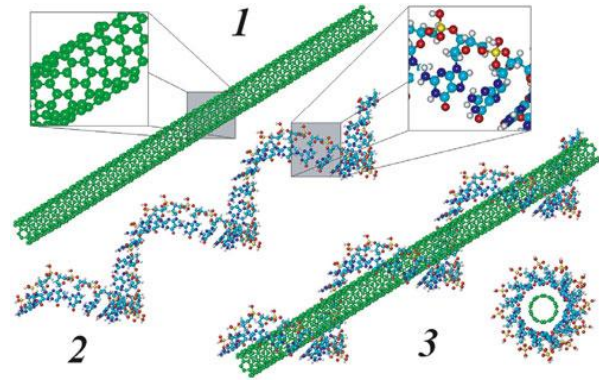
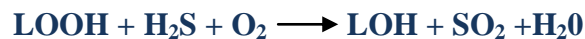


Figure 7- model of carbon nanotube wrapped in DNA<sup>33</sup>

### Formation of H<sub>2</sub>S

The vapour space above sodium hydrosulphide (NaHS) solution contains hydrogen sulphide gas, the level of H<sub>2</sub>S gas above the solution can be increased by heating of the solution<sup>34</sup>.

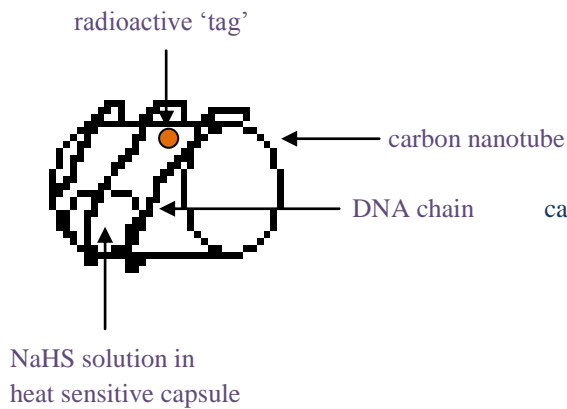
My suggestion is to transport NaHS solution encapsulated in a heat-sensitive material within a CNT to the atherosclerotic lesions through the veins of the affected individual. Upon heating of the capsule, the NaHS should release H<sub>2</sub>S which, according to Muellner [*et al* 2009] should reduce the atherogenic compound LOOH to LOH. A method must be devised by which the heat-sensitive capsule can be directly heated without damaging healthy cells in the process, and I believe the key to this lies in the properties of near-infrared light (NIR). A ray of NIR light, when shone at the human body will not damage healthy cells, but will be absorbed by the CNT<sup>35</sup>. As mentioned previously, the exact location of the nanoparticle can be established by its radioactive tag, so when the CNT has reached its destination, the ray of NIR light will be absorbed by the CNT as heat energy which in turn will release the hydrogen sulphide, which in turn should reduce the highly atherogenic LOOH to LOH. However, as shown below, the reaction involving H<sub>2</sub>S and LOOH also produces sulphur dioxide (SO<sub>2</sub>), another acidic gas which, upon dissolving in the water formed, will form sulphurous acid (H<sub>2</sub>SO<sub>3</sub>).



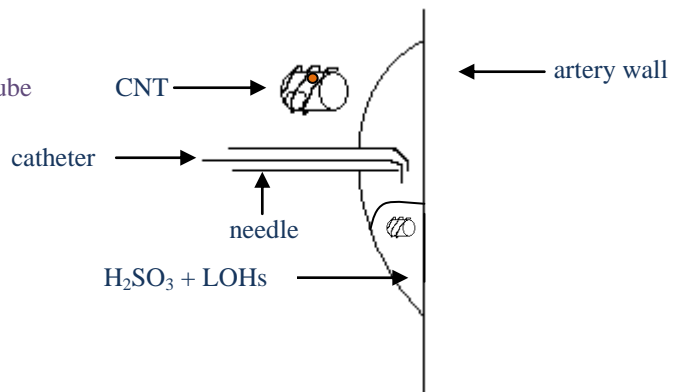
My suggestion for the removal of the sulphurous acid formed is to essentially use a reversed catheter system. The catheter would be placed using a needle; the needle would have to pierce the fibrous cap of the lesion in order to reach the area within the plaque affected by the H<sub>2</sub>S – the LOOHs. The catheter would then be inserted through the needle (see figure 8), and would drain the sulphurous acid out of the lesion.

This process would have to take place either as soon as a *Stary I lesion* is detected, or at some point during the formation of the *Stary V lesion*, so that the sulphurous acid can be held in one place while it is drained. Since atherosclerosis progresses over a period of 10-15 years, the chances of detection of a *Stary I lesion* are very slim, so the optimum time for a process such as this to be carried out is between the fourth and fifth *Stary lesion*. In removing the atherogenic compound within oxLDLs (LOOHs), the chances of the lipids accumulating again to form lesions should be significantly reduced.

In order to have any effect on the lesions, a significant volume of hydrogen sulphide must be deposited, and this would result in a large number of CNTs left in the body. Due to their size, there would be no way of removing the ‘empty’ or ‘used’ nanoparticles from the body, and as yet, the effect of nanoparticles on the cells in the body is unknown.



**Figure 9 – diagram of CNT prior to heating with NIR light**



**Figure 8- diagram of needle with catheter placed prior to draining of H<sub>2</sub>SO<sub>4</sub> and LOHs**

## Conclusion

Theoretically speaking, the medicinal use of nanotechnology carries with it the potential to give us qualities we wouldn't otherwise have - the capacity to rapidly heal oneself and night-vision, for example. But in striving for the ability to heal ourselves with technology, are we pursuing a goal which will defy all the ethics and morals laid out thus far? If your heart has been replaced with what is essentially a piece of metal, are you still human?

Aside from the many ethics on the use of nanotechnology in medicine, and in particular in its use within the human body, there are various other difficulties to consider: for one, there is a possibility of incompatibility with the human body – CNTs do not occur naturally in the human body, so even with the presence of a DNA 'disguise', there is a large risk of the body's immune system attacking the nanoparticles. For another, many scientists are concerned that the size of nanoparticles may allow them to cross the blood-brain barrier; the membrane that protects the brain from exposure to harmful chemicals in the bloodstream<sup>36</sup>.

Despite the challenges and difficulties it brings up, I believe that nanotechnology has thrown open a set of doors in medicine which we, until now, didn't know existed.

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