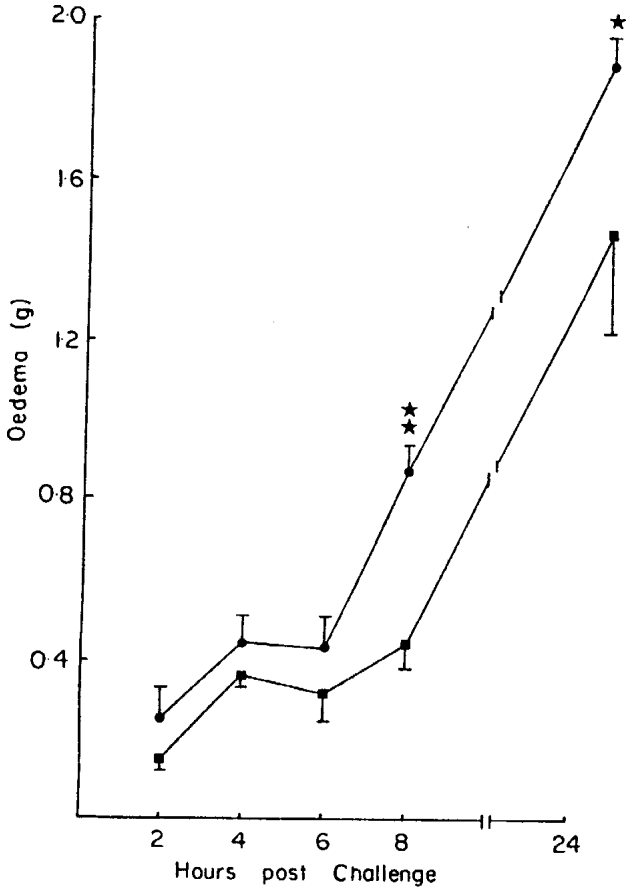

FIGURE 11. A comparison of the development of foot pad oedema in iron deficient and iron supplemented rats after challenge with Freund's complete adjuvant. Solid squares = iron deficient, solid circles = iron supplemented. * $p < 0.05$, ** $p < 0.01$ (Student's Test).

perhaps people have thought. Maybe in the future we will be seeing copper complex non steroidal agents.

Mr Christian Narkowicz

Is there any way of binding free the iron in the joints?

Dr Fiona Andrews

There has been some work to suggest that infusion of desferrioxamine into a model of inflamed synovial-like tissue, namely the allergic air pouch in rats, reduces the inflammatory reaction although I am not aware of studies where desferrioxamine has been infused into the human arthritic joint.

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This is an edited transcript of a recording made at a Free Radical Workshop during the joint SPUMS and Royal Hobart Hospital meeting on Hyperbaric and Diving Medicine in November 1988.

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FREE RADICALS IN HEALTH AND DISEASE

Janet Vial

An alternative title for my talk today would be oxygen, friend or foe. I am sure Joseph Priestly in 1775 never really appreciated the implications of his words when he wrote, "Though pure dephlogisticated air (which was his name for oxygen) might be useful as a medicine it might be not so proper for us in the usual healthy state of the body for as the candle burns so much faster in dephlogisticated than in common air so we might as may be said live out too fast and the animals powers be too soon exhausted in this pure kind of air". So from the very beginning Priestly perhaps appreciated the mixed blessing that oxygen is. Although we can point to many substances in our environment which are both good and bad, perhaps oxygen is unique in being essential to life but also being so potentially toxic to living cells.

I would like to go back in time. Back five billion years to the beginning of the earth. When the earth was

young it was a rather inhospitable place; very geologically active with volcanoes and fumaroles. There was no protection from ultra violet radiation and other radiation from extra terrestrial sources. The atmosphere consisted of small organic molecules like methane, ammonia, hydrogen, sulphur, and some water vapour. Although rather inhospitable to our eyes that combination of substances, plus the fact that there was no protection from extra terrestrial radiation set up the circumstances in which life could evolve. It has been shown in the laboratory that if one combines the substances which were in the early atmosphere with radiation one can produce amino acids which are the building blocks of proteins. With time, increasingly complex organic molecules were synthesized from the combination of simple molecules and still later molecules which had the ability to reproduce themselves developed. These were either DNA or substances like DNA and there may have been several trials before life as we know it evolved.

In the beginning the DNA and cells, when they came along, depended for their energy on the breakdown of the complex molecules around them. In time algae evolved which had the ability to synthesize carbohydrates using the energy from the sun and carbon dioxide. Photosynthesis had arrived. This was a very important stage in evolution because the by product of this photosynthesis was oxygen. For the first time significant amounts of oxygen appeared in the earth's atmosphere. This was toxic to the organisms that had never been exposed to oxygen before and I am sure many forms of life disappeared at that time. Those that survived either had to find niches that were away from oxygen or else they had to develop mechanisms to defend themselves against oxygen damage. Those organisms that learned to live with oxygen had many advantages, because metabolism using oxygen was very much more efficient than the previous anaerobic metabolism. This improved ability to generate energy was important pre-requisite for the development of multi celled organisms. Oxygen was important in another way. Ozone is derived from oxygen. Up until this time there was no protection for the surface of the earth from ultraviolet radiation. With increasing amounts of oxygen the ozone layer was able to develop and the surface of the earth was then protected to some degree from UV radiation. This allowed the evolution of life on land. Oxygen and development of organisms that both released and were able to use oxygen was a very important part of the evolution of life on earth.

I have mentioned cellular metabolism that uses oxygen. Most reduction of oxygen in cells occurs through the addition of four electrons to oxygen. That is important because it means that free radicals are not produced. Before I go further I will explain what free radicals are. That perhaps will explain why oxygen was toxic to those primitive cells that had no defence against it. So what are free radicals? Remember the structure of an atom or a molecule. The nucleus of an atom consists of protons, positively charged particles, and neutrons which have no charge. They form the nucleus and spinning around the nucleus in orbitals are electrons, the negatively charged particles. These electrons usually occur in pairs. These electrons, as well as spinning around the nucleus, also spin on their own axis which creates magnetic forces. However the two electrons that make up a pair spin in opposite directions, so their magnetic forces cancel each other out effectively. A free radical is a molecule that has only one electron in an outer orbital. As a result it is unbalanced and has the potential to act as a magnet. Because this is an unstable state the radical tends to grab other electrons to make its outer orbital stable. So free radicals tend to be very reactive and tend to react very readily with other molecules.

Oxygen is interesting in that it is a biradical. An oxygen molecule consists of two atoms of oxygen and the two atoms are each radicals in that they each have an unpaired electron in their outer orbital. One might ask why do not the two electrons pair up? Unfortunately they have parallel spins so they are not able to pair up because only electrons with opposite spins can pair up. That makes oxygen an unusual molecule as even if one adds another electron to oxygen there is still one unpaired electron. In fact one needs to add four electrons to the molecule to get a stable situation. So oxygen, and metabolism of oxygen, has a great propensity to produce free radicals. This is overcome in most cellular metabolism by an enzyme called cytochrome oxidase which adds four electrons in a single step therefore avoiding the production of free radicals. However some of the oxygen in the cell bypasses this system and electrons are added one at a time producing free radicals. So from every cell there is a leak of free radicals as part of cellular metabolism.

Other enzymes in the cell, which act on oxygen, also produce free radicals. This is an inevitable side effect of the production of important cell messengers and the metabolism of a number of drugs and chemicals also result in the production of free radicals. Exposure to ultra violet light and to ionising radiation also can produce free radicals. These are some of the sources of free radicals in the body (Table 1) that are known and there may be others that as yet we do not know about. The production, in the body, of free radicals is something that is happening all the time as part of its normal functioning and it is essential that the body has means of dealing with them to prevent potential damage.

Why are free radicals potentially harmful, why do we have to worry about them? The major oxygen free radical product of biological reactions is superoxide. It is an oxygen molecule with an extra electron and because it has an extra electron it is negatively charged.

In itself the superoxide does not seem to be particularly damaging. In the laboratory it is very difficult to show that superoxide does any harm to tissues so it is thought that it is a product of this superoxide that is responsible for free radical damage. The superoxide radical in the presence of

TABLE 1
Sources of free radicals in the body

Cellular metabolism
Enzymes (oxidases)
Metabolism of drugs and chemicals
Exposure to UV light and ionizing radiation

iron Fe+++ donates an electron the iron molecule producing Fe^{++} (Figure 1). Superoxide in the presence of hydrogen ions produces hydrogen peroxide plus molecular oxygen and then the combination of this hydrogen peroxide and Fe^{++} results in the production of hydroxyl radical (Figure 1) which is thought to be one of the villains of the piece. The hydroxyl radical has been shown to be a potent cause of damage in the body.

HABER-WEISS REACTION

$$O_2^{\cdot -} + Fe^{3+} \rightarrow O_2 + Fe^{2+}$$

$$2H^+ + 2O_2^{\cdot -} \rightarrow H_2O_2 + O_2$$

$$H_2O_2 + Fe^{2+} \rightarrow OH^{\cdot} + OH^- + Fe^{3+}$$

FIGURE 1. The chemical reactions by which the relatively harmless superoxide radical, the major oxygen free radical product of biological reactions, is thought to be converted to the tissue damaging hydroxyl radical ($OH^{\cdot}$).

How does this hydroxyl radical cause damage to the body? The next players in the saga are polyunsaturated fatty acids. Polyunsaturated fatty acids are fairly ubiquitous substances. They are very important constituents of cell membranes. Cell membranes are vital for function. If the cell membrane is destroyed then very shortly thereafter the cell dies. Polyunsaturated fatty acids are particularly prone to free radical attacks. They consist of a carbon backbone but they have a number of double bonds, or unsaturated bonds between the carbon atoms, and free radicals can attack at these points. When an hydroxyl radical attacks at a carbon double bond the result is the production of a lipid radical. In the presence of oxygen the next product is a lipid peroxide radical (Figure 2). This radical can break down, in certain circumstances, to form a number of different substances which in themselves are toxic to cells. They are responsible for the bad taste and bad smells of rancid fat and of food that contains fat when it goes off.

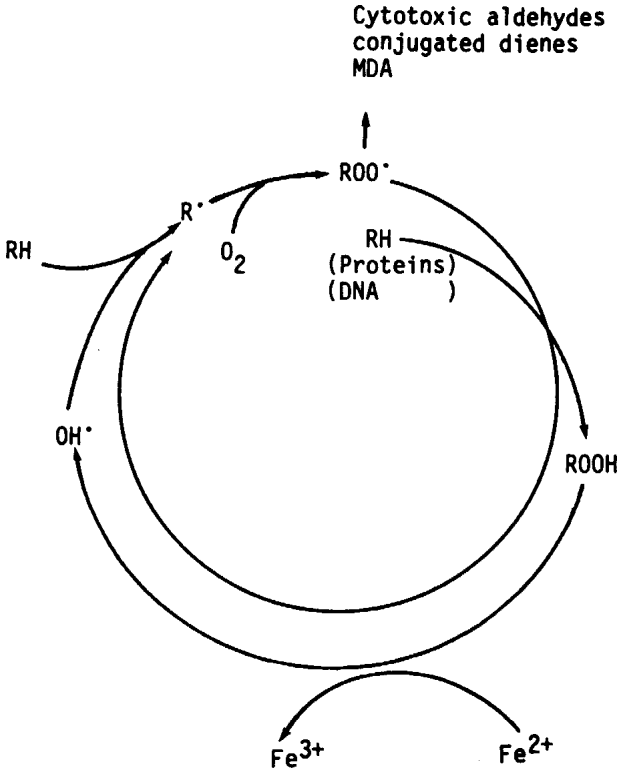

FIGURE 2. The reactions by which polyunsaturated fatty acids (RH) and the hydroxyl radicals ($OH^{\cdot}$) produce lipid radicals ($R^{\cdot}$), lipid peroxyl radicals ($ROO^{\cdot}$) and lipid peroxides (ROOH).

If that does not happen the lipid peroxide radical in the presence of more polyunsaturated fatty acids can produce lipid peroxide and at the same time produce a further radical from the polyunsaturated fatty acid (Figure 2). At this stage in the cycle other sorts of compounds can come in. Proteins or DNA can be introduced into the system and radicals can be generated from them. This can become a self sustaining reaction with eventual destruction of the organism if there is not some block in the system.

What happens to the lipid peroxide? It can hang around for a while in cell walls not doing much at all. But in the right circumstances and in the presence of small amounts of iron it can break down with the production of hydroxyl radical and the whole process can start all over again (Figure 2).

This damage particularly effects lipids which are very important in cell membranes, for cellular integrity, but as it also involves proteins and DNA, one can see very easily how radicals, if they get out of control, can wreak havoc at many levels in the cell and result in cell destruction.

Before getting carried away with the damaging effects of uncontrolled free radicals one should look to see if

there is another side of the coin. Interest in free radicals and related compounds as is something necessary to life is fairly new so there is not a lot of research in this area. It is becoming clear in a couple of areas that a certain low level of free radicals is needed for good health. For some enzymes full activity requires a low level of lipid peroxides. this applies to the cyclooxygenase enzyme which is responsible for producing prostaglandins, important mediators in inflammation, clotting and control of blood vessel diameter. The white cells are very important in defending the body against bacterial infection and a group of the white cells, the polymorphonuclear leukocytes, have the ability to release packets of free radicals in the right circumstances to kill bacteria. The body has thus used free radicals for its own defence against bacteria and people who do not have this ability are very prone to bacterial infections and often die prematurely as a result.

There are a couple more speculative areas where free radicals may be necessary for normal health. There is some evidence that free radicals are involved in the control of blood vessels and blood flow. An even more speculative area is in brain function. People with Down's Syndrome have an extra chromosome 21. Chromosome 21 contains the genetic code for superoxide dismutase which is a very important protective enzyme that prevents free radical generation. So people with Down's Syndrome have at least 50% more superoxide dismutase in their brain than normal people. It has also been found that some people with chronic psychiatric conditions have more superoxide dismutase in their brain than normal and it has been speculated that perhaps a certain level of free radicals is necessary in the brain for normal brain functioning. That is an area that is going to need more research but it is interesting to speculate.

How can one prevent tissue damage due to free radicals? First, by reducing production of free radicals through reducing exposure to oxygen, other chemicals and radiation that might produce free radicals. Reduction of the pool of labile transition metals will also reduce free radical production. I indicated before how iron could promote the production of hydroxyl radicals and other transition metals like copper and manganese can do the same thing. Protective enzymes and antioxidants are also important for preventing and reducing tissue damage.

Defence mechanisms vary in different parts of the body. Let us first consider the blood stream. Protein in the blood stream is important in defending against free radical damage. Some of the body's waste products which are carried in the blood stream actually have a function. Bilirubin, which is the breakdown product of red cells and uric acid, which is a breakdown product of DNA and nucleic acids are both important scavengers of free radicals in the blood stream. The antioxidants, Vitamin C and vitamin E are also important blood stream defences against free radicals (Table 2, page 135). In the cell membrane, Vitamin E seems to be the main factor protecting against damage, and is very important in breaking the lipid peroxidation cycle (Table 2).

Inside the cell, some of the proteins are important as are several protective enzyme systems. The glutathione system, which is a complex enzyme system, is involved in preventing free radical damage, as are the enzymes superoxide dismutase and catalase and the antioxidant vitamin C (Table 2, page 135). These multiple mechanisms tend to be overlapping. If there is a deficiency in one, free radical damage does not necessarily follow because often the others can compensate to some degree.

How do some of the enzyme systems in the cell work to prevent free radical damage? Superoxide is the first free radical product and superoxide dismutase converts it to hydrogen peroxide. Then catalase or glutathione peroxidase converts hydrogen peroxide to water preventing the production of hydroxyl radicals and damage (Figure 3). What about the lipid peroxide radicals and lipid peroxides? The oxidation of Vitamin E results in the lipid peroxide radical becoming a lipid peroxide and then glutathione peroxidase converts the lipid peroxide into innocuous alcohol that can not do any damage. Vitamin C transforms the oxidised Vitamin E back to reduced Vitamin E (Figure 4). This illustrates some of the interlinking of the different free radical defence mechanisms.

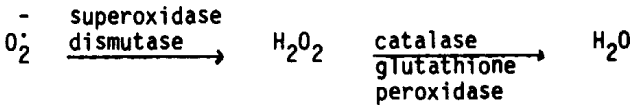

FIGURE 3. Dismutation of superoxide to hydrogen peroxide (H_2O_2) and conversion of hydrogen peroxide to water by either catalase or glutathione peroxide.

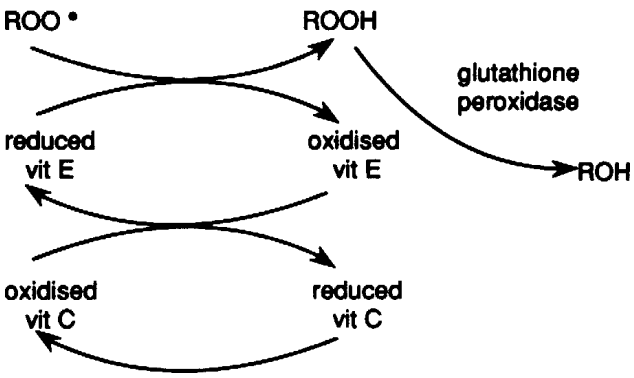

FIGURE 4. The lipid peroxyl radical ($ROO^{\cdot}$) is reduced to lipid peroxide (ROOH) by vitamin E and the lipid peroxide is converted to an alcohol by glutathione peroxidase. The oxidised vitamin E is reduced by vitamin C.

TABLE 2
Free radical defences in the blood stream, cell membrane and inside the cell.

Blood	Cell Membrane	Cell
protein	vitamin E	heme proteins
bilirubin		glutathione system
uric acid		superoxide dismutase (SOD)
vitamin C		catalase
vitamin E		vitamin C

Free radical damage occurs if there is an increase in production of free radicals or a reduction in free radical defence mechanisms. Some of the diseases where free radical mechanisms have been implicated are listed (Table 3). Aging is something of interest to most people, oxygen toxicity, atherosclerosis, reperfusion damage and cancer I will discuss in more detail shortly. There is some difficulty in finding out exactly if and to what degree free radicals are involved in human disease. The first difficulty is that they are often hard to measure. Many of them are very short lived so they are hard to capture, particularly in biological systems. So much of the evidence comes indirectly through studies which involve increasing free radical defence mechanisms or reducing free radical defence mechanisms. This makes the involvement of free radicals difficult to prove absolutely for many diseases, though the techniques are improving all the time and this is an area of avid research at the moment.

TABLE 3
Some diseases in which free radicals have been implicated

Aging	
Oxygen toxicity	lungs
	retrolental fibroplasia
Cataract formation	
Atherosclerosis	
Rheumatoid arthritis	
Parkinson's Disease	
Reperfusion damage in heart attacks and strokes	
Cancer	
Drug toxicity	

To deal with oxygen toxicity first. It has been known for a long time that patients exposed to very high concentrations of oxygen for a long period get damage to their lungs. It has been shown in premature baby nurseries that if babies are exposed to high concentrations of oxygen they get damage to their eyes sometimes producing blindness and also to a lesser extent damage to their lungs. Because exposure to high concentrations of oxygen has the potential to produce free radicals this has been suggested as a mechanism. Certainly there is quite a lot of indirect evidence from laboratory studies where free radical defence mechanisms have been reduced or enhanced and this has altered the extent of oxygen damage. Premature babies are thought to be particularly sensitive to oxygen damage because they have very low levels of vitamin E. Studies have been done to try to increase their levels of vitamin E to reduce damage.

We have been interested in this area of oxygen toxicity and have done some studies in collaboration with Dr Peter McCartney. The hyperbaric chamber is particularly useful for studying oxygen toxicity because one can expose people or animals to high concentrations of oxygen in a controlled environment. Our studies also have implications for hyperbaric treatment itself. Hyperbaric oxygen is increasingly being used to treat a number of medical conditions, but there is always a worry that perhaps some of the potential benefit could be counteracted by an increase in oxygen free radicals. So for maximising the value of this treatment it is important to know whether in fact free radicals are produced and whether there is some way of preventing the production of free radicals. So we have been interested in measuring free radicals. What we have been doing is measuring free radicals in blood. We have been taking blood and snap freezing it in liquid nitrogen. This has the advantage that it stops any further free radical processes. Also it is easier to examine free radicals using the techniques that we use, in a solid state rather than in a liquid state. We have been using electron spin resonance to measure free radicals.

The principal behind electron spin resonance (ESR) measurement of free radicals is that the unpaired electron in a free radical can act as a magnet and if put in a magnetic field it will line up in that magnetic field. If one then applies energy, in the form of microwave radiation, there may be a change in the energy level of the "magnet", i.e.. it will change its orientation in the magnetic field and this will be picked up as an absorption in the microwave radiation.

We have found that in the blood of volunteers in the hyperbaric chamber breathing 100% oxygen at 3 atmos-

pheres there is an increase in the ESR peak height compared to room air indicating an increase in free radical concentration. Not only does the peak increase but its position changes slightly, suggesting that the radical produced during hyperbaric oxygen treatment is perhaps different from the base line radical present before the subject went into the chamber.

We have now studied a number of police divers in the hyperbaric chamber. They breathe 100% oxygen at three atmospheres for three periods of 20 minutes with 5 minutes break breathing air. There is an increase in free radical peak height at the end of each oxygen period in the chamber. The encouraging thing is that the increase in height comes back to normal very quickly after re-exposure to room air. I think this demonstrates that the healthy human can tolerate an increase in free radical stress and cope with it quite readily.

There has been a lot of interest in free radicals and aging. Scientists have done some interesting calculations. They took a number of species of animals and measured their superoxide dismutase level, superoxide dismutase being an important free radical defence mechanism, and measured their metabolic rate. They divided the superoxide dismutase level by the metabolic rate and they found that this correlated roughly with the potential life span of the animals. This seemed to be good evidence that maybe free radicals were important in determining the life span of different species. Since then there have been a number of laboratory studies, depleting or increasing the free radical defence mechanism of experimental animals to see whether this makes any difference to their life span. I am sorry to report that it does not seem to make much difference to their potential life span. So perhaps swallowing vitamin E and vitamin C is not going to be the elixir of youth we thought. But one thing that did come out of these sort of studies is that many of the degenerative diseases that stop individuals from reaching their potential life span do seem to be free radical mediated. So it may be that enhancing free radical defence mechanisms will have some value in allowing more individuals to reach their potential life span without degenerative illness.

A major degenerative disease is atherosclerosis. The risk factors of cigarette smoking, hypertension, diabetes and high cholesterol, are well known. These risk factors are well established from the epidemiological evidence but how do these risk factors actually cause the atherosclerosis? On the surface of it, it might look simple, there is cholesterol in atherosclerotic plaques and perhaps the cholesterol just crosses into the blood vessel wall but it is not quite as simple as that. Cholesterol can not just pass by itself into the blood vessel wall, it does so inside macrophages. As macrophages normally do not take up cholesterol there has been a bit of a mystery as to how the cholesterol gets inside. There has been a lot of progress recently in this area. If one exposes cholesterol to oxygen or other oxidants and damages it, and makes a radical or a peroxide out of it then macrophages do take up the cholesterol. Macrophages take up damaged cholesterol but not normal cholesterol. This damage to cholesterol may be a very important point along the sequence of cholesterol to atherosclerosis, and so now there is increasing interest in looking at anti-oxidant treatment to prevent atherosclerosis. Certainly it has been shown in the laboratory that depleting the anti-oxidants, such as vitamin E, vitamin A and betacarotene, increases the oxidation of cholesterol. This is an area for interesting future research.

Another important group of diseases that limit the potential life span of many people is cancer. DNA can be damaged by the lipid peroxidation process I mentioned previously and damage to DNA certainly is a precursor for the development of carcinogenesis. What of the evidence of the involvement of free radicals in human cancer? There are a number of animal studies where animals have been depleted in anti-oxidants like vitamin A, C and E and it has been shown that these animals have an increased tendency to develop malignancies. Humans who eat a vegetarian diet which is high in betacarotene and vitamins A and C have less risk of both ischaemic heart disease and cancer. There have been a number of epidemiological studies where blood has been taken from normal populations and these various vitamins and anti-oxidants have been measured, the people have then followed for many years and then when some of them eventually died of cancer their blood levels have been compared with those who did not die of cancer. From these studies evidence is emerging that those who die from cancer or certain forms of cancer often do have lower levels of anti-oxidants than those who do not. It has been shown with lung cancer and breast cancer that those who get it have lower levels of vitamin E, for example, than those who do not get these malignancies. With gastrointestinal tumours it has been shown that those who get these malignancies have lower levels of vitamin A, C, E and betacarotene than those who do not. So some circumstantial evidence is starting to accumulate that these free radical processes may have something to do with cancer.

I would like to briefly discuss reperfusion damage in heart attacks. It is now clear that a heart attack usually results from a clot in one of the arteries supplying the heart, often at a point of atherosclerosis. There is increasing interest now in trying to limit the damage from heart attacks by getting these people to hospital very soon after their heart attack and giving them therapy to break down the clot and re-establish blood flow. Drugs such as streptokinase and tissue plasminogen activator are being increasingly used for this purpose. There is a potential problem in this treatment. When a tissue is not receiving blood it does not receive oxygen so it can not make free radicals. However it can not metabolize normally either and this results in the breakdown of the free radical defence mechanisms. So when the blood supply is restored and oxygen reintroduced there is a sudden burst of free radicals and the tissue has no way of defending itself against them. There is certainly some evidence that this period of reperfusion when blood flow starts again is a time when there can be damage. Some of the benefit of reintroducing the blood flow may be counteracted by the

disadvantage of this reperfusion damage. Because we are using this sort of treatment there is increasing interest in using free radical scavenging mechanisms to prevent damage. There are clinical trials, I know, going on in the United States looking at treatment with free radical scavengers. It remains to be seen how beneficial it will be in presenting reperfusion damage.

This brief outline shows that free radicals have the potential to be very important in many human diseases including some of the most common diseases that are likely to stop us from reaching our potential life span. I hope that I have provided some insight into how free radicals which were once the domain of academic chemists now have implications for medical research and hopefully in the future understanding of their role in disease will result in improvements in prevention and treatment.

This is an edited transcript of a recording made at a lectureduring the joint SPUMS and Royal Hobart Hospital meeting on Hyperbaric and Diving Medicine in November 1988.

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DIVING SAFETY MEMORANDA

Department of Energy
London SW1P 4QJ
May 1989

DIVING SAFETY MEMORANDUM NO. 4/1989 EXPOSURE LIMITS FOR IN-WATER DECOMPRESSION

Diving Safety Memorandum No. 5/1988 recommended that all surface decompression dives should be arranged so that the planned bottom times did not exceed the exposure limits defined in the table attached thereto.

At that time there was only limited data available on the experience of using in-water decompression techniques in the UK sector. Hence diving using this technique was not included in the safety memorandum.

From the 1988 dive data, it is evident that there has been an increased use of the in-water decompression technique, and that long bottom times using this technique have resulted in serious cases of decompression sickness. Though the amount of information available is limited, it is felt that the industry should be made aware of this trend.

It is therefore strongly recommended that the guidance on exposure limits given in Table 1 to DSM 5/1988 is also followed when using the in-water decompression technique.

R. GILES
Chief Inspector of Diving

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Faculty

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