FREE RADICALS - Curated Transcript of BBC In Our Time podcast

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In Our Time is hosted by Melvyn Bragg. Melvyn's guests on this podcast are:

Nick Lane

Professor of Evolutionary Biochemistry at University College London

Anna Croft

Associate Professor at the Department of Chemical and Environmental Engineering at the University of Nottingham

And

Mike Murphy

Professor of Mitochondrial Redox Biology at Cambridge University

Producer: Simon Tillotson

Transcript:

[Melvyn Bragg] Hello. We'll be talking about free radicals. Free radicals are highly reactive atoms or molecules, and we can't live without them or sometimes live with them. If all their electrons were paired up, they'd be stable. But some have one electron which is unpaired and are always looking to strip an electron from a nearby molecule to make up the pair. And that neighbor then takes one from another, and so it goes on and on. It's a chain reaction that's great for sending signals throughout our bodies or making long molecules, such as for polythene. But it's also highly destructive if unchecked. And it's when the free radicals have free rein that they're linked to disease and cell damage. Sometimes they've been blamed for the entire aging process, so that's contested. With me to discuss free radicals are Nick Lane, Professor of Evolutionary Biochemistry at University College London, Anna Croft, Associate Professor at the Department of Chemical and Environmental Engineering at the University of Nottingham and Mike Murphy Professor of Mitochondrial Redox Biology at Cambridge University

[Melvyn Bragg] Nick Lane, can you define what a free radical is?

[Nick Lane] Yes. It's really any atom or molecule that has a single unpaired electron. So usually electrons like to be in pairs. They're far more kind of comfortable as a pair. And if you have a single unpaired electron, it really wants to either find a partner and push itself onto another molecule or grab another electron from somewhere else, and so it then forms a pair, but it leaves that other molecule with a single unpaired electron, which is why you have these chain reactions.

[Melvyn Bragg] Can you give ...the listeners some idea of the number of transitions that might be going on in this industrial plant which is inside our skin? The number, the size of the cells, the number, and all that sort [of thing]... just give us a context there?

[Nick Lane] Well, there are something in the order of 50 trillion cells in the human body. Inside those cells, there are usually hundreds, if not thousands, of mitochondria. The mitochondria are the places where respiration is taking place, and respiration is where we're burning food in oxygen. And a lot of the free radicals that we produce are effectively reactive bits of oxygen, and we're producing a lot. We don't really know exactly how much, but in the order of probably in a year, certainly grams, if not kilograms worth of free radicals.

[Melvyn Bragg] What do we need to know about oxygen for this discussion?

[Nick Lane] Well, oxygen itself, funnily enough, is a free radical in its stable state. And curiously, that's one of the reasons why it's not so reactive. They don't always have to be reactive. I mean, it's easy to think of free radicals as being reactive, but oxygen is very reactive if you can feed it one electron at a time, and something like iron will do that, which is why things rust so easily. But mostly it's not reactive enough to yank electrons out from other places, and so we can have an atmosphere full of oxygen and coexist with it. And if it, if you [did] have slightly more reactive forms of oxygen, you could never have an atmosphere that's composed of 21% of oxygen.

[Melvyn Bragg] How much of this is going on? How much of this yanking, as you use a word which is very helpful,... how much of this yanking of electrons is going on as we're talking now?

[Nick Lane] Well, it depends a lot on just how much oxygen there is. So in our cells, the level of oxygen is much, much lower than it is in the atmosphere. We're down around about one to 5% of the oxygen that's in the atmosphere is getting through to the mitochondria, possibly even less than that. And so the original experiments that were done to try and work out what's the quantity of free radicals that are produced were done usually in cell cultures sitting there under the atmosphere of oxygen. And the answer was lots and lots... we would be producing if those calculations were correct, in the order of hundreds of kilograms a year. But because the levels are so much lower inside our cells, we actually produce vanishingly small amounts, probably, and that's why we now think in terms of signalling rather than just pathology.

[Melvyn Bragg] Are we in an area where there's much more research to be done, although a lot of exciting things are known?

[Nick Lane] Yes, there's always a lot more to know, but I think in the case of free radicals, we're actually right at the beginning, ... of our understanding of how they're acting in normal physiological circumstances. We've had 50 years of studying them as pathology, as something going wrong, as something destructive, and they do do all of that, but we've had much less time and it's much more difficult to study, to try to understand, well, how are they influencing the normal workings of the cell by signalling slight changes in, I suppose, the flux; the normal flux of how respiration is working, how you're making new molecules, new building blocks, new DNA, new proteins and so on. All of this is controlled by a kind-of steady state of production of free radicals.

[Melvyn Bragg] I hope we'll come back to signalling a bit later, but to cover a bit more basic ground. Anna Croft, how were they, how and when were they discovered, these free radicals?

[Anna Croft] So radicals were kind-of known about, or kind-of hypothesized in probably the 1800s already. And I think the breakthrough with respect to carbon based radicals, as opposed to the radicals of oxygen, came in 1900, when a guy called Moses Gomberg created a molecule that seemed to be incredibly reactive, but yet still stable. And this was triphenylmethyl radical. Lots of people had been trying to make derivatives and he really hypothesized at that point that these were carbon based species that would contain a radical and would be stable. So Moses was quite an interesting person. He came from the Ukraine and moved across to America, to Michigan in the late 1800s, and worked with some of the leaders in the field in Germany before going back and making this very stable molecule. He was originally trying to get a degree in physics, and he turned up to try and get into the program at Michigan and was thrown out because he didn't know enough trigonometry. So he showed up three days later and was tested again, and he'd learnt all that trigonometry, so he was a really clever guy.

[Melvyn Bragg] When he discovered this free radical in the first place, was this thought to be in his area of science in that world, ... a "eureka" moment? At last we cracked something very important? Here's a new area of science?

[Anna Croft] I think it was a new area of science, and in fact, on his paper, where he put down, he actually, what was quite common at the time, put down something along the lines that says, "I hereby claim this entire field for myself".

[Melvyn Bragg] [laughter] Imagine a poet saying, "I hearby claim all poetry for myself"!

[Anna Croft] Yes, something along those lines...

[Melvyn Bragg] I wonder about that really, it might have a good consequence..[laughter]

[Anna Croft] But I don't think he actually realized how important this would all become. So it was fairly controversial early on, but then, by about the 1920s, people had managed to make methyl radical, which is one of the smallest carbon radicals that you can make. And building up on that work came radical polymerisation, which then has obviously major industrial impacts. So many of the polymers that we come across today. So PET, PVC, polystyrene, these are all products of radical chemistry that was developed in the 1930s and just beyond.

[Melvyn Bragg] So the first application was in plastics?

[Anna Croft] Yes.

[Melvyn Bragg] And does that take it up immediately? Did people say, whoopi, we've got a new material, we can change the world?

[Anna Croft] I think... so plastics and polymerization was developing, not just the radical form at the same time. And I think it was really during World War Two, in the post WWII era, that people really latched on to... this was a new material or new way of making materials that were very strong and robust, because one of the very good things with the carbon-based radicals, definitely, you can make very strong bonds that meant that the material itself was hard to break apart. So very robust and useful materials.

[Melvyn Bragg] Thank you. Mike Murphy, it seems that radiation sickness ... provoked interest in free radicals. What was the connection there?

[9:12]

[Mike Murphy] The connection was very interesting. As Anna and Nick have explained, radicals are important because of their great reactivity, and they're extremely reactive with all sorts of molecules. And this was used early on from the work of Moses Gomberg and other people like that, to develop this radical chemistry for polymerization. But people didn't think it was going to be involved in biology. In parallel, in the 1950s, people were very interested in the effects of radiation on the body. And it turns out...

[Melvyn Bragg] Is this anything to do with atom bombs?

[Mike Murphy] Exactly. Because what was happening is there was a lot of funding available for people to try and counteract the effects of the atomic bomb and the hydrogen bomb and the effects of radiation on humans. So in the 1940s and 50s, people were exploring, how does radiation damage the body? And one of the ways it does this is through radical reactions. What happens is this huge amount of energy coming from, say, a gamma ray, gets absorbed by the water in your body, and that makes free radicals out of the water, because water is the dominant species in your body, and those radicals then go on to react with the protein, the DNA or the lipid, and those sort of reactions propagate through and cause damage. Now, that was obviously a pathology from an external source. But what one guy called Denham Harmon noticed, which was very interesting, was that the damage associated with radiation damage to tissue was quite similar to what he was seeing with aging and with some pathologies. So he suggested back in the 1950s that maybe some of the damage in the body, particularly that associated with aging, is due to a parallel process. At that stage, we didn't realize if free radicals were present in the body at all. But then this led onto other work where people in the 1960s found an enzyme called superoxidismutase, that its only job is to stop radicals causing more damage in the body. So that suggests that they must be in the body

[Melvyn Bragg] If he made the connection between free radicals and aging, yet you said they didn't realize that free radicals were all over the body. I don't quite get it...

[Mike Murphy] Well, it was a leap of imagination on his part. So he was saying, this damage is similar. Maybe there are free radicals being produced in the body, and maybe those free radicals are contributing to aging and pathology. At the time, there was no real evidence for free radicals being present, except in a few very specialized situations.

[Melvyn Bragg] Isn't extraordinary, all this stuff going on, and then these free radicals pop up. Who knows what's going to happen next? Never mind. Let's go with this...

Mike, how do free radicals damage cells?

[Mike Murphy] What happens is that, as Nick and Anna were saying, free radicals... their major property, is [that they are] extremely reactive. And that means that as soon as they're produced, they'll react with the fat or the DNA or the protein right beside them, so they're not controlled or regulated. The other issue is that that just initiates a chain reaction, because typically, when a radical pairs up with another electron by stripping it off a protein or whatever, it makes another radical, which then can react with oxygen to form more radicals and so on. So you end up with ...

[Melvyn Bragg] When will that stop?

[Mike Murphy] Well, what will happen is that that, in theory, could propagate right the way through indefinitely. What you have is antioxidants, which act to stop that. They quench the radicals by sacrificing themselves and reacting with the radical to form another radical that's stable and not reactive. Things like vitamin E and vitamin C, the antioxidants we have in our bodies, they do that, and that way they stop this propagation of this damaging chain reaction. So it's always this kind of fight between the production of free radicals and these special protective mechanisms we have in our bodies to stop them causing more damage.

[Melvyn Bragg] So surely being over simplistic, it's a fight, isn't it? They get going and the antioxidants come in and stop them.

[Mike Murphy] Absolutely.

[Melvyn Bragg] Without anybody telling him to do that.

[Mike Murphy] Well, evolution selected the antioxidant.

[Melvyn Bragg] Yeah. Extraordinary. Nick, let's go back to.... you want to say something?

[Nick Lane] Well, one thing....

[Melvyn Bragg] I want to ask you about the theory of aging. So if you can wrap it up in a theory of aging, that would be great.

[Nick Lane] Okay, well, one difference, I suppose, between radiation poisoning, as it was seen in the 1950s, and free radicals, which have been produced in the mitochondria, which was first suggested in the 1950s, is the starting point. So with radiation, you're starting with water, and you split water and you get one of the most reactive of all free radicals, called the hydroxyl radical. And that really will react with essentially anything immediately.

[Melvyn Bragg] A promiscuous radical.

[Nick Lane] It really is promiscuous, yes. Now, with breathing, you're starting at the other end, you're starting with oxygen, and you're producing something which is much less reactive, called the superoxide radical. It sounds pretty destructive, and in fact, it's quite meek in comparison with the hydroxyl radical. And then there's another molecule in between called hydrogen peroxide, which is not technically a radical, but it's also quite reactive, moderately reactive. So you have these three intermediates between oxygen and water. And you can produce them from either end. You can produce them from oxygen or from water. And if you've got radiation poisoning, you're producing them from water essentially anywhere. Whereas if you're producing them when you're breathing from oxygen, it's in a very specific location in the cell inside the mitochondria. They're far more mild in terms of their effects. So although there's this parallel between radiation poisoning and breathing, I think the whole field had that in its frame for decades, that free radicals are just reactive. As Mike said, some of them are not. Vitamin C, vitamin E are radicals, oxygen itself is a radical, but they're all pretty stable. So there's one thing that we've learned, I suppose, over the last couple of decades is really big differences in reactivity.

[Melvyn Bragg] Anna, can I come to you about these antioxidants? How are they supposed to work? Can you tell us more about those, please?

[Anna Croft] So we've had already, Mike, describe, I guess, something like superoxide dismutase, which essentially kills off a radical process, I guess, more or less before it starts. And then, I guess, the more common antioxidants that people know about from, I guess, their diet ...

will be things like the vitamin Es and vitamin C. So vitamin E, for example, is a very fat soluble vitamin that will capture radicals within fat membranes, and so that way it will stop damage there. And it holds it in a very stable way for long enough for something like vitamin C, for example, to come and take it away. And vitamin C is very water soluble, so then can be moved along, as it were, and again holds the radical in a very stable way. And these stop this chain process by creating this sort of more stable platform that can then be, I guess, more managed in terms of getting rid of it. And we've got lots of other sort-of antioxidants that we may use either, for example, in food to make sure that food stays fresh for longer. ...And things that we have, I guess, like in green tea, we've got sort of molecules there which act as antioxidants. We have other sort of food products, although it's unclear, I think, at this stage, whether all the antioxidants that people keep getting told they should eat fruits and vegetables for are necessarily... in high enough quantities to make a huge impact. But what's very interesting is some of these antioxidant-like molecules do have different effects that we know contribute to stopping damage and aging anyway. So eat your vegetables, I think, is the moral of the story.

[Melvyn Bragg] Just in case, you mean?

[Anna Croft] Yeah, but not. Well, no. I think they do have an effect, but whether it's purely an antioxidant effect is still up for debate.

[Melvyn Bragg] Mike, can we get back to ... this theory of aging, which is very prevalent and brought up and by yourself, that it was said this is similar to what was happening in vascular dementia and so on. Can we develop that and talk about it? Because it lingered on for a very long time and still it's still...contested, but it's still not entirely deleted.

[Mike Murphy] It's a very interesting theory because it's a very beautiful theory ...very simple, in its elegance. The original free radical theory of aging was that as you age, your body is producing these damaging free radicals, and then what would happen is the free radicals would cause damage to your mitochondria and other parts of your cell. Then the damaged parts of the cell would produce more free radicals.

[Melvyn Bragg] What did they think happened before they got onto free radicals? What was happening in the body before the year 2000?

[Mike Murphy] Well, this was actually a long time ago when people were thinking these. There were many other theories for why aging occurred. Some of these were related to the number of breaths hypothesis that you could consume so many oxygen molecules, or the rate of living hypothesis, which related to how fast you're metabolizing, the idea that we have that a mouse lives two or three years, whereas a human lives 80 or 90 years. So those were some of the ideas that rapid metabolism is associated with shorter lifespan than slow metabolism.

[Melvyn Bragg] So can we get back to what you were saying before I rudely interrupted you?

[Mike Murphy] No problem with that. Then this idea that you would have this damage accumulation, that then formed this kind of vicious spiral, that more damage produced more free radicals, produce more damage and so on. A beautiful theory, but the problem was that when you tested this in experimental animals, it doesn't seem to be borne out. And the original theory from Dunham Harmon was then extended in the 1970s, saying it's the mitochondrial radical production. This was tested quite recently in various mouse models. And what they could do was that they could induce damage in the mitochondria and see what would happen. And that, remarkably, produced very rapid aging. So people thought, oh, that's interesting. Maybe that damage means those mitochondria producing more free radicals, but it turns out they're not producing any large amount of free radicals. So the issue with really understanding aging is to think about how you would know if something was causing aging. It's very easy to make something live a shorter period of time - what you do is if you want to damage something, you can hit it over the head, that will kill it off. But the real test for hypothesis of something that causes aging is if you intervene in that and extend lifespan. We haven't really found any good ways directly related to free radicals and the simple idea of damage that extends lifespan. We've got many other ways that expend lifespan, and these tend to be by things like caloric restriction and nutrient sensing. And when we manipulate some of the genes involved in those processes, we can extend lifespan, and they don't seem to be related to free radical production.

[Melvyn Bragg] Nick Lane, the idea of it being an explanation for aging held on for a long time is still not... it's contested, but still not entirely eliminated, is it? Where is it at the moment?

[Nick Lane] Well, it's in some kind of limbo, I would say. I think most people now would see free radicals as being a part of aging, but not the driving cause of it. And the simple reason for that is that you add antioxidants in the hope of interfering with the process, and they've never worked. If anything, they tend to be slightly detrimental. And it's partly that the body response...

[Melvyn Bragg] Are you should not eat your vegetables, Nick? [laughter]

[Nick Lane] No, you should definitely eat your vegetables, but you should probably not take large doses of Vitamin C or Vitamin E or beta-keratin or things like that, because they can distort the balance, the body's natural balance, and you end up kind of suppressing the antioxidant enzymes, the proteins that detoxify these things. You suppress them instead. So everything you do has a kind of a counter effect in terms of physiology. And that means it's very difficult to interfere in these processes. Now, does that mean that free radicals are not relevant to aging or only just an effect of aging? I don't think so. I still think that there's some truth in the idea that free radicals are driving aging. But definitely interfering with antioxidants does not work. There's no question about that. It's the signalling and it's the.... I mentioned this word "flux" before...the rate at which we are...

[Melvyn Bragg] Can you tell us about signalling and signaling? You're big on signaling, Nick.

[Nick Lane] I think of it a little bit like a fire alarm, I suppose, or a smoke detector, perhaps, is a better analogy, that if you're over producing free radicals, it's a little bit like producing a certain amount of smoke, and you set off the fire alarm or the water sprinkler or whatever it might be. And so that adjusts the system back to where it was. So without these signals, which is to say, like the smoke, which might say "you've been infected by a bacterium, you better respond now", or "you've had some stressful episode, or something, you better respond now". These are the signals that say "danger" in effect, and if you cut them out, then you don't respond properly to the danger, and then you're more likely to be in trouble.

[Melvyn Bragg] And where does flux come in?

[Nick Lane] Well, flux is the way I think about it, I suppose, is we're breathing continuously. And as we're breathing, we are getting the energy to live, but we're also in the same process as making all the building blocks that we need to replace the contents of cells or to make hormones or...everything that goes with living. And that's a continuous process over time. And all of this time, we're producing very small amounts of free radicals, almost undetectably low amounts of them, and they're giving a kind of a balance to how healthy a cell is. It's on this kind of danger scale, and gradually, as life goes on, we get slightly further up the danger scale. Maybe it's not them by themselves. it's also everything else. How much energy do we have? How many of the building blocks themselves do we have? How healthy are the mitochondria themselves? But I think the free radicals are part of that overall health report for how a cell is doing. And if we try to fiddle with them, we tend to mess up that health report.

[Melvyn Bragg] Thank you...Anna Croft, another way free radicals use it in living things is with enzymes. Could you tell us about that?

[23:51]

[Anna Croft] Yeah. So these are, I guess, "not so free" radicals. So there are loads and loads of enzymes....

[Melvyn Bragg] On day release, you mean? [laughter]...

[Anna Croft] No, they're incarcerated, more or less, or encased within enzymes themselves, which use the power of the free radical then to do numbers of different types of reactions. And I guess we didn't quite realize how beneficial a lot of these processes were ... it wouldn't have started till even, I guess, as late as the 1970s, really. And there are processes such as with P450s, which detoxify lots of material that if you've got, like, toxins coming through, it'll get rid of

those from your liver by doing reactions there. We have things like cyclooxygenases, which make prostaglandins, which are very important in a lot of these signalling processes. And then we have a huge range of other enzymes that, for example, are involved in antibiotic synthesis, involved, we think, in defence against viruses and in making a lot of the cofactors that we actually need for everyday life. And I think in terms of one of the most important examples of where radicals are absolutely essential in order to make the stuff of life is essentially we have this very specific enzyme called ribonucleotide reductase, which in every walk of cellular life uses a radical. And that can be an oxygen based radical, as the others have described, or we have other types of radical that are generally mediated by metals in order to generate them. And this enzyme itself takes precursors that are usually used for making RNA, which is a long polymer, which is used generally for making proteins, and it makes the precursors for DNA. And without these radical processes, we wouldn't have those building blocks for DNA and we wouldn't have that sort of beautiful genetic storage that we have in all organisms that use DNA for that.

[Melvyn Bragg] Thank you very much. Mike Murphy, what's happening at the level of mitochondria?

[Mike Murphy] Well, mitochondria are particularly interesting, and it's an area that Nick has described elegantly already, that what we know about mitochondria is that they take the food that we eat and they strip electrons off that food and react with the oxygen that we breathe in. So about 95% of the oxygen that we breathe in goes to mitochondria. And the reason that that's quite important in terms of the radical production, is that people always knew that mitochondria could produce radicals. The original idea was that this was a damage process because it's a bit like a bit of copper wire with rubber insulation around it. You put an electron in on one end and it goes down the wire, and the mitochondria are like that wire, and if you scratch the rubber, then some of these electrons might leak out, react with oxygen, become free radicals. But in some areas now, we can extend this a little bit and show that it's not just random damage, it seems to be a controlled process. One of the areas that's very interesting at the moment is something called ischemia-reperfusion injury, and this occurs in heart attack or stroke. What happens is that when you block blood supply to the heart, electrons build up, and then when the oxygen comes flooding back in, say in the hospital where you unblock an artery and blood comes back in to restore life to the damaged tissue, at those few minutes, you get this burst of free radicals hit by mitochondria, that cause the heart to be damaged...

[Melvyn Bragg] Is that damage, a consequence of the cure?

[Mike Murphy] It's ironic, really, that a lot of the damage that occurs in a heart attack is that when you remove the blood clot and the oxygenated blood comes back in, inevitably that causes a lot of damage. So that's caused that reperfusion injury, where you reperfuse the tissue, is one of the most damaging aspects. We're really keen to try and understand that. But the assumption a few years ago was that damage was random damage to the mitochondria. Now, we think we understand that that is actually a process that's normally used by mitochondria to

produce free radicals, and it just gets abused during this extreme situation. And it turns out that process, we think, is involved in signalling, as Nick was saying before, but also as a way of sending on other pathways, such as in the inflammatory process, where the mitochondria are a key part of how the cell senses inflammation, because that can send out signals saying that the cell has been infected or damaged and that can switch on inflammatory processes. And coming back to the theory of aging, that may be one of the ways in which free radicals are affecting aging through altering inflammation, which is probably a key player in aging.

[Melvyn Bragg] It's wonderfully sophisticated in there, isn't it? Nick, how are free radicals a component of breathing?

[29:09]

[Nick Lane] Well, as Mike was saying, it's not so much the breathing, so much as how we process oxygen inside the mitochondria. And as they pass down this wire, they can leak out. And we originally thought years ago, with the original version of the free radical theory of aging, that effectively a fixed proportion would escape, that maybe 5% of the oxygen that we respire would actually escape as free radicals and do this damage. And it's almost certainly a lot less than that, but it also varies. So if, for example, if we're doing exercise, you're breathing maybe ten times as much oxygen, and you would think then you'd have ten times as many free radicals, but in fact, you don't have any more because the flow down, effectively the current down, the wire in the mitochondria is just faster. And so there isn't really a good correlation between the rate at which we're breathing and the rate of free radical production. And also it varies from tissue to tissue, and it varies from species to species. So birds and bats, for example, which live a surprisingly long time, relative to their metabolic rate and their body size, tend to produce fewer free radicals relative to equivalently sized mammals, like a rat or something. So this is purely correlative, but we still have this feeling that there's something about the way in which we're processing oxygen over a lifetime, which is affecting the rate at which we age. And as Mike was saying, we've moved away from the idea of direct damage, towards things like inflammation, so indirect forms of damage, but there's still this rate factor.

[Melvyn Bragg] In other words, there's more research to be done?

[Nick Lane] There's a lot more research to be done.

[Melvyn Bragg] Anna, how, with enzymes, do free radicals rid the body of toxins?

[Anna Croft] Right...so in the sort of enzymes that I was talking about earlier, the cytochrome P450s, these are really, really reactive, so ...they are able to really pull off hydrogen from very unreactive molecules. And by doing this, they can incorporate oxygen and thereby make the molecule more soluble, and thereby you can excrete that molecule from your body. So this is

one of the ways where we can remove toxic molecules from the body by doing this sort of oxidative process in order to get rid of them.

[Melvyn Bragg] Mike, how are free radicals used therapeutically?

[Mike Murphy] There are a couple of ways in which free radicals can be used therapeutically. One of the things about free radicals that we've mentioned is that they can actually cause damage to biological molecules. So in some situations, our body's cells actually use free radicals to...kill off bacteria. Some types of phagocytes that engulf bacteria, they actually produce some of these free radicals around the bacteria to try and kill off that bacteria. So that's one way in which our body naturally uses free radicals to cause damage. In addition, there are some drugs which we think could also be targeted to kill off particular types of cells. Now, radiotherapy actually works because it produces free radicals that if you can target the radiation to a particular area, the free radicals are produced there and kill off that cell locally. And hopefully, you're just killing off the cancer cell. We can extend that to cancer therapies in other ways. If you think about light often interacts with particular molecules, and it will produce a sort of free radical form of oxygen, called singlet oxygen, that's essentially a di radical that's extremely reactive. And what you can do is you can target a drug to a tumor and then you can shine laser light at that drug, and that will produce a burst of this thing called singlet oxygen that then damages the cell. So you can have the drug in your body and then you can localize the tumor just by having the laser. And the final version could be in many tumors the problem is that the core of the tumour has no blood supply. So inside ...the tumor, there's no oxygen and that [tumor is] still there and causing damage, but the traditional drugs, which require oxygen to produce free radicals, don't work. So there are some particular drugs that form other sorts of free radicals that are only stabilized in the absence of oxygen, and there they're produced just in that anaerobic environment in the centre of a tumour, and there also wreak havoc and try and kill the tumour. So a number of different ways that we can use natural or artificial free radical production to enhance therapies.

[Melvyn Bragg] Well this loops back to the original idea, one of the original ideas, that it was to do with radiation,

[Mike Murphy] Of course, yes, it's all connected.

[Melvyn Bragg] Yeah. Is there much more to be done in a therapeutic area? Do you think there will be much more ways discovered of using free radicals?

[Mike Murphy] I think there will be. Bearing in mind, at the moment, our understanding of what goes on inside our bodies, inside cells, is very crude. And the way we're using free radicals,

[Melvyn Bragg] What's crude? It's crude, what we know or it's crude, what's going on?

[Mike Murphy] It's crude about what we know and the way the tools that we're using are relatively crude, because at the moment, our therapeutic interventions tend to be to kill off that cell. So we select the cell and we try and kill off that cell. Really, if many of the important pathways in inflammation, for example, are involved in pathology and those involve mitochondrial or other types of free radicals, for those signaling pathways that Nick alluded to, we want to be able to directly intervene in those, in more subtle ways, to, say, act as anti inflammatories, for example. Those sorts of things were just scratching the surface about trying to develop new therapies.

[Nick Lane] So one aspect that I think could become very important is exactly how the mitochondria work between different individuals. So mitochondria have their own genes and they're responsible for making part of the proteins, which are part of this wire for respiration, where we're passing electrons down the wire. But half these proteins, more than half of these proteins, are encoded by genes in the nucleus, and so they have to work properly together, otherwise the wire doesn't work properly. And there can be effectively slight differences in that wiring between different individuals, and that can affect the way the signalling systems work and the way that cells respond to it and the kind of stressors that they respond to or fail to respond to. It can differ between men and women, it can differ between one tissue and another tissue, and it can differ depending on the diet. So lots of drugs will work very well for some people and be quite bad for other people. And those differences we've been thinking about in terms of genetic differences between individuals at the level of genes in the nucleus, where there's 20,000 of them, but these interactions with the genes in the mitochondria, where there are only 13 protein-coding genes in the mitochondria, but they're so central to everything that the cell is doing, that very, very subtle kind-of misinteractions there can affect the whole of the signaling and the whole way that cells work, and then ultimately tissues work, and so that will be important, I think, in the future.

[Melvyn Bragg] Can I switch from the micro to the macro? How inseparable have free radicals been to evolution? To the origin of life?

[Nick Lane] They've been hugely important to the origin of life. Probably oxygen free radicals...[are] probably not particularly important to the origin of life.

[Melvyn Bragg] We're talking about 2-3 billion years...

[Nick Lane] Yeah, 4 billion years ago, for the origin of life. But oxygen ... began to build up in the atmosphere from around about 2.2 billion years ago. And again, it's a long time ago, we don't really know exactly what happened. There were kind-of calamitous stories of bacteria dying out as a result of being poisoned by oxygen. There's some truth in that they adapted to it. And we

can see the way in which cells have adapted. We can see that in our own cells as well, that a lot of these systems that we can find in bacteria... Mike mentioned superoxide dismutase as an enzyme. It's all across the whole of life... even things like body size. There were periods where oxygen levels may have been higher, may have been as high as 30% in the carboniferous period, 300 million years ago. Again, we don't know for sure, but we see at that time giant dragonflies in the fossil record. And there is some very nice work suggesting that one of the reasons they can get larger is that that effectively lowers the amount of oxygen in the tracheal tubes that are supplying oxygen to the tissues themselves to the flight muscles [of insects].

[Melvyn Bragg] Anna, your notes are full of enthusiasm for the positive things that free radicals do, as if you want to shake off this thing, that all they did was damage stuff. So can you tell us a bit more about that?

[37:52]

[Anna Croft] So I guess one of the things, as I've briefly said, about the enzymes, and some of these enzymes do predate the massive oxygen event that Nick was describing. So we think that because they're based on iron and sulfur, that they've built up in these undersea vents, where that was a very rich iron sulfur area, and we see those traces in enzymes all the way through from, I guess, bacteria that are still hiding under there, hiding from the oxygen into humans themselves, that actually the body has had to come up with very clever mechanisms for protecting these particular radical generating species from oxygen. And this is part of the

[Melvyn Bragg] Oxygen was seen as the enemy, was it?

[Anna Croft] In some cases, because oxygen will react with any free radical and if you have a beneficial free radical that is helping you, maybe to break down metabolic products or generate a new type of compound that you want as part of metabolism, then you need to stop oxygen from destroying it. And certainly some of the enzymes, they even harbour a free radical on the protein itself, and this needs protection from oxygen because otherwise the protein itself degrades.

[Melvyn Bragg] Are there any particular areas ... in which free radicals are having a positive role? Areas that people listening would know about - ... commonplace stuff?...

[Mike Murphy] I think the ....

[Melvyn Bragg] I mean... I'm looking for commonplace stuff. Okay?

[Mike Murphy] I think the idea that how new types of drugs will intervene in this, so with many areas of new drug development, are based on trying to understand these processes and intervene in subtle ways. We mentioned heart attack and stroke. Many of the new types of drugs that have been developed are trying to understand those processes and come in with new interventions that will block some of the damage caused by free radicals. And related to that, I think new drugs based on inflammation will also be involved in trying to understand those signalling processes caused by free radicals. So those are the areas that I think will be hopefully commonplace in years to come, but they're just emerging over the last few years.

[Melvyn Bragg] So what we're talking about.... Did you want to say something [Anna]?

[Anna Croft] Oh, well, I guess one of the things is with these radicals actually damaging bacteria as part of infection. So this is, I guess, a very tangible positive where you have the radicals coming in and they're actually doing something for the body.

[Nick Lane] And analogous to plastics we were talking about earlier on, oxygen radicals are used to make the long chain polymers that give lignin its strength in the bark of plants, for example, the connective tissues of plants. And collagen, which is really has been called the tape and glue of the animal world, but it basically holds all animals together, and again, it's a free radical process that's building these strong cross links between them. So they've been used in an extremely positive way. And for the most part, they don't cause any serious damage. It's only when there's conditions like a heart attack or something where it's out of control or the very gentle process of aging, which is kind-of uncovered by the unusually long human lifespan.

[Melvyn Bragg] Finally, Mike Murphy, are we at the beginning of the understanding the place and worth of free radicals? Is there a lot more to find out?

[Mike Murphy] I think we're just starting because it's a huge leap to go from the chemistry in a test tube and the experiments we've done up to now with, say, isolated enzymes and isolated mitochondria, to really understand how that works inside a body, inside a patient, that's a real challenge. And we're only just beginning to understand those processes now.

[Melvyn Bragg] From the body and the patient to society...

[Mike Murphy] Exactly.

[Melvyn Bragg] Yes. Well, thank you very much, Mike Murphy, Nick Lane, Anna Croft. ...Thank you very much for listening.

And the in our Time podcast gets some extra time now with a few minutes of bonus material from Melvyn and his guests.

[Melvyn Bragg] Well, thank you. I mean, I understood that. [laughter] Amazing, what an education I got. Now I've got to remember it, [laughter] that's the second bit. Now, what did, what do you think? Did we miss out? Did you miss out anything? We miss out anything essential?

[Mike Murphy] There's, I guess, the free radical chemistry. One thing that people outside might be interested in is that it's actually a key part of, say, how the ozone layer works, how smog is produced. So a lot of this other aspects of radical chemistry occur in the atmosphere that we've completely bypassed. I don't know whether Anna, being a real chemist, would know more about these things.

[Anna Croft] Yeah, I'm not an atmospheric chemist, but, I mean, these are extremely important processes. And we see sort of, as you mentioned, the ozone layer, which I think is one of the big ones where that's come into play, but also, I guess, as part of air pollution. So radical formation there and the worries behind what that might be doing to both people, I guess, and other molecules generating all sorts of other,

[Mike Murphy] I think it was the chlorofluorocarbons and their disruption of the ozone layer that was because of radical chemistry going up high in the atmosphere that was disrupted by these molecules.

[Anna Croft] So this takes us back to the radiation, because, obviously, you've got much more radiation up in the atmosphere that allows those processes to happen and allows that energy to break the molecules apart in order to generate the radicals.

[Nick Lane] One thing you touched on as well, in hydrothermal vents, these iron and sulfur conditions, they produce radicals as well. And in the absence of oxygen, they're extremely important in organic chemistry in ... crafting new molecules and so on. So it's only when you have oxygen there that it becomes really dangerous. And most, I hesitate to say, "primitive" cells, but very early bacteria are absolutely stuffed full with these iron sulfur complexes. They're like little minerals, almost. And they work brilliantly, if you're in a stagnant conditions where there's no oxygen and we still use them. I mean, it's extraordinary that we still have in our mitochondria, all these little iron sulfur clusters. There's tens of thousands of them in every

single mitochondrion. And they're dangerous as hell when you've got oxygen around. But we need them because you've got to feed oxygen electrons one at a time, and iron is really good at doing that. And so they've stayed there for ... that reason. But you have this tension between carbon, which wants to have two electrons at a time, always an oxygen, which can only take one electron at a time. And effectively, life can only work if you're going between this one and two electron chemistry. And so it's there. It's a really difficult tension right at the heart of everything.

[Mike Murphy] One interesting point, moving on to a slightly different topic, is the free radical theory of aging. It's been a fascinating theory, and often you can think of theories as not just being right or wrong, but being rich and productive. And the free radical theory of aging has been very productive because it's forced us to do very interesting experiments. And as we refine our understanding, it's helped us do that a lot. Even though the classical, original view is almost certainly wrong, it's actually inspired very many new interventions that we're trying to understand. And that's been a really interesting insight from Dunham Harmon all those years ago.

[Nick Lane] Another aspect to that, in terms of the free radical theory of aging is a lot of the measurements were done at "normoxia", which is to say, under the atmosphere of 21% of oxygen,

[Melvyn Bragg] On a bench..?

[Nick Lane] On a bench. You can measure on a bench and you can measure free radicals under those conditions. But for decades, if you put those same cells at one or one, two, three, 4% oxygen, you can't measure any free radicals. We can now, because we have more sensitive technology. We really have no idea... do you need grams of these things, or milligrams or micrograms? But a theory has been built on evidence which was the best that we could do and is good, but it doesn't really tell us.... you know, we don't actually know if there's a correlation between these gram quantities of free radicals or microgram quantities of free radicals. Does it matter that it's thousands of times less in terms of the total rate of formation of these things? We don't really know that kind of question. So I won't say it's misleading, but a whole field of medicine can be kind-of questionable because of the conditions under which it was done. And those conditions are effectively the only practical conditions under which you can do it.

[Melvyn Bragg] Anna, you want to say something?

[Anna Croft] Yeah. So we also, I guess, one of the other things is this complex interplay of different molecules as well. So, interestingly, vitamin E, which we talked about earlier as an antioxidant, under certain conditions, if you haven't got the right molecules in place, can also be a pro oxidant. That means it will help to oxidize and damage things. So, again, the conditions

under which you measure things, the complexity of the system, really matters in being able to understand the exact processes that we see happening.

[Melvyn Bragg] What I liked about, and I didn't like, because you were so interesting, and we're talking about it, was, how do you do this? How do you measure this? And these are so tiny, and these trillions were rather daunting at the start, quite exciting but quite daunting. How do you measure it? What are you doing?

[Mike Murphy] Well, it's very difficult, but what you can do is you can set up situations in isolated systems where you have very sensitive detection molecules, maybe a fluorescent molecule. Extending that in vivo is quite difficult because a fluorescent molecule means you can shine light on it and emits light at a different wavelength that you can detect. That's how we would do it in cells or in isolated bits of cells. In vivo, light can't get into our body so easily. So there are a few other methods that we can use. These tend to be indirect, because the free radicals, by their nature, are very short lived. So what you tend to do...

[Melvyn Bragg] What's short lived?

It could be milliseconds or microseconds.

[Melvyn Bragg] Oh, that's short lived.

[Mike Murphy] So that's quite short lived, so if they're generated inside one part of a cell, they would usually be disappeared before they've diffused more than a few hundred nanometers... depending on the lifetime. So what you often try and do is you detect them indirectly by a footprint that they would leave behind either damage or a change in a local reaction and from that infer what was going on in vivo - in the patient or the experimental animal.

[Anna Croft] And this is one of, I guess, the difficult things, is that you see a lot of the free radical damage under certain disease conditions ... even in things like diabetes, you can see that footprint, but it doesn't necessarily mean that the radicals caused the disease. It's just... there are other processes working alongside, but we can still measure the footprint, and this is why people think that, or can come up with theories that say, okay, radicals are involved in this, that or the other, but it's all correlation, not causation.

[Nick Lane] You try and interfere in the process by throwing in antioxidants and they don't work. They don't work as you expected them to work. And the reasons for that are really very subtle. It boils back down to all of this signalling and the responses, and they throw a signal of danger and

the cell responds to quash that danger. So throwing in an antioxidant can be the worst thing to do sometimes.

[Melvyn Bragg] Are you thinking of an improvement in technology which will improve technological improvement you're looking for?

[Mike Murphy] In our lab, for example, we spend a lot of our time trying to develop better techniques to measure these things in. For example, some of the work on the heart attack that relied on mass spectrometric techniques that we were able to develop to be able to see what was happening inside the heart during a heart attack. So those sort of things... and always new techniques and new approaches give us new insights and allow us to fine tune our ideas a little bit better. But always better techniques and better measurements are a huge benefit in all areas of science, especially in these areas.

[Anna Croft] And always the cross comparison between, I guess, whole systems as you're working on, and the model systems in order to build up at least the tiny picture to work out what, what's happening as well.

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In our time with Melvyn Bragg is produced by Simon Tillotson.