Episode Transcript

Danny Lennon: Professor Paul Sharp, thank you so much for taking the time to join me on the podcast today. How are you doing?

Paul Sharp: I'm doing very well, Danny. How are you?

Danny Lennon: I'm doing great, and I'm very much excited. Can you maybe start by giving us an introduction to your academic background your work in this field and then currently what you're doing?

Paul Sharp: Yeah, sure. In the last millennium I did my first degree in in physiological sciences at the University of Newcastle, up in the northeast of England. And from there progressed to a PhD in biochemistry at St. Thomas's Hospital, which is now part of King's College London. And both of those areas I was very interested, both as an undergraduate and as a PhD student in the mechanisms that were involved in digestion and absorption of nutrients.

So from the end of the PhD, I went to a post-doctoral position at the Royal Free Hospital, again in London to work on mechanisms of carbohydrate and iron digestion and absorption in various gut models. And then really got into the sort of major academic background. And I guess my first academic position was at the University of East Anglia.

And that was quite an interesting move because that wasn't just funded and run as part of the university. Part of my remit was also to develop collaborations with what was then called the Institute for Food Research, which is now the Quadrant Institute Biosciences in Norwich. So that, that really introduced me more into the sort of mainstream of nutrition, if you like.

And then moving on from there, I was at the University of Surrey in the nutritional sciences department for four years, and I've been at King's College London since 2004 and have progressed through the ranks. I was made a full professor in 2017. And since 2016, I've been the head of Department of Nutrition and Dietetics at Kings which is the education department that delivers our undergraduate and master's level taught programs in nutrition and in dietetics.

Danny Lennon: There's a whole host to your CV when people go and look at it. And as you mentioned, some of the work that you became really well known for is some of the impacts of specific nutrients and looking at their absorption. And within that, there are so many different layers to that, different types of studies we can get into.

But specifically today I wanted to focus in on iron. And of course there are some relationships with other minerals here that we may bring up. And this has a number of important implications, not only at a cellular level, but now big conversations that are happening in nutrition around sustainability of different types of diets and food sources. So I think quite a pertinent question at this time.

So before we get into any of the details I guess again, to bring everyone up to speed, how would you introduce them to why iron is such an important nutrient to consider? What are some of the primary functions in the body? And why is this often formed as such a crucial nutrient to consider?

Paul Sharp: So I guess that the most people will know that the main reasons that we need iron are for a number of different metabolic functions. Probably the main one is for the synthesis of hemoglobin, which circulates in our red cells and is the oxygen transport molecule that delivers oxygen to all the metabolically active tissues.

We have a related protein in the body called myoglobin. Which is the oxygen storage molecule that you find typically in skeletal muscle. We need iron also for energy production. So the cytochromes, which are part of the electron transport chain, which is the final processing metabolism that converts the energy that we derive from the metabolism of the macronutrients from carbohydrates, proteins, and fats, ultimately into the main energy molecule ATP, and that transport of electrons in the mitochondria that allows the generation of ATP, those complexes in their contained cytochromes.

And those are also iron dependent enzyme processes. So typically we would need iron for all of those different metabolic processes. And you can see quite quickly if somebody becomes iron deficient, then the main symptoms that you would see in an adult, for example, would be lethargy, lack of physical activity, poor work performance, and those tie in directly to perhaps the reduced activity of the cytochomes reduced capacity of the red blood cells to deliver oxygen to the metabolically active tissues.

And it's estimated that if we want to look at the instance of iron deficiency worldwide, then it's the most common nutritional deficiency disorder globally. It's estimated that may be a third of the world's population are iron deficient. Similar number of people globally have anemia and about 50% of anemia cases globally are directly attributable to iron deficiency. So it is a major problem worldwide in terms of metabolic health.

Danny Lennon: Yeah. And there's a number of different kind of sub-components I'm sure we'll circle back to later of what you just said. I did want to touch a bit on metabolism and iron homeostasis for a moment. And at the risk of this may being too broad a question for people that first come across this, we're struck with this very odd situation almost, where, as you've just noted, iron is this very crucial mineral for our health. But then on the flip side, if we have too much of it could be toxic. And we'll certainly maybe get into some of the effects of too much iron. But it seems that we don't really have a really effective way of getting rid of some of that. And so it speaks this critical or delicate nature of homeostasis in humans. I'm wondering, can you just speak a bit more to that and elaborate on iron homeostasis and some of the main things people should be aware of?

Paul Sharp: Yeah, sure. So I think, going directly to what you said, that there are no defined excretory mechanisms to get rid of excess iron from the body.

So the control of iron homeostasis really takes place at the level of the intestine in the amount that we absorb from diet.

And if we think about the mechanisms that are involved in iron absorption it's quite interesting. When I first started working on iron metabolism if I tried to produce a cellular model showing all the different transporters and enzymes that are involved in the absorption of iron, then it would've been a pretty blank box, so we only actually characterized the first iron transporter, the one that's responsible for the absorption of iron from the intestinal lumen, taking the iron into the cells lining the intestine.

That was only first cloned and characterized in 1997. So I guess, the whole field of. Iron metabolism and the understanding of iron absorption is really young in nutritional and biochemical terms. But what we do know is that there are two forms of iron that we find in the diet.

We have heme iron. And I mentioned earlier the heme molecules; they're hemoglobin and myoglobin. So typically we would get our heme from animal tissues, animal products, and obviously if you are vegetarian or vegan, then heme won't be a component of your diet. And we absorb what we call non-heme iron. And that covers a whole range of different compounds from iron oxides, iron salts, but also the storage molecules for iron in both plants and again in animal tissues.

So we have a protein called ferritin that stores up to 4,500 atoms of iron. And it's the main storage protein in all cells; in plants and in animals. And we can release the iron from ferritin and we can absorb that in the intestine through a transporter that is known as the divalent metal transporter or DMT-1. And that sits on the luminal membrane of the enterocytes in the duodenum. And one of the features of DMT one is that it is what we call a proton coupled transporter.

So it needs acid to drive the absorption of iron. And it's localization is ideally situated for that. It's right in the proximal part of the duodenum, which is the first part of the small intestine. So it's receiving the acidic outflow from the stomach. Acid makes iron more soluble. You've got plentiful amounts of protons there to drive the absorption of iron.

And again, what we know is that really that first part of the duodenum is the only section of the intestine in which we absorb iron efficiently. So that's the sort of mechanism for how iron crosses the membrane. But another crucial feature is that when it comes to the non-heme iron, we can only absorb it in its reduced form.

So one of the main biological functions of iron is that it can exchange its oxidation state very readily between its oxidized form, which is Fe3 or Ferric iron, and the reduced state, which is Fe2 or ferrous iron. And we can only efficiently absorb the ferrous iron. So we have to reduce the iron before we can absorb it in the intestine.

Danny Lennon: One thing that I did want to circle back to was, and this may be something that people will see if they start looking at some review papers in this area, is it's quite common to see that when it comes down to the mechanisms of absorption of heme iron and non-heme iron, at least typically it gets reported that there's an asymmetry in how much we know about each of these things. Is that currently a fair assessment of the state of things? And can you maybe speak a bit to that?

Paul Sharp: So there, there have been a number of proposed mechanisms for the absorption of heme iron. What we know is that we absorb heme intact, so we take in the entire heme molecule and dti. Inside the intersite we have an enzyme called heme oxygenase.

And that is there basically to break down those heme molecules and release the iron that's contained within the heme. I was mentioned in a few moments ago the mechanism for non-heme iron absorption that it's absorbed through this divalent metal transporter mechanism.

The interesting thing is once we get over that initial barrier to the absorption of he and non-heme, then our bodies really don't distinguish between the dietary source of iron. So the heme iron, once it's liberated from the heme molecule. It is treated metabolically in exactly the same way as the non-heme iron. So it's just that first step of absorption from the intestinal contents into the enterocytes that differentiates between the absorption of heme and non-heme.

Danny Lennon: Where are we in the state of our understanding of the actual iron requirements for humans? And of course, if we first take, let's say a Western population and we look at iron requirements, what is, number one, I suppose typically recommended? And two, how much of a clear consensus or confidence do we have in the current recommended intakes, do you think?

Paul Sharp: So we can look at that in two different ways. So the first way is to look at how much iron do we need for metabolism to maintain these the function of these different proteins and enzymes in the body.

And that is essentially a function of three components. So growth, we need iron for growth of all cells and organisms. It's quite interesting that every organism worldwide that's ever been known apart from a couple of species of bacteria have an absolute requirement for iron for growth. So it's not just humans, it's down through yeast and into bacteria that you need iron for cellular growth and cell division. So that's one of the things that we need to cover metabolically. The other one is that we lose small amounts of iron. So this is different to a regulated excretory pathway. We lose iron from cells that line the gut, line the urinary tract, skin cells, hair cells, all contain small amounts of iron.

There's nothing that we can do about that as the sort of daily renewal process of cells and tissues. We're going to lose small amounts of iron as these cells die off. They're sled off and lost into the environment. So we need to cover those losses as well to maintain our homeostasis. And then the third factor for females is that we need to cover the amount of iron that's lost as a consequence of menstrual blood loss.

So those are the three factors really that determine how much iron we require on a daily basis to meet our metabolic requirements. And that amounts to a roundabout for an adult male, a roundabout one milligram per day to replace these losses and these growth requirements. And for adult females around about 3 to 3.5 milligrams per day.

And then across the question is how does that translate into the amount of food iron that we are going to need to meet those metabolic requirements? And I guess this is where it gets slightly more complicated for iron and some of the minerals and other micronutrients than it would be, for example, for simple carbohydrates or proteins and fats.

Where we absorb virtually all of the easily digestible carbohydrate that we ingest in the diet, we only absorb a small fraction of iron that we ingest. And typically the estimate is that it could be between 10 to 15% of the iron that we ingest, depending on what else is present in our diet. So using those estimates in the UK there are the Dietary Reference Values that have been established for iron and the, what we call the Reference Nutrient Intake, which is the amount that should satisfy the metabolic requirements of about 95% of the population. For adult males that's 8.7 milligrams of food iron per day. And for adult females it's 14.8 milligrams of food iron per day to meet those metabolic requirements.

Danny Lennon: People are probably thinking now, we've differentiated between heme and non-heme iron, and there's this difference in absorption. And it's quite common for people to hear the recommendation that, okay, if you are following a plant exclusive diet where you're not getting any heme iron, then there may be a requirement for more of that to account for this. Is that still where we would recommend and is it as straightforward and simple as that to, to work out?

Paul Sharp: Nothing's ever straightforward. So it's true if you look on a like-for-like basis that heme iron is more bioavailable, it's more readily absorbed than non-heme iron. But actually in people who eat meat on a regular basis, heme is still only a relatively small amount of their dietary intake.

So it accounts for maybe five to 10% of the total amount of iron that somebody who's a meat eater will ingest. And one of the things that's often overlooked is I think that people often think that all of the iron that's present in meat is heme iron. And actually more than 50% of the iron that's present in meat is non-heme. It's in proteins like ferritin. So a relatively small amount of our total iron intake comes from heme even if you are a very regular meat eater. The vast majority of the iron in everybody's diet, whether you are vegan, vegetarian, or a carnivore, comes from non-heme. So the same sort of principles apply regardless of which dietary regime you're following, in terms of the absorption; the vast majority from non-heme. And it's the non heme iron that is directly affected by other components of the diet.

Danny Lennon: So far you've mentioned that we have this average figure in terms of the typical absorption we could expect, but that is dependent on a number of factors that could perhaps increase or decrease that.

And I think there's probably going to be some dietary factors and then non dietary factors. So if we first look at some of those dietary factors, and I'm sure if people have ever experienced having low iron and they've been given dietary advice by a dietitian or otherwise, they may have came across this, but there is certain things that may enhance one's absorption of iron. Can you maybe start with some of the most well known and ones that we have the best literature on?

Paul Sharp: The factors that increase the absorption of iron tend to be factors that will favor the reduced iron state, so will favor iron being in its ferrous form. The most powerful of those agents is ascorbic acid or vitamin C, and that's a very potent reducing agent and very readily reduces the ferric iron which is the oxidized iron into the ferrous iron.

And that will make the ion available in a form in which it can be absorbed. That's the most potent of those stimulating agents. But there are also effects from other similar compounds, so other small organic acids. And thinking about things like malic acid or citric acid that we find in fruits and vegetables.

They will also favor iron being present in the ferrous state and will stimulate the absorption of iron. And to a certain extent digestion products of meat as well, carbohydrate digestion products, certainly some protein digestion products, certain amino acids. And there's some evidence that some lipid digestion products as well can also favor the absorption of iron, but by far and away ascorbic acid or vitamin C is the most potent of those factors that will stimulate the absorption of non-heme iron.

Danny Lennon: Yeah, and I certainly have some follow up questions on that but first to round things off nicely in a coherent fashion. Perhaps let's talk about some of the things that could inhibit iron absorption. And there's probably a few important ones here because this will have implications for some questions later on. But what are the primary compounds or nutrients that we tend to associate with inhibiting iron absorption?

Paul Sharp: Yeah, so one of the things that I tell the students when I'm talking about iron we talk about the main dietary sources of iron, particularly in the UK diet. And I give them a basically quick quiz question of whether they think that most of the iron comes from red meat or from green vegetables, or from cereals or from beer, particularly Guinness? And we get a fair spread; not

many people choose the Guinness. But there's a fair spread of people who think that green vegetables, particularly things like spinach are important sources of iron a lot will think that it's red meat and probably half the class think that it's cereals and cereal products.

And of course they're right: about 50% of our iron on a daily basis comes from cereals and cereal products. The reason I tell them this is be to highlight that the main inhibitory factor that can limit the amount of iron that we absorb the amount of non-heme iron that we absorb is a molecule called phytic acid.

And phytic acid is abundant in cereals and cereal products. So we've got this paradox where we've got the main dietary source of iron, also contains the most potent inhibitor of iron absorption. And again, there are other things that can inhibit iron absorption. So there are oxalates, which are another group of organic acids, they will readily bind iron and other similar divalent metals, so things like calcium and will stop the absorption of that. There are polyphenolic compounds, I'm sure most of your listeners will be familiar with polyphenols that are present in various fruits and vegetables, but they're also very good at binding iron and stopping it being absorbed. And to a certain extent, there's some evidence that calcium might be involved in the inhibition of iron absorption. That might be to do with forming a tighter complex with things like the phytates so that the iron's even more tightly bound and less available for absorption.

Danny Lennon: And something when it comes to some practical recommendations that we'll get to later I'll have some questions about how maybe the influences things can be changed via cooking methods and preparation and so on. But for now, for maybe more of a question for those really interested in nutrition science and understanding that when you look at this literature, there's an interesting discrepancy that sometimes comes up that goes beyond this field, really into everywhere nutrition of looking at mechanisms versus outcomes.

And so in relation to any of the things to do with inhibition or enhancing of iron absorption, there can be this discrepancy between what we see in a acute single meal study and looking mechanistically what's happening at iron versus a whole dietary pattern or a whole diet intervention with "harder" outcomes. Can you be speak to some of this discrepancy? How much of an issue that is, and then potential reasons why we see this crop up.

Paul Sharp: And I think that's a really important point that you raised in terms of the nutrition science studies that have been carried out. A lot of the studies that have looked at the mechanisms and the factors that increase iron absorption or inhibit its absorption have come from single meal studies or looking at one compound and how that affects the absorption of iron.

Absolutely, when you look at these acute studies, you can see quite clearly that meals that are rich in ascorbic acid and low in phytic acid, then the fractional absorption of iron will be much higher. And if you flip that on its head that you've got a meal that's high in phytic acid, but low in ascorbic acid, then the absorption of iron, the fractional absorption of iron will be decreased.

The complexity comes when you try and reproduce that over a period of time. So you have a long-term intervention over a period of weeks and months where you're feeding meals that are rich in ascorbic acid or meals that are rich in phytic acid. And what you tend to find at the end of that inter intervention period is there's no net effect on iron absorption.

So there is quite a ready acute effect on absorption. But the longer term implications mean that things tend to go back to the normal resting state. And perhaps one of the reasons for that is that we're actually very good at adapting. Are mechanisms of absorption. So if we need iron on an acute basis, then we can increase that quite rapidly.

But over a period of time, if we've started to build up our iron stores, then the net effect of a longer term intervention isn't going to be as manifest as it would be in a single meal acute study. So we do tend to, once we've got to the sort of limit of our stores, if you like, once we've replenished our stores, then we're not going to see any further benefits in terms of those meals that are rich in ascorbic acid or rich in phytic acid.

Danny Lennon: Yeah, I think that's a really important piece of context for people to keep in mind when trying to look at some of this literature. So if we can continue on with some of these factors that can influence absorption maybe beyond just specific nutrients that have been included in that.

We've mentioned so far one of the areas that you have published in and has been quite interesting reading is in relation to zinc. And zinc in itself is quite

interesting, and we could probably spend a whole podcast talking about that and the absorption there. But for it's relationship with iron, it seems that there's at least some degree of an association with zinc status and iron homeostasis.

And there's this maybe coexistence of deficiencies in certain populations we see, but what do we actually know about this relationship between them and what to this point has been worked out? And what do you think is the best way to. Think about this relationship sh should I say, in relation to how that might impact iron status?

Paul Sharp: So I think if we go back to the the discovery of the the DMT-1 transporter back in 1997 one of the reasons it was called a divalent metal transporter is that the protein was thought to transport multiple metals, and it would naturally facilitate the interaction between those metals at the level of absorption and you would get competition perhaps between iron and zinc or iron and some of the other developent metals.

One of the things that we shared early on back in the early 2000s was that there isn't competition between iron and zinc at the level of the divalent metal transporter. So they use completely different transport processes. One thing that is certainly the case is in populations that are iron deficient, there will quite often also be zinc deficient, and there seems to be a beneficial effect of giving zinc supplements as well as iron supplements on things like the repletion of hemoglobin, so the ability of the bone marrow to produce new red cells and utilize efficiently the iron that's been absorbed from supplemental sources.

And so some of the mechanisms of those interactions have been looked at in a little bit more detail. There seem to be effects of zinc. on the expression of the developent metal transporter and on some of the other enzymes that are involved in iron absorption. And I think this really comes down to zinc is a really important signaling molecule.

So we think of zinc as just a mineral. And we need it for growth and we need it for immune function. At the cellular level, it's a really important signaling protein. And what we've been able to show, at least in cell culture models, in some animal models in collaboration with colleagues in India, is that zinc can enhance the activity of some of those intracellular signaling cascades that

are important in ultimately modifying gene expression. So zinc seems to, for example, interact quite readily with the PI3 kinase signaling pathway. And that's perhaps some of the ways that zinc can influence the absorption and utilization of iron.

Danny Lennon: Do we see genetic differences in iron absorption capabilities relative to these typical numbers we've talked about so far related to any of those potential mechanisms? Is there a genetic variation here? If so, how wide is this? What do we currently know in, in that area?

Paul Sharp: So there certainly are genetic variations that can affect the way that we absorb and metabolize iron. Perhaps the best known of those is hereditary hemochromatosis, which is very common in Northern Europe particularly in Scandinavia and in Ireland. Where as many as one in 10 of the Northern European Caucasian population can carry a mutation in a gene that's present in the liver that can lead to hyper absorption of iron.

So we're absorbing much more iron than we actually need for metabolic purposes, and that can lead to deposition of iron in the liver and can ultimately lead to fibrosis and cirrhosis and liver cancer but also affects a number of other different organs in the body.

So that's perhaps the main example of a dysregulation in metabolism that can stimulate the absorption of iron. There are also a number of other rarer inborn errors of metabolism that can affect iron absorption. So there are mutations that have been documented in the the dive developent metal transporter that can influence how much iron we absorb from the diet and how much we utilize.

There are also mutations identified in the iron export protein which we haven't mentioned so far, which is a protein called ferroportin. And you find that on all iron absorbing and iron metabolizing cells it's the only way that iron can efficiently get out of cells to be utilized. So there are those inborn errors of metabolism, but by far and away the most important genetic component to iron metabolism is this link with hereditary hemochromatosis.

Danny Lennon: Something that I think gets looked at for every nutrient because of the way we absorb nutrients and because of the field itself and the hype around looking at things like probiotics and prebiotics. Iron is no

stranger here either, that this has been something where there's been some initial interest and at least some early trials to, to my understanding, what's the current state of that literature? Is there anything strong that suggests that there could be any meaningful impact? Or what is the best way to think of that literature?

Paul Sharp: I think it's fairly mixed. I think that there may be effects of some of the pre and probiotics on absorption of iron in the small intestine. Really some of the work has looked at whether these modifying agents, whether it's adding directly the gut bacteria, whether it's adding compounds that can influence the growth of gut bacteria looking to see whether that can affect iron absorption in the colon. And really there's no evidence that there's significant amounts of iron that's absorbed in the colon.

So there, there may well be some indirect benefits of modifying the gut microflora on the way that we absorb and metabolize iron. But really the jury's out in terms of direct effects on the absorption in the small intestine directly attributed to these pre and probiotic factors.

Danny Lennon: To circle back to supplementation, because this is a particularly important topic and is incredibly common. And as you've outlined, the problems with both iron deficiency or even suboptimal iron status is quite significant and can be quite a pressing issue for people to attend to. Of course, for someone that has maybe just slightly out of range iron, it's possible that through dietary changes that can be brought back up.

But that is a slower process and more often than not, if people get a test and then are going to be placed on supplementation or other forms, which we maybe can go back to. But if we look at supplementation, first of all, do we see different forms of iron used here in supplements? If so, what are maybe some of those main differences? And in terms of an effectiveness or efficacy, is there a particular form or type of supplement which tends to be considered the best using clinical practice?

Paul Sharp: People who are prescribed supplements and you should be prescribed them by a GP or some medical practitioner. They are prescribed because that person is anemic. The way that you would measure that is by measuring their hemoglobin levels in blood. And that's actually probably the worst biomarker that you can measure in terms of iron status because it's the

endpoint measurement. You've basically gone through the situation of iron deficiency and have arrived at your full-blown clinical anemia.

And at that stage, you need to intervene quite dramatically to try and restore the iron levels in the body. So the gold standard supplement, I guess the one that's been used forever, is ferrous sulfate. It's used because it's relatively soluble and it's quite readily absorbed. There are other iron salts that are used, so ferrous fumarates. Various conjugations with amino acids; so there's ferrous bisglycinate compound that's used. They're all essentially serving the same purpose. They're trying to deliver iron in a bioavailable form that would be readily absorbed by the intestine.

The big question, comes with the amount that's prescribed in these supplements. So typically you would be getting 65 milligrams of iron within a clinically prescribed supplement, and that is a huge amount of iron. If we think about that in terms of diet, that is a week's worth of iron in one go. We've only got a finite capacity to absorb by the intestines. So actually yes, some of that supplement will be absorbed, but actually there's going to be a lot of it that is just going to pass straight from the small intestine and into the colon.

And we go back to the gut bacteria issue. Now there are species of bacteria in the colon that are specifically target iron. They're iron sulfur bacteria. So one of the common side effects for people who take these high dose iron supplements is not only the nausea and the gut pain that they can induce, but also the fact that they'll start to notice very quickly that they've got black tarry stools.

And that's directly due to the production of iron sulfide by these iron sulfur bacteria. So actually the compliance with these very high dose iron supplements is limited because people don't like the side effects. And that really roses the question of whether, we should be looking at different dosing regimens for the use of iron supplements.

Whether we give lower dose forms of iron, whether we give the same dose on a twice weekly basis rather than on a daily basis, or whether it's some combination of those different regimens. But I think, we've used this high dose supplementation protocol for many years and maybe it's something that needs to be looked at.

Danny Lennon: Yeah. This is an interesting question because as you've outlined, if we have significant side effects here, and maybe that leads to a loss of adherence to taking the supplement or even if someone persists with it, it's not nice for them to have that degree of side effect. And so this question of if we use alternate day (dosing) that I've seen looked at, or there's even more intermittent use of that. Could we still get status bumped up to an appreciable meaningful degree? Does that line of research look promising that yes, you actually can do so with these more sparse intakes?

Paul Sharp: I think it does. And there, there's some work by Michael Zimmerman's group in in Zurich, and they've looked quite carefully now at different levels of iron given in supplements, whether you can give it daily or twice daily if it's a smaller dose or whether you can give it every other day.

If you're using a slightly higher dose and what they see from those studies is that actually the rate of absorption, the amount of iron that you absorb if you give a lower dose iron supplement every other day is at least equivalent, if not better, than giving a single high dose supplement on a daily basis and one of the reasons for that is that if you overload your gut with iron, you get a phenomenon that's called mucosal block. And basically what that means in a nutshell is that you completely swamp the transporters that are responsible for the absorption of iron. And they will down-regulate, they will move away from the cell membrane.

And it can take up to 24 to 36 hours for those transporters to move back towards the cell membrane. So if you take a really high dose supplement, the chances are that the next time you have a meal containing iron, you won't derive any benefit from it. You will only absorb a limited amount of that iron because you've downregulated those transporters.

And at a more systemic level what we also know is if you give these high dose iron supplements, then you induce the production of an iron regulatory peptide that's produced in the liver, that's called hepcidin. And hepcidin is the main systemic regulator of iron metabolism. It basically locks iron up inside cells.

When you've got high levels of hepcidin, it binds to this ferroportin transporter, which I mentioned previously is the only known efflux protein; the only way the iron can get out of cells. Hepcidin binds to that ferroportin

transporter and basically blocks the efflux of iron out of cells and back into the circulation for utilization in the different metabolically active tissues.

Danny Lennon: And again, correct me if I'm wrong, we have these two issues that can are doubly problematic that when we have this daily very high intake of iron: first of all, you said with this high level you can get this at least acute downregulation of iron absorption. And so it may benefit then to have that spaced out more because you're not really getting an added benefit from going high dose every day. But on top of the downregulation and absorption, you get this production of hepcidin, which is essentially keeping the iron that is there locked up. So it can't be used in the tissues as we would wish.

Paul Sharp: That's absolutely right. Yeah.

Danny Lennon: One of the other interesting questions that comes up and in both in clinical practice and has been looked at maybe in the literature relation to supplementation, is in cases where people do have low iron status are put on a consistent supplement regime and it doesn't really seem to budge their iron status much. From cases like this, do we know if these people are actually true non-responders to supplementation or is there something else going on that's preventing their iron status from improving?

Paul Sharp: It's likely that people who aren't responding to oral iron supplementation have something else that's causing their low iron status or causing their anemia. And I mentioned right at the start that about 50% of the cases of anemia were due directly to iron deficiency. The other 50% are due to anemia that results from chronic inflammation. The way that we should treat those diseases is completely different. So iron deficiency anemia, we can give all reliant supplements and they tend to be absorbed, and you can restore the iron status, the iron homeostasis of the body.

In anemia of chronic disease, you've got very high circulating levels of cytokines, so these pro-inflammatory molecules, you've also, again, got high levels of hepcidin. So hepcidin isn't just induced by high intake of iron, it's also induced by inflammation. And again the hepcidin will be to block the recycling of iron through macrophages, which the the cells that are responsible for digesting are senescent and aging red blood cells and recycling the iron.

And it also blocks the absorption of iron from the gut. So basically it will bind to ferroportin in the intestine and stop you absorbing the iron. So there's likely to be other underlying causes of the the anemia that you see in some of the other population. It doesn't just have to be people who've got a notifiable chronic disease, so people with kidney disease or arthritis or cancers, it can be at the level of somebody who's overweight. So we know that obesity is basically a state of chronic low grade inflammation, and in people who are overweight, we also see high levels of hepcidin that can affect the ability to absorb iron from the diet, but also from oral iron supplementation

Danny Lennon: At a more population level, the use of food fortification. And as you noted right at the bat, if we look at most of the general population the primary or where we're getting a large proportion of our dietary iron is from cereals and otherwise. And food fortification seems to be an interesting and important route to look at because of the widespread consumption of the products that we're trying to fortify.

And then also going into the future of, people are looking at things like changing overall dietary patterns. Are we going to make sure that we're not doing so to the detriment of something like someone's iron status? H how widespread, first of all, do we. Iron in terms of food fortification, and what is the things that we know so far from those larger programs that have been put in place?

Paul Sharp: In the UK we, we have an Act of Parliament called the Bread and Flower Regulations, which were initially set up after the Second World War that require the fortification of white wheat flour with iron, calcium, thymine, and niacin. And that basically recognizes the fact that when you produce white flour, you are removing the outer brand layers and some of the other more superficial structures.

And that's where most of the iron and calcium reside. So essentially as you produce white flour, what you're doing is denuding that flour of iron. So there's this mandatory requirement to add 1.65 milligrams of iron into white flour to basically restore the iron level back to what you would see perhaps in a whole wheat flour.

The question then is how bioavailable, how easy is it to absorb the iron? And one of the issues if you're going to do a countrywide fortification is that you

need to use a relatively cheap form of iron and something that's not going to have sensory characteristics. So you don't want your bread to taste of iron, you don't want the product to be discolored, you don't want it to reduce the shelf life of your product.

So we tend to use something in the UK that's fairly inert, it's elemental iron. To think about it in a different way, it's essentially iron filings; it's just a ground iron powder. And that meets all of those characteristics that are required: it's a very pale, gray color. It doesn't taste of anything.

Part of the reason for that is that it's not very soluble. And of course if you're going to absorb iron, you need it to be in solution. And if it's not in solution, you're not going to absorb it. So there's a big question about whether there's any efficacy associated with the fortification programs. And there's some evidence from Scandinavia where they've, I think in Denmark they stopped fortifying with iron, and in Sweden they started fortifying with iron. And they saw in Sweden when they started fortifying, there was an initial benefit of the iron fortification that has now regressed back to the sort of normal situation. So there were fewer cases of iron deficiency and now they seem to have gone back to the original resting state before fortification was implemented.

And in Denmark, when they stopped fortifying, basically it had no effect on the number of cases of iron deficiency. So there are big questions about whether we're using the most or a suitable bioavailable form of iron for these countrywide fortification programs. And I guess that opens up the question of, how can we do it?

One of the things that we've been looking at in our research more recently is whether we can actually make the iron that's present in cereals more bioavailable. And one of the limiting factors too, iron bioavailability in wheat, for example, is that the cells that contain the iron. Those cell walls are very resistant to digestion in the gut.

So we can ingest a whole wheat flour with the cell fraction that contains the iron and it'll pass through the gut and be excreted in feces. So the amount of iron that we can absorb is quite limited. And one of the things that we've been looking at is to see whether we can "micro mill"; we can micronize the flour. Basically to break up and the cell walls with the hope that the iron would be more available for absorption so that endogenous iron perhaps

could be utilized better and absorbed better. And I can't tell you the answer to that at the moment. I'm afraid that's still ongoing work.

Danny Lennon: I look forward to seeing some publications on that in the future. But essentially with this process, you are attempting to have this barrier of the cell wall taken care of to some degree so that more of the iron is available. D oes that change much, the characteristic of the actual whole wheat? Would we consider it just the exact same? What is the best way for people to view that?

Paul Sharp: So we've done some studies looking at what happens to to bread when we bake it using this micronized flour versus a standard milled flour. And there are differences in the the volume of the loaf. So the micronized flour produces a slightly denser loaf. And I guess, what we'd have to do before we could take that much further is work out whether that was something that would be a barrier to the public perception. Would it spoil their enjoyment? The change in perhaps the texture and the mouth feel of the bread?

Yeah. So experimentally it looks quite interesting, but obviously, to, to roll that out on a more commercial basis that would need a lot more sensory type studies about whether that was acceptable to a population.

Danny Lennon: That's actually a nice segue to maybe my final question before we start wrapping up here. And that was in relation to future research questions in this area or anything related to iron in the diet or otherwise that we've discussed today. And this could be from your group or others, but to you, what are some open research questions now that you think over the next number of years there could be hopefully some work done that would hopefully shine some answers on what would be ones you'd like to see some answers to?

Paul Sharp: There's a lot of work going on looking at biofortification, whether we can basically select varieties of rice or maize or wheats that naturally have higher levels of iron in them than the ones that are currently grown for commercial purposes. A lot of that has been in low and middle income countries trying to improve the the intake of buy-in, but also of zinc and of vitamin A.

But that's something that really could translate, I think, to more developed countries like the UK. The use of alternative crops that might have higher endogenous levels of minerals. And of course that would beg the question then about whether those minerals were bioavailable. I think the oth the other big question that will be addressed over the next few years is how we get around a growing population that really wants to consume meat.

And the development of the the plant-based meat substitutes is going to be a really interesting sort of area to follow and hopefully to work in as well. Whether we can get plant-based meats or alternatives that have high levels of iron that's also highly bioavailable. I think that's going to be another big area for growth in the the food industry and in nutrition science.

Danny Lennon: Professor Sharp, for anyone who is interested in finding you or your work on the internet, are there any places on social media, websites et cetera, that you'd like to send their attention? Where are some places that they can find out more about you and your work?

Paul Sharp: So if you want to read a very sort of basic introduction to iron and some of the other important minerals that are in the diet, that there's a chapter that I have written in a textbook called Human Nutrition, edited by Catherine Geisler and Hillary Powers. And I think that's just up for a another edition coming up maybe next year. On social media, you can follow me at SharpProfessor (Twitter) . And there are some links to some of the work that we've done there. There's a webinar that's on the the British Nutrition Foundation website which was not just about the work that we're doing on Iron, but was in general about food processing and whether that's always a bad thing. So it's called "NutriBabble: is natural or always best?" And basically discusses iron, but also some of the other work that's been going on at Kings in terms of looking at legumes and how they might control carbohydrate digestion and absorption, and also interest certified fats and how they might be used by the food industry.

Yeah, there are links on PubMed. You can also look up on the King's College website. We've got a repository called Pure. So if you look at KCL Pure, and I guess I can send you the link to that, Danny, and you can perhaps, post that in the notes. It will give a link to all of the the recent work that we've published looking at iron metabolism both at the cell and molecular level, but also some of the more applied aspects that we've talked about today.

Danny Lennon: Fantastic. Yes. And for everyone listening, all of that will be linked up in, in the show notes and I'll pick out some of the particular publications that relate to much of what we've discussed as well as everything else Professor Sharp has just mentioned. So with that, we come to the very final question I always end the podcast on, if you could advise people to do one thing each day that would have a positive impact on any area of their life. What might that one thing be?

Paul Sharp: I'm going to throw away the iron and I'm going to put my head of department hat on and I think it's looking after mental wellbeing. I think in particular during the the covid pandemic as we, we change the way that we work. A lot of us now, when we used to commute, so my commute into London used to take me about an hour and 20 minutes each way. And that was really useful as d downtime when you are preparing for the day ahead, thinking perhaps about a lecture that you're going to be giving. And also reflecting on how the day had gone on the way home. That really now has just become additional working time as we, we're still working in this hybrid model and we see it with academic staff, but also with students and the sense of isolation that they felt throughout the pandemic.

And I think that there tends to be this approach now; everybody's back at work, that's all in the past and it really isn't. I think the effects on mental health and mental wellbeing are going to be seen for a number of years to come. So what I would ask people to do is take time for yourself, step away from your computer, have lunch in a completely different environment. Try and get out and go for a walk in the fresh air every day. And I think that is a way that we can be nice to ourselves and look after our mental health a little bit better.

Danny Lennon: Extremely well said. With that professor Paul Sharp, thank you so much, first of all for giving up your time to come and talk to me today. I've really enjoyed this conversation and really enjoyed reading a lot of your work.

Paul Sharp: Thanks, Danny. It was a great pleasure.