Academy of PHYSICAL MEDICINE

Transcript

Cryotherapy
With Colin Brown

APM: My guest this evening has been an analytical chemist for the last 30 years, looking primarily into pharmaceutical products and in particular, the method of delivery of those products whether it would be by pill, injection, topical products and so on. For 11 of those years, he's worked with a company called Mentholatum which I think you may be surprised to learn that you know more about than you think. In that company, he has acted as their research and development head for a number of years and he's travelled down from Scotland to be with us this evening. Colin Brown, welcome to our studio.

CB: Thank you.

APM: You've traveled down from Scotland where it's pretty damn cold, you said. I'm freezing in this studio and you think it's lovely and temperate. Good. You've been in R and D at Mentholatum for a long time. What does that job entail exactly?

CB: Well, I have a group of about 25 staff, most of them are scientists and the remit is very broad. So we're looking at research and development in the conventional sense, looking at new products, looking at generating claims for existing products, the legal and scientific affairs of the company, the safety of the products such as pharmacovigilance and all the quality aspects of the products that we manufacture and produce for our consumers.

APM: Now, we know that we are going to be talking about Mentholatum's products quite extensively this evening for reasons which will become very, very apparent but in terms of pharmacovigilance, yours are topical products and that's not something we would normally associate with topical products. This is something we would think of as being medical devices like pacemakers or drugs such as anti-inflammatory, steroids. Yours are creams, gels, sprays. Why are they subject to these controls?

CB: Well, some of the products that we have are licensed medicines and some are medical devices and in either case, we have a responsibility and a duty of care to make sure that the products are safe in normal use. So we're constantly reviewing the intelligence that comes from the normal use of those products

from consumers and looking to refine the instructions, the label instructions on the packs to make sure that they're used safely.

APM: What's the difference between a medical product and a medical device then?

CB: So a licensed medicine requires a marketing authorization from the Medicines and Healthcare Products Regulatory Agency in the UK, the medicines agency who have to be persuaded that a product works pharmacologically and in doing so, it's safe, efficacious and is made to the appropriate quality. A medical device is similar but different. It must work principally by a physical action rather than a pharmacological one but it may be assisted in the action by a secondary pharmacological action. So a medical device works by a physical effect.

APM: What sort of things are we talking about?

CB: So within our product range, we have products branded as Deep Freeze. We have a patch, a spray and a gel and all three of those products are classified as medical devices because they work principally by the evaporation of solvent. So that's how they exert their cooling effect.

APM: What else would constitute a medical device? These are level one medical devices you said —

CB: Class one medical devices, yes.

APM: Class one.

CB: So that's represented to have the lowest risk to the user on normal use and it goes up to class 2A, class 2B and then the highest regulated class represents the highest risk to the user, class three and those would be things like a pacemaker, for example, which is an invasive device.

APM: You mentioned Deep Freeze. You left out Deep Heat which is also one of your products. That's not a medical device then.

CB: Well, some…Deep Heat is a brand. So within the brand, it's called an umbrella brand and within that brand, we have medical devices and medicine. So the Deep Heat, known and loved by many people in sports changing rooms, comes either as a rub or as a spray and both of those are licensed medicines. There's another one called Deep Heat Maximum Strength which is a licensed medicine but we also have Deep Heat Patch and that's a charcoal activated patch which is applied direct to the skin but it's a medical device because it works principally, simply by heat transfer. So it's a principle physical effect.

APM: Our viewers this evening are primarily physical therapists. So, you know, for years and years and years, we have been using or advising our patients to use ice or heat or a combination of the two and for all the years I've been in this business, I have done that rather on what I think is a hit and miss basis because I'm not actually seeing very much evidence for this. What is the history

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towards advising people to use let's just say hot and cold for now rather than particular products or devices?

CB: Well, I think you're right to say that there hasn't been a lot of evidence. There have been lots of reviews, lots of meta-analysis of clinical trials and various other data and the general consensus is that there isn't a consensus. So there is a lot of confusion. I think what we do know is that everyone, at some stage, will suffer from a soft tissue injury or will know someone who has and we know that consumers understand that there are topical hot products and topical cold products but we also understand that there's a lack of clarity in the mind of the consumer about the correct circumstances in which they should use hot or cold. We also find this from GPs, pharmacists and other health care professionals who contact our organization looking for advice for the right circumstances in which to use hot or cold.

APM: So pharmacists as well are not well informed about what should be applied and I can imagine why there's been little research done because frankly, people will say, "Well, I can get a bag of ice out of the fridge, the freezer and stick that on my leg if that's what I've injured," or, "I can warm up a hot water bottle and use that. So why should I waste money looking at products or medical devices to do the same thing?" And is that the approach that you find that physical therapists are taking, "Get some ice. Get a hot water bottle"?

CB: Yes, and some people will say, "Take some ice," but of course, practically speaking, ice isn't always available. So people will be looking for some alternative to ice, something that's going to cool but I do accept that in order to make a recommendation, professionals will want to recommend something that they can put stock in because they're persuaded and compelled by the evidence that supports the use of that product.

APM: And of course, Mentholatum have an interest…your company has an interest in selling a product. So there's got to be something in that for you, hasn't it? There's got to be something that…there's a return on the investment that you put into the trials that are necessary to satisfy not just the regulatory authorities but the public and the professionals and the public who are using this.

CB: Yes, of course. It's not entirely a philanthropic exercise—

APM: Of course not.

CB: --to do these studies but what we do want to do genuinely is to inform the consumer and to inform the recommender in some cases that the products that we're offering have a purpose, have an efficacy and in specific circumstances are appropriate for use.

APM: Now, you're a chemist and you've admitted of not being a biochemist but can you tell us what is the theory behind the application of heat or cold to an injured muscle?

CB: Sure. We tried to communicate this by talking about healing. So when

someone has a traumatic injury, there are three phases to recovery. The first phase is inflammation which is the body's natural response to an incident of trauma. The second phase is one called proliferation and the third one which the physiotherapist will be well aware of but the public tend not to be and that's called remodeling.

APM: You don't offend anybody because I'm sure the osteopaths and chiropractors—

CB: Osteopaths.

APM: --and the sports therapists will all be very familiar with those terms.

CB: Beg your pardon. No offense intended. But physiotherapists, of course, are involved in the manipulation of soft tissue in order to prevent recurrence of an injury. So in looking at each of those three phases in turn, it's easier to compartmentalize the use of cold or hot. So our recommendation is to use cold when someone first experiences an acute injury and cold can be used for up to 72 hours. If you think about why cold would be applied, that's a very important part in the understanding of what we're seeking to achieve by using cold. The tissue's damaged. The body's natural response is to flood that area with inflammatory markers to control and to start the healing process.

APM: So it could be bleeding as well, of course.

CB: Could be bleeding, yes, of course. What cooling is going to seek to do is to minimize blood loss in damaged tissue because blood loss will equate to stiffness, swelling, pain and —

APM: Stiffness because of the swelling and the compression of the muscle fibers.

CB: Exactly. So the tissue physically has less volume available for it to move. So that's not ideal. What we're looking to do in that case is to use cold, so that, we apply vasoconstriction. By applying vasoconstriction, the consequence of that is that blood has its viscosity changed. So its viscosity increases as a result of cold. Cold is a well-known pain relieving mechanism but one of the points I'm really keen to communicate is that cold isn't only about analgesia. It's not just about pain relief. There's a physical function to cold and to heat that can't simply be delivered by products that are only providing pain relief such as non-steroidal anti-inflammatory drugs, for example.

APM: Do you remember…I said that I had very little training in…I felt very inadequate training in advising on cold and heat. I attended one lecture by Professor Tim Watson who is a physiotherapist at University of Hertfordshire. I remember him saying that he would say cold for 24 hours to get that vasoconstriction effect so that the blood vessels could heal. Thereafter, you wanted as much blood as possible to provide nutrients and wash through the inflammatory exudates and so on. You're saying 72 hours?

CB: Yes. So the published literature is recommending 72 hours and the purpose of

that is to make sure that the small blood vessels are entirely intact again because if heat is introduced too quickly, the original situation will be exacerbated. The condition's clearly going to worsen and that will cause the patient a longer time to recover to normal function.

APM: You said something that we all assume and that is that cold has an analgesic effect. What's the mechanism?

CB: Well, cold triggers a nervous response on the skin and there are specific receptors on the skin which are responsible for the perception of hot and cold and that mechanism is described as counter-irritation through the pain gate. So I think most people will be familiar with the pain gate mechanism and by flooding the sensory system with different senses other than pain, pain is diminished.

APM: So we established that in the first phase, in the inflammatory phase, we need cold on the skin to cause vasoconstriction. It will also cause a bit of pain gating. So it's reducing the pain felt, experienced by the casualty. How long do you need the cold on there for?

CB: The interesting point here is it's very difficult to determine that because thus far, nobody can quantify what cold really means. Cold is —

APM: I know. That's the next question, isn't it? What's cold? Is it ice or is it just cool water or…?

CB: Indeed. So cold has no specific meaning. That's a relative term and individuals will perceive cold to different extents. We all know that when we get into our bath. Someone will feel a bath to be very hot. Someone else will feel it to be not quite so hot. So that's a perception which is very difficult to gauge. We do know that cold is beneficial and we're told to use cold in first aid. Government tells us to do that. The National Health Service —

APM: That's quite different from us knowing that it actually works is in fact, we're being told to do it.

CB: No, I accept that but one of the endeavors that we've embarked upon is as a campaign to generate object of data to make such arguments compelling. People may say, "Well, you would say that, wouldn't you?" because our products are efficacious but people want evidence, people…and the best kind of evidence, of course, is objective evidence.

APM: And, you know, I'm not apologizing to anybody if we're getting a company representative in here. You've got a history of research and development and investigation objectively. The company you worked for before was —

CB: It was a company called Syntex Pharmaceuticals that then became a contract research organization called Quintiles.

APM: Quintiles, that's it. So I mean…and their job was to do objective research for

pharmaceuticals. So they weren't paid to get the right results, if I could use the words that way.

CB: Well, definitely.

APM: Well, it's so unheard of, is it? You know, there's plenty of evidence of pharmaceutical companies engineering research to get the results that they need or hiding the research that they didn't like.

CB: I don't think there's plenty of evidence. I think there have been some…

APM: A fish out of book or two for you, if you like.

CB: I think there have been some examples of that and I think in every walk of life. There are less scrupulous organizations than others, of course, some bad eggs but generally, the environment of which pharmaceutical companies are operating, it's heavily regulated.

APM: But then we're talking about objective research and so you've got a background in objective research. And when Mentholatum are doing research, how are you maintaining that objectivity?

CB: We're using instrumentation and pioneering techniques increasingly in order to generate data. The instruments tell us the answer to rather than asking people what they think might be happening to them.

APM: Well, we'll come back to the latest research in a little while. Let's go back to the mechanisms and the duration and so on. Given that you've just admitted that we don't really know what cold is and we don't really have any data on which to base our prescription of cold for treating the inflammatory phase of an injury, what do you say to people? How often do they apply cold and for how long and at what basis do you make that advice?

CB: What we say to them, first of all is understand that a joint or a piece of soft tissue in the body is inflamed and how do you tell if it's inflamed and a GP will be told that there are four signs of inflammation in addition to range of motion loss which are calor, dolor, rubor, tumor, classically. So in other words, calor being heat and we ask people to check the application site to determine with the back of the non-dominant hand if they feel warmth. If it's warm, assume that it's inflamed and if it's inflamed, apply cold until they can feel the cold no longer. So it may be 24 hours. It could be 48, 72 but when there is heat residual, we should assume it's inflamed and while it's inflamed, we shouldn't be applying heat.

APM: Back of the non-dominant hand. Never heard that before. That's because…?

CB: Just because it's a different temperature from the dominant hand.

APM: But even so, you said apply cold until you don't feel that heat. Well, you know, constantly? Foot in a bucket of ice water for 24 hours?

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CB: Well, you certainly won't be able to tolerate ice for 24 hours but the products that we have are designed to be able to offer different levels of cooling. So some may act quite aggressively for a short period of time, others will provide a lower level of cooling, in other words less cooling but for a longer period of time, more consistently and depending in the circumstances, the site of the body, the extent of the injury, all of those things will be factored into the advice that's given.

APM: Moving on then to the proliferation and remodeling phases. So what's the difference in the advice then? We're moving on to heat now.

CB: We are. So at this point, assuming that there is no residual heat and there's no longer an inflamed site, our recommendation is that people use heat and the purpose of doing that, as you increase the metabolism again of the injured site and the injured cells…I should've said in cold, the metabolism of cells is reduced and that's incredibly advantageous because there's a secondary so called hypoxic effect on cells that causes additional damage to the site in a traumatic injury, simply because of swelling and the lack of oxygen that's available to the healthy tissues. They become starved —

APM: So reduced metabolism means less demand for oxygen —

CB: That's right. So the supply and demand is attenuated. We want to do the opposite of that one when we apply heat. We want to increase blood flow to cause a vasodilation and that assumes that other capillaries and other tissues are intact and during this proliferation phase, the body is determined to put scar tissue down and it does so in a fairly haphazard way and a disorganized way. So we end up with piece of scar tissue which is important in the third remodeling phase. I'll come back to that but heating becomes very important in transporting nutrients and oxygen to the damaged site in order to help that healing process, proliferate, as the name suggests.

APM: It was very popular, it still I believe, to recommend contrast bathing and in my training, it was always start with cold and finish with cold and alternate as much as you like in between. Does that mean that that's just somebody trying to get the best of all worlds despite the different needs of the different phases or is there a role for it?

CB: There may be a role for it. Although there's no empirical evidence that we can find in the published literature to support its use, that doesn't mean that it's not effective. It just means there's no evidence. And so we are not recommending contrast therapy simply because we don't, yet, understand the magnitude of hot or cold and the extent of which they should be contrasted.

APM: But it would seem to fly in the face of the biophysical description of what's going on and if you've got damaged tissue, you don't want vasodilation so why put any hot on at all? And if you've got tissue that needs a greater blood flow, why apply cold to it? So, you know, that seems to indicate that contrast bathing is never going to be useful.

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CB: It's not going to be useful in a traumatic injury, for sure but some people may find it useful. For example, in episodes of arthritis where the non-inflammatory phase of arthritis, people can experience pain without inflammation and it may be the contrast between hot and cold and a pumping system that that's purported to generate may be beneficial but there's no empirical evidence that we can find in the literature for it.

APM: I do remember being told that actually, when you apply cold, for the first…I think it's seven minutes, you achieve vasodilation but thereafter, you get…sorry, vasoconstriction. Thereafter, you get vasodilation. So if you leave cold on for long enough, you will get vasodilation which would then seen to achieve what the heat was doing but also, still apply the analgesic effect.

CB: The difficulty with that though is that the definition of cold is ill-defined. So if someone were to apply extreme cold then there will be a demand on the body to return to homeostasis to try and scavenge back to the original starting temperature. However, with small decreases in temperature, the lowering of the temperature moderate way, that's very unlikely to trigger that hunting response.

APM: And you said you call it a hunting response earlier on. This is the body looking for…you know, homeostatic way for some sort of balance but overshooting you described it I think earlier on.

CB: So it oscillates too much in the opposite direction and that, of course, can be counterproductive and this attempt, this oscillation continues as long as the therapy continues. So I think there's reasonably good evidence in the published literature now to suggest that excessive cold is not desirable because it produces this hunting response which is not desirable in our —

APM: And do you know if that research did define what they meant by excessive cold?

CB: The absolute temperatures are defined in some cases and not on others and the modalities of the site are defined in most cases and the durations vary wildly which is why we're not subscribing to that point of view until we generate evidence of our own.

APM: Excuse me, which is going to be difficult, isn't it? Because there are so many variables in all of this and of course…now, I don't know anything about the finances of Mentholatum but you're not a massive drug producing company. I should imagine that the amount of research that you can afford to generate for this is fairly limited given the margins on the products. I'm not going to ask you to comment on that because that's an assumption I'm making but we have got a question from the audience. Someone has asked, "Has anyone studied the difference between using cold or heat in different areas of the body to get better responses?" And they give the example that they've had good response from cold in low back pain but not for acute cervical pain.

CB: It's a very important question too as some of the information that I'm going to talk about later on will reveal that. You mentioned, as the…I think is implied in the question from the viewer that there are so many variables, age, sex, muscle-fat ratio in the body, a whole series of factors and of course, location on the body where the product is being applied. These are all variables that make defining hot or cold very, very challenging. Together with the…let's call it the dose of hot or cold, unlike in medicine which is clearly defined, the application of something subjective is ill-defined and one of the quests that we're trying to embark upon just now is to quantify that to a much greater degree.

APM: I think I probably should apologize to the audience at this stage because the train seems to be much louder than usual and much more frequent than we've experienced in the past and I'll apologize for that. We'll try to speak up through it but also to reassure you that we are looking at other venues that we can use, other studios that we can use where we don't suffer that problem. At the moment, we're kind of tied to the studio we're using for technical reasons but we will try to overcome that. In the meantime, you and I will try to speak a little bit louder. OK, so in terms of the research that's going on, what are you doing at the moment to pursue this sort of objective evidence that we need?

CB: We have extended our reach as an organization by collaborating with research institutions and universities. Some universities in Scotland, we have a very close relationship with now and we're also sponsoring, for the first time as an organization, PhD studentships which, of course, are three-year programs, looking at pioneering technology in medical imaging techniques which will allow us to generate non-invasive, harmless to the patient, and objective measures of the effectiveness of these products and to demonstrate that topical applications aren't simply about pain relief and they're not simply about superficial effects, that they actually do more. They have a physical action which is penetrating. That's very important as a compelling argument for someone to recommend a product.

APM: Well, let's have a look at the products now, shall we? Because I mean people are going to be very familiar with these products, I'm sure and they are products which…they're in every rugby changing room. They're on every football field, at the side of the pitch. What's the range of topical products that we're talking about?

CB: Within the range, we have a product brand called Deep Freeze and that comes in three different formats currently. One is a spray, the magic sponge, if you like that's used on football and rugby pitches and for acute injury and that's pain relieving. That's a medical device. We have a Deep Freeze Pain Relief Cold Gel which is, as the name suggests, a topical gel, an aqueous alcoholic gel which is applied to the skin and we have a patch product called Deep Freeze Pain Relief Cold Patch.

APM: Held in place by?

CB: It's just an adhesive substrate that holds it in place.

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APM: That's part of the product, is it?

CB: Yes.

APM: So we'll have a look at these. We've got some on the table here.

CB: So this is the spray product.

APM: Now, as you say, I've always been really suspicious of this because, you know, I have acted at the side of rugby pitches as the injury, sports injuries chap as well as the osteopath. You see football coaches rushing on with these things or physiotherapists rushing on with these things and a quick squirt of this on somebody who's theoretically pulled a hamstring. Now, it'd have to be a very, very minor tear for this to do any good on the pitch if the guy's going to carry on work, isn't it? Wouldn't it?

CB: My colleagues in the marketing team will talk about "Spray On, Play on". That's the message that is tried to be portrayed —

APM: By Mentholatum?

CB: By Mentholatum, yeah and in the absence of ice, not…certainly in an amateur setting, not everyone has ice bags available at the side. So the philosophy then is to use something that's going to be pain relieving and allow that person to get on and continue with the sporting activity, whatever that is. So the principle of how that…as a vapo-coolant product, it contains organic solvents which when applied to the skin together with water causes a cooling and evaporative effect which is a physical action which makes it a medical device.

APM: And this has been thoroughly researched?

CB: It has been thoroughly researched and is being even more thoroughly researched at the moment and I've got some information which I can show you later.

APM: So what about…you mentioned patches. What have we got in the way of patches that do the same thing?

CB: So this is the patch product.

APM: Let's have a look at this.

CB: It comes in a foil pouch and the patches are folded inside there with a re-sealable —

APM: And what does it contain?

CB: So it's a fabric cloth which has a gelatinous aqueous base and that is adhesive and it's applied with some compression because the application of that in itself

causes occlusion of the skin and that adds to the penetrative cooling that it delivers.

APM: And this has nothing to do with sports injuries but I mean it sounds very like the sort of thing you would apply to a burn if you had a burn dressing, for example, except that it wouldn't be adhesive. Is that the same mechanism?

CB: They'll be the same mechanism but we, of course, for our products can't recommend them on broken skin. So they certainly wouldn't be using that on a burn.

APM: And you said you had a gel as well.

CB: And this is an example of a gel.

APM: Now, I've always thought with gels, whether they be heat or cold, that most of the beneficial effect comes from rubbing them in.

CB: Well, we can —

APM: This is long before I met you, I have to say. So what's your answer to that?

CB: It's always something that's a challenge to conventional thinking because people do have this received wisdom that the physical act of massage has some positive therapeutic effect and it may well have but we are conducting…we have conducted studies and we're conducting studies that show that any effect of massage are corrected for and extended by these other products. So it's not simply the act of massage that's causing the efficacy.

APM: This one, the patch here has got an expiry date of April 2018 on it. What happens in 2018 in April? Is there something —

CB: Well, we have this part of our data package to satisfy the regulators. We have to justify the shelf life and the stability studies that we conduct support a shelf life for three years.

APM: So what are the corresponding products for your heat products?

CB: So we have…in the same order, we have a heat spray which is a licensed medicine. It contains four active ingredients and it causes vasodilation when it's applied to the skin. So it doesn't feel cold in the way that the cold spray does. In fact, initially, the user may feel it cold because of the same evaporative effects but that's very transient and ephemeral, for a few seconds. The so called rubefacient effect of the active ingredients causes local vasodilation and that begins a cascade of penetrative heat.

APM: I've always been puzzled by this how something, which is not hot, can make the user feel heat and this is primarily through the vasodilation and then is that irritation of the skin? Is that sending what the brain perceives as a heat signal —

CB: Exactly.

APM: But if you put the back of your non-dominant hand against the skin when that had been applied, would it feel heat?

CB: Not initially, it wouldn't but subsequently, it does and we've shown in an infrared thermometry and thermography studies that the absolute temperature on the surface of the skin does rise considerably.

APM: Who's using the spray then? Because I can see that, you know, your physio or your sports injury therapist on a football field is going to rush on and spray somebody with this because it's nice and easy and you can't strap ice to people if they're going to carry on playing football but they're also not going to do this because it's an acute injury. Therefore, we don't want heat. So why would you use the spray as opposed to the other products?

CB: Well, vasodilation ultimately results in a change in the vascularity of the underlying tissue which causes that soft tissue to become suppler, more extensible and that's less likely to result in someone suffering an injury.

APM: But you'll get this with the other products as well. So why use the spray since —

CB: Yeah.

APM: Time is of the essence when you run onto the picture of an injured football player. In the latest stages of injury, time is not of the essence. You've got the time to rub in a cream or apply a patch or whatever. Is it just convenience that people want to use the spray?

CB: Some of it's personal preference. Some people perceive the heat from the spray to be more aggressive, more aggressively hot. It is convenient because there's nothing being applied by the hand. So there's no need to wash the hands afterwards and it is also quite convenient for those difficult to reach areas of the body such as the back and so on.

APM: The other products, the gels and the patches for heat?

CB: So this is Deep Heat Rub—

APM: Deep Heat Rub.

CB: --which is very well known —

APM: Anyone who's been anywhere near a rugby or a football changing room would be familiar with the smell of this stuff, I'm sure.

CB: And that's a licensed medicine which we manufacture in our own facility in Scotland.

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APM: It's a licensed medicine because it has pharmacological properties?

CB: Correct.

APM: But it's an over the shelf medicine because —

CB: Yes. It's over the counter. It doesn't require supervision from a physician. So someone will self-diagnose that they require to use this product and they will go and purchase it.

APM: Sorry, just…yeah. I just had to have a reassuring sniff of Deep Heat because I quite like this stuff. Right and we've got a patch and I'm not going to open that because it's presumably pretty much the same as the blue one.

CB: It's actually quite fundamentally different from the blue one. The patch has itself a pouch. So it would look like a large plaster and it's got an adhesive layer in the way that a plaster does and that applies direct to the skin and it delivers a controlled amount of heat which we measure by temperature at about 43^{o}C to direct to the skin and it lasts for about eight hours, that perception of heat.

APM: And it says, "Open here," is it? Tear open or —

CB: Yes, so when you…tear like that. So when you open it, it's being manufactured in an oxygen-free environment and the pouch that you've just opened is hermetically sealed. So as soon as oxygen from the air permeates the patch, there is a classic high-school exothermic reaction that takes place —

APM: And which side goes down, do you peel this off and stick it to my skin?

CB: Yeah.

APM: I'll do that because…it can't work though because it doesn't smell.

CB: It does work.

APM: Deep Heat's no good if it doesn't smell of Deep Heat, surely but isn't that a problem? It's a problem, isn't it? Because people don't want to smell of DEEP HEAT. Personally, I like it but…

CB: Not everyone does like the smell but they like the effect. To that end, we introduced a non-medicinal version of Deep Heat quite recently which we call Deep Heat Muscle Massage Roller Ball and it comes in a roller ball format, again, for convenience, to allow the person to massage it directly and without using the hands. So if people remember the deodorants from some time ago with the roller ball, it's a similar format —

APM: Which is what you've got here.

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CB: Exactly. So that there doesn't contain the same active ingredients that cause the heating which are pharmacological in basis. This is heating by a different mechanism and —

APM: Why?

CB: The chemistry, there's not a pharmacological action —

APM: Then why did you choose to go down that different route?

CB: Because some people like the warming effect but don't like the smell. So this has got a completely different fragrance and the smell of this product is more herbal and therefore, for some sections of the population, particularly with ladies who may want to benefit from the effects of heat, they won't want to smell perhaps in the office of Deep Heat.

APM: Actually, there's quite a lot of other times when even the hardiest of blokes would not want to go around smelling of Deep Heat, don't they? So I'm not feeling any heat from this yet but I'm —

CB: So it takes about five minutes to warm up.

APM: I'm living in expectation. I've had some questions. This one is, "Leaving aside the situations when using a bag of peas is not possible, real cold is more effective, is it not?" So why spend money on gels when these gels really just make you feel cold? There's plenty of other ways of feeling cold. We probably need to look at some of your latest slides for this, don't we?

CB: Probably. What I would say is that a product, of course, is a controlled entity, something which can be reproduced and therefore, the control mechanisms and its manufacturer allow it to give a performance repeatedly. If someone takes something else that's cold that's not a product that's not been designed to do that job, then the performance is going to vary each time they use it.

APM: There are other products on the market, particularly cold products. I mean would one of our viewers…would a physical therapist looking for a product for their patients be able to discern which products are going to have a better therapeutic result? Because we're interested, obviously, in the clinical outcomes here. So why would…I'm trying not to put you in a position of having to criticize any of your competitors but what should we be looking for in a product which claims to give you that therapeutic approach…result from heat or cold?

CB: So I certainly don't want to denigrate any of the competitor products but rather speak more positively about the evidence that we are generating as a company. That's very important to us because we do want to persuade the user the correct circumstances in which they should use a product rather than a different product. Even if that's a different one of our products, it's really important that the person gets the benefit, the intended outcome from the use of a product. The only way to do that is to generate data and ultimately, those

data will be translated into consumer language on to the pack so that someone seeking to buy a product will be able to determine from the pack exactly what it does.

APM: You're in quite a fortunate position I think, aren't you? With Mentholatum because your Deep Heat product was devised before the regulations came in which would've made it very difficult for you to jump through the medical regulation hurtles, is that right?

CB: That's true, yes.

APM: So run us through what that means and how that came about.

CB: Well, Deep Heat, the rub product, the cream was developed in 1956 and the Medicines Act in the UK didn't come into play until the late '60s and enacted in the early '70s. So Deep Heat has a license from MHRA in the UK and in 37 other countries around Europe, Middle East and Africa. Those regulatory authorities have been persuaded that the product has the appropriate efficacy, safety profile and quality of manufacturer in order to grant a license. If someone were to set out today to develop a product to mimic Deep Heat which contains four active ingredients, the burden of proof on that company would be quite extraordinary because the regulator would demand clinical trials and efficacy to demonstrate the efficacy of each of the active ingredients and each of the active ingredients in combination to demonstrate that there's a synergy. In other words, that it's greater than the sum of its components but that would be cost prohibitive.

APM: I've been thinking about this since you first mentioned this before we went on air and I'm wondering why that's important. Surely, the critical thing about any product is its safety. It mustn't make a patient worse or any way affect their health adversely. So why is it necessary to prove the efficacy of each component? Surely, it's up to you if you want to put in a couple of components that don't do anything in your product or aren't as effective?

CB: Absolutely not. The medicines regulators would be very unhappy with that sort of opinion.

APM: But why is where I'm going for.

CB: Why —

APM: If it is safe.

CB: Sure.

APM: Because you aren't…all right, you answer the question.

CB: So a medicine has a therapeutic range. So the concentration of an active ingredient…let's envisage a medicine with one active ingredient. It has a concentration of the active ingredient so that when it's delivered to the user in

whatever form, it falls in, say, the therapeutic range and then the frequency of use determines the continuation of the effectiveness of that product. That becomes complicated when you add a 2nd, a 3rd or a 4th. So the accumulative effect of those active ingredients, if they have different mechanisms or if they have the same needs to be understood and the regulator would say that if we give someone an agent that's providing no effect then that's an unsafe medicine and therefore, wouldn't grant a license. So —

APM: That I think was the nub of what I was saying there, that the lack of an effect doesn't mean something is unsafe. It may mean it's not proven to be safe but it's not evidence that it's unsafe, is it? And isn't that creating an unfair burden on companies like yours to develop new products especially where the profit margins are not as great as they might be in drugs, for example?

CB: It's certainly creating a burden. There's a debate as to whether it's an unfair burden because ultimately, a medicine's granted a license because it does what it says most of the time although that can't be guaranteed nor can its safety be guaranteed but there's a duty on the license holder of a medicine to make sure that it minimizes the risk to the patient and that the benefit-risk ratio is in favor of the benefit. So the regulator will argue giving an active ingredient that's not efficacious as an unsafe medicine. I think everyone accepts that if we give too much of an ingredient to someone, they'll experience side effects and overdose. If you give too little, you'll have no effect and the regulator doesn't differentiate between those two entities.

APM: Well, I was going to ask, actually, when…my test would be, for the regulator, well, if I rub a bit of Deep Heat into my quadriceps since we'll be talking about those later and it doesn't hurt me and I rub a bit more and I keep on doing it until I'm rubbing a whole tube on it for a period of 10 minutes, am I going to suffer an adverse reaction?

CB: You may. Yes, you may. So we have posology that the frequency, the administration instructions for a medicine's part of the license. In other words, the condition on which the product is allowed to be marketed. And so instructions are given to the users to how best to use products. Those need to be further refined all the time. Part of a pharmacovigilance responsibility is to monitor suspected adverse events, most of these are topical skin irritation and, you know, low level burns and so on which one would expect to get from the application of topical hot or cold products.

APM: Because you could get a burn from Deep Heat.

CB: It's plausible, for sure. Anything that you apply to the skin that can cause vasodilation or increased temperature has the potential to cause —

APM: How bad could that be? Could you get what would be called an intermediate thickness or that blistered burn from it?

CB: Yeah, you can. It's possible.

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APM: So there are dosage guidelines in the packets that come with these.

CB: There are and we try…what we try to do is to constantly review those to make sure that the company and the regulator are both satisfied that the benefit to risk ratio is always in favor of the benefit. That's a license requirement.

APM: Out of curiosity then, what do they say? When should a sportsman, for arguments sake…although it could be anybody, when should they use this? How often for and how much do they put on their skin?

CB: So we recommend that they apply a thin layer because it's difficult to measure a unit dose of a topical product like a cream and we apply the product up to three times a day.

APM: Somebody has asked if there's…it might seem as a silly question but I know what's meant by this. Is there a difference in the active ingredient between Deep Heat and Deep Freeze? One you've already said, Deep Freeze works by evaporation. So it's causing cooling. I think you said earlier on that there is a chili pepper component in most heat compounds that you put on the skin. Some of them, as you said, are prescription only because the…capsicum?

CB: Capsaicin.

APM: Capsaicin component is so strong. What's the difference, precisely, between these? There's four in Deep Heat, you said and you mentioned —

CB: There's none in Deep Freeze because Deep Freeze is…well, the Deep Freeze products in that range are medical devices and as medical devices, you have to work by a physical action, not a pharmacological one. So if they did contain an active ingredient in a pharmacological sense that would be classified as a medicine or actually a class three medical device and it's neither of those.

APM: It's a mechanism which is evaporation.

CB: Correct.

APM: And the four ingredients here?

CB: So we have something called methyl salicylate, ethyl salicylate, methyl nicotinate and the fourth one which has a long name.

APM: We'll take your word for that.

CB: So those active ingredients are all vasodilating and the —

APM: Which one is the smelly one, the long one?

CB: No. Methyl nicotinate has a particular smell but actually, the salicylates all have an oil of wintergreen smell which I think is what most people would associate with the Deep Heat smell.

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APM: Of course that name, we would all associate with aspirin as well. There is a connection presumably.

CB: Yes, there is and methyl and ethyl salicylates are both aspirin-like drugs. So —

APM: What's the technical name for aspirin?

CB: Acetylsalicylic acid. And so acetylsalicylic acid —

APM: Sorry, it's sounding like a quiz, isn't it? I'm not trying to test you on your —

CB: No, not at all. Acetylsalicylic acid is the chemical name for aspirin. The active part of that when it goes into the body and is changed by the body into the thing that does the job, that is salicylic acid. That's exactly the same ingredient that methyl and ethyl salicylate convert to in the skin when you spray it on or rub it in.

APM: And that component is an anti-inflammatory component.

CB: It's a non-steroidal anti-inflammatory action, yes.

APM: So is this a non-steroidal anti-inflammatory product?

CB: It technically is.

APM: I had never realized that.

CB: So the action's non-steroidal anti-inflammatory. So it's an aspirin-like drug with four active ingredients. The other one's 2-hydroxyethyl salicylate. That's the fourth one.

APM: Good, thank you. We'll write these down in the text summary and we'll include them, hopefully, after the broadcast. A question here is about treating a chronic problem or a long-term problem such as disc prolapsed. Do you still recommend ice for 72 hours and then heat thereafter?

CB: I would go back to the default position which is if we feel that the site of injury is hot and is inflamed, we would apply cold. I would recommend cold. If it's not, we would recommend heat.

APM: That's fairly straightforward then. I find this…it's actually quite reassuring that there is a bit of evidence behind the…what was almost old wives' tales I thought we were being told when I went to training. Do you want to talk a bit about this sort of research which is currently going on in to these products?

CB: Of course. So we have conducted studies at the University of Stirling which is Department of Sports Medicine and we were looking specifically at Deep Freeze range of products, so the patch, the gel and the spray in the context of ice, as the benchmark product. And so we recruited healthy subjects and the

determination for this study was to demonstrate that topical cold has a penetrating cooling effect. In other words, they are working physically but not simply superficially. It's not a study to measure pain relief. Pain relief is well established in cold through the gate theory of pain as we've mentioned in counter irritation. However, penetrating cold is usually something that practitioners come back to us and say, 'well that doesn't really go below the surface of the skin, does it?' So we conducted a study in which we recruited healthy subjects and we measured skin temperature following the application of these products.

APM: Going back to your earlier comment, I presume these were all students. So we're talking about a very tight age demographic.

CB: We are. They were all male and they were all 18 to 24 and because they were from the Department of Sports Medicine, they were all —

APM: Quite healthy.

CB: Pretty healthy and, you know, live and toned.

APM: And I know we can't extrapolate legitimately from that population to an elderly or a female, many things like that but I'm tempted to say logic says that our physiology isn't going to differ too much. Would that be unreasonable?

CB: No, I don't think it is but I think further definition would be helpful so that we can look at different patient populations or different cohorts so that we can understand the influence of body fat, for example, or age —

APM: It's actually quite well understood, isn't it? That the very elderly respond very much differently to cold and heat. They're much less able to regulate their own body temperatures. So do you think that practitioners perhaps ought to be more cautious if they've got an elderly patient with what would otherwise be termed as sports injury but they're thinking about advising ice or Deep Heat or anything like this?

CB: For sure and also, the sensitivity of the skin in the elderly and the very young, of course, as well. It's different from…let's call them normal adults. So they are not contraindicated but special precautions need to be taken to make sure that we don't change the benefit-risk in that particular cohort.

APM: And those precautions would be?

CB: I think trying a small area first would always be a good piece of advice to make sure that if we're applying a product that that person isn't particularly desensitized to either hot or cold. With other patient population, people with Raynaud's disease, people with peripheral neuropathy, anyone who can't perceive hot or cold, we wouldn't want to be trying hot or cold products on them.

APM: Do you think that…I understand why you wouldn't want to try them particularly peripheral neuropathy. Would it still work if you could get the dose right?

CB: Certain aspects of it would work because if the heat is penetrating then…or the cold is penetrating then for sure. So it's just that person's ability to perceive hot or cold. So if someone is burning, so maybe an easier example, it's good that we can feel burning because we can do something about it. If someone is desensitized to that effect, then the risk to them is greater.

APM: This is a very interesting…I have two questions here. I'll answer the second one first. It says is my hand warm. My hand is lovely and warm, thank you. I wish I had a few more patches because the studio is actually quite cold because we don't have heat generating lights in our studio. We only have LEDs. So my hands are nice and warm.

CB: Good.

APM: Comfortably warm. The question though is if Deep Heat has similar properties to a non-steroidal anti-inflammatory, is it safe to use it if you're using non-steroidals?

CB: No, for the same reason that we…when I say no, it's very difficult to say that any medicine's safe. In fact, the regulations prevent us from making such a claim. No medicine is safe entirely. However, we contraindicate the use of other salicylates and other non-steroidal anti-inflammatories at the same time as we're applying —

APM: So if somebody's taking aspirin as a blood thinning medication, you'd say, "Don't use Deep Heat."

CB: Yes, we would say that.

APM: But they'd be alright with deep freeze because that's a device, right?

CB: Correct. An important point there is that we don't want to suggest that no active ingredient, salicylate, penetrates the skin because we know that it does and the circulating concentrations are proportionally very, very small when compared to an oral administration but nevertheless—

APM: They are there.

CB: --it's an additional incremental increase in what would be administered orally. So therefore, it's outside the scope.

APM: So in your…going back to your study, the students at Stirling University, how did you go about measuring the effect of what was taking place? And this is cryotherapy specifically, wasn't it?

CB: This was, yes, cryotherapy. So the key thing for us was to generate objective

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data. Subjective data has its place in some circumstances but it's much more compelling if you can have an independent object of measure. So we placed a thermistor on the denuded skin of each subject.

APM: We could look at this on our slide, I think, couldn't we? Which is —

CB: So here's an image.

APM: On our screen now.

CB: Here's an image of one of the subjects, the thigh has been waxed and denuded. The blue gloved hand from the investigator there is just checking the femoral artery for blood flow using ultrasound. The thermistor is the black disc that you can see with the green cable and that's measuring surface temperature. And then further down the leg, there are two fine wire thermocouples which have been inserted into one of the quadriceps. One of the fine wire thermocouples has been inserted at one centimeter depth and the other at three centimeters deep.

APM: Which answers the question why you only had 20 volunteers, doesn't it?

CB: Exactly.

APM: So the same muscle on all the volunteers?

CB: That's correct.

APM: And there were 20 of them which obviously means it's a very low power study because there's only 20 people in it.

CB: That's usually something that people challenges on but the statistical power…and I'm not a statistician but I did get advice, indeed.

APM: Thank god.

CB: The statistical power of a study is directly influenced by the object of measure that's used on it, the level of objectivity. So a classic example I would say to counter the suggestion is if you want to do a subject of assessment of pain, in other words ask —

APM: A visual indicator scale.

CB: Yeah, 1 to 10 on a scale, that's lacking in power because it's highly subjective. What is 7 out of 10? What does that mean? Even to that individual, in an hour's time, what does that mean? Let alone between individuals. So to correct for that lack of statistical power, it has to be a large number of subjects in the study. We are…objective measures are taken. You have an image; you have a data output. Those are statistically much more powerful. So the number of subjects should require in a subject…in a study, require to be much smaller.

APM: So in the slide which you've just shown, the gloved hand is measuring her blood flow through sonography. We've got temperature being measured at 1 centimeter and 3 centimeters depth in the muscle. So you're looking to find out the penetrating effect of the cold and the effect on blood flow through the muscles. Can we pick this apart for its weaknesses or defend it against those allegations? One is, of course, that it is only a small demographic. So it's 18 to 25 I think you said. It's 20 people. You justified the small number. One criticism that would be alleged perhaps is that, well, what are we comparing this with? How do you go about that?

CB: So we used ice as the standard gold, gold standard.

APM: I asked the question because, you know, in a lot of studies, drug companies notoriously are renowned for comparing their product against the wrong dose or an overdose of their competitor's products that shows up favorably. Using ice, I think is quite a strength here, isn't it? Because that is the usual best alternative.

CB: Yes, and it's the one that's recommended. So there's a presupposition that ice does something and that's why it's recommended. So ice being the benchmark and the modality of choice if ice were to be available, our interest was to compare the product penetrating effect of cold versus ice so that we can have a direct comparison but also to show that there may be a differentiation between each of our modalities. So the patch may be different from the spray which may be different from the gel.

APM: We've covered already how the gel, the patch, the spray would be administered. How is the ice administered?

CB: So the ice was applied as crushed ice in an ice pack directly over the muscle for 10 minutes and then removed. The entire study lasted, regrettably with the benefit of hindsight for only 80 minutes. That was the ethical approval that was granted and really, what we were looking to do was to look for a cause and effect. So we're looking to demonstrate here that topical application is cooling underlying tissue to a greater extent than simply a superficial effect.

APM: So one way you could have fudged the results here is by using ice for an inappropriate period of time. Why did you pick 10 minutes?

CB: Ten minutes is what we were granted ethically and 10 minutes was what was recommended to us by the Department of Sports Medicine.

APM: And I was about to say it's probably what most people would suggest to their patients, isn't it? So again, it's the usual treatment.

CB: Yeah and ice is, of course, not tolerated for very much longer than that before you start to experience unwanted effects.

APM: And throughout that, you had ice or an ice solution. So it was at 0^{o} throughout the whole time it was applied —

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CB: Yes.

APM: What did it all show then?

CB: Well, I have a series of graphs that will tell you of what the results were. So if we were to look at the flush charts here, this is the maximum skin temperature decline. So down the left-hand side here and the…on the Y axis is the temperature change and each of the four products is represented by a bar chart here. So the blue on in the left-hand side is ice and then we have…going from left to right, red is gel, green is spray and purple is patch and this is the maximum skin temperature decline and it clearly shows that skin temperature fails maximally using ice.

APM: So that could be good.

CB: That could be good. So that's perhaps an expected result.

APM: So is there a more meaningful result that we can look at beside from that one then?

CB: Well, what we found was that at the end of the 80 minutes of the assessment period, we found that the patch in purple described here was much colder than it was for ice. Remember, the ice had been removed, as would be expected and therefore, the body is determined to return the skin temperature back to its original —

APM: The patch was still on at 80 minutes.

CB: Patch was still on because the patch is intended to be worn over the affected area. So it still got moisture in it. So it's going to be wet, cold and therefore, it's likely to be beneficial for longer.

APM: Now, people might say that it's an unfair trial because you've kept the patch on for 80 minutes. You didn't keep the ice on for 80 minutes but I guess the answer to that is, well, you can't physically keep ice on for 80 minutes. You can't walk around with an ice pack strapped to your leg for that length of time.

CB: Exactly.

APM: And as you said, it probably wouldn't be tolerated because the temperature is so low. What was the temperature underneath your products here? Because these are all Mentholatum products, weren't they, that you were trying?

CB: Yes.

APM: What was the temperature under the patch as opposed to the ice?

CB: On the skin or on the muscle?

APM: Both.

CB: So the value here is that at the end of 80 minutes, the maximum decline was four degrees on the skin. At 80 minutes, the patch was about half…the ice, rather, was about half of that, about 1.4 I think that says.

APM: And deeper down?

CB: So deeper down, we've got some very encouraging results. At one centimeter depth, these are temperature profiles which are telling us for each of the four products, how they behaved at one centimeter in the muscle. So these results are being taken periodically through the duration of the assessment for up to 80 minutes and you can see on the blue chart which is the ice at one centimeter, ice is applied and those are quite a profound drop at one centimeter in the deep tissue but when ice is removed, that's the determination for the body to return heat back into that system. Because those Deep Freeze products are applied to the skin and not removed, we get a completely different profile and the one of most interest to us and the one that gave us the greatest joy, if you like, was the purple one which is for the patch and it shows that the patch is providing gradual cooling effect. It's having an effect at one centimeter in the first place which is the first time that evidence like this has been demonstrated objectively but it's also showing that it's getting toward the temperature in the muscle that was achieved by ice. The other important point here is that whereas the ice result was starting, of course, to rise again back to its original state, that's the trend. The trend for the patch is a downward one. So it still hasn't reached its platus It's quite intriguing to wonder what may have happened had this —

APM: It does look as though it's more or less leveling off there but of course, I imagine that the ice would continue to increase in temperature and I'm assuming that that endpoint there is at 80 minutes.

CB: That's right, 80 minutes.

APM: But even so, it's still convenient to wear a patch for that length of time. Which is the red one? Is that the gel?

CB: Red one's the gel.

APM: So that's actually not done too badly either. It's gone down to a lower temperature early and it stayed fairly constant. You made an assumption earlier on that a gradual decrease in temperature was better than that sudden drop that you get from the ice.

CB: It's not an assumption. It's a position. There's plenty of evidence that suggest that very rapid changes in temperature can be counterproductive. So prolonged use of very cold results in a rebound effect and the scavenger effect, the hunting effect which can be counterproductive.

APM: The ice graph is not prolonged cold, isn't it?

CB: No, it's not.

APM: It's a sudden drop but then relatively rapid and then gradual rise. Does that have that effect?

CB: I don't understand the question.

APM: Well, you said that a prolonged application of cold would lead to that hunting effect but in your grafts, the ice effect was not a prolonged application of cold. It just got down to a low temperature quickly.

CB: So had ice been left on for longer, at least the published literature would suggest that the temperature would continue to drop and therefore, the demand to return it to its normal temperature would be even more rapid. So the shape of the graph would be more extreme.

APM: Well, what can you say about where we go further with this research then?

CB: Well, this was only at one centimeter, of course and we looked at…yeah, this is a representation at the end of the study and it showed that…whereas in ice, we've got a maximum temperature drop of about 4.1 degree I think that says in Celsius, we have a very appreciable drop at one centimeter after 80 minutes of continuous wear of the path but if three centimeters deep and looking at the equivalent graph, at three centimeters deep after 80 minutes, we can see that the temperature decrease resulting from the continuous wear of the patch, actually starts to overtake the temperature achieved by ice. So that's to make a compelling case that the patch is a product that is having an effect deep in the tissue and going back to the discussion we had at the beginning, one of the desirable aims of applying cold to a traumatic condition is to try and minimize exudate, minimize swelling and you can only do that if the product is having an effect, a vascular effect deep down.

APM: So far, your graphs haven't shown any vascular effects. Simply, they've shown a temperature effect. What was the sonographer giving you at this stage? Do you know?

CB: We had no statistical difference in the vascularity change between any of the products from ice.

APM: Over the whole 80 minutes. That surprises me.

CB: So the mechanism, how this is achieved is of course…requires to be evaluated further but the hypothesis is that cooling must be the result of changes in blood flow.

APM: I suppose one question which is begged by all this is regardless of…it's very satisfying to see that ice and your products will reach a depth of three centimeters but do we know what the optimum depth is and do we know what the optimum temperature that we need at those depths is in order to achieve

the most beneficial effect?

CB: No, we don't know nor does the published literature arrive at a consensus on that. So as mentioned earlier, the dose of cold or heat hasn't been elucidated. Nobody has been able to suggest what that should be and therefore, should it be a short, sharp treatment of cold that's extreme cold for a very short period of time. Is that good? Well, it may be in some circumstances depending on the site of the body and the extent of the injury but it might be that on a different site of the body, a different dosing of cold and duration of action might be desirable.

APM: Do you know…there's some real parallels here with ultrasound therapy in that…and I don't expect that you've done any sort of in depth research into that but when we were talking to Tim Watson about ultrasound, he was saying that, you know, there are two therapeutic doses of ultrasound. One is 1 megahertz, one is 3 megahertz and the only reason that we have those doses is because they're convenient to produce though it's actually worked out what the best frequency to use is and it seems similar here, isn't it? That, you know, ice is convenient so we're using that as a benchmark but it's probably an almost impossible question to answer, isn't it? At what depth, at what temperature do we get the best result on every individual part of the body that might be injured?

CB: Yes, I think that is where we are at the moment. Our ambition though is to shed some light on that because we have other research tools at our disposal. We are looking to evaluate and to bring to bear for hot and cold applications.

APM: Is there more we should learn from your Stirling study before we go on to this?

CB: I think probably the final slide that we could look at is the one that compares the maximum intramuscular temperature change at 1 centimeter and at 3 centimeters. So you can see that whereas in the other ice gel and spray applications, the one centimeter maximum temperature fall is greater than it is at three but that's not the case in the patch study and since we know that the patch was continuing to fall and that was the trend, it would be intriguing to know what would happen had the study gone on for more than 80 minutes. So at three centimeters deep, the patch generated cooler temperatures than it did at one centimeter.

APM: That's fascinating. It's also…looking at the graph and I can't see the scale on the graph but it's not far short of the effect of ice at three centimeters either in terms of temperature drop which is, you know, very interesting and I'm sure it's reassuring to all of us who are trying to achieve the best we can for our patients. Although, you know, we come back to that surrogate endpoint thing we were talking about before and that is that we're talking here about temperatures, that doesn't necessarily relate to a clinical benefit or the best clinical benefit and earlier on, you said that the research was confusing and yet, you still are asserting, not assuming, that cold is good for you.

CB: Well, I think there's evidence that cold is good. I think we know that there's chemistry and biochemistry and physiology that tells us cold is good. The thing that people are grappling with is quantifying what cold means and what that dosage should be. What I would like to say perhaps is that this type of study also allows us to crack the particular nut that you've describe. If we can use these data in an intelligent way, we can understand what that…rather than the surrogate effect, can understand what the clinical effect is and by doing that, we can then develop intelligent products that allow us to optimize the profile in order to optimize the clinical endpoint.

APM: I need to drag you back to an earlier question, actually because we've had a follow-up to that. Someone has asked for clarification about aspirin and Deep Heat. If someone is not allowed to take aspirin, should they be prevented from using Deep Heat?

CB: Yes, and similarly, if a person was taking aspirin, they shouldn't take Deep Heat for the same reason.

APM: Slightly different question, about Deep Freeze this time. Does this need to be washed off after a certain period of time, for whatever reason, as you would remove ice after a period of time? Eighty minutes would seem to be acceptable or could you just leave it on until the effect wears off?

CB: Just leave it on. There's no requirement to wash it off, unless the person's experiencing an unwanted effect in which case, we would recommend, you know, the patches removed or the contact areas —

APM: How long do you recommend the patches, the Deep Heat patches are kept on for?

CB: The Deep Heat patches. Well, the Deep Heat patches are kept on for eight hours —

APM: And I should've asked about the freeze ones as well because you were about to tell me that.

CB: I was. The Deep Heat patches kept on for eight hours. We did a consumer study which is not our research study or the type that we're talking about here but we did ask consumers if they continued to feel the beneficial effects, what I describe the legacy effects, of having worn the heat patch.

APM: After the eight hours.

CB: After the eight hours. So wear the heat patch for eight hours. Remove the heat patch at eight hours and then report if there's any continuing legacy effect and therefore, we had a regulatory approval to make a claim that the product has a 16-hour effect, 8 of which is directly responsible from the wearing of the patch and 8 are legacy hours arising from the consequential benefit of having worn the patch.

APM: Your study would've been difficult to conduct over 18 hours, wouldn't it? Yeah. I'm not quite sure how you would do that. Final one here that's come in so far is…it's a bit of a cheeky question. Can we trust the study which is financed by the industry? Is it truly an independent and objective study?

CB: Yeah and I can understand why someone may ask that question. The study requires approval. It requires ethical approval and all of the measures that are taken are objectively measured. So we're conscious that people want evidence. I'm a scientist. You know, my raison d'etre is to generate data and objective data are far more compelling than subjective data. So anything that takes out either subjectivity or any suggestion of impropriety is attractive and there's nothing…I assure the audience there's nothing sinister in any of these studies.

APM: Now, I'm sure there isn't. I mean just because there are unethical studies being conducted or have been conducted in the past doesn't mean that any of these studies are. It's hard to see from what you've described so far how you would go about making it more objective. Perhaps we could ask some suggestions from the audience but it seems to me that you're doing the best you can because let's face it, there isn't anyone else who's going to go out there and do it for you. So it's got to be the industry that carries out the study, hasn't it? OK, so you talked about what's coming in the future then. We've got a few minutes left. So what you've talked about, less invasive studies I think.

CB: So we have a collaboration with the University of Edinburgh where we are sponsoring PhD studentships and we're looking at medical imaging techniques, the project…we've described it as Project ARTEMIS. Artemis was the Greek goddess of —

APM: Goddess of the hunt.

CB: Indeed, so which seemed appropriate but ARTEMIS is an acronym and it stands for Advance in Research and Technology with Elastography and Medical Imaging Techniques, medical imaging signs it would be in the end. So that's what ARTEMIS is for and —

APM: Is there a big committee somewhere that spends all this time working on acronyms for studies?

CB: This is entirely my fault.

APM: She was also the goddess of the moon as well.

CB: She was.

APM: Are you shooting for the moon?

CB: Well, we're shooting for something that pioneering that no one else is doing and that's an exciting area for us to be in. In all seriousness, medical imaging science is advancing all the time. We're using a technique which is genuinely

pioneering. It's only available in the musculoskeletal system in Edinburgh. That's the only research institute in the world that's using this technique for this purpose. And so therefore, we're very excited about the potential that it has for allowing us to understand exactly what our products do and being honest, what they don't do because we are asking serious questions about what our products are doing and how they're behaving. We may get answers that we don't want but I would rather, as a scientist, know those and do something about it.

APM: So can I ask, before you tell us all about what these studies are actually going to be, are they studies or are you looking at methods of conducting studies at the moment?

CB: Both.

APM: Both, OK. So for the studies, I take it you've published your objectives and your endpoints in advance so that people will know that when the results are published, they were what you intended to look for.

CB: Yes. So we don't want pilot study which we've completed and that's given us evidence and information now which allows us to go to the…if you pardon the pun, it gives us a nice, warm feeling to go to the next iteration of a study. So it allows us to evaluate more what products are doing and therefore, what they're not doing. So that allows us to focus the gun more accurately on our targets. So it's a little bit like a pyramid and we're at the base of the pyramid at the moment trying to identify the apex.

APM: So what are the mechanisms you're using?

CB: So we're working with the Clinical Research Imaging Center in Edinburgh which is our fantastic facility located in the Royal Infirmary in Edinburgh, a spanking new hospital and that image, you can see just now, is three floors of research. The top two floors are university space, for research. The middle floor's entirely dedicated to information research which, of course, is of interest to Mentholatum and the bottom floor is called the Clinical Research Imaging Center which is a shared partnership between the university and the National Health Service in Scotland and it has…because it's embedded in a clinical setting, it has some wonderful medical imaging techniques. So magnetic resonance imaging, PET scans, CAT scans and so on. Now, part of that venture was to look at a new technique called Magnetic Resonance Elastography. Now, three institutions in the world are helping to develop that technology. So it's adjunctive to magnetic resonance imaging. It uses an MRI scanner.

APM: And we can see one of those…an image that we've got up on the screen.

CB: So the top left-hand image that you can see there is an MRI scan.

APM: We're all familiar with that. There's nothing new in that.

CB: There's nothing new in that.

APM: Where does the elastography bit come in?

CB: What magnetic resonance imaging does is it show anatomy and that's very helpful in the diagnosis of tumors and various other systems in the body. Magnetic resonance elastography is measuring the viscoelastic properties of tissue and it does that using sound. So in the images, you can see here the bottom right-hand image is a carbon fiber rod which is attached to the patient's leg and that leg has got an actuator on it. At the other end of that carbon fiber pole is essentially, an exotic loudspeaker which delivers controlled sound waves at a particular amplitude and frequency.

APM: That's a seriously long pole.

CB: It's a long pole. Yes, it is a long pole and I'm sure there's good physics behind it for doing that.

APM: And how is that…that's connected to the patient. I can see that the top right image has got —

CB: It's got an actuator device there that houses the one end of the carbon fiber rod and you can see at the bottom left-hand image there, the full assembly and that person would then be rolled into the scanner.

APM: So remind me what we're measuring here?

CB: So this is measuring the viscoelastic properties of tissue. So the working hypothesis here is that whereas MRI's looking at anatomy, if someone passes sound waves through a tissue then the passage of those sound waves will alter according to the viscoelastic properties of those tissue. So if someone had, for example, a stiff tissue because of trauma or some injury or some scarring —

APM: And by stiff, we mean inability to stretch the muscle —

CB: For example, yes. So the viscosity of the muscle or the stiffness of the muscle was different from healthy tissue. Then it follows that it could be possible that applying topical heat, for example, assuming that topical heat was penetrative, might change the extensibility of that tissue and consequently, we should be able to measure the effect of topical application deep in the tissue non-invasively. Because it uses sound waves, so there's no x-rays involved, there's no ionizing radiation —

APM: And no three-centimeter long probes.

CB: No probes into people. It's non-invasive, completely. Really, we're only talking about sound and magnets. So as long as the person doesn't have a pacemaker then essentially, everyone's available to go inside a scanner.

APM: And what's the mechanism of the study? You've got somebody who has an

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injury, in this case, we're presuming quadriceps and you're going to apply a heat pack, a heat pad, take them into the MRI and monitor the changes over an 80-minute cycle?

CB: So it could be done in real time. So the idea that we have for a study using this particular technique is…for example, let's imagine someone had delayed onset muscle soreness. They're done some sort of exercise and have overexerted. It would be interesting to know that if the person applied heat prior to doing that would affect the outcome, would delay the onset of delayed onset muscle soreness or would it reduce the extent to which it develops. So in other words, a prophylactic use of a heating product.

APM: Let's talk about delayed onset muscle soreness for a little while, for a moment there because for a long time, the theory behind DOMS was that it was a buildup of lactic acid. Now, I think that's been widely dismissed in the literature now. So tell us about the mechanism for DOMS.

CB: Well, the mechanism is attributed to microtears of the very fine structures in the soft tissue. So the muscle structure…and I've got a slide I can show you at the end of this passage.

APM: I'm looking forward to it. Very good slide, that one.

CB: That shows an exquisite detailed individual muscle fiber. So if those are damaged…we're talking about small scale damages here rather than something traumatic like, you know, a sprained ankle or something which might cause swelling and bleeding and so on. We're talking about microtears and after a few hours of those and up to perhaps 48 hours, people will experience exudate and therefore, inflammation, pain and swelling.

APM: And the delay in this is caused by the fact that the tears are so microscopic that the buildup of exudate is much, much slower than in, as you say —

CB: Exactly.

APM: So dismissed the lactic acid theory and we're now looking at inflammation around microtears and again, I'm still not familiar how we're going to do this. This study here in the MRI, are you taking people who have got DOMS, for example, and sticking them in there periodically during the period after exercise to see what happens or —

CB: Yeah. So one study design could be that we assess them at baseline before they do some exercise. They apply a product, let's imagine a hot product, and then they do exercise and they should experience delayed onset muscle soreness at periods up to 48 hours or there around. By monitoring them in the scanner, periodically, we should be able to see, in real time, the microtears. We should be able to measure changes in stiffness of the affected muscle. What we've done in a study here on an image that I can show you on the screen just now, we have the rectus femoris quadricep. EIMD stands for exercise induced muscle damage. And so the image on the left-hand side is a cross-section of

the thigh. The white disc in the center is the femur which doesn't show up on MRI because it's bone and the top of the image is a white layer of fat which goes all the way around the thigh and then we have the quadriceps working down to the bottom of the image which is the hamstrings. So that's the anatomy. The rectus femoris muscle is clearly highlighted on the right-hand image there because that's after exercise induced muscle damage and the protocol is designed to deliberately target and damage that quadricep over others.

APM: When you say exercise induced muscle damage, are we talking DOMS, delayed onset muscle soreness or a more significant —

CB: It's more significant than that. Yeah, this is serious edema and pain.

APM: Sorry and this is a T2-weighted image. What we see…the white shading that we're seeing there is a buildup of fluid within the muscle as a result of that injury.

CB: Exactly. So what that shows is that by deliberately targeting and damaging a muscle, it's possible to identify differences in the anatomy of the before and after which is quite powerful but it doesn't quantify anything and this is where magnetic resonance elastography has the potential to reveal lots. So in this next image, the magnetic resonance images are overlayed with so called elastograms. So these are the outputs from magnetic resonance elastography and on —

APM: This is the echo sounding from your carbon rod.

CB: Exactly. So on the left-hand side there, not only does it have a color that colors it, it can be attributed to a scale, a bit like a weather map can or a temperature map and on the right-hand side image, the colors are different because the stiffness is different. And so therefore, for the first time, it's very possible that we will be able to quantify the extent of which damage continues or is prevented as a result of using topical products. So if a topical product is to have a deep effect and change the muscle structure deep down, this is a technique that we'd be able to identify that.

APM: When do you expect that trial to be complete?

CB: In the course of our financial year, this year which started in March through to the end of February next year.

APM: And do you have any idea how many people have been recruited into the study?

CB: We did our pilot study which looks at 20 subjects. Again, we found some statistical outcomes which were very interesting to us and we want to use those to further refine what our study might look like. So I think something of that order, 20 subjects. Again, using a placebo. In that particular pilot, we used the placebo back to the point you were making earlier about the effect of

massage. I think it's very important that a placebo is used to correct…take into account the effect of massage so that we can have a null hypothesis there. So something of the other of 20 has shown using these objective measures to generate data that of are statistically significant.

APM: And where else are we going with your research?

CB: So in the next image, what we were able to do is to…this is a simulation in this particular case and you can see it's a movie of time lapsed magnetic resonance elastograms and this is showing the passage of sound through tissue which has been deliberately stiffened or relaxed.

APM: So when this is done for real, this would be a functional MRI giving you real time feedback of what's going on in the muscle.

CB: Not functional MRI which I will come on to but this is MRI with magnetic resonance elastography superimposed and what that will allow us to do is to look at real time about the effects of either our hot or cold products, whichever we select and understand the speed of onset and the duration of action of those and the extent to which they help in limiting damage in tissue.

APM: You better get us on to your last couple of slides. I think we're rapidly running out of time here and I know you've some really interesting stuff to show.

CB: So this is an active piece of technology that we have very recently, in fact, since the beginning of May, been looking at. So we've sponsored a new PhD student at the University of Edinburgh, microwave radiology is what it's called. It was developed for breast cancer. The hypothesis of how it works is that it detects temperature and the seedlings, for want of a better phrase, of the beginnings of a malignant tumor are detectable by mammograms and the conventional ways but this non-invasive technique uses a device that measures emitted infrared heat, in other words. So what it's capable of doing is non-invasively giving us three dimensional temperature mapping of any part of the body that we choose to apply our products to and therefore, allow us to differentiate between products that we're offering and also, compare the effect of our product with those of our competitors. What's really exciting for me as a researcher is that we can use this intelligently in order to identify next generation versions of our products by using the information that we're generating to optimize formulations.

APM: And what's actually good for you commercially as well is that you can make claims for the efficacy of your products but actually, that's very useful for us because it's very hard sometimes to know whether products are a little more than a placebo. But take us through what this thing actually looks like when we see this in…

CB: So this is an example of sort of outputs are for microwave radiometry. So you can see the bottom of the chart, there's a temperature scale which is divided into colors in the way that the weather map would be. On the left-hand side, that's the ambient condition of muscle or skin, it happens to be a muscle in

this particular case. If someone were to apply a cold product, as a function of time, we'd. expect to see the temperature decrease if the product is having a penetrative cooling effect. So rather than sticking needles into people's legs which are objective, this is a non-invasive way of achieving three dimensional temperature mapping from within the tissue. So that will allow us to talk about speed of onset and depth. "How deep is Deep Freeze? How deep is Deep Heat?" will be answerable. You mentioned functional magnetic resonance imaging. That's looking at the brain and one of the great goals is to measure objective pain relief. At the moment, as I mentioned earlier on in the article, we measure using a visual analog scale. On a scale of 1 to 10, how painful is it? It's not very powerful. It's not necessarily very helpful and meaningful. If MRI looks in a part of the brain that's responsible for interpreting pain, it produces a signal which is a magnitude and therefore, it follows that if you apply a topical analgesic product that the magnitude should diminish and therefore, you have an objective measure of pain relief.

APM: And your final one?

CB: And the final one is the technique.

APM: I just love this image. It's fantastic, isn't it?

CB: It's a lovely image. So this is the thigh and the left-hand side of the image which is multicolored and green all the way down the left-hand side, these are the hamstrings and then it goes across the thigh to the right-hand side of the image and you can see the top right-hand side of that thigh is…one of the quadricep muscles that has been deliberately damaged and targeted and that has shown up in a different color because lots of the individual muscle fibers which you can see in exquisite detail here have been damaged and this —

APM: And those threads we can see there, you're telling me are muscle fibers, is that right?

CB: Yes.

APM: Which is…yeah, it's actually quite phenomenal I think.

CB: So it's easy to suggest therefore that if that particular patient has experienced that type of trauma, were we to apply ice or a cold product, we should expect to see, in real time, changes in the color of those fibers, indicating that they're less damaged.

APM: I think that's all really exciting. I'm sorry. Normally, we stop dead on the hour but the last time…on the hour and a half. Last time, we did an hour's broadcast and we cut it short to see if that was better suited to what we deliver and everyone said, "No, go back to an hour and a half," and here we are, we're run on over time but it's been fascinating stuff, Colin. I'm really looking forward to seeing the results of all this because it directly effects what we do in clinic and the advice we give our patients. So thank you very much for your time. Hopefully, we'll keep in touch with the results. You will keep in touch

This transcript will shortly be replaced by a concise text summary.

with us and let us know what we should be advising our patients and what you're seeing from all these studies but in the meantime, that's our CPD for this evening. That's 90 minutes up. Next broadcast, don't forget, is on the 23rd which is a Monday. We have Dr. Nathan Hasson who is an expert in juvenile hypermobility and chronic regional pain syndrome. In all probability, we will have one of his patients in the studio with us on that occasion and I'm very much hoping it won't be the studio because the trains have been really working hard to interrupt us as you've probably noticed. So we will have at least one patient in the studio. I hope we will probably two people who have experienced these problems, who are not practitioners, they are patients, joining us for that broadcast and I'm sure that it is something which will be of direct relevance to all of you in your clinics. Don't forget our courses. We have two new courses about to be posted with Simeon Niel Asher. We're doing a dry needling and trigger point course in Bristol in September and we are doing another shoulder course in Manchester also in September but we have still got places on the Laurie Hartman course in October and on Eyal Lederman's course in September. Hopefully, you can join us for some of those and hopefully, you'll —

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