Transcript Running rats and healing hearts

Nancy: It's October, 1998, and a young, fit individual in a laboratory at St. Olavs Hospital in Trondheim is running hard on a treadmill. For part of the workout, the incline is set at 25 degrees — the equivalent of running up a steep ski slope. Week after week, this individual and her 17 other companions have been training 2 hours a day, 5 days a week, in the service of research.

After only two weeks of training, the study participants are so eager to begin their sessions that they literally leap onto the treadmill when the time comes.

But here's the thing. Those treadmills — they're only 40 centimetres long.

And the pay for each session? One tiny piece of a Crispo chocolate bar. Because these exercise fanatics? They're RATS.

And their job is to help a young PhD student named Ulrik Wisløff answer an important question: can high-intensity exercise help people who have heart disease live longer, healthier lives?

Ulrik:
I was working with Olympic athletes in Cross Country skiing and how they trained and gave advice to them, and we found really smart ways to do exercise training, endurance training. And when I started here at the Faculty of Medicine in 1997, I thought, why shouldn't we use the same principles in cardiac patients as we do an athletes?

Nancy: The specific kind of training that Ulrik is talking about is called High Intensity Interval Training, or HIIT. High intensity means you train at at least 85 per cent of your maximum heart rate. And the interval part means you only have to train for a relatively short period — commonly just a series of 4 minute intervals.

Ulrik had seen just how powerful high intensity training had been in training elite skiers. It really strengthened their heart muscles. Researchers could actually measure this change with a cardiopulmonary exercise test called VO2 max. Why couldn't the same technique help heart patients, too?

At the time, cardiologists knew that it was good for heart attack patients to exercise, to improve their quality of life and possibly reduce the risk of additional heart attacks. But the conventional wisdom in 1997 was to prescribe moderate exercise — not high intensity training.
So in 1997, is your doctor going to recommend you go out and peg your heart rate nearly up to its max, even if it's just for a few minutes at a time? As Ulrik found out, the answer was definitely not.

Ulrik:
What happened when I started at the Faculty of Medicine I asked the cardiologists, couldn't we use the same principles as we do in athletes in heart failure patients? And they said yes, let's do that. But you are crazy. You can't do it in humans. You have to start in rats.

Ulrik: I had never seen a rat before. At least not a laboratory rat. So, that was the start. And we built treadmills for rats.

Nancy: Yes, the little tiny treadmills! With the ability to measure the rat's oxygen uptake!!

Ulrik: Long, long story short, we found really nice results.

Ulrik:
I presented at American College of Sports Medicine and, and the auditorium was full and there were a lot of wows. And then I said in the end, okay, now we have got approval to do this in humans.
And then one famous cardiologist in the back of the auditorium said, you have a great study, Ulrik, but you can't do this in humans. ….

You will kill them.

Nancy: I'm Nancy Bazilchuk, and this is 63 degrees North, an original podcast from NTNU, the Norwegian University of Science and Technology.

We all know that exercise is good for us, but just how good? What kind of exercise? And for whom?

Today I'm going to tell you a story of how exercise — actually, high intensity interval training — went from being a way for elite athletes to get faster and stronger, to doing everything from improving the lives and longevity of heart patients to helping seniors age better. And maybe, just maybe, it can also help Alzheimer's patients — but not in the way you might think.

It's a story about a huge Norwegian health-related database called HUNT; a website that attracted millions of users who willingly entered information for researchers about how they train; and 1500 people aged 70 and older signing up to be human guinea pigs. And of course, there are the rats, training like crazy on their treadmills. And behind all of this is the big mystery which is only just beginning to be solved: Can exercise really be the magic pill that medical researchers have hunted for, for decades?

Many researchers across the globe have looked at exercise, and high intensity interval training in specific. In Norway, however, the undisputed leader in this field is NTNU's Ulrik Wisløff, now a professor and head of the Cardiac Exercise Research Group here at the university.

Nancy: After Ulrik went to the American College of Sports Medicine conference, he did exactly what that famous cardiologist told him not to do. He recruited 27 patients with heart failure, with an average age of 75. One-third of them did moderate training, one-third did high intensity training, and the last third served as the control group, and was just given the standard advice regarding physical activity.

It wasn't easy, though. No one had actually studied the effects of high intensity training in human heart patients. But Ulrik, as you heard, had already studied this in rats — that was the study he presented to the American College of Sports Medicine.

And not only had he studied high intensity interval training in healthy rats, he had also looked at physiological changes that happened in rats that trained this way after having had massive heart attacks. In all cases, high intensity training radically improved their cardiac functioning. Nevertheless, you might reasonably wonder if he was a little nervous about getting 75 year old heart patients to train intensively.

Ulrik:
I was not, because I knew that the intensity is relative. So heart failure patients that works at, let's say 90% of their peak capacity, they're walk walking at 2.5 kilometers per hour, whereas an endurance athlete runs at 30 kilometers an hour.

Nancy: Even so...

Ulrik: It was hard to convince the cardiologists that this was safe. And it was also hard to convince the patients in the beginning, because that intensity we want them to train on so that they breathe heavily and they get really sweaty. And the first two, three sessions, they were quite nervous, but after two, three sessions, they did it themself and just showed up and saw that everything was okay. And it was a huge change in the cardiology area because just a few years before I started, the advice was that these patients should be at rest. They shouldn't have exertion that raised their breath or heart rate.

Nancy: That particular paper has been cited nearly 3000 times since it was first published in 2007.

Ulrik is quick to point out that many other people have, and still work with, interval training.

Ulrik:

We didn't invent interval training. They have done that in Germany for many years, at least in athletes.

But what our contribution has been is, what can we expect on the cellular and organ level when you do different types of exercise training?

Nancy: Ulrik and his colleagues began to publish a series of papers describing the benefits of high intensity training in people with heart disease. They also began looking at the benefits of high intensity training on something called metabolic syndrome, which is a combination of high blood pressure, obesity and high blood sugar levels, all of which put people at high risk of cardiovascular disease. They looked at how the heart muscle improved in people who have already cardiovascular disease when they exercised at high intensity. They looked at dementia.

Ulrik: Athletes do a lot of high intensity training, but they also do a lot of moderate intensity. So we thought it was a good idea to compare those in different types of populations with metabolic diseases, cardiac diseases, dementia, and so on.

Nancy: And they found some dramatic differences. As just one of many examples, when they studied the effects of high intensity training compared to moderate exercise in patients with metabolic syndrome, they found high intensity training significantly reduced the number of risk factors that cause metabolic syndrome compared to moderate exercise. Basically, in all cases, the benefits came from really working up a sweat.

Ulrik: What we find is that, sadly, is that you need to raise your heart rate. Yeah. Which is sad because it's much harder. It would've been much easier if you just could walk the dog and do the gardening.

Nancy: But Ulrik and his colleagues still didn't know exactly what it was about high-intensity training that was so important. Here's where fate stepped in.

Wisløff and his colleagues were invited to participate in this giant Norwegian health study called HUNT. Briefly, the Trøndelag Health Study, or HUNT (the acronym is from its original Norwegian name, if you are curious) began in 1984, with four waves of data collection, the last of which was in 2017.

In total, researchers have collected detailed data on 250000 individuals from northern Trøndelag County. There were questionnaires about everything from health-related behaviors, illnesses, socioeconomic conditions and more, collected multiple times over the four decades since the study began. Plus participants underwent a range of medical tests, and in many cases, researchers collected biological samples like blood, saliva and DNA, all of which are now frozen in a biobank and available for research.

Ulrik: And we were asked if we would like to do something in that study. And I said, yes, we would like to test VO2 max on healthy people, and see how will this go.

Nancy: VO2 max is your maximum oxygen uptake, and is a standard measure of how fit you are. To do this particular test, you run on a treadmill or ride a bike wearing a mask that measures the amount of oxygen you breathe in and the amount of carbon dioxide you exhale. And then you run or bike as hard as you possibly can until your VO2 measurements flatten out.

Ulrik: Is it so that those with high fitness live longer and healthier than those with low fitness and so on? And so we tested 5,000 people, and we have followed these people up to now. We have blood from them. We are able to study the genetics. We have access to journals, we have access to the quality registry.

Nancy: One of the advantages of the HUNT studies is that Norway has socialized medicine. Your medical records are linked under something that's called a fødselsnummer, which is like a US Social Security Number. That number links you to all of your health-related information: the medicines you are prescribed, and to different health registries, including the death registry.

Ulrik: So we can see, did this man or woman, did he or she get heart attack or what about dementia, diabetes, everything. So I think that's a gold mine.

Nancy: And the HUNT studies led to something that became a worldwide sensation: the World Fitness Level calculator, where you enter a few bits of information about yourself to find out how fit you are compared to the population at large.

Ulrik:
So we used the data from the 5,000 that we actually tested and matched those with questionnaires about exercise habits and adjusted for marriage, not marriage, alcohol, no alcohol and so on. And we developed a calculator that can be used anywhere in the world as long as you have internet access. That was the only requirement. And then we thought, okay, that's cool. And then I realized, of course, we have the same questions from HUNT in HUNT three and HUNT one.

Nancy: HUNT 1 started in 1984. HUNT 3 started in 2006. So 22 years apart!

Ulrik: And I thought, let's go back to the eighties. And then we plotted the data for, for the 30,000 men, 30,000 women. And we linked their fitness number to death registries. And we saw that those with the highest fitness level, lived longer than those with the low fitness level.

Ulrik:

And based upon that, we developed the fitness calculator that has been used by millions of people worldwide. To do a real test of a VO2 max or max oxygen uptake requires trained people and very expensive equipment. So I had this idea that it should be possible to predict this in a good way. Not of course accurate enough for athletes, but for 99% of the world's population.

Nancy: Here, Ulrik had a little help from The New York Times, where reporter Gretchen Reynolds, who had begun writing about Ulrik's work, described the existence of the fitness calculator, along with the publication of a paper that showed that it worked in identifying people who might be at increased risk of premature cardiovascular disease.

Ulrik:
Gretchen told me that when she wrote about that, it almost crashed the server for The New York Times. So she also realized that this is a topic that is of interest for many, many million people.

Nancy: Right around this time, one of Ulrik's colleagues began looking at another, related question.

Dorthe: So in 2011, Ulrik and I discussed the possibility to perform one of the largest study ever on exercise, a randomised control trial looking at the effect of exercise on morbidity and mortality.

Nancy: That's

Dorthe: Dorthe Stensvold. And I work as a professor in exercise physiology at NTNU in a research group called CERG, which stands for the Cardiac Exercise Research group.

Nancy: A randomized control trial is the gold standard for medical research.

Dorthe: Until then, every study looking at the effect of exercise on morbidity and mortality was from observational studies, which gives us a clear clue that there is a relation between health and longevity and morbidity. But the thing about an observational study is that they tell us about the association, but not about the cause and effect.

Dorthe: And in 2012, we initiated Generation 100, which is the first study that evaluated the effect of long term exercise on harder endpoints such as morbidity and mortality

Dorthe: We invited all people born between 1936 and 1942, with a permanent address in Trondheim. So they got an invite in the mail. With all inclusion-exclusion criteria, we ended up including a 1567 participants, approximately 50% women which we are very, very happy about.

Dorthe: So we actually did a randomized control trial. Half of them were randomized to supervised exercise and the rest half was in a control group with no supervision. Ideally, this control group would have been sedentary, but that's impossible to get through to the ethical committee. There are so strong evidence that exercise may protect for different diseases and increase longevity so, so we couldn't get that through to the ethical committee.

So the control group were asked to follow the recommendations for physical activity given by the health authorities. And then the other half were given supervised exercise twice a week. For the supervised exercise group, we also split them into two, where half of them were getting supervised exercise with continuous moderate intensity. And the other half trained with high intensity interval training.

Nancy: So the youngest of the people who were invited to participate in the study were 70 at the time. Dorthe said many of them, especially the women, had been active but mainly just by walking. High intensity training was not something that was on their radar.

Dorthe: This was a new thing. Some of them said that they've never actually performed structured exercise, they've been walking. Many, many of the participants were walking a lot every day. But structured exercise, and especially with higher intensity was very new for most of the participants, I would say. So I think they were surprised. And we are surprised. And I think the entire research, society has been very surprised how, how well, the participants have been able to perform this type of exercise, how well, they have tolerated it, but also that they were actually able to perform it for five years.

Nancy: And

Dorthe: We have a lot of different findings from Generation 100, I think we actually now have published maybe 34 papers so far. But in general, we saw that all three groups had a much lower mortality rate than what is expected in this age group.

So we have a theory that, of course, there is a selection bias.

Nancy: In this kind of study, where researchers invite a huge group of people, the people who are going to say yes are the people who are already active. So makes it more likely that these people would be in better health to begin with.

Dorthe: But we also see that all three groups, including the control group, increased their activity levels, and actually were very active during the study, which is kind of a headache for us as researchers because it was a bit hard to compare them.

The expected mortality in this age group in the general population is between 10 and 12%. The mortality rate in all three groups was 4.7 after five years. So much lower than what is expected.

Our data demonstrate that those who exercise with high intensity had more health benefits compared to the other groups, they had a lower mortality rate compared to the moderate group. And also there was a significant higher fitness level after five years or throughout the study after one three and five years, the high intensity group had higher oxygen uptake, maximal oxygen uptake, which is very clear indicator for future future health. And we also found that they had they reported higher levels of quality of life actually, after five years than the two other groups.

Nancy: But how much exercise is enough? It's one thing to set up a research group and offer them structured training, like Dorthe and the Generation 100 study, but how do you translate this information to the average person on the street? Ulrik, of course, has thought about this — a lot.

Ulrik:
When I started out as a researcher in exercise and public health, when I read the recommendations from all health authorities worldwide, I thought, Hmm, do people understand this? And what is three METS or six METS, or what is brisk walking?

Nancy: A MET is a ratio of your working metabolic rate relative to your resting metabolic rate. Your metabolic rate is the rate of energy expended per unit of time. Yeah, not user friendly.

Ulrik: And I thought if you ask my mother to walk at six mets, she will never understand that. So I thought that the recommendations were really inaccurate, and I thought that heart rate reflects what your body undertakes. So if you go uphill, your heart rate increases, if you go on a flat surface, it doesn't increase a lot. And I thought, is it possible using the HUNT data to make a meaningful metric out of heart rate that can translate into health?

Nancy: Once again, those four decades of information from Trøndelag Country come into play.

He had a huge dataset, from HUNT.

And he knew that heart rate was key — because he had already shown that the harder and faster your heart beats while you're exercising, the better it is for your overall health.

The one piece they needed was the ability to measure a person's heart rate. And then…

Ulrik: In 2014-ish, uh, all the wrist-worn wearables came along and all measured heart rate, but no one told you what that heart rate meant. And, and I thought, okay, let's try it in HUNT to see can we find a heart rate pattern over a week that translates into good health.

Nancy: Still, that wasn't quite enough.

Ulrik: And so we started testing that, and in the beginning we counted how many heartbeats do you have during a week? I thought it was that easy, but it was not. So everyone has about 700,000 beats if you're an athlete or not, per week.

Nancy: In the end, it was the HUNT data that made the difference.

Ulrik: We managed to make an algorithm that based purely on heart rate and gender and age so that we saw that when they had this pattern, they had good health, they had good cholesterol, they had low blood pressure, they were not obese, and so on.

Nancy: And the algorithm was built into a metric called PAI.

Ulrik: PAI stands for Personal Activity Intelligence.
And we made this scale from zero to 100. And we saw that, uh, if you had above 100, you didn't have any improved health compared to if you had hundred. So a hundred was sort of the optimal point. Of course, if you had 200 PAI points per week, you had higher respiratory fitness and so on. But you, you were not healthier in any other ways.

Nancy: There's an app under development that will allow people to use data from their sports watches to calculate their PAI. It's called Mia Health and is being rolled out globally this year. It's fun, because the algorithm that Ulrik and his colleagues developed can also tell you your fitness age. So the smarter you train the younger your fitness age becomes!

Nancy: At the top of the podcast I mentioned that high intensity interval training might help Alzheimer's patients. One of Ulrik's postdocs is looking at this exact question.

Atefe: My name is Atefe Rafi Tari and I'm a postdoc at NTNU in the Cardiac Exercise Research Group. The title of my thesis is do Physical Activity and Cardio Respiratory Fitness Hold the Key to Prevent Dementia?

Nancy:
And the answer?

Atefe: (
I think so, yes. We're still working on it. We don't have a definite answer yet, but a lot of evidence points towards that, especially these studies that we have done in HUNT.

Nancy: Yup, HUNT again. Four decades of incredibly detailed health data from more than 250000 people.

Atefe:
And so, we realized that there's also a health and memory study where they have diagnosed a group of people with dementia who also participated in HUNT in the 1980s and 1990 and were diagnosed around 2010, 2011. So, with that, we thought that, okay, we can go back to the eighties and estimate their cardio respiratory fitness or their PAI level, and then also in the nineties, and follow them over time and then see whether or not this is associated with later risk of developing dementia.

Nancy: You probably won't be shocked at this point to hear that they found an association.

Atefe:
We found that having a high estimated cardio respiratory fitness, or a PAI level of a hundred, which is our go-to level, that they have about 40% reduced risk of developing dementia later. And then we saw that if they didn't have that in the eighties in HUNT 1, but they had it in HUNT 2, so that they improved their fitness or their physical activity level, then that was also associated with risk reduction just as much.

Nancy: However, if the HUNT study participants had high fitness in HUNT 1 but low fitness by HUNT 2, then it was the same as if they had never been fit.

Atefe:
It's like fresh meat. So you really have to maintain it, improve and then maintain it. Otherwise, it seems like the effect will be lost.

Nancy: It's one thing to find an association, but that doesn't prove that there's causation.

So Atefe and Ulrik and their colleagues decided to follow up on some research that had been done in mice at Stanford University, in the US. There, researchers did studies where they found that old mice that got blood from young mice were rejuvenated. But what if the blood came from trained individuals? Or in this case, rats? Given all the causal evidence from the HUNT studies, might that make a difference? Atefe and Ulrik decided to check it out.

Nancy: That's right, bring out the tiny rat treadmills!

Atefe:
So we have rats that are genetically, uh, manipulated to have Alzheimer's disease. They have some Alzheimer's pathology in the brain. We had healthy young donor rats, which we trained for 10 weeks high intensity interval training on the treadmill, five days a week. And we took the blood from these healthy, trained rats. And then we had sedentary rats who had just remained in their cages. And then we took our Alzheimer rats and divided them into three groups. One of the groups got injections with the exercise blood plasma, and one group got the center plasma, and we had one saline group.

Nancy: Atefe and Ulrik are still writing up their results, but they did find that rats who got the exercise blood plasma showed the formation of new neurons.

Now they've started an experiment called ExPlas, for exercise plasma, where they are recruiting 60 people with Alzheimer's who will get one of three treatments. One third will be given plasma from donors who exercise, one third will be given saline and one third will be given plasma that has been collected from many different donors.

Atefe: For this study, our primary outcome is safety and tolerability and feasibility. But we do have the secondary outcome. So we will have an idea of whether it has an effect or not. And, of course we believe in it, it's our hypothesis, that's why we're doing it. But we might as well find that there is no effect. There are so many confounding factors here. Is it the dosage? Is it the timing? Is it the duration of the treatment?

Nancy: It will be two years or more before Atefe and her colleagues get their results. But there's still a lot they do know. Remember PAI, that fitness calculator? Ulrik and his team have now published a series of papers that show that people whose weekly score is 100 or more

Ulrik: ....they lived longer, they get less heart attack and so on compared to those with lower than 100 PAI points. And we have shown that it's lower risk of getting heart attack, lower risk of developing dementia, if you develop dementia, you get it later, you live three years longer without dementia and so on.

Nancy: Essentially

Ulrik Wisløff:
cardio respiratory fitness is the key.

Nancy: So as Ulrik will tell you — and as the science clearly shows — there's no reason to wait to exercise — and really break a sweat.

Nancy: I'm Nancy Bazilchuk, and you've been listening to 63 Degrees North, an original podcast by the Norwegian University of Science and Technology. Our guests on today's show were Ulrik Wisløff, Dorthe Stensvold and Atefe Tari. For more information and links to academic articles about this research, check out our show notes. And yes, there is a link to a photo of a rat on a treadmill! Editorial help and sound design by Historiebruket. Thanks for listening.