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Norman Swan: Hello, and welcome to the Health Report with me, Norman Swan.

Today, does stress affect the onset or severity of breast cancer? Fascinating findings which suggest that doctors can't be quite so dismissive as in the past.

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And another thing doctors used to be dismissive about: psychotherapy in psychosis. Even Freud thought it was a waste of time and he treated almost anything. Well, it turns out there is a role for talking therapies in conditions like schizophrenia.

That's all later, after what's becoming a typical good news bad news dilemma. New treatments are coming on stream for hepatitis C infection which can cure almost everyone carrying the virus. They come as pills and have few side effects, apart from their cost that is.

One of Australia's leading authorities on hep C is Professor Greg Dore who's head of the viral hepatitis research program at the University of New South Wales.

Greg Dore: Hepatitis C is a chronic viral infection that affects the liver and causes a progressive scarring process that can **lead** to cirrhosis and complications, including liver cancer.

Norman Swan: And how do you catch it?

Greg Dore: In Australia the predominant means of infection is injecting drug use, so people who share contaminated injecting equipment. On a global scale however the most common means of infection is actually contaminated injections within the healthcare setting.

Norman Swan: There used to be this cascading notion that of 100 people who got hepatitis C, so many got liver disease and so many ended up with liver failure and a liver transplant or dying. What's that story?

Greg Dore: So those that become infected, three-quarters go on to develop a chronic infection. And of those people we think about 20% to 30% will progress to cirrhosis.

Norman Swan: And is there any sexual **acquisition** of hepatitis C?

Greg Dore: Minimal. I mean, in the context of men who have sex with men, particularly HIV-infected men, there seems to be an emerging sexually transmitted epidemic. But in the heterosexual setting we very rarely see cases of sexually acquired infection.

Norman Swan: And living in the same home as somebody with hepatitis C?

Greg Dore: Almost never seen.

Norman Swan: How many Australians have chronic hepatitis C infection?

Greg Dore: Around 230,000.

Norman Swan: So it's a lot.

Greg Dore: And it's increasing in terms of the burden of disease. So a lot of people have been infected now for 20, 30 years. People who became infected through injecting drug use in the '70s, '80s and '90s, and that's producing more and more advanced liver disease.

Norman Swan: And it's almost universal on exit from Australian prisons.

Greg Dore: It is very high prevalence. So around a third of inmates would have hepatitis C, so it's a big problem in prisons across the country.

Norman Swan: So things have changed. It used to be untouchable, incurable, we only barely had a test for it.

Greg Dore: Enormously. I remember giving a presentation at a conference in the late 1990s and I said back then that no one should be treated for hepatitis C because the results were so poor and the success rate was only 5% to 10% and there were significant side-effects. But it looks like in the near future we will be curing more than 90% of people who commence therapy, if we can get access to these new regimens that have been recently developed.

Norman Swan: So what's changed?

Greg Dore: A couple of key things. Treatment has been Interferon based for the last two decades.

Norman Swan: Interferon is a drug that has some antiviral effects but also influences the immune system.

Greg Dore: Exactly, and it's given subcutaneously, so injections once a week in combination with tablets, and the main tablet being ribavirin.

Norman Swan: Which is like an antibiotic for viruses.

Greg Dore: Yes, exactly. So that sort of combination has cured around about half the people we treat. But it's had significant side effects, it’s required at least six months, often 12 months of therapy.

Norman Swan: And what's new?

Greg Dore: This amazing turnaround. We've moved from that era to an era where we look like we are going to completely remove Interferon from the treatment regimen.

Norman Swan: Because that's the cause of a lot of the side effects.

Greg Dore: Absolutely. And we will have regimens that will be all oral, will require generally only 12 weeks of therapy, will have very limited if any side-effects, and provide cure rates above 90%.

Norman Swan: And what the technology that's done that?

Greg Dore: There are classes of drugs now that directly inhibit the key enzymes that are involved in replication of the virus. Unlocking the way that the virus replicates has enabled people to develop therapies, as I said, that directly inhibit these enzymes. So combining a couple of those inhibitors together provides a very potent effect on the virus.

Norman Swan: Now, I should have a declaration of interest here; I have spoken at symposia sponsored by the drug **company** that produces the latest drug. Have you got any conflicts of interest you'd like to declare before we go on with this?

Greg Dore: I'**m** an advisor for several pharmaceutical companies that are developing different regimens.

Norman Swan: And having said that I was at a symposium sponsored by this, they're charging an outrageous price. They are charging…what is it, $100,000 for a treatment, just extraordinary sums which are hard to explain.

Greg Dore: So the first key direct acting anti-viral that I think will be part of the main treatment armoury over the next decade or so is a drug called Sofosbuvir, and it's listed…it's just been approved in the United States…listed at a price of $84,000 for a 12-week course. There is another agent, a protease inhibitor called Simeprevir, $66,000 for a 12-week course. And a lot of clinicians in the United States, now that those two drugs are approved, are in fact combining those two drugs, which is a very effective regimen, but that's $150,000 for a curative course of therapy.

Norman Swan: And of course the drug **company** will say, well, I've saved somebody from liver failure and liver cancer and saved their lives and how much do you value that, therefore it's cheap at the price. But it's a lot of money.

Greg Dore: It is a lot of money if you want to treat a lot of people.

Norman Swan: So you're saying you've got 230,000 people with chronic hep C, when do they qualify for this drug if it was approved?

Greg Dore: I think that's the key difference. To date we've only been treating 1% to 2% of that chronic infection pool per year, so only a few thousand people in Australia per year have been able to be treated, and part of the reason why the treatment numbers are so low is because of the toxicity of therapy and the difficult course of therapy. So now that we're going to transfer from that paradigm to an incredible paradigm potentially with limited side-effects, high cure rates, and therefore we expect a huge demand of those people coming forward to access that therapy. I think the government is going to be very concerned about that potential wave of the new demand and the high cost of therapy. So the next year or so in terms of evaluation of these regimens as they move through by the Pharmaceutical Benefits Advisory Committee will be obviously crucial in terms of the broad strategy.

Norman Swan: It's going to be very hard for them because it's going to be a vast amount of money in a shrinking budgetary environment. What I don't get is why don't doctors, specialists like you, rise up in arms? This is what happened at Memorial Sloan-Kettering a couple of years ago, a new cancer drug comes on, the cancer specialists there thought it was completely outrageous, the price, and hard to justify, and they just said, 'Sorry, we can't afford to buy it and we're not going to buy it.' And because they were the key opinion leaders in the United States in terms of this drug, the drug **company** immediately or relatively soon dropped their price quite dramatically. Why don't specialists get together and say to the drug **company**, 'Jack off and reduce your price, because we are not going to prescribe it. It's unfair.' You're not going to be able to afford the drugs for your HIV patients.

Greg Dore: I think it's an important point. What is happening at the moment is that there are some good partnerships across the sector between the community-based organisations, the key peak bodies in terms of clinicians, to try and come together to develop an advocacy strategy around this. We all want the best possible therapy for people affected by hepatitis C, there's no doubt about that.

I think Australia at least has a reasonable system in terms of pricing. So we won't pay those premium prices that are paid for in the United States. We always pay significantly less than that, but it still will be a sizeable amount of money. And if the bucket is not able to be enlarged in terms of the total spent on hepatitis C, we'll still be restricted in terms of the total number of people we'll be able to treat. And those restrictions will probably be based on either people with more advanced liver disease or what we call a cap on the total numbers of people who can be treated per year. So you're right in the sense that if we could help to negotiate a considerably lower price, clearly the number of people able to be treated would be expanded significantly.

Norman Swan: But it's hard to justify. I mean, I think that somebody did what the cost of, including amortising the cost of development, and it's in tens of dollars, not thousands or tens of thousands of dollars.

Greg Dore: Absolutely, there's been some really nice work recently done coming out of the UK that has stated that the production price for a 12-week course of highly curative therapy is maybe $100 to $200.

Norman Swan: They deserve to be reimbursed for their research and development.

Greg Dore: Sure, that will be the pharmaceutical industry argument, that there needs to be return on investment. It's a huge investment to bring these agents right through to licensure. But what is happening I think globally is a range of advocacy movements to try and sort out how we can improve access, and access in different settings, so access in low and middle income countries. The interesting thing about hepatitis C is that the majority of people actually live in middle income countries such as India and **China** in terms of the global burden of disease, but also access in high income countries like Australia. We have a constrained fiscal environment, as you pointed out, so we need to develop a strategy that will give us the best potential access and the best solution for people affected by hepatitis C.

Norman Swan: Of course another argument from the pharmaceutical industry I presume is, well, you know, 12 weeks and they're cured and then we don't have further use for this drug. Are there likely to be other uses of drugs such as these? Are they only active in hepatitis C or are they useful in HIV and other viral infections?

Greg Dore: They are really only active in hepatitis C in terms of their activity. I think one of the other arguments they use is that treatment for hepatitis C over the last decade or so has been expensive. So Interferon, the monitoring of that therapy, the management of the toxicity of that therapy, the length of that therapy is equal to a fairly large spend. But as I said before, the total spend has been constrained by the…

Norman Swan: Narrowness of the base.

Greg Dore: Exactly. So now in terms of a public health approach, if you really want to impact on this rising burden of advanced liver disease, we have to treat three, four, five-fold the number of people we've been treating over recent years, that's what we want to achieve at a population level. So we are only going to do that if we can get the government to increase their investment several-fold in hepatitis C or, as you say, get a much cheaper price and enable expansion in terms of the numbers that we treat.

But I think part of the solution is there in the fact that we have several companies that have what I think will be very competitive successful regimens moving through towards licensure. If it was only one or two companies it would be problematic, but if we have five or six companies that have very effective regimens, there will be competitive pricing, there will be no doubt about that.

Norman Swan: In a sense there is a big stigma around hepatitis C, that you think it's just…I shouldn't have used the word 'just'…but you think it's just people who are out on the streets mainlining heroin or cocaine or what have you, but it is much broader than that in the population.

Greg Dore: Yes, I think that's a really important point, there's enormous stigma around hepatitis C and that clearly is related to the alignment of hepatitis C with the main mode of infection being injecting drug use. But the reality of people with hepatitis C is that they are an incredibly diverse population. I see people in different clinical settings. And sure, I see people who are still injecting and have significant social and health issues related to that injecting, but I see many, many people who might have injected for a very short period of time and are what you would call…

Norman Swan: Lawyers, doctors…

Greg Dore: Exactly, like us! Very much part of…

Norman Swan: Are you about to tell me something, Professor Dore?

Greg Dore: No. Very much part of mainstream middle class Australia. And they are a very, as I said, diverse, interesting population of people, and it's a real privilege to be part of the care for those people.

Norman Swan: Greg Dore, thank you very much for joining us on the Health Report.

Greg Dore: A pleasure, Norman

Norman Swan: Professor Greg Dore who's head of the viral hepatitis research program at the Kirby Institute at the University of New South Wales.

You're listening to the Health Report here on RN with me, Norman Swan. Still to come, is breast cancer made worse or even caused by chronic stress? That's later.

A group of psychologists and researchers at the University of Technology Sydney has published what they call a manual designed for both mental health professionals and consumers about an area which until only relatively recently was frowned upon as useless and a waste of time and resources: psychotherapy for people with psychosis.

Psychosis is a loss of contact with reality involving, among other things, delusional thinking and even hallucinations. It can be chaotic and certainly scary for the person experiencing an episode and the people around him or her. Freud reckoned that psychosis was too hard for talking therapies to crack. But there's growing evidence some of them can help.

Tony Kidman leads the group which produced the manual and has been practising and researching cognitive behavioural therapy—one of the best studied forms of psychotherapy—for many years.

Tony Kidman: The work that's been done over the last 20 years now, particularly in the UK but also in the US, saying that the use of psychotherapy in conjunction with medication can be very helpful, and sometimes with medication-resistant psychosis.

Norman Swan: And you've had a particular interest in cognitive behavioural therapy. So just remind us what cognitive behavioural therapy is.

Tony Kidman: Right, yes I have. Essentially the core principles are that we can think about our thinking. So if we have negative thought about our health, our future, job or whatever, that is not necessarily a complete fact. There may be elements of it that aren't quite as bad as you think, and being able to challenge it and talk back to yourself, that can be a very helpful strategy. It is only one of many strategies, but that concept of being able to think about your thinking, challenge it, dispute it, can have a profound influence on your mood and on your actions.

Norman Swan: Now, that's hard enough to do when somebody is depressed and they think, 'I'm worthless, nobody likes me, and I have no future in the world,' and you challenge their thinking, saying, 'Well, you're not worthless, look at the world you've got around you, you're a successful person,' et cetera. And you start reframing your thinking in that sense.

Tony Kidman: That's correct.

Norman Swan: But the reason that people say that's impossible in psychosis is that, if you like, psychosis is much further down the track in terms of unrealistic thinking because in fact what you're dealing with are delusions.

Tony Kidman: You are, and hallucinations. I'm not suggesting that that can be applied in the middle of a frank episode, but psychosis and schizophrenia (which can follow) are episodic, and the evidence is that if people receiving medication can be engaged in therapy then slowly but surely these techniques not only of challenging negative thinking but other behavioural techniques, distraction techniques and a whole lot of other things, they can realise that when they are heading up for an episode (and they often realise it) these techniques can help. They are also very useful for compliance.

Norman Swan: Sticking to treatment.

Tony Kidman: With medication, people coming off, because they don't like some of the side-effects. So there's a whole range of benefits.

Norman Swan: So what do you do? Do you confront somebody, say, if you're starting to believe that the world is against you and people are talking about you, for example, recognise that…

Tony Kidman: Well, we do, but of course we don't challenge necessarily the fact that they say, 'people are trying to kill me', or 'there's people from the CIA or ASIO across the road in a car sending me messages'. The therapeutic approach is to say, well, 'what does that really mean', or 'just elaborate on how you feel about that', without saying 'that's a load of nonsense'. But not accepting it either.

I was talking to somebody the other day who I've been seeing for many years. She was telling me that the people who had been hounding her for the past 20 years have started to come back. But in the end she allowed those thoughts, which I said, 'I'm sorry to hear that they're there…' or I don't know whether I used that phrase but let's just see what you can do as you normally do when those sort of people or voices start to come back to you again. So at the end of the conversation she agreed that those voices could sort of drift to the back of her head, and she was better than when she started.

Norman Swan: So have there been randomised trials of cognitive behavioural therapy?

Tony Kidman: Oh yes.

Norman Swan: And what do they show?

Tony Kidman: Good. I mean, it's not magic, but the evidence is certainly accumulating that CBT…I mean, there are other therapeutic models as well that can be used, but the evidence is that it has benefits. Of course the problem is that schizophrenia and psychosis has had a bad brand. Depression and anxiety, a lot of people come forward, celebrities and others, but not many people come forward and say they suffer from schizophrenia. There's a tremendous stigma because the press attributes are many violent crimes to people suffering from schizophrenia.

Norman Swan: Does it lower the relapse rate?

Tony Kidman: Yes, it does, and the intensity of the episode.

Norman Swan: So one of the problems in schizophrenia which hampers rehabilitation is that drugs, albeit that they have side-effects, are quite good at controlling what they call the positive symptoms, which are delusions, hallucinations, the things that we've been talking about. But what stops somebody really getting better, back to work and so on, are what are called the negative symptoms, which is that you lose social skills, you become apathetic, you find it difficult to motivate yourself. There's no drugs that affect that. Does CBT help that?

Tony Kidman: It most certainly does. And in our study that was one of the main things that we focused on, and treating them in that way, using all the repertoire of skills from cognitive behavioural therapy, social skills, distraction techniques, scheduling activities, pushing oneself, you know, when you feel demotivated and so on. But again, that requires engagement and trust between the therapist and the client.

Norman Swan: And you've had experience yourself with schizophrenia in your family.

Tony Kidman: I have, Norman. My brother, who was two and a half years younger than me, was diagnosed in the late '50s with schizophrenia. He'd been down training to become a religious in the Jesuit order and unfortunately that didn't work out and he was sent back, came back, and he started to hear voices and so on.

It was a very, very difficult time, and I'm not suggesting that that's been dramatically improved for family members, because when a family member gets diagnosed with this there's tremendous stigma, there's fear, a whole range of negative emotions arise and it can throw the family into a very, very difficult situation. It did in my case, in our case, and my mother in particular had a very, very difficult time over many years in which he was in and out of hospitals. And of course the treatment then was very basic, and he had a great deal of electric shock and so on, and drugs that were not particularly effective.

So I had an experience of that. And seeing people in the unit…my colleagues of course are doing all the work these days and I try and just keep the show on the road, and they wrote this manual and papers that are emerging from it, they are the authors, have come up with suggestions in that, particularly the manual, even though it's written for professionals, for family members to take some hope about how they can help manage their son, daughter, relative suffering from schizophrenia and from an initial episode of psychosis. So I'd like to think there are some good tools available, and also there's a lot more help available than there was. Not enough, by any means, not enough. And I'd just like to think and hope that anyone listening to this program can get some benefit from that.

Norman Swan: So if somebody is listening to this and they want this kind of care, they need to talk to their GP about getting referred to a psychologist…?

Tony Kidman: Yes, that's exactly right.

Norman Swan: …who does cognitive behavioural therapy. And if they want your manual we'll give some details on our website of how to get it.

Tony Kidman: Yes, we're happy to do that. Of course the Australian Psychological Society has a telephone number and people can be contacted there to find out clinical psychologists that they could seek help from. But the GP-psychology symbiosis is very good.

Norman Swan: Tony Kidman, thanks for joining us on the Health Report.

Tony Kidman: Good to see you and talk to you again Norman, thank you.

Norman Swan: Tony Kidman is director of the Health Psychology Research and Treatment Unit at the University of Technology Sydney.

Now to stress and breast cancer.

Women who develop breast cancer are often to be heard claiming stress had something to do with it because of disruptions in their lives prior to being diagnosed. And while cancer specialists are sometimes sympathetic, they generally have rejected the idea of a link.

But research from the laboratory of Professor Suzanne Conzen at the University of Chicago should make the experts think again.

Suzanne Conzen: Well, it is an interesting story. My laboratory was studying a type of breast cancer which does not depend on the oestrogen signal for its growth. And we decided that we wanted to look at a number of different compounds to see if they affected the growth of this type of breast cancer. It's known as triple negative breast cancer.

Norman Swan: So just to explain here, you can typify breast cancer in lots of different ways: by the genes, but also by whether or not they've got a lock and key mechanism for hormones. And so one is oestrogen, one is progesterone, and I forget what the third one is.

Suzanne Conzen: The HER2, or human epidermal growth factor receptor 2.

Norman Swan: If you're positive for some of these then there are drugs which can treat you relatively easily. But if you're negative to them all, the prognosis can be quite poor.

Suzanne Conzen: That's exactly correct. And I was interested in receptor negative breast cancer because we tend to see that type of breast cancer here on the Southside of Chicago. There is an association, for reasons we do not understand, with this triple negative breast cancer and young African American ancestry.

Norman Swan: And we should just explain, we're sitting here at the University of Chicago, it's on the south side of Chicago which is really the poorest part of Chicago.

Suzanne Conzen: That's correct. And so I was seeing a lot of young women with this type of breast cancer, which tends to be very aggressive.

Norman Swan: And while these women's breast cancers were negative for those three hormones, the women who relapsed and did badly tended to have breast tumours which carried receptors, lock and key mechanisms if you like, for a stress hormone called cortisol, part of the glucocorticoid family. Glucocorticoids are associated with long-term chronic stress of the kind experienced by people who feel they've lost control of their lives. So Suzanne Conzen and a collaborator created experiments which induced chronic stress in female rats and mice from around puberty.

Suzanne Conzen: And these rats she worked with first become very anxious and one can measure that objectively, and they stop grooming themselves and eventually they become quite ill. And in one of those cases of scientific serendipity she found that socially isolated female rats developed mammary gland tumours, or breast cancers, earlier than group housed female rats. And we actually did find that their glucocorticoid levels were very, very high in response to a superimposed stressor, and they did not return to normal after the removal of the superimposed stressor for a very long time. So their total exposure to glucocorticoid was quite high.

Norman Swan: And on the tumour?

Suzanne Conzen: And on the tumour they were larger tumours and they did express the glucocorticoid receptor. But we hypothesised that it is responding to this stress hormone. And we also found that they developed earlier and larger tumours when they were socially isolated, and we were able to show that some of the gene expression changes within the mammary gland happened very early on, even before the tumours were actually detectable.

Norman Swan: What Suzanne Conzen thinks is that first comes the stress, then the stress hormone, then the receptors, then quite profound changes in the way the breast functions. And the breast cells which seemed to be the first responders to stress are the fat cells, which may, in a woman with a genetic predisposition to breast cancer send signals which induce malignant change in the breast ducts, the lining tissue where cancers arise. But not everything that happens in a mouse or a rat happens in a human.

Suzanne Conzen: There are some interesting clues. There are other groups and they have looked at fat and other cells outside of the ducts in women who have either oestrogen receptor positive tumours or oestrogen receptor negative tumours in the other breast, the non-affected breast. And what they found is that there are very different characteristics to the fat tissue in these two types of patients. And so there are some clues that fat is actually an important thermostat of what's going on in the body

Norman Swan: Of course women have said anecdotally for many years that they're convinced that they had this episode of stress: somebody died, their husband left them, they lost their job, and they got breast cancer a year later. And traditionally cancer specialists have said it's just a coincidence. It might actually not be a coincidence.

Suzanne Conzen: I think for certain types of breast cancer it's something that deserves a lot more investigation. Many of my patients have asked me if stress contributed to their breast cancer without me ever asking and I always of course previously said no, of course not. I think as we learn more about the sub-types of breast cancer and understand the biology better, we'll be able to put these two pieces of the body together.

Norman Swan: So the question then is whether intervening in some way by reducing the stress, giving a single woman more support with her three kids, whether that's going to change the outcome or whether it's too late at that point because she's already got the cancer.

Suzanne Conzen: Yes, I think that our mouse models at least suggest that the intervention should be early, and that the stress in the younger woman is very important because that's when the mammary glands are finishing their development. But I do believe that there is evidence, and some of it is conflicting, that even after a woman has breast cancer that there is a role for social support.

For example, there is work from Ohio State which has randomised women with breast cancer to social support or no social support and found a benefit in breast cancer outcome, and it was particularly significant among the women with oestrogen receptor negative breast cancer. So there are some tantalising pieces of information.

The other possibility of course is actually blocking this receptor pharmacologically in either patients who have breast cancer or are at risk of getting breast cancer. Right now we have glucocorticoid receptor blockers and we are studying them in more advanced breast cancer here at the University of Chicago.

Norman Swan: Have you got any sense at all of whether this story's true for women who might be oestrogen receptor positive, progesterone receptor positive or even HER2 positive?

Suzanne Conzen: It's…

Norman Swan: You're going to tell me it's complicated.

Suzanne Conzen: No, I'm going to try and explain it, because I should be able to. So what's really interesting about this observation about the high glucocorticoid receptor expressing breast cancers is that when we looked at oestrogen receptor positive tumours that were high glucocorticoid receptor expressing, we actually saw the flip side. We saw that those tumours tended to not recur as quickly. And we believe (and this illustrates how complicated breast cancer is) that that is because the oestrogen receptor and the glucocorticoid receptor can speak to one another.

One way of looking at it is if you walk into a room and there is the oestrogen receptor there, the glucocorticoid receptor might behave quite well. But if you walk into a room and the oestrogen receptor is absent, the glucocorticoid receptor does not behave nicely and causes a lot of changes in the cell that it wouldn't if the oestrogen receptor was present.

So we think there's actually a big difference between the two types of breast cancer and how the glucocorticoid receptor is acting.

Norman Swan: Suzanne Conzen is professor of medicine and cancer biology at the University of Chicago.

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