

The New Mind–Body Science of Depression

A David Van Nuys interview with
Charles Raison, MD

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Dr. Raison is internationally recognized for his studies examining novel mechanisms involved in the development and treatment of major depression and other stress-related emotional and physical conditions, as well as for his work examining the physical and behavioral effects of compassion training. Dr. Raison received the Raymond Pearl Memorial Award from the Human Biology Association “in recognition of his contributions to our understanding of evolutionary biocultural origins of mental health and illness”.

Dr. Raison’s book *The New Mind–Body Science of Depression* was published by W. W. Norton in 2017. In addition to his other activities, Dr. Raison serves as the mental health expert for CNN.com.



Dr. Dave: Dr. Charles Raison, welcome to Shrink Rap Radio. You and your co-author, Vladimir Maletic have written the 2017 book *The New Mind-Body Science of Depression*. I must say it's a real tour de force on the topic of depression.

Raison: Thank you. It took us five years to do it.

Dr. Dave: What led to the writing of this book?

Raison: Well, it's interesting. Vlad and I are colleagues. We've been colleagues and friends for years. We do a lot of medical education stuff, a lot of lecturing to mental health people. Vlad is a walking encyclopedia of neurobiologic and clinical knowledge. I have been in awe of him for years. Back, six, seven years ago, we began to talk about the fact that we should try to get some of this down. We were wandering around talking about it and people seemed really, really interested. So we decided to capture this program of education we've been doing for years and put it in print form. That's what really launched the book.

Dr. Dave: I think it's a really important book, but it seems like things are moving so fast in the field that it may not be a classic because the information will change.

Raison: I've already thought about how if and when the time came that we did a second edition, it'd be a major rewrite. From when we started the book to when we finished it, we had to go back and rewrite part of it. There's been a lot of interesting discovery in the last four to five years.

Dr. Dave: Well, I have to say your book is very carefully argued, is evidence-based, and it presents a complex picture which makes for challenging reading.

Raison: Yeah, I know. It's hard. Parts of it are very dense, you know. The book runs a gamut. We have some case studies in the back that are very approachable. We've got some sections about the neurobiology—there's a lot in there. Very dense and detailed.

Dr. Dave: Well, I'm going to try to lead you through much of the book. Can you give us the highlights to start? Your focus is on major depres-

sive disorder as opposed to what? There's major and there's?

Raison: There's minor, there's all sorts. The manual of psychiatry, the DSM, that codifies diagnoses. It has a number of new disorders. We focus on major depression because it's the sort of standard depression. But one of the key arguments we make in the book is that it's not—even though it has a code and we call it an illness, it's not a discrete thing. In fact, we explicitly say that we prefer to use the word depression because we recognize that depression far exceeds the more limited bounds of major depression and that depression, in almost all of its forms, is very, very painful and can be very problematic for people.

I've come to prefer the word depression better. It's not as clinical, not as exacting, but it gets closer to the fact that there is a phenomenon out there that is not one thing. It's more like a cloud of symptoms, and something that is very common. You see something like it all around the world. You can see it in hunter-gatherers. It's a thing. It's not a thing that has hard boundaries, but it is a thing, and it really is depression.

Dr. Dave: I was really struck by what you just said, going back to hunters and gatherers, because you make the point that it's not a symptom of western culture which many people might assume, but it goes all the way back.

Raison: Yes, as far as we know. We know it is in historical times. There's a couple of ancient papyri from about 3,000 BC from Egypt that articulate something that we would clearly recognize as major depression. Mood disorders were beautifully described in the ancient world. Hippocrates did a good job. There were others. There's a famous guy from Turkey ... his name escapes me ... who laid out mood disorders beautifully and recognized bipolar disorder as a type of mood disorder. Beautiful descriptions of depression in the renaissance. But more recently, there's been some interesting work, part of which was done to test one of the theories that we talk about in the book, having to deal with why depression may have evolved.

A group of anthropologists out at the University of New Mexico went down to one group that may not be fully hunter-gatherers, but they're pretty close, and did very, very rigorous depression screening there. It found a number of interesting things. One of them was that the biology of depression there looks like the biology of depression here, and second, that the symptoms look the same. The people had very much the same symptoms and they had the symptoms from many of the same reasons. There's a little cadre of reasons for why humans tend to get depressed. I think the best evidence suggests that those reasons are very ancient. Depression evolved probably as a response in one way or another for coping with those reasons.

Dr. Dave: I was also surprised to learn that individuals who have experienced more than one major depression show lasting cognitive decline. I wasn't aware of that. That's rather alarming.

Raison: Very alarming. I mean, for those of us that have struggled with depression.

Dr. Dave: As I have.

Raison: Yeah, I have too. If you've had a depression, if you think about it, you probably recognize that it impairs your thinking, it makes you feel sluggish, you have a hard time remembering things. Then there's this indecisive thinking that comes up, but we don't sometimes think of that as cognitive, but you have a hard time making decisions, things seem overwhelming that way. There's older data that those symptoms take longer to clear up than mood symptoms do. They're not always as responsive to antidepressants, they linger, and they are a major source of morbidity in the disorder.

Part of what nails people with depression is it screws up their ability to think and remember. It's a huge problem, and it's a problem that we're becoming more aware of in the last few years. Certainly, it's become of more interest since we started writing the book because it's become a focus of the pharmaceutical industry. There are a couple new antidepressants that target a serotonin receptor that has been associated with improved cognition,

you know, so all of a sudden, people are very interested in this idea, "Oh, man. Maybe we can specifically do something about it." Not so clear if that's true, but anyway, it's a big deal.

Dr. Dave: One of the things that you take on is the DSM-5 which has some coverage of depression. What is it that they've got wrong there?

Raison: Well, they've got a couple of things wrong, but they've got a couple of things right. What they have wrong is that it's built upon an idea that is extremely admirable and it was the idea of one of my main mentors. I went to a school in a place called Washington University in St. Louis. That was really one of the two primary founding sites for what became the DSM. The chairman of the department Samuel Guze along with Eli Robins felt and provided some evidence that psychiatric conditions were really diseases. That if you look at their symptoms and if you follow their symptoms over time, that it would be like discovering a bacteria and saying, "Oh, hey, that's what causes tuberculosis."

So, they thought that something like major depression was a disease state and that it was a disease state that differs, say, from something like bipolar disorder or differed from something like schizophrenia. Why did it differ? Because it had different symptoms and tend to have different outcome over time. It's not that that's exactly wrong, but it's pretty clear now that it's really not true. That in fact, as we have come to understand the mechanisms for these disorders, both genetic and systems within the body. There's a huge overlap between many of these disorders. For instance, the genetic risk



factors for depression are largely shared with something like bipolar disorder and even with schizophrenia.

When you look at the mechanisms that underlie these disorders, there's some evidence that there's some differences between them. But what strikes me is the fact that so many of the changes were reminiscent of each other. We look at brain changes or immune changes. What is emerging now in psychiatry, is that in ways we never would have guessed 30, 40 years ago, these disorders we label as being separate have powerful genetic and biological overlaps. We don't know how to cleave nature at the joints. What we don't know how to do though is to take these emerging scientific data and say, "Oh, well, let's come up with a whole bunch of new disorders." If two people with depression have got the same symptoms and one of them has a problem with their immune system, with TNF (tumour necrosis factor alpha), that's an immune molecule then they've got a TNF disorder, so hey, what we used to call it major depression, we can now call it TNF disease.

Another person has got a problem with their cortisol, so we're not going to call it major depression, we're going to call it cortisol disorder. But that's what we cannot do yet. Even though we've begun to understand that there are complex overlaps in the biology of these disorders and within each disorder, we have not yet come up with anything frankly, better than the DSM. That's why in our book, and this eventually is what the National Institute of Mental Health has recently decided too, is to recognize that the DSM with its description of things like major depression is a useful clinical document that helps people use the same language. You and I can diagnose the same thing if we see somebody with something like major depression. But that these are not disorders like rheumatoid arthritis or pneumococcal pneumonia. The diseases in the DSM are clinically useful suggestions, although they may not be God's truth.

Dr. Dave: In fact, you talk about the National Institute of Mental Health and IMH in the book. You say that for the purposes of funding research, they're sort of ignoring the DSM-5 and requiring a different type of research. Can you briefly characterize what that different type of research is?

Raison: Another colleague of mine, a very famous guy named Tom Insel became the head of NIMH. He is no longer there, but about 15 years ago, this brilliant, bold controversial man came in and said, "When we look at research in general, if we look at cancer, we see a significant decline in deaths from cancer over the last 20 years. If we look at heart disease, even more impressive. We look at, say, depression, let's say suicide as a proxy for depression. Rates haven't dropped, they've gone up. We are failing." More recently he said, "I don't know what



the number was, like \$20 billion during my tenure in IMH. We did some really cool work, but I don't think we accomplished anything." So he decided to take the bull by the horns and say he thought part of the problem was that we're trying to study these DSM disorders and they don't exist. That they don't exist that way. They don't have a single mechanism.

So they came up with a system called RDoC, which stands for Research Domain Criteria, and, basically, instead of reaching into the DSM, they said, "We're going to have these domains that we think characterize mental disturbance more generally, so a cognitive function domain, a stress resilience domain, a negative affect valence domain." You're only going to get grants if they propose to study those domains. But you can see you're now setting up another set of these sort of criteria. So if you take something like stress resilience, there are probably a hundred ways to get stress resilience, right? Calling that a sort of a mechanism, it's a step forward, but the problem is we don't know the hundred ways.

The brain and the body in these regards are so complex that although we've learned a lot, really trying to zero in, is always the problem. But yes, NIMH has really changed things in very interesting ways in terms of they will now really only fund projects that use these sort of criteria and try to look at a mechanism. So, if I got a new treatment for depression, they're not very interested in me just trying it on depressed people. What they want is for me to say, "I think it works by blocking inflammation." So first show me that it blocks inflammation and then show me that people get less depressed. It's a very logical idea, right? They're really trying to get to be like the rest of medicine and try to find mechanisms.

Dr. Dave: I'm thinking of phenomenology as the experience, the inside experience of depression.

Raison: Yes. It's often used to mean a "descriptor of symptoms", like a description of what is it that people that have depression experience. There is no doubt that we need that, and there is no doubt that I have no idea what it is.

Dr. Dave: Okay.

Raison: We all have some ideas, but this is the huge challenge and ... It depends on how you look at it. This is one of the things the book says too? If you try to go in up close and really hone in on details, it sort of is like a Buddhist feel in the world when you try to find solid objects, things just vanish into these complex interrelationships. If you try to be very specific about the phenomenology of something like depression, you cannot figure out where it starts, where it ends, what is what. But one of the things that Vlad and I realized in writing this book, was that if you step way back, you actually can get a sense of the phenomenology of depression. Then we can say some things.

One is that it's remarkably common. Two is that it doesn't really tend to come out of the blue. Most of the time it is in response to certain types of environmental adversities. It tends to hit men and women in different ages. In general, it tends to have a set of symptoms. Not everybody has all the symptoms, so if you go back, that turns out to be quite useful. It's different than a simpler medical illness and it's got a code. Because if you look at it this way, it has a narrative. It turns out that it has causes. It has effects too, but it has causes.

One of the arguments in the book is that the causes of depression are fairly stereotyped, suggesting that they're ancient in human evolution, and they're not random. That gives you a sense that we can call it a disease. Pragmatically, it might as well be a disease, it wrecks lives. But it's not just a disease, it actually turns out to be an evolved response to adversity and that opens some really interesting doors for thinking about it and for thinking about its phenomenology.

Dr. Dave: Yeah. You mentioned bipolar, and I was wondering where does that fit in? Does that complicate the picture?

Raison: It does.

Dr. Dave: So is it more of its own thing or is it part of this thing?

Raison: Yeah. Oh, yeah. Well, so in the old days, in the way old days, people would kind of lump

everything together. They thought everything ran together. There are modern people who think that all disorders of mood are bipolar. Most of us don't believe that, but I admire that position. I don't agree with it fully, but I really admire it. It's old, it's an ancient, it goes back to the ancient world to that guy whose name I'm not thinking of from Turkey. But more recently, and certainly in the DSM, there was this sharp distinction. Unipolar disorders, just depression, is one thing. Bipolar disorder is something else. That's not true. We know that's not true. They're clearly not the same thing. Because to have bipolar disorder, you have to have a manic episode or hypomanic

of time as an adversity, but it is. It's quite an adversity, actually.

Dr. Dave: Getting older?

Raison: No, not that. Getting up everyday, going through the day, going to sleep. The literal passage of circadian rhythms is a powerful stressor, right? The most stressful thing you do most days that aren't terrible is get up in the morning and your body prepares for it a couple of hours. It activates the stress system. That's why there's a surfeit of death rate at dawn. The reason people die at dawn is because it's really rough to get up. Ask any teenager, they know that. But it turns out to be true, right?

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episode. Those can take various flavors, but when they're extreme, people are psychotic, they're hearing voices, they don't sleep, they can't stop talking, all the time. It looks like the opposite of depression.

Clearly, it's not the same thing as depression, but bizarrely, it's not altogether different either. Many of the biologic changes you see in mania, you can see in depression. It's weird. Many people that seem to have depression, specially when it's recurrent, when it happens to somebody a lot over the years, many of those people will eventually have something like a manic episode. As we've learned more, we've understood less in some ways. That's one of the ways we've understood less. The clear demarkation of just regular old depression from a bipolar disorder has softened a little bit. Now I'll tell you one way I think about the distinction is that depression tends to be response to certain types of adversity, largely social and often immune infectious related adversity. Bipolar disorder is often a response to the adversity of time. Most of us don't think

Dr. Dave: I was thinking of teenagers.

Raison: Most of us manage that. In bipolar disorder, one of the classic things that induces episodes in bipolar disorder is disruption of circadian functioning, so missing sleep. For people with a bipolar disorder, all you need do is keep them up for a night and they'll frequently go fully manic. If you put them asleep for 12 hours ... When I used to do a lot of clinical work I ran a large inpatient service in California. Several times we took people that were doing things like running around naked in public, screaming, and stuff like that. Put them to sleep for 12 hours and, literally, when the people woke up the next morning and said, "Oh my God. Where am I? What happened?", they were perfectly normal.

Some manic people have outbreaks when they get on a plane and fly to Europe. Bipolar disorder is more of a brain disorder. When it's really severe, it really looks like there's something wrong with people's brains. But it's not just that, we also know that the episodes of

bipolar disorder are sparked by the environment, but they're also sparked by the stress of time, circadian time, in a way that depression, regular old depression is not.

Dr. Dave: Now one of the things that you emphasized in the book is that depression is not a unitary disorder, and that there's a complex interaction between genetics and environment.

Raison: That's right. Although, that's not novel. I think the whole field now recognizes that psychiatric disorders arise at the interface of genetic vulnerability and environmental conditions. The conditions that produce depression are often conditions of adversity. It's a continual model and a simple way to think about it is that there's some people whose essential makeup is largely driven by genes and the way those genes are expressed through epigenetic changes. There's other people that take a lot of grief to get unhappy and get depressed. There's a famous story from ancient Athens about a king who had everything until the end of his life when he lost his wife, he lost his children, he lost his kingdom. On his deathbed he said, "Call no man be happy until he dies." Meaning that there are things that can happen that can probably upset everybody, but some people need a lot of push from the environment.

Other people are genetically vulnerable. They're more sensitive to environmental perturbations. They need much less push from the environment. Because life is difficult, as the Buddhist said, "All life is suffering," you are going to suffer in life. The more you're vulnerable to that, the more likely you are to get de-

pressed because the world is just not ... it's not a bowl of cherries, right? Most of us fall somewhere in the middle, but that's a way of thinking about a continuum where the genes and the environment talk to each other that way. One of the things we do in the book that's really interesting is we raise the point that even the dichotomy of genes and the environment is in many ways false. Because if you think about what a gene is, it's a chemical structure, but it's really an encoding of information.

If you say, "Well, what's that information?" It really isn't encoding. It's information about past environments. Because those genes are there mostly, not always, but mostly because they were selected by past environments. From a genes point of view, everything outside the gene is environment, right? If you're a gene and you wanted to survive and reproduce, your body is outside environment. If you're a human, then there's a lot more on the inside. You think your guts are on the inside, and your genes are on the inside, and the environment starts with your skin. But it really turns out that there's another continuum which is genes and environments. They're also married to each other and they're ciphers for each other. One element to environment is a new element to a gene.

Think about an individual gene. Its environment includes the chromosome. It includes the entire genome because it's fighting with those other genes. They get along but they also fight. Then if you look at a chromosome, well, its environment is the cell. You look at the cell, its environment is the body. When you really get into it, you begin to realize that al-



though it's very difficult to model these things, what really is going on is that all these levels are in constant interaction with each other, and the interactions are largely bidirectional. You get these extreme, complex systems. When you get complex systems it's hard to make simple predictions. That's why we can't accurately forecast the weather. They become so complex that actually finding what they're doing becomes either intractable, meaning you don't have enough computer power to do it, or nearly impossible. That's one of the challenges for thinking about why depression is so difficult. The simplest thing to say, and when I started with this, we know the genes and environments interact with each other.

Dr. Dave: Are we talking about multiple causal pathways.

Raison: Yes. Multiple causal pathways that are also interacting with each other in ascending levels. You get 12 pathways and these 12 pathways interact with each other, then those interactions can interact with each other. Some levels are going to be much more important for intervention than others. That's how we can do anything in life. But still, in this way, it's a little like a quantum understanding in that it's a cloud of causes. Some of them are more important than others, but it's very complicated. In some circumstances, a cause that wasn't so relevant in another circumstance becomes very important. That's another complication. I think one of the things writing the book did for me was making me realize, with a certain humility, that we're learning a lot. What I'm saying to you now, wouldn't have been said 20 years ago. Even the articulation of our ignorance has become more knowing, but it's a very humbling thing.

Dr. Dave: Another eye-opener for me was—and it really relates to what you've been saying about systems within systems and everything being connected—is that there's a high degree of comorbidity among individuals of major depression as well as among their families.

Raison: Yeah, absolutely. So, these things certainly run in families. There's no doubt about that. That is a strong argument that there is a ge-


netic underpinning. Now me and one of my other close buddies argue about this constantly. He's a total genetic guy. I'm much more of an environmental guy. But we know there's something genetic even though finding a single gene for depression is proved thus far impossible, but we know there's something genetic. But then other things get passed down in families. Environment gets passed down in families, and now we know from animal studies that in fact, how your genes are expressed can get passed down through generations. That the experiences of one generation can get encoded in the epigenetic markings of the next generation. It runs in families for both genetic and environmental reasons. Then the psychiatric disorders run together. They're also a family, right?

Many, many people with major depression will have other psychiatric conditions. Often, anxiety disorders. Most people that are really depressed are going to be anxious as well. But most people that have chronic anxiety will eventually get depressed. You see this bidirectional thing that people that have other significant psychiatric conditions will usually end up with depression at the end of the day. The explanation we'd offer for that from the book's perspective is that these disorders are terrible stressors. So, they're fertile seeds for the development of depression. Depression is a big risk factor for other disorders. We know for instance that depression is a risk factor for substance abuse. But more disturbingly, and I hate to say it, but we know that depression over time is a risk factor for cardiovascular disease, a huge risk factor. It's a risk factor for diabetes. It's a risk factor for dementia. All these things are increased in people that have depression. It's comorbid with all sorts of things, and all sorts of things cause it, and it contributes to the cause of all sorts of things.

Dr. Dave: Wow. That was kind of an eye opener to realize that these things go in such clusters and it's a grim outlook, actually.

Raison: Sadly, in part, yes.

Dr. Dave: You talk about a loss of evolutionary fitness resulting from environmental adversity.



Raison: A fair proportion of the book tries to address potential evolutionary understandings for why depression exists. There's a riddle. The riddle is this. Even though we haven't found a gene for depression and even though we know there's environmental contributions that are huge, there's a lot of evidence that there's genetic underpinnings to this disorder. You've got genes that set you up for depression. Depression seems to be so inimical to optimal functioning, certainly in the modern world, but we see from the hunter-gatherers who get depressed that they're not really benefiting from depression. They often commit suicide. Depressions strike, it's partly genetic, it really looks to be inimical, you know, bad for survival and reproduction. It strikes people early in life, especially women, right in the middle of the years when the Darwinian burden of sur-

vival and reproduction is maximal.

Why hasn't it been removed from the human genome by adaptive forces, by natural selection? We propose two answers to those questions. One more direct and the other less direct. The less direct answer addresses your question. One of the things that we noticed over the years was that there's an odd thing about the types of adversity that make people depressed. They're largely social and they're largely immunological, by which I mean, if you made a list of what makes people depressed around the world, one of them is being sick. As you say, "Well, what's being sick about?" Well, it's partly a stressor, but most illnesses are also a manifestation of activation of the immune system, something called inflammation. We and others have shown in many studies that if you take people that are not inflamed and begin to inflame them through something like a medicine that activates the immune system, they have a huge rate of getting depressed. They get major depression, they get minor depression. Inflammation makes people depressed and so that's-

Dr. Dave: Let me just cut in with a personal experience here. Often, I can tell that I'm getting sick because I'll start to get depressed. I'll start to have kind of depressive thoughts or something and it turns out I'm getting a cold.

Raison: Yes, absolutely. In some people, I've had this experience, can actually have bizarre joyous kind of hyper mood states getting sick too, which again points to the fact that very high mood and very low mood are driven by underlying similarities. But we know it's true. It's been shown in studies. We begin to wonder why it is that getting sick makes you depressed? Why is it that certain types of social things make you depressed? What are those things? They have a lot to do with losing status, being shamed, losing options, losing valuable loved one, losing resources, being trapped in situations that are horrible for you emotionally but ones that you can't escape. Why are these things so depressogenic? Why are they so unreasonably depressogenic The

answer we suggest in the book is that in fact, although nowadays, many of these things are not at all risks to survival or reproduction, they really were across most of human evolution.

Here's a thought experiment that I give in lectures. I suggest that the things that make people depressed are the things that reliably signal that you as an individual were in danger of not optimally surviving and reproducing. That's not consciously why you're upset, but evolution's tricky. It likes to take the proximal causes and use them for ends that we don't necessarily want to do. The classic example is sex, right? Evolution uses the pleasure of sex to get people to procreate. Evolution uses our sense of needing to be important, of needing to be more important than other people, our need not to be shamed. Evolution uses all these things to drive certain types of behavior that were adaptive across human evolution given the kind of creatures that humans are.

What we suggest is that the things that make us depressed today were things that were signals to us in the old days, back before modern times. In hunter-gatherer times it signaled that you were at risk of dying and/or not reproducing. Think about depression as if it was really about survival and reproduction in the modern world. Every time you see a car go by, you should become utterly despondent because, especially early in life, cars are a major source of killing you, so you won't survive and reproduce. Yet, none of us feel that way. Many do, however, do this when they got in an airplane. People can feel terrified, even though your odds of dying on any one flight are something like 20 million to one. Why are we terrified? Because people have been dying from falling from heights across all of hominid evolution. We have evolved fear of heights. It's unreasonable in the case of an airplane, but it's emotionally powerful.

The things that make us depressed in the modern world are like fear of heights. You know, you become depressed because you lose status in front of a boss or you're fighting with a co-worker. Now, you know, what the modern world lets you do is get another

boss quick. You often have other options. You're not usually going to die. You're children aren't usually going to die. But if you look at foraging hunter-gatherer societies, if you fall in status, especially if you become ostracized, you will die. Ostracized people die. Children whose parents died or were excluded from the group were often killed or much more likely to die. There's really nice anthropologic data on this. The idea is that one of depression's purposes from an evolutionary point of view is as a signaling mechanism. It signals that you are in danger, you're an evolutionary danger, and evolution gets your attention by making you feel horrible. You feel like you're in personal danger. That was literally true a hundred thousand years ago. It's not really true now. That's the way in which depression has become an evolutionary mismatch.

Dr. Dave: I was just thinking it's unconscious, but deeper than in Freudian sense.

Raison: It's more Jungian. It's more Jungian this way. It's like a collective unconscious except it's wired in biological mechanisms, social mechanisms, and genes. What it means though, treatment wise, is that part of what we need to face when we treat depression is to recognize that we're in a lucky moment. The things that are making us depressed are actually, most of the time, not going to kill us. They are often, in fact, far more minor in the modern world than they were in the world of our ancestors.

You may end up not living in a giant mansion, but there's other things that matter more and recognizing that these thoughts don't line up so well with reality in the modern world. That forms the basis of meditation. It forms the basis of cognitive behavioral therapy. This provides an evolutionary underpinning to some of these treatments of just recognizing that we are burdened with an ancient physiology and an ancient psychology. We were burdened but there's also some great opportunities, some of the positives we need to recover in the modern world. Faulkner said, "The past is dead. The past isn't even the past." That is the truth when it comes to both the biology and the psychology of depression.

Dr. Dave: You mentioned inflammation earlier, and that was one of the really intriguing things for me in the book as I'm also reading in various places about inflammation and how we are carrying a certain amount of inflammation in our bodies. It sounds alarming. Chronic inflammation tends to cause depression because the brain detects the threat? Do I have that right?

Raison: You got it. That's our little contribution to the world of brain immune stuff. The argument of the book is how these things tie together. What inflammation tells a person is, "Hey, guess what? You're going to die." You've been infected, or you have a cancer, or you've had massive tissue trauma. So, what are the things that activate inflammation? It's a signal that something has happened, or is happening, that's about to increase your risk of dying. Of course, from an evolutionary perspective, dying, especially before your children are secure in their lineage, is a big bad way to end your Darwinian mandate. Evolution is a sort of subtle signal that you are in trouble in that regard, and it makes people depressed. There's some really interesting evidence that this is the case. There's some evidence that inflammation is more likely to make people depressed when they're younger which makes sense because that signal that you're going to die is of more evolutionary relevance when you're younger in terms of survival and reproduction.

The other interesting thing is we did a study a number of years ago. Really, my mentor, a guy named Andrew Miller, who is one of the great fathers of this field. He trained me up. I owe much of my thought to him. But together we did a number of studies where we showed that indeed, if you looked at people who are getting inflamed because they were taking a drug called interferon, which activates inflammation, these folks get depressed. If inflammation makes you depressed, you should be able to treat depression by blocking inflammation. So we set out to put our money where our mouth was to prove this. We did a study where we took people that were healthy but depressed, very depressed. They had failed a couple antidepressants. We gave them a very power anti-inflammatory. It's something

called infliximab. It used to be marketed as Remicade. These are really interesting drugs because they don't do anything but block inflammatory molecules. So, infliximab has no other effects on the body, this drug we used, other than to take out the most potent inflammatory molecule, a thing called tumor necrosis factor alpha or TNF. There's no other side effects that could explain it's effect. If it works, all it's done is kill inflammation.

We did this study. We compared it to placebo, just salt water. We saw that a lot of people were getting better. We figured we were going to get rich and famous. When the study was over, we looked, and placebo worked a little better than the drug. Blocking inflammation in depressed folks in general did not work. In fact, salt water was a better antidepressant in these people. It was quite striking. But when we looked, we had another idea that we tested which was we thought that if inflammation does make you depressed, the people who have higher inflammation should get a better response from having it blocked. That was absolutely true. There's a straight line. If you were depressed and you had high inflammation, infliximab worked better than placebo. It looked like an antidepressant. If you had low inflammation and you were just as depressed, the placebo worked much better. There's a whole story there we don't understand, but for today, the thing that's interesting is infliximab is too big to get into the brain, it works in the body.

What does this mean? It suggests that you take people who are depressed and you as-



sume that their brains must be abnormal because the brain is creating their consciousness. U treat them with a drug that doesn't get into the brain. What does it do? It turns off that signal of danger from the body. When that happens, people start feeling better. How is that possible? What I've argued is the only way it's possible is that the brain is no longer getting that signal. The brain, you see these "abnormalities" in depression and how the brain's functioning, maybe they're abnormalities or maybe they're fairly reasonable responses to a signal that you're going to die. You know, of course, the abnormalities in the brain, the brain patterns are producing the depressed emotions and thoughts. But you turn off the signal from the body and the brain all of a sudden goes, "Huh? Wow. Shoot. Kind of a beautiful cloud that I don't feel so bad." It's amazing, right? It's so sure. In a way the brain is the proximal cause of depression, but if you can turn it off by turning off a body signal, you could say, "Well, no. It's actually the signal from the body." This really highlights the fact that inflammation makes people depressed because it's a signal.

Now that's not the only reason inflammation makes people depressed, but we think that the other thing is that it actually serves an adaptive purpose. Depression looks a lot like sickness. If you make a list of what happens to you when you're sick and what happens to you when you're depressed, in fact, many of the symptoms overlap, including weird things like changes in iron and changes in zinc, and things like this that don't seem to serve any social function for human beings. I mean, if depression has to do with managing the scary boss of the tribe, why would your zinc drop? But it turns out that when you look and you ask another question which is why does sickness exist, I mean, who wants to be sick? The answer is sickness is an evolved response to pathogen danger. The reason we get sick is because the symptoms of sickness help us survive. Why do you get a fever? You get a fever because higher body temperatures ramp up the immune system and they make bugs fall apart. Bugs don't do very well at higher temperatures. You can

make a list of all the symptoms of sickness and many of them have that function.

Well, it turns out, depression has almost all of the symptoms of sickness. For instance, we think fever is really a classic symptom of sickness. Fever's a classic symptom of depression. Depressed people, on average, in many studies actually, run their body temperature a couple of degrees higher. Depressed people have changes in zinc. Depressed people have changes in iron. We begin to realize that depression looked like what's called an acute phase response to infection. Then when we began to look, we realized, the genes that have been most implicated in depression, if you look at the form of the gene that's associated with depression, you can almost always find evidence that it helps people survive one or another very serious infection, suggesting that in fact the types of genes and the types of immunological processes that seemed to promote depression, seemed to also promote pathogen defence against infection.

We and others have elaborated something that we call the pathogen-host theory of depression or path-host B, which just basically says that one of the reasons that depression evolved in part to help us manage our relationships, but not so much manage our relationships with other people, manage our relationships with the microbial world. From that perspective, in areas before modernity, when 50% of everybody who is born died of infection by age 15, and when babies had nothing but these inflammatory processes between themselves and death for the first two years of life, anything that is selected for an inflammatory bias in our genome would likely be selected because whatever the costs of an inflammation are, if you're going to die when you're a kid, if this keeps you alive even marginally, the selected benefit over time is huge. This is why you see this suite of behaviors and genes in human beings that have this inflammatory bias. That inflammatory bias, there is a respect for depression. That explains why depression, in part, why depression persists.

Dr. Dave: Because it's adapted.

Raison: Definitely. We talked about those foragers down in Bolivia that turned out to have the same type of depression that we do. They went down there to see if they had the same types of inflammatory changes, and they do. They did an interesting thing where they showed that the depressed people had a better immunological response to certain pathogens that are relevant down there. It's kind of a beautiful story. We think that the link between inflammation and depression is ancient, that's it's the involved adaptive strategy. We also think however that it's been made hyperacute in the modern world because it's been unmasked by the loss of something else which is our connection with other types of microorganisms that we and others have called the old friend of microorganisms. Many environmental organisms that used to be common in the human world have been removed because of

sanitation and changes and all sorts of things, many of these microbes had very powerful anti-inflammatory properties.

Across most of human evolution, you had this inflammatory bias that was being pushed by the selective advantage of inflammation helping you survive infection, but it was held in check by the fact that you as a human being swam in a environmental world or microbial organisms, that didn't want to be destroyed by the immune system, over time taught the immune system to be tolerant. In the late 1700s, things started getting clean in Western Europe and there's an explosion of hay fever and these soft of asthmatic things. We've been off to the races ever since because we and others think that we've lost this moderated influence of these other types of microorganisms. The link between inflammation and depression is ancient but is exacerbated by the modern world.



Dr. Dave: That's fascinating. Now another thing that we read a lot about these days is the biome. It sounds like that would play in there somewhere.

Raison: There's been these really interesting studies in the last few years. I'll briefly describe the microbiome for folks that don't know. Ten years ago, we thought of ourselves as discrete entities, just, sort of, human beings. We now know that it's equally valid to look at each of us as a community or a universe. In fact, if you counted up the total number of cells in your body, only one out of 10 are human. The rest are mostly bacterial, but there's also fungi and parasites. About 90% of the cells in your body are bacterial. If you look at the DNA in our body, only 1% of the DNA in our body is human, 99% is bacterial. Each of us is a community. We're a compromise between the cells of our own body, with their DNA, and the cells of these little other creatures that live within us that are with us but not of us. We increasingly think of our behaviour as a sort of a compromise of that. The vast bulk of these microbial organisms, to the tune of trillions and trillions, live within our guts. It's been said that the most complex ecosystem known in the universe is the gut. There's also huge numbers of cells of bacterial and viral and fungi cells in the lungs, on skin. Anywhere where the human meets the world, there is this powerful community of microbial species that we call the microbiome. That's what the microbiome is.

It turns out that the microbiome of modern humans is profoundly different than the microbiome of the last hunter-gatherers. This has been tested on a tribe in Africa called the Hadza. Their microbiome is just remarkably different. Western folks go live with them for a few days and they already begin to look more like the Hadza. It's interesting, so it's not something genetic. It has to do with the way they live their life. But that microbiome that is so abnormal in the modern world is almost certainly contributing to a whole bunch of modern problems, allergies, asthma, autoimmune conditions, all these immunologic conditions that are running rampant in the

modern world. Now that's interesting. But what's more interesting is that it hasn't been shown so clearly in humans yet at all, although it's beginning to, but in animals, you can take something like a mouse or a rat, and if you clear out all those bacteria in its gut and put in new ones, you can totally change the behavior depending on where you took the fecal matter from.

There's two classic studies. One is they had a strain of very anxious timid mice and a strain of very bold exploratory mice. They cleaned out their guts, but they collected poop, faeces, from both those species and swapped them. When they did that, the mice that had been timid became very brave. The mice that had been brave became very timid. After the faecal transplant, the mice that got the brave faecal matter had changes in their brain that you see when you give somebody or if you give a mouse an antidepressant. The bugs in the gut, they look around, and they say, "All right. Hey, we want to survive, so we need to change. Clearly, we don't want to be in this nervous little mouse here." So they begin talking to the brain and they change the way the brain functions. There's a study in mice showing that if you take mice that don't have a microbiome, so they've got completely clean guts, and you give half of them fecal matter from depressed humans and half of them fecal matter from normal humans, the mice that get the depressed human poop started acting depressed.

Dr. Dave: Wow.

Raison: There's a small study recently which is published with autistic kids. Not very large, about 20, but these are severely autistic adolescents mostly. They didn't do anything to their brains. They just cleaned out their guts and gave them a faecal matter transplant. They collected faeces from normal humans and transplanted into the guts of these autistic kids. They began behaving more like normal people, and they had a significant improvement in their autistic symptoms. Now I'd be less inclined to believe this but there is evidence now that you can do bone marrow transplant for autism. You heal

the head. You do anything to the head, you radiate the body. You kill all the immune cells and then you transplant normal ones. The kids have a huge improvement in their autism. In animal models, bone marrow transplant can totally change the behavior of an animal. In other words, what we know is that the immune system is a second brain that is a messenger system, back and forth, between us and them, and that we are compromised between us and them. What I call me is part me and partly the bugs.

Dr. Dave: Amazing, amazing.

Raison: Yeah, it is amazing.

Dr. Dave: Has there been a faecal implant study relating to depression in human beings?

Raison: You know, I wanted to do that starting about 10 years ago. People thought I was out of my mind.

Dr. Dave: I can imagine.

Raison: But, I just had to wash it. It could damage my career. So, no, not that I know of, but it's begging to be done.

Dr. Dave: Oh, yeah. It seems like an obvious next step from what you said.

Raison: It is. It breaks my heart that I won't be the one to do it. You can't just waltz into this stuff. Probably somebody's doing it now. It's such a clear thing to do. I'm in contact with folks that do faecal transplants medicinally down in Mexico where it's legal. It's all anecdotal data, but many people that come in with things like bad allergies or autoimmune conditions seemed to have big emotional response, feel

better. Now we're even more interested not so much in things that are residents of the gut, but in microorganisms that come from the environment. They used to pass through us all the time, but now they are gone. There's one in particular that has been a long fascination of my colleagues and I, something called mycobacterium vaccae. This has been in development, and its related species, for a number of years as treatments in the UK and Britain. There's some very striking studies that when you add this to chemotherapy, you'd get a huge improvement in survival. I mean, it's quite striking.

In animal models, if you kill the microorganism, you just take its chemicals. If you inject mycobacterium vaccae into the tail, say, of a mouse or a rat, it works as an antidepressant. It's quite remarkable. In humans with cancer there's some pretty interesting data that it actually has some pretty powerful mood enhancing effects. We don't just think it's things like probiotics and faecal matter transplants that are promising here, but in fact, some of these species that were once rampant in the environment that are now missing, that have very powerful immune moderating effects, may even have more promise as antidepressant strategies.

Dr. Dave: Now we're kind of into the realm of therapy. One of the things that you talked about was WBH, whole body hypothermia.

Raison: Hyperthermia, yeah.

Dr. Dave: Tell us about that.

Raison: One of the things that I recognized a few



years ago is that in pursuing this link between the mind and the body and my interest in this idea that bodily processes like the immune system could be used to alter brain function, I began to notice that some of the things I was studying have been around for a long time. We've come to call them ancient practices. I sometimes call them ancient practices and associations. For instance, we can talk all this stuff about microbes, about bugs. Well, we're talking about ancient associations that have been ruptured, right? Humans function best when they're back in relationship with the microbial world. Not in the ways before, we don't want to be dying by the age of 15, but we've thrown the baby out the bathwater. There's a bunch of good guy bacteria that we'd want to get back in relationship with. That's the ancient associations.

Hyperthermia, whole body, this heating people. So, heat, really high heat, hyperthermia, is a paradigmatic example of an ancient practice. Think about all the cultures in the world that use some sort of heat application as a therapeutic modality. In the new world, things like sweat lodge, temescal, they were ubiquitous. Why would somebody voluntarily subject themselves to the stifling heat of a sweat lodge? You see it across the ancient world. Heat was used widely for medicinal purposes in the ancient world. I'm fascinated by this phenomenon of hot yoga. Why in God's name when you could go do yoga on a nice sunny day out on the lawn, why would you voluntarily lock yourself up in a stinky miserably hot room? There's an answer for this. The reason they use sweat lodges is for healing, for stress resilience, for the induction of these sort of elevated emotional states, is because heat does that. Heat is another example of a peripheral sensory process that can be harnessed to change how the brain functions. It's a kind of deep brain stimulator.

We realized a number of years ago that heat might have antidepressant properties. How did we realize it? Well, my friend and colleague Christopher Lowry, who had done the experiments with mycobacterium vaccae, realized that heat should have the same signaling ef-

fect on the brain as that bacteria. So, we set out to test it, and we just recently published his paper. He took rodents, and he half of them heated up, hyperthermia, and half of them he didn't. Then he gave them a standard antidepressant test for animals that they use to identify new antidepressant therapies. Heat worked just like an antidepressant. Around the same time, we had the opportunity to do a small study in depressed humans in Europe. We did and we saw that if you just put them in a fancy box that has these big heating lights, and you heat them up for an hour, hour and a half, you get the body temperature up to 38.5 centigrade, which is hot, it's 101 or something. If you do that, people feel better very rapidly and they seem to feel better for a week or two afterwards. I mean, it looked like an antidepressant.

When we're at the University of Arizona, we did a much better randomized study with a fancy hyperthermia machine. We gave half the people the real heat, and we gave the other half fake lights and fake sounds, although we warmed them up a little bit, so they thought they were getting something. The vast majority of them thought they'd gotten the real treatment. We looked at the real hyperthermia versus that sham fake treatment. Hyperthermia had a profound antidepressant effect, big antidepressant effect. It was immediate and it lasted for six weeks.

It's two things. It's a peripheral sensory pathway. We think that heat activates immune and neural processes in the body, then go up and talk to the brain. We haven't done neuro imaging studies yet. But one of the things we have done is look at what hyperthermia does to the immune system. It activates the immune system in a way that looks identical to what exercise does. In our first study, we've seen that the more it does that, the more undepressed people get. For everybody that goes and then gets hyperthermia, the more you have that certain type of immune response, the more undepressed you're going to be in one week later, two weeks later. It's a pretty big effect actually. We know that there's something about the immune system that is at least re-

lated to whatever heat hyperthermia is doing in the body and brain to make people feel so much better.

Dave: Now I'm getting a little confused between hypo and hyper. In the case of mania, hypomania means a little bit of mania. Hypermania means a lot mania.

Dr. Raison: Yes, exactly. With thermia, hyperthermia means heat, hotter. Hyperthermia means that you're in an environment that is hotter than your body wants to be. Hyperthermia is going to make you sweat. Hypo with an O thermia means that you're in an environment that's colder than your body wants to be. Now hypothermia is also very interesting. It's never been rigorously studied, but now there's a craze to take people with things like autoimmune conditions or pain disorders and stick them briefly in liquid nitrogen which is a couple hundred degrees below zero. A colleague of mine who has rheumatoid arthritis did it. It seems to be quite effective. People report feeling less anxious and less depressed. It may be that hypo with an O thermia may also have therapeutic potential. Some of the most esoteric Tibetan Buddhist practices in the world try to harness hypo, with an O, thermia to change brain function. It's a complex thing, but it's very interesting. We've spent the last few years studying hyper because fate led us that direction, but infinite money and time, there's something interesting with cold as well as heat.

Dave: Now I have to ask you about shock therapy ...

Dr. Raison: ECT, electroconvulsive therapy.

Dave: Yes. I think it's out of favor now, but it worked dramatically for some people. Why?

Dr. Raison: It's still unfavored. In fact, it's more unfavored but it is by far the most effective treatment for depression. We all wander around. Back in the '40s and '50s and even '30s, they gave ECT without anaesthesia. They'd come up and you have a seizure. I knew patients that had remembered that and were terrified of it. Nowadays, you put people to sleep. It's safe, it's benign. It has some side effects with memory, but oh, it's way more effective than any

other treatment that we know of. The problem is it's not always long lasting, but it is rapid.

I've seen many people over the years that were so depressed they literally couldn't move, they couldn't speak. After a single treatment, they would be walking around. Now, they'd often relapse, but by the time a week was up and they'd had multiple treatments, it was just amazing. There's certain types of very severe bipolar and depressive symptoms that are life threatening, we call them lethal catatonia, that ECT is the absolute mandated treatment. Nobody knows how it works. That's the funny thing. If you made a list of everything that antidepressants have all sorts seem to do, and if you ask from that list, does ECT do it? The answer is almost always yes. It just does all sorts of stuff. It's not a subtle treatment. It's like a bomb. It seems to shake everything at once.

Dr. Dave: It sounds like it's a reset button in a way.

Raison: Yes. We think it's a reset button. It's interesting it's an unconscious reset button because people are asleep when they get it. It's not like they have an experience that's transformative. I'm involved with some work now with agents that we think operate by changing people, giving people a certain type of experience. But what's interesting about ECT is it is unconscious, you're out. You wake up and you don't know why you just feel better.

Dr. Dave: Ketamine infusion is something that I've become aware of that supposedly had good results for depression among other things.

Raison: Absolutely.

Dr. Dave: And transcranial magnetic stimulation?



Raison: Yes and yes. Transcranial magnetic stimulation has been around for a while. It is different than ECT. You apply a magnet to the head. Usually on this side, left entry of frontal cortex. It sends a little jolt. The magnets had a little bit of electricity that goes about this far (2-3cm) into your brain. You don't have a seizure, but the idea is that you're stimulated that part of the brain that's kind of not working so well in depression. We've gotten better at it as the years passed. So, recent studies where they have ways of trying to zero in on the spots you want to put the magnet on, result is pretty good. They're pretty good in people that have failed antidepressants. If you are depressed and if you have not tried TMS, your list is too short.

I now believe that if you are depressed and you haven't tried ketamine, your list is too short. The data shows that it produces a rapid antidepressant response in people that have failed everything. Not everybody, but a large percentage of people. Those data are very strong. A single dose on average makes people feel better for a week. If it gets approval from the FDA, it'll see light of day as a repeated treatment. We don't have great data on giving yourself ketamine once or twice a week over extended periods, but we do have a great data that being catastrophically depressed is a killer. Ketamine is showing a great deal of promise. It's very interesting. We thought we knew how it worked. Now we're not so sure. Something that I am much involved with in terms of part of my research work is looking at the potential for other agents that alter consciousness as means of antidepressants. Things like psilocybin which is the active ingredient in magic mushrooms or MDMA.

Dr. Dave: I'm very interested in that whole area as well.

Raison: I serve as a director of research for folks that we're working to try to really show that this might be FDA approvable. Very, very interesting treatments. There's some early studies. They're small. There's a couple of them. The results are somewhere between dramatic and jaw-droppingly dramatic. What's really inter-

esting, is that it looks like it has to do with giving people certain types of experiences, conscious experiences, that change how they look at the world.


Dr. Dave: Let's raise one more little area of inquiry here. What about psychotherapy? You had mentioned CBT, cognitive behavioral therapy. Is that it in terms of the "best approach for depression"?

Raison: No. No.

Dr. Dave: Do you have any thoughts about that?

Raison: Oh, yeah. There are a number of treatments that have been shown in good studies to be generally as effective as antidepressants. CBT has been the most studied. I am very interested in something called MBCT, mindfulness-based cognitive therapy. It mixes the methods of CBT, cognitive behavioral therapy, with the methods of mindfulness. It's been shown to be especially interesting for folks that have struggled with recurrent depression and is useful in keeping them from having a relapse. There's dialectical behavioral therapy for folks that have more personality issues. There's something really interesting, I think it's called rumination-focused therapy. It's come out of Europe, but it's a type of CBT but it focuses on challenging your negative ruminative thoughts. In folks that have ruminations, it looks to be very promising. There are a number of interesting therapeutic options that are emerging. Many of which now are beginning to have data.

One of the most interesting studies in the literature of depression are findings where you take people who are depressed and you give them either an antidepressant or psychotherapy, let them get well, and then you take away whatever they were on. You get rid of the antidepressant. You get rid of the psychotherapy. For the people that got the antidepressant, a huge number of them relapsed. They get depressed again and do so fairly quickly. The people that got psychotherapy are much less likely to get depressed. In fact, even without the psychotherapy being ongoing, they are about as protected as people stayed on in



medicine. One of the really interesting advantages of psychotherapy is it's a social practice, and it's a conscious practice. One of its apparent advantages is that it seems to induce resilience that our pharmacologic agents do not seem to do.

Dr. Dave: Wow. What a fascinating person you are to talk to, I must say.

Raison: Well, you have great questions. I'm not always this fascinating. I mean, you asked exactly the right questions.

Dr. Dave: I think probably we should wrap it up here. Dr. Charles Raison, thank you for being my guest today on Shrink Rap Radio.

Raison: This was a blast. Thanks for having me.