December 2010 Issue: Andrew Scull, PhD UC San Diego

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Welcome to *Functional Medicine Update* for December 2010. What an epic issue we have this month. I'm so excited about it because it's an area that we have hit upon on a number of occasions during our 28 years of existence, but today I think we are taking a different approach. The subject this month is psychiatry-the history of psychiatry. We've got a magnificent expert to help guide us through the labyrinth of history of psychiatric conditions, psychiatric management, and the profession of psychiatry. I think it is a very interesting case study for the general evolution of medicine. I hope you'll be able to extrapolate beyond psychiatry to other areas of medical innovation, thinking, paradigms, and how concepts are shifted.

We're going to have the chance to speak with Dr. Andrew Scull in a moment, who is the author of some extraordinary publications on the history of psychiatry. I've read a number of his books and papers, which are fascinating reading. He is a marvelous writer. One book is titled *Undertaker of the Mind: John Monro and Mad-Doctoring in Eighteenth-Century England*(University of California Press, 2001).[1] His work, *Museums of Madness: The Social Organization of Insanity in Nineteenth Century England* was published by Allen Lane Publishers in 1979.[2] And his most recent book is *Madhouse: A Tragic Tale of Megalomania and Modern Medicine*.[3] I think all of these are extraordinary reading. By listening to my discussion with him I think you are going to connects to the evolution of thinking and how it translates into medicine and the standard of care.

Interview

Researcher of the Month - Andrew Scull, PhD
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Here we are once again at our clinician/researcher of the month section. This section really sets the tone for the whole issue, as you may have noticed over the last several years. The context of each issue is framed by these people who are remarkable. They are defining visions, perspectives, technologies, or procedures that relate to the direction of medicine: creating a more effective, patient-centered-based medicine as we move into the 21st century.

I'm so excited that we have the chance to talk with Dr. Andrew Scull, who is a professor of sociology at the University of California at San Diego. That might sound, at first blush, to be a departure for me. You might say, "Sociology department? That doesn't seem to fit into the kind of Jeff Bland-left-hemisphere-of-the-brain-reductionistic-analytic-Newtonian model of trying to understand the piece parts. It seems like

that's a broad brush, bigger picture perspective." The answer is "Yes. It is and it fits together beautifully with our whole concept of function-function at every organizational level."

Dr. Scull got his undergraduate degree at one of the colleges in Oxford University, and then came to the states and got his PhD at Princeton in sociology, and then went back and did a postdoctoral fellowship in medical history at the University College in London. Now he is a distinguished professor of sociology and social science studies at the University of California, San Diego.

Books by Dr. Andrew Scull

I wish I would have known of Dr. Scull earlier, but it was only as a consequence of reading his article that appeared in The Lancet (April 10, 2010) that I became acquainted with his work. The article that he authored was titled "The Art of Medicine: A Psychiatric Revolution."4 I did cite this article in a previous issue of Functional Medicine Update in 2010. Since then, I have become a "Scull-ite." I've been reading everything I can find that Dr. Scull has written, including Madhouse: A Tragic Tale of Megalomania and Modern Medicine, which reads like the greatest thriller novel that you'd ever imagine. You can't believe that it is actually a true story. We'll be talking more about that. His book Museums of Madness: The Social Organization of Insanity in Nineteenth Century England was, I think, one of his first books, published in 1979. And then I most recently read Hysteria: The Biography(Oxford University Press, 2009).5 Dr. Scull has to help us understand-through the lens of the past-what the future of medicine might look like as we as we try to ferret out systems improvement.

With that as a long-winded introduction, Dr. Scull, thanks so much for being part of Functional Medicine Update. We really appreciate it.

AS: Thank you so much for that awesome introduction. It's most kind. I'm very pleased to be able to talk with your listeners.

The Significance of the Diagnostic and Statistical Manual of Mental Disorders

JB: Let me, if I can, start down the path. There are many ways to get into this hologram of understanding the things that you have been investigating and talking about for these many years. Let's start with psychiatry, because that is one that you have done such in-depth work in (the history of psychiatry). In one of your publications you talk about the use of medicines in anglo-American psychiatry, and how that really interrelates to the Diagnostic and Statistical Manual of Mental Disorders (DSM4), and what is a disease? Those questions are all tied together. Maybe you can help us by guiding us down this path.

AS: Yes, let me try to talk a little bit about that situation. American psychiatry, in particular from World War II onwards for about a 20 or 25 year period, was heavily dominated by psychoanalytic ideas. During that period there existed two editions of the Diagnostic and Statistical Manual, but they were neither very large nor terribly important, in part because those diagnostic categories didn't mean much to psychoanalysts; that wasn't something that concerned them.

During the 1970s, the American Psychiatry Association put together a task force to re-write that manual, and it turned out to be a very groundbreaking document, something that I think reoriented not just the field in the United States but all across the world. By way of context, of course, psychiatry had already experienced a tremendous shift in therapeutics with the advent (beginning in the mid-1950s) of so-called antipsychotic drugs, the first of which was Thorazine and the whole category of phenothiazines.

Subsequently, as we know, the category of anti-depressant drugs came to the fore as well. There is actually a synergy between the DSMIII as it appeared in 1980 and the subsequent edition, DSMIV. Four has been revised and there is a fifth edition in the works; it will be out in a couple of years.

When that manual was rewritten for the first time in 1980, it really began to...it is often referred to as a "neo-Kraepelinian" kind of document, after the famous late 19th century German psychiatrist, Kraepelin, who would distinguish between dementia praecox (later relabeled "schizophrenia") and manic depressive illness. The dividing up of the mental illnesses that occurred in that manual really, to some degree, reflected the drug revolution, and then as the manual has evolved over the years, it has continued to be a central focus of the way in which disease is being conceived by psychiatry and the way, increasingly, it is treated. So it has helped to cement the re-biologization of the field: the attempt to claim that mental illness is a primarily biological event that can be treated by specific classes of drugs, so that those diagnostic categories in turn link up with different forms of therapy. But it turns out, as the manual evolved, we see new drugs in a sense creating new diseases, if that makes sense to you. That is, the advent of a class of drugs that potentially has some effects is then a search for ways reconfiguring the way we think about mental illness and to link those two things together.

I think in general if we look at the evolution of psychiatry over the last four or five decades, what we see is a shift away from a period where social and psychological factors were considered as central parts of the picture to one where increasingly we move towards biology. If you look at the pattern with psychiatric training programs in major medical schools, in 1970 virtually every major department in the United States, with the exception of Washington University in St. Louis, was headed by either a psychoanalyst or what we might think of as a psychoanalytic fellow traveler. And if you look now, none of them are. Everything has moved in the direction of neuroscience. Everything has moved in the direction of biological research and drug-related research. So the field has moved very sharply away from where its center of gravity was three or four decades ago, and that's not unprecedented in the history of psychiatry.

If you look to the 19thcentury, when the large asylums first come on the scene, the logic behind them is the notion that a therapeutic environment (largely a social psychological environment) will be the primary mechanism of cure. But by the end of the 19th century (by the last third of the century), we'd moved to an era where a much more pessimistic, hereditary account of mental illness is abroad. Mental patients are largely seen as people whose biological mechanisms have gone awry.

Oddly enough, from 1870 to past 1900 you have this very strong emphasis on the biological roots of mental illness, and then almost exactly 100 years later we see exactly the same phenomenon emerging. It all depends, of course, I suppose, how one assesses that. It depends on whether one believes: A) the science is sufficient to justify that engagement, and B) that things aren't being lost when the social and psychological dimensions of mental illness get diminished attention. I think, in lots of ways, the DSM is both a symbolic event, and, practically, tremendously important. It marks a decisive move within psychiatry. It has not just been an American event. It has been something that has had worldwide significance.

JB: That's a wonderful platform and context. I think you were very politically gentle and gracious in the way you described that, because there seems to me-and I may be over over-reading this, so I will stand corrected if you think so-that there is an interesting bifurcation that occurs from this concept of psychiatry as focused on the mind to psychiatry focused on the body. It seems like this body/mind duality got kind of

shifted over. Rather than looking at it as body/mind or a mind/body as one whole, we went from one part which was the mind (psychoanalytical Freudian psychology), over to another part which is the psychobiology of psychotropics. Am I exaggerating, here? It seems like we missed something in the middle, which was the connection of the holograph of mind/body.

Psychoanalysis versus Biology: Shifting Perspectives

AS: Yes. Well, I think largely not. I mean, there's always danger, of course, when one is describing a complex reality and you paint in broad brush strokes, but I think it's fair to say that overwhelmingly we've had exactly that kind of shift occurring. It was always difficult for me to comprehend, as I looked at the history, the sense that psychoanalysis could be an effective therapy for schizophrenia, for example, although there were Americans who claimed that it was. Likewise it is hard for me to imagine we can move into a world where we ignore the mind side of the equation and the contextual part of mental illness.

As I read the literature, at least, the etiology of most of the major mental disorders is still very much up in the air. We have some suggested hypotheses. We have some clues. We have some hints. But part of the discord is not only do we not have much more than palliative therapy for these conditions, but our level of understanding of them is really quite primitive. Yet, when these enthusiasms take hold in either direction, there tends to be a neglect of the limits of our knowledge and we get carried away with enthusiasm for what, at best, are partial solutions. And those enthusiasms, in the longer lens of history, can come to seem rather odd, if not downright bizarre.

Since physicians are trained predominantly to think of illness as a biological event, there is always a tendency to move back in that direction. And certainly during the time when psychoanalytic perspectives were dominant, it is clear that the relations between psychiatry and the rest of medicine sometimes got quite strained because the notion of talk therapy for illness seemed a very odd one to most doctors, not to mention some of the details of psychoanalytic theory that many of them found difficult to swallow.

You know, the same tendency to pull back towards the body in the past has led to some really-what is seen after the fact-very odd kinds of intervention. Not that some of them don't sometimes seem to have had purchase. One of odd things about the history of 20th century psychiatry is there have been two Nobel Prizes awarded to psychiatrists. One was the invention of fever therapy for tertiary syphilis, which produces a multitude of psychiatric problems. And the second was for lobotomy in 1949. Oddly enough, no prize for any of the drug therapies that now would dominate psychiatric practice. If we look at the 30s, for example, you see a period of extraordinary drastic sorts of physical therapies that are introduced on a very casual kind of basis, things like insulin comas, and metrazol to produce seizures, and ECT, which still survives as a treatment modality (almost alone among these things), and of course lobotomy itself.

Not to equate modern therapies with those, but it is important to understand that with psychiatric drugs there are limits. We often forget (unless we're on the shop end of these things) that these drugs can, in many instances, carry severe side effects along with them. There are many patients who fail to respond to the drugs, and even for those who do, what they do is control symptoms. I don't mean to minimize that. That's an important accomplishment. But they certainly are not a psychiatric penicillin. They don't make any of these conditions go away. One of the things that troubles me about the way in which we seem to lurch from one extreme to another is that we lose perspective, and we get overly enthusiastic about whatever the fad of the day is, and that is certainly a concern I would have in the present climate.

JB: Yes. You said many, many things that are very interesting. I want to follow up on one that I think spawns many other issues. I may not be quoting exactly what you said, but something like, "New drugs create new diseases." You can think of agoraphobia, or you can think of attention deficit hyperactivity disorder, which didn't exist as a disease entity decades ago. I even think of-and I may be stretching the envelope a little bit, here-cholesterol. Cholesterol is almost seen like a disease. The number one selling drug in the Western world is a cholesterol-lowering drug for which the drug is being used to treat no disease. It's being used to treat a number, which has a relationship-in statistical association-with a disease, but once you start to define cholesterol elevation as a meta-disease, it takes on a life of its own and creates its own mythology, it creates its own technology, its creates its own standards of care, it creates its own economy. It seems, if you use psychiatry (what you've observed) as kind of a model, that that same phenomenon of new drugs creating new diseases...I mean, look at erectile dysfunction-there's an interesting one. It just springboards down. So it raises the question: Do we use biology as a stocking horse for the sale of drugs?

AS: Yes, I would think so. And if you look actually at the statistics on the larger-selling categories of drugs, both anti-psychotics and antidepressants rank in the top five in terms of sales and profit. It is fairly obvious there is a huge incentive there. If any of your listeners have been following the medical journalism that has been emerging and the lawsuits, a lot of evidence of the drug trials being manipulated in ways that are quite alarming so that findings that Big Pharma doesn't like get suppressed and those trials don't see the light of day-we see only a very selective sample of what's going on-and that's not something confined to confined to psychiatry, obviously. So these are deeply troubling events. On the one hand, whether it be the misery of psychiatric illness or the degradations of other kinds of illness, we're desperate for cures, but in the search for them, what we fail to realize is that interventions always come with a price, and sometimes that's a price worth paying, but we do need to be cognizant of that fact. To use a famous phrase from another social science, "There's no free lunch here." One does worry that indeed it seems like that with the statin situation. Frankly, for healthcare budgets at a time when, in the United States, healthcare is now absorbing .17 of every dollar, the explosion of those new things-constantly one wonders where that's going to lead down the road.

To come back to the point you made at the outset of that question, though my work is largely focused on matters psychiatric, psychiatry is not so different after all from much of the rest of medicine. It's different and it's not. Some of the things we see in the psychiatric realm do carry over into other realms of medicine.

JB: Let's pick up on that, following on that train of thought. Let's look at the DSM and this concept of the primacy of disease. As we get into more granularity of differential diagnosis and start defining specific conditions as diseases-let's use autism as an example, which really, mechanistically, is a variegated presentation of all sorts of different distortions of neuronal function that we try to lop into one diagnosis and then hopefully make that so it could be treated with one drug. This construct of what I call reductionistic medicine seems like it drives us into a model that is very, very limiting, relative to the way that the new biology talks about networks and talks about connections. In fact, it even drives us into the organizational structure of medicine of guilds, which become specialty boards that do standards of care, in which everybody is sitting around speaking the same language and patting one another on the back, saying "This is what we believe to be our truth for the reasons of expediency." It seems that there is a whole social nexus that derives out of this conceptual framework of taking complex issues and reducing them to simple diagnostic criteria and calling that a disease. Am I wrong?

The Politics of Establishing Psychiatric Categories

AS: No, I think that is absolutely right actually. What we have learned about DSM-V, which has yet to appear, is that there is an attempt to broaden the diagnosis of autism to talk about autistic spectrum disorders, which potentially sucks many, many thousands of new patients into this ambit and with that label, which has obviously very profound consequences for people who are given it and for parents who are struggling with children whose maturation may be different than the norm. That's certainly a valid observation. And I think if you look at the construction of the DSM, it purports to be a scientific document, but in fact the construction of those categories was often a heavily political enterprise, where horses were being traded to get to a consensus that really was relatively artificial, but then once it exists, it is ratified. It acquires a significance in all kinds of ways that perhaps its creators neither fully intended nor anticipated. That, too, is a big, big problem.

The difficulty of defining the boundaries of disease-and particularly a psychiatric disease-goes back a very, very long way. There was a time in my nominal home discipline of sociology where sociologists talked about mental illness as the product of labeling, which I think was romantic nonsense. But at the margins, you can see what those people were getting at. I think all of us encountering somebody who is completely dissociated with reality-whose cognitions, whose emotional reactions are far beyond anything we've experienced-as competent members of the culture, we don't need to be experts to know there is something radically different about those sorts of people. But where do we draw the line between eccentricity and madness, for example? That's been contested all through history, and the problem with these diagnostic categories is when you get the blurring at the boundaries. For example, if you start talking about-as has happened in the past and is again about to recur with DSM-V, depending on how the final negotiations go-preventative intervention, that is, looking for the precepts of the psychosis and treating patients before they actually become unhinged, that is a real slippery slope and potentially something that creates the very thing you want to avoid. If you start treating people differently because of what you assume may be the developmental path in the future, you're creating a situation which can kind of rebound on them and on you.

The Social Context of Disease

JB: Yes, and I think you said earlier something that's really an important takeaway from this discussion, and that is the social context of disease. I think in psychiatric disease, the social context becomes very probably more obvious than maybe other diseases, but they all have a social context. We live up here in the Pacific Northwest in Seattle, andthere is an ancient tribe of first nation people in British Columbia called the Haida Indians. The Haida Indians were the carvers-they did the totem carving. A lot of people wonder why the faces of many of the figures in these totems seemed so distorted. What I have read is that in their culture, individuals who were born that might today have what are called psychiatric disorders or diseases were considered unique in their insight. You know, they were speaking closely to a spiritual being and therefore they were more revered. And they were actually carved not as disfigured human beings, but as unique features in their society. What would have been their DSM back in that time?
I know you have written on this-you're actually an expert on this in your book Hysteria: The Biography -the word "hysteria," in language, has an interesting context because I believe, if I'm not mistaken, it comes from the Greek root that has something to do with the womb.

The History of Hysteria

AS: "Hysteria" is the Greek for womb. It had, for much of its history, a kind of gendered context to it. It was seen, perhaps peculiarly, as a disease of women, and then at times not. Beginning with Thomas

Willis in the late 17th century when you get a neurological account of hysteria's origins, when once again it's a real disease and the root is in the nervous system, That opens up the disease as something that both men and women can experience. At various times in the history of hysteria we see that kind of rediscovery of male hysterics from many people, including physicians at the time.

Shell shock in World War I was often seen as a form of hysterical disorder. That was certainly true among German physicians, and it was true among the French, and for some British, who were coping with this epidemic of apparently psychogenic disorders in the troops. That was a huge military problem. And, of course, now anticipated because of what we have seen in every industrialized theater of war. Fortunately, in my view, the appalling things that people witness and sometimes have to do on the battlefield are things that most of us recoil from in normal times and have a very hard time processing and dealing with. That, I think, well may have something to do with all the psychiatric troubles that flow from war. In World War I it was shell shock. In World War II, it was combat fatigue or combat exhaustion. And, of course, by Vietnam it had become Post-Traumatic Stress Disorder. And that concept which began as something applied to these military casualties has spread to victims of trauma in civilian life and it has acquired a life of its own, as categories tend to do.

How the Gut has Factored into the History of Psychiatry

JB: I think you really described this-historically--very beautifully in the book, Madhouse: The Tragic Tale of Megalomania and Modern Medicine. You talk a little bit about the turn of the last century, with Pasteur and the infectious disease revolution, getting to Elie Metchnikoff, the father of immunology (winning a Nobel Prize in medicine in 1903), and how Metchnikoff talked about prolongation of life through this gut connection to the body. There was a dominant theme that the gut had something to do with systemic health through infection and endotoxemia, which then spread into psychiatry and became a dominant theme for abdominal surgery in the 20s and 30s in America. All of this history tends to point me in a direction that says something about our tendency to medicalize changes in functional status. Without looking at cause, we jump into medicalization by quantifying, naming and blaming (as Dr. Sid Baker calls it), and then producing a procedure before we understand where the dysfunction really originated.

AS: Yes, I think you can actually push that even further back. It is very much the case that with the rise of bacteriological models of disease the gut became very suspect, not just among some psychiatrists. A lot of other fields of medicine looked at this, and particularly the notion of what was called focal sepsis: chronic, low-grade, untreated infections producing illness at a distance, so to speak, and the connections not being made. But you can push that back even further if you move to the two millennia or more of Western medicine where Galenic and Hippocratic notions of the four humors were dominant. That was a period, as well, where notions of defects in the digestive system and the bowels were obviously the focus of a lot of attention-bleedings, and purges, and vomits very much the central remedies against disease. In some ways, that notion of kind of inner cleanliness--you can see it exploited by ads for constipation remedies today--it's got a resonance both in folk belief and in medicine that sometimes can produce a pretty gross effect.

There were a number of major figures, like Franklin Billings, who was the Dean of the University of Chicago Medical School back in the nineteen teens, who became general advocates of this notion that much of ill health could be traced back to problems in the bowel and the digestive system in general. So when Henry Cotton comes along and applies those notions in psychiatry, you know, in a certain sense,

they are part of the air almost at that time. We develop models of disease and we sort of push everything to fit in. At the time of bacteriology, it was assumed that pretty soon disease would be amenable to intervention and many of them would cease to be very problematic. Unfortunately, that has turned out not to be true, not to minimize the importance of that revolution. It has given us some purchase on disease we didn't have before, but it by no means is it a panacea.

JB: Let me close. This has been-by the way-a fascinating discussion for me and I think the listeners are really getting a whole conceptual framework. What we often focus on is the moment of what we should do rather than the context in which we are doing it, so I think you are really helping us to see, contextually, some of the ways that we ultimately are directed into what we do.
I'd like to have you talk about your views on what I see as a paradigm shift that is occurring (or recurring-I think it occurred at the turn of the last century to some degree, but it's now gaining a lot of momentum)-and that is this genes/environment connection: that we carry with us this pluripotential in our genes that is expressed as a consequence of the environment in which we find ourselves-the psychosocial, the chemical, physical, molecular, and electromagnetic environment where we find ourselves. That, to me, produces a different kind of thoughtfulness about medicine, because rather than single diseases existing individually, what this does is it connects together different dysfunctions so that diseases become less important and the origin of the dysfunction becomes more important. We are moving from isolated points that lead to specialization in medicine to looking at connectedness, and networks, and how normative behavior influences these. Do you see this as an issue?

AS: I think what you are painting is what one sees in one's optimistic moments perhaps. Obviously it is what one hopes will happen. I think these would be the growing interests in genomics and genetics in relationship to medicine. This is often fueled among the public--and to some degree the earlier enthusiasts--with much too simple a model of how genes and disease might be connected, so that there would be a simple one-to-one correspondence between some kind of genetic abnormality and the appearance of a particular kind of disease. I think increasingly we are realizing-rather along the lines that you were suggesting-that it is not just one site on the genome, but a bunch of things may contribute. And what they provide is a context within which disease may or may not materialize depending upon a host of other factors, including environmental ones. And as long as we keep that in mind and don't assume that there is going to be some simple-minded kind of unlocking of the key of disease that excludes those factors, then that indeed could be a very positive development.

JB: So let's go back 360 and finish with the last question. Given all of this landscape that you've taken us across, coming back to psychiatry, what's your vision as to where psychiatry is going as a discipline? How do you see it changing-if at all-over the visible future?

Thoughts on the Future of Psychiatry

AS: You know, most of us turn out to be pretty bad at forecasting the future, so you are asking me to go out on a limb here. What I think will happen probably over the next two to three decades is that what I see as a swing of the pendulum too far in a single direction will probably exhaust itself, and we'll see a revival of a more complex picture of mental illness that brings some of these other elements back into being. Part of what's happened is that the psychotherapeutic part of the enterprise, for lots of reasons (including what insurance companies are willing to reimburse and so forth), has tended to move into another professional arena: into the hands of clinical psychologists using cognitive behavioral therapy and the like, and psychiatric social workers. So that end of things, within psychiatry, has tended to be

minimized. I don't think that's sustainable over the long haul. I would guess it will prove not to be sustainable. But we shall see. It's always impossible to predict what kinds of research breakthroughs may occur.

We talked earlier about how autism is sort of spreading and becoming much more amorphous as a category, and I think a lot of the categories we use to think about psychiatric disease don't really cut nature at the joints, so one of the things we may see is we may discover some things that allow us to move beyond creating diagnoses by committee, which is basically what DSM has done for some fraction of mental disorders.

After all, in the past, if you lived in 1880, people thought of what they call general paralysis of the insane as simply a subtype of insanity, and only in the early 20thcentury did we definitively begin to understand that it had its roots-in this case-in tertiary syphilis. So I don't know whether those things will be forthcoming. None of us, I think, is able to peer that clearly into the future. But I think looking at the way, over the past couple of centuries as medicine has consolidated its interests in mental illness and has striven to cope and understand it, we have seen these kinds of broad oscillations between emphasizing the mind, emphasizing the brain, and we are presently in the midst of one of those brain moments, but I suspect that the underlying reality is so much more complicated that eventually the profession will be forced back to recognizing that.

JB: That's very, very interesting. When your students come to you and say, "Dr. Scull, I really enjoyed being your student. I've enjoyed this whole field, and somewhere along the line I'm going to have to make a living and I'd like to do it in the social sciences. Where do you think I ought to put my footprint?" Is there a place, as you see it, where in the immediacy this model of thinking is going to have applicability in social work, or social sciences, or in medicine?

AS: That's a hard one to call. A number of my students with that orientation have ended up going into public health programs, actually. Others, off to medical school. I had an absolutely wonderful student about three or four years ago who is presently at Stanford in an MD/PhD program, but before he went to Stanford he said to me, "I really want to do more medical history. I think it's going to make me a better researcher and a better clinician." And he went off to London and did a master's in medical history before he went off to medical school, and I think many of his science professors-because he is a quite brilliant student-thought, "What on earth are you doing? Why don't you jump straight in?" But, in fact, he came back from that experience, won the William Osler Medal for writing the best essay on the history of medicine after simply one year of graduate training, which was extraordinary, and students like that give me hope about students going into medicine more directly, but with a more contextualized understanding of disease and its history, may be the ones that help us move in a more balanced direction.

JB: That's a beautiful way to finish this discussion. What a great optimistic perspective. Thank you so much, and, again, I'm going to follow everything you write. I encourage our listeners to. If they want to start with a spellbinding book, Madhouse: A Tragic Tale of Megalomania and Modern Medicine is that kind of book. I couldn't put it down myself. It's such a fantastic history of psychiatry from this perspective of the anatomical/physiological relationship of infectious disease to neurological function. Keep doing what you are doing. It's really a good guidepost for us and I appreciate it so much.

AS: Thank you so much. I've really enjoyed the conversation. I hope your listeners will find something of

value in it and I much appreciate you getting in touch with me. Thanks again for the kind words.

JB: Thank you.

Dr. Linus Pauling's Writings on Psychiatry

I hope you enjoyed that discussion with Dr. Scull as much as I did. What an amazing personality, teacher, historian, and communicator. As I listened to him and had a chance to read his books and papers, I was reminded of the extraordinary journey of psychiatry, even in the area of molecular medicine, and the pioneering, almost-paradigm-shifting paper that appeared in *Science*magazine in 1968 titled "Orthomolecular Psychiatry. Varying the Concentration of Substances Normally Present in the Human Body May Control Mental Disease."[6] Of course, the author of that paper was none other than Dr. Linus Pauling, two-time Nobel Prize-winning laureate. It is interesting to note that when I talk about Dr. Pauling now to some of the younger people coming into the profession, they are not actually familiar with his name, which I think is a tragedy. He still remains, today, the only person to have won two independent solo Nobel Prizes in different disciplines, one in chemistry and the other in peace. He was the father of so many ideas that come into our culture now as kind of well-accepted paradigms: the mechanism of anesthetic drugs, and the concept of immunology that he developed with Delbrook while he was at Cal Tech, protein structure (i.e., the structure of collagen, even the Watson and Crick double helix was born in part-as you know, if you read The *Double Helix*by James Watson-through exchanged communications from his son, who at the time was in England with Watson and Crick, about his father's x-ray crystallography work on what later became known as the double helix (Pauling thinking at the time that it might have been a triple helix).[7] These impacts he has had, and then going on into the area of peace and the nuclear atmospheric test ban treaty that he and Albert Einstein and Albert Schweitzer, which was a very fundamentally important step for scientist's advocacy in getting the ban on atmospheric testing. All of these are historically interesting parts of the social fabric of our society and the great mind-the social mind, the mindfulness-of our society.

The article that appeared in *Science* really set a tone for reviewing the nature of mental illness-where it came from-suggesting that concentrations of various substances within brain biochemistry that are unique and normal to human physiology could help explain the origin of schizophrenia and other mental diseases, and that by modulating the environment using natural substances one could restore improved function. In the article, Pauling wrote: "The functioning of the brain is affected by the molecular concentrations of many substances that are normally present in the brain. The optimum concentrations of these substances for an individual may differ greatly from the concentrations provided by his normal diet and genetic machinery." This would be what we call the biochemical individuality concept that Roger Williams spoke about in the 40s and 50s. "Biochemical and genetic arguments support the idea that orthomolecular therapy, the provision for the individual person of the optimal concentrations of important normal constituents of the brain, may be the preferred treatment for many mentally ill patients. Mental symptoms of avitaminosis sometimes are observed long before any physical symptoms appear."

It has been said that neuropsychological effects are some of the first signs of chronic vitamin intake below the levels necessary for optimal function, well before you get into the deficiency symptoms of scurvy, , or pellagra. Pauling also wrote: "There is a possibility that for some persons the cerebral spinal concentrations of vital substances may be grossly low at the same time that the concentration in the blood and lymph is essentially normal. A physiological abnormality such as a decreased permeability of the

blood-brain barrier for the vital substance or increased rate of metabolism of the substance in the brain, may lead to a cerebral deficiency. Diseases of this sort may be called localized cerebral deficiency diseases. It is suggested that the genes responsible for abnormalities (deficiencies) in the concentration of vital substances in the brain that may be responsible for increased penetrance of schizophrenia. The so-call gene for schizophrenia may itself be a gene or a series of genes that leads to a localized cerebral deficiency in one or more of the vital substances."

Dr. Abram Hoffer and Orthomolecular Psychiatry

That was Dr. Pauling's contribution in 1968 on the orthomolecular environment in the mind. It is another chapter in the history, explanation, and understanding of the etiology of neuropsychiatric disorders. Following up on that is the other founding member of this field of orthomolecular psychiatry. This is a person I interviewed and his interview was in the December 2009 issue of *Functional Medicine Update*. I'm talking about Dr. Abram Hoffer, now unfortunately deceased, but certainly one of the individuals who is credited with birthing this concept.

If you go back and look at Dr. Hoffer's work, he talked about orthomolecular treatment of schizophrenia back in the 1970s, and was actually a colleague of Dr. Pauling in the development of this concept. We can go well back before the 1970s, however, back into the 1950s, when he first observed the role that niacin had in modulating schizophrenic symptoms in some patients. In fact, if you go back to the *Acta Psychiatrica Scandanavica*, you'll find articles by Dr. Hoffer and Dr. Osmond, his colleague, about the treatment of schizophrenia with nicotinic acid, a 10-year follow-up in the early 60s, from the work they did in the 1950s.[8] It's a very interesting chapter in understanding the etiology of neuropsychiatric disorders.

If you listened to Dr. Pauling and Dr. Hoffer in the December 2009 issue, you recall they both said that these concepts are not good for everyone. In other words, there is this genetic heterogeneity, and schizophrenia has multiple causes with multiple molecular mechanisms that can contribute to it. Some of these causes may be related to this preclinical, pellagrous condition that we call schizophrenia. Niacin therapy may be a useful tool in modulating the intramolecular environment of the brain and stabilizing critical neuroregulatory substances and improving function. In fact, it is not only niacin. Perodoxine, cobalamin, and ascorbic acid have all been found, in different individuals, to play potentially important roles in the orthomolecular environment of the brain.

The Research of Dr. Michael Maes

With that in mind, let's move to a more contemporary view of this. Another colleague I've had the privilege of meeting and spending some time with is Dr. Michael Maes. He is an MD, PhD psychiatrist and a molecular geneticist from Belgium. Dr. Maes has an amazingly productive background in terms of his both clinical and research work, publishing well in excess of 100 papers over the last several years. I think if you trace through Dr. Maes' work, it gives another context of understanding the development and origin of neuropsychiatric disorders and the connection of systems biology to the brain. In medicine, we often tend to isolate organ systems as if they are compartmentalized from other organs and they have their own pathologies that are separate from other pathologies. Therefore, they have their own diseases, and

their own treatment regimes, and their own molecules that are using those treatment regimes, that are owned by certain subspecialists in that medical discipline. Psychiatry has its own drugs to treat its own diseases, as if the brain was really isolated from the rest of the body.

As we move forward in our understanding of systems biology, we recognize that what we used to consider to be comorbidities, where disorders would serendipitously line up together and have similar overlap, was maybe actually related to the fact that these comorbidities share common mechanisms of distorted metabolism. As an example, the arthritis connects to the osteoporosis, which connects to the heart disease through alterations in mechanisms of the immune system that trigger inflammatory response that can be seen in different patients as different degrees of presentation of either heart disease, osteoporosis, or arthritis (or a combination thereof). Rather than call these comorbidities, they really should be called outcomes of the same altered metabolic system.

By a similar token, if we look at the DSM (the direction as it relates to the diagnosis of mental illness), those diagnoses tend to be very broad and descriptive diagnoses that are more related to presentations than they are related to molecular distortions that lead to the individual presentation. So there may be multiple paths towards those different diagnoses. What we call them may be the same, but how we got to that name may be very different from patient to patient. It is that differentiation--that cohort kind of compartmentalization--helps us to better understand not just what we call it, but how the patient got to that state of signs and symptoms on presentation. It also helps to guide us as to how to individualize or personalize the treatment to the specific need of the patient. Rather than treat the name of the disease, we're treating the individual situation in that patient.

Research on Functional Deficiencies and Cerebral Metabolism

That is the model characterized by Linus Pauling and Abram Hoffer with the orthomolecular concept, but it now goes into other themes, beyond that just of the traditional vitamins-these functional insufficiencies or deficiencies-in terms of cerebral metabolism. That is what Dr. Maes and his colleagues have been helping us to better understand. It has been his observation that these conditions such as depression, or dysphoria, or various types of schizophrenias, or even autistic types of diagnoses, really relate, in part, to alterations in the neuroimmune system of the individual, and better understanding of the origin of distortions in neuroimmunology helps us to tailor a program of treatment to the individual needs of the patient. This cuts across into a whole family of companion comorbid situations that we consider related to alterations in neuroendocrine or neuroimmune function, including such things as fibromyalgia. I think it is very interesting that the drug LyricaTM, which has recently been approved for the treatment of fibromyalgia, works as kind of a gabapentin activator of function, which suggests an immune-neurological connection that is central rather than peripheral. So the trigger point pain found in fibromyalgia patients may have a central-mediated problem at the connection between the nervous, immune, and endocrine systems (this neuroendocrineimmune dysfunction).

As we learn more about neuroendocrine dysfunction, it helps us to understand how that interrelates with immunity and immunological function, and how it then goes out into a wide variety of diagnoses that are both in the psychiatric as well as in the immunological categories. Dr. Maes and his colleague, Dr. van West, first wrote about this in an article they published in BioDrugs in 2001, in which they said that fibromyalgia is "a form of nonarticular rheumatism characterized by long term and widespread musculoskeletal aching, stiffness, and pressure hyperalgesia at characteristic soft tissue sites called soft tissue tender points. The biophysiology of fibromyalgia, however, has remained elusive."9 Now there is

increasing evidence to suggest that there are various serum activities of neuroendocrineimmune disturbance that is then seen as muscle energy depletion, as it relates to altered mitochondrial function that is related to altered immunological function that is tied to inflammation. These concepts that we would go upstream and start actually looking at the origin of why you would have these interruptions in mitochondrial function that produces pain, some of which may be related to the social environment and others relate to the physical environment, is a different way of approaching the etiology and ultimately the treatment of fibromyalgia.

Dr. Maes has followed up on this concept of the neuroendocrineimmune system being a kind of combined system for regulating all sorts of intercommunication among centrally mediated processes, immunologically and peripherally mediated processes, and endocrine-related processes, and it ties together through the inflammatory response. He has published papers showing that the inflammatory response is amplified in women who previously suffered from major depression, suggesting that depression is accompanied by sensitization of the inflammatory response system.10 This could be like a dog chasing its tail: there may be something that starts the depression moving, that then alters the immune system, the immune system becomes more proinflammatory in its response to a perceived hostile environment, that then further circles back and causes more alteration in neurological function, which then sets more depression in place.

In his work, inflammation markers have been found to be associated with altered cognition and altered affect in aging populations. This was published in the Journal of Neuroimmunologyback in 2003. The suggestion is that if you start looking at things like high sensitivity C-reactive protein, and do testing of word learning tests and word recall tests in individuals, you will find there is a very close correlation between increasing inflammatory markers and decreasing memory and cognition, suggesting, again, that there is this interrelationship between nervous system function, and immune system function, and inflammatory signaling.

The Metabolism of Serotonin: Neurotoxins

As you probably know, serotonin is derived from the amino acid tryptophan, through metabolic conversion through kynurinic acid. These intermediary molecules in the metabolism of serotonin can be considered neurotoxins in their own right, and can have-in animals-effects on their mood and their nervous system activity. If you had an alteration in the metabolism of neurotransmitters coming up from the precursor tryptophan into serotonin and its byproducts, it would be possible to induce autotoxicity, which then could activate the immune system.

This is very similar to what Dr. Hoffer talked about back in the 1950s with his constructs of orthomolecular psychiatry. He talked about the alteration in metabolism to produce hallucinogenic substances that could induce, endogenously, schizophrenia. The chemistry at that time was not sophisticated enough to allow complete understanding of the various intermediary metabolites and all the orthomolecular environment. But today, as a consequence of multi-analyte testing and all of the high throughput screening we can do, and the ability to do analyte testing at a very low level of concentration, some of these intermediaries in this alteration-the web of physiology-are starting to be understood.

This autointoxication concept is getting more traction, and that's what Dr. Maes talks about as it relates to how these substances may interrelate with immune system activation and then be like a circular effect on

depression, anxiety, mood changes, and inflammatory mediators all working together. It is not just in the mind; chronic fatigue syndrome, fibromyalgia, and depressive disorders all swim together, work together, through the inflammatory pathways. You'll see increased NF-kappa-B activities as a gene transcription agent for activating the genes that are associated with proinflammatory cytokines. There is this sense that agents that amplify the inflammatory pathway may be aggravant substances for depression, mood, and behavior dysfunctions, for which we then treat the effect rather than treat the cause. In fact, if you look at some of the hallmarks of activation of gene expression of inflammatory mediation, like the activation of genes that regulate nitric oxide synthase and prostaglandin E2, you find that there is an activation of inducible nitric oxide synthase and cyclooxygenase 2 in chronic fatigue patients, and fibromyalgia patients, and depressed patients. This was actually published in *Neuroendocrine and Endocrinology Letters* in 2007.[12]

This model is another part of our evolving understanding of the origin of neuropsychiatric and neurophysiological disorders. If you start looking at tryptophan metabolites along the pathway of ultimate excretion of indoleamine metabolites from the metabolism of tryptophan through the serotonergic pathway, you see there is some relevance in individuals to the autointoxication concept that was first born out of work from the middle of the last century. By modulating the metabolism of these substances and improving their throughput into serotonin and their exit ultimately out of the body through detoxified intermediates, we improve the molecular milieu (the orthomolecular environment).

Eosinophilia Myalgia Syndrome: Tainted Tryptophan Resulted in Autoimmune-like Reactions

For those of you who feel this sounds like it doesn't have anything other than theory behind it, let me remind you that we had a condition called eosinophilia myalgia syndrome that was of extraordinary concern some 20 years ago. EMS led to the death of a number of individuals-more than 10-in the US, and literally thousands were adversely affected by this autoimmune-like reaction that had neurophysiological, neuropsychiatric, and neuromuscular relationships, symptomatically. The origin of EMS, which was virtually epidemic for awhile in its prevalence, was the consumption of tainted tryptophan that was manufactured by the Showa Denko Corporation in Japan by fermentation using microbiological production. These organisms that they were using were genetically modified, and unfortunately the final tryptophan was not cleansed of a small contaminant called peak-E, which was a tryptophan-type of dimer that with formaldehyde produced this very toxic effect on the immune and nervous systems that ultimately led to what we diagnosed and called eosinophilic myalgia syndrome, leading to death and very serious disability (sometimes lifelong disability) of people who consumed this tainted tryptophan. The amount of this peak-E amount of tryptophan dimer was very, very small. In fact, it was missed in the first analysis because it wasn't high enough in concentration until they went to a more detailed chromatographic analysis to find material in it. It was almost like a trace contaminant that had this very dramatic effect on immune and neurological function.

This tryptophan contaminant demonstrates, I think, that there are substances that even in very small amounts may have very profound influence on neuroendocrine immune function. The autointoxication concept is not so far away from what we observe factually, from clinical experience, to be thrown out as ridiculous. In fact, if you look at another condition called hepatic encephalopathy, I consider that an interesting example of autointoxication as well. This is often seen in hospitalized geriatric patients. They develop hallucinations and psychoses. The treatment of choice for that condition has historically been something like lactulose oral therapy, which causes diarrhea. It's a gut detoxification, and basically by

reducing the load of toxic metabolites from the gut, which are often protein byproducts from bacterial fermentation in the gut, it lowers the load on the liver. The liver of an older-age person that is hospitalized may not be able to completely remove these substances, and therefore they are delivered to the blood and then ultimately to the blood-brain barrier, where they have this effect of producing hallucinations and psychoses. Hepatic encephalopathy should really be called gastrointestinal hepatic encephalopathy, in which the gut and bacterial debris that comes from metabolism of various food stuffs and protein amino acids into secondary metabolites are not properly detoxified or regulated at the hepatic level, and then travel to the brain where they can have an adverse effect.

I think if we look at a little bit broader view of neuropsychiatry as it relates to the concept of autointoxification and take a more contemporary and modern view of it, it doesn't look quite as strange as it did back in the early 1900s. In fact, I think it is also interesting to note that the management of this is not gastric resection, as was discussed in *Madhouse* by Dr. Scull (how this was managed in psychiatric hospitals by surgery-by shortening the bowel), nor by giving antibiotics, but rather by regulating proper metabolism, and proper barrier function of the gut (the so-called gut mucosal barrier), and proper hepatic detoxification function. So the strategy-using the orthomolecular model of Pauling and Hoffer-would be to provide adequate levels of orthomolecular substances to manage the natural processes of regulating these substances.

I think this is a very interesting conceptual shift, from a surgical invasive intervention that was being used in psychiatric hospitals in the 1920s and 30s to a more orthomolecular modulation of the molecular milieu. Dr. Maes, in some of his more recent work, has looked at this gut connection to things like chronic fatigue syndrome and fibromyalgia. I'm very pleased about this because it was back in the early 1990s that our group first started talking about and publishing papers on the gut-brain connection and the gut-immune connection and its relationship to chronic fatigue syndrome and fibromyalgia. At the time, it was considered totally heretical thinking. I recall presenting at a number of meetings where it was considered absolutely ridiculous to consider the fact that there would be some connection between the gut and the immune system that would been seen as either chronic fatigue syndrome or fibromyalgia. Yet, in 2008, in *Neurology and Endocrinology Letters*, Drs. Leunis and Maes published an article titled "Normalization of Leaky Gut in Chronic Fatigue Syndrome is Accompanied by Clinical Improvement: Effects of Age, Duration of Illness, and Translation and Translocation of Lipo-polysaccharide from Gram-Negative Bacteria."[13] That's a very interesting title and I don't know if it completely resonates with you, I think it is a very important title, clinically.

We have this barrier function called the gut mucosal membrane. That gut mucosa is not only actively involved in excluding the translocation of bacteria, but also in engaging in detoxification and selective transport of nutrients while excluding toxins. So there is a detoxification process going on in the gut mucosa, as well as (obviously) in the liver. When you get a breakdown in the gut barrier function and you get this paracellular leakiness, it can lead to translocation not only of bacteria, which can induce immunological effects, but also to middle molecular weight molecules, things that were previously excluded and had to be detoxified before they were passed into the blood. This leakiness, which can be measured clinically in patients with things like the lactulose-mannitol oral challenge test to look for gut permeability, is a very interesting concept that ties to endotoxemia and relationships to quality of diet, environmental agents, stress factors, all of which can alter the integrity of the gut mucosal membrane. These portals of entry through a leaky gut to the gastrointestinal associated lymphoid tissues of the gut-immune system allow exposure to foreign molecules, which then initiates various types of immunological

responses, including the production of proinflammatory mediators.

I think that what Dr. Maes and Dr. Leunis are talking about in this *Neuroendocrine and Endocrinology Letters* article is the fact that if you look at chronic fatigue syndrome patients and examine inflammation and gut function, you find there is a very strong interrelationship. What they found is that by administering agents that help to improve gut immune function and gut mucosal integrity, such as the amino acid L-glutamine given therapeutically, N-acetylcysteine, and zinc, in conjunction with a low gluten diet and a diet that is not high in solutes, like salt and sugar and saturated fat, that you can actually restore proper gut immune integrity (mucosal integrity), lower inflammatory mediators, and reduce the symptoms of chronic fatigue syndrome.

This has been re-studied by a number of other investigators and we've spoken to some of these studies in previous issues of *Functional Medicine Update*. We have talked about how one high fat, high sugar meal in apparently healthy people has been demonstrated to increase post-prandial bacteria lipopolysaccharide in their blood, to increase pro-inflammatory cytokines like TNF-alpha and IL-6 in their blood, and to activate immunological response.[14]That's just one high fat, high sugar meal. What happens if a person eats that day in and day out, meal in and meal out? They are-to use kind of a descriptive term-driving holes through their GI mucosal membrane and increasing the exposure of their gastrointestinal immune system to these immune active substances that can then generate more proinflammatory mediators.

All of these things, I think, are very interesting as it relates to a systems biology process of looking at how the gut, the diet, the environment may interrelate to various psychiatric diagnoses. We're not-again-talking about the necessity for gastrointestinal resection or surgery. We're talking about appropriate orthomolecular provisions for function at the gut immune level, the hepatic level, and circulating white cells in the blood-brain barrier.

How would you compare this type of an approach? We call it the 4R approach-remove, replace, reinoculate, repair therapeutic approach. Removing the offending agents that are causing alteration in gut mucosal integrity, things that would be considered like parasitic organisms, or food allergens, or toxins. The second "R" is that of "Replace" (replacing digestive enzymes and acid where necessary to stimulate proper digestive function). The third "R" is "Reinoculate" (adding pre- and probiotics-symbiotics-to stimulate proper friendly bacteria and push out the toxic parasitic bacteria. And lastly "Repair" is the fourth "R" (to add those nutrients like glutamine and zinc and essential fatty acids of the omega-3 family that are necessary for repairing proper gut mucosal integrity).

How does this 4R approach contrast to the generally accepted approaches to chronic fatigue syndrome, things like cognitive behavior therapies? There is a nice paper that has been published-again in *Neurology and Endocrinology Letters* -in 2009, in which the effect of cognitive behavioral therapy in chronic fatigue was examined and it was found that although a lot of people feel this is the standard of identity and the standard of care, in this treatment trial, there was no significant benefit of the cognitive behavioral therapy, and managing, in the long term, chronic fatigue syndrome symptoms and severity.[15] In fact, in a study in *Current Opinions in Psychiatry* in 2009, volume 22, it was found that people with chronic fatigue syndrome actually did best when they were placed on a program that was lowering inflammatory burden, improving gut mucosal barrier function, and reducing things like cyclooxygenase II activities and inducible nitric oxide synthase activities, and that that had an effect also on their mood.[16] This not only

improved somatic symptoms like aches and pains (muscular tension and fatigue), but also it had a very positive effect on reducing irritability, sadness, and a subjective feeling of depression. Again, this is the body/mind connection through this kind of a systems biology approach.

I think this cytokine hypothesis of depression and its relationship to inflammation and oxidative and nitrosative stress and leaky gut really represents a new target for adjunctive treatments in depression. I think the concept that there are secondary metabolites of various biomolecules that may be considered neurotoxic is not an unreasonable thing to consider given the expanding body of understanding we have about the molecular milieu of the mind. We're starting to see much more of the interconnection between the gut-brain barrier in major depression, how intestinal mucosal dysfunction is associated with increased translocation of lipopolysaccharide from gram-negative entero bacteria and how it plays a role in the inflammatory pathiophysiological role seen in depression and maybe other behavioral and psychiatric illnesses. So I want to go back and give credit to the founding figures upon which this field is being built, Dr. Pauling and Dr. Hoffer. Dr. Maes' work continues to extend this concept, and also-I think-the 4R program, a therapeutic concept we developed in the functional medicine model some 20 years ago. People now see that this really has a tremendous opportunity to advance successful outcome in patients with these chronic neurochemical, neuroimmune, endocrine dysfunctions, like chronic fatigue syndrome, fibromyalgia, and other depressive disorders.

I want to once again thank Dr. Scull for his extraordinary history lesson that gave us a timeline upon which we viewed advances that are being made in this field and recognize that we shouldn't throw a baby out with the bathwater. We ought to look at the best that exists and assemble new information into new therapeutic tools that will help alleviate these very complex disorders of the mind.

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