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Overview of Alzheimer's disease

The program provides insight into the current understanding of the disease processes underlying Alzheimer's disease; namely:

- **Recent advances in genetic markers**
- **Risk factors and lifestyle as risk factors for Alzheimer's disease. The medications and potential therapies to prevent and slow the progression of Alzheimer's disease**

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JON MERRIL: This podcast is on the topic of the nature and treatment of Alzheimer's disease. We are honored to have Constantine Lyketsos, MD and Master of Health Sciences. Dr. Lyketsos is a Professor of Psychiatry at the Johns Hopkins University. He is also the Chairman of Psychiatry at the Johns Hopkins Bayview campus. He is The Academic Director of the Copper Ridge Institute.

Our first question for Dr. Lyketsos is the question of medications to prevent Alzheimer's disease. Are there any medications that effectively prevent Alzheimer's disease Dr. Lyketsos?

DR. LYKETSOS: No, none.

JON MERRIL: Well, how about food products? Are there any food products that have proven to be effective in preventing Alzheimer's disease? Are there any merits to claims about blueberries helping to prevent the disease?

DR. LYKETSOS: Several things have merit. It is very complicated to do prevention studies to prove that things work. We've been studying anti-steroidal anti-inflammatories. We're about seven years out from a study looking at Aleve which is commonly available and Celebrex celecoxib, the study has cost many millions we're just about where we have an answer but I can't tell you what it is though because it hasn't been published yet. But the bottom line is one of the reasons we don't have an answer yet of many of the promising compounds like antioxidants which is the mechanism that involves blueberries and high dose vitamins etc that is so hard and costly to get the answers.

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JON MERRIL: So, in summary are there any studies or any evidence that suggest that blueberries are effective in preventing Alzheimer's disease?

DR. LYKETSOS: I don't know is there is specific evidence for blueberries and Alzheimer's but any evidence that exits is what we would call observational. I am quite sure that there has never been a clinical trial with blueberries, so is not quite antidotal but its sort of a level above that but it's not definitive.

Curcuminoids which is what I believe is what you find in turmeric and related foods that are eaten in India they are being studied. In test tube bottles and animal models they seem to be quite good at treating some of the elements of Alzheimer's that relate to amyloid and how it amyloid damages tissue. But you're right we actually have some ideas about compounds we'd like to test but it's very

hard to get what's called the intellectual properties around those, so you can then find individuals who will spend many tens of millions necessary to do the development.

JON MERRIL: Let's switch gears now to prescription medications. What are the names of the medications that aim at slowing down the course of Alzheimer's disease? How do they work and how effective are they?

DR. LYKETSOS: Well the answer to that question is the same as the one I already gave you so for the first three bullets prevent, arrest, and cure they all fall under same rubric as we don't have medicine many things are under study depending on where in the phase of Alzheimer's you want to introduce the medicine. The cost of showing that a given drug works in that phase differs. So if you take people who already have symptoms it cost less to show that a drug works or doesn't work. If you look at people in early symptoms first memory loss later in life for example, it cost a little bit more. And if you're looking at preventing it, it cost even more. How you prevent it or how you treat it whether something is arresting progression or curing it's almost I need to ask you to define your terms there because this is such a complicated disease there isn't clear agreement on what it means to arrest progression or cure. In fact those two might be synonymous for some people.

All the meds we have now in some way affect the chemistry of the brain. We have three groups of medicines and they each have slightly different mechanisms of action.

One group are what we called acetylcholinesterase inhibitors and they are marketed under the brand names such as Aricept, Exelon, and Razadyne and what those three medicines do is they stop the breakdown in the brain of a chemical called acetylcholine. This chemical is produced by nerve cells that die off early on in Alzheimer's and by virtue of the nerve cells dying on there is less acetylcholine around which is important to memory signaling. So by using a medication to stop the breakdown or to slow the breakdown of that chemical more chemical is available even though neurons have died. So for some time period memory seems to function a little bit better. But eventually other neurons that are making the acetylcholine chemical die off, so there is nothing around, so inhibiting the breakdown of nothing around obviously doesn't help you.

Other mechanisms of action have to do with a medicine called Namenda. That medicine probably inhibits the toxicity that dying nerve cells have for other nerve cells so certain nerve cells as they are dying release big amounts of their chemicals and kill other nerve cells around them and that is one way that Alzheimer's is thought to spread. So Namenda probably interferes with that spread and might therefore delays the progression of the disease a little bit.

The third mechanism of action has to do with traditional psychotropics like antidepressants, antipsychotics which are often use in Alzheimer's disease to treat some of the psychiatric symptoms like depression, delusions, agitation and the like and each one of those has its own mechanism of action again relating somehow to manipulating chemicals in the brain.

JON MERRIL: Let's focus now on what types of symptoms we can expect to see disappear or decrease when a patient is on a particular medication for Alzheimer's disease.

DR. LYKETSOS: Well it is different for each for each type of medicine the cholinesterase inhibitor a caregiver, a patient and a clinician can in some cases expect improvement in memory symptoms and functional symptoms. Patients might do the things that they weren't doing as well for a period of time or there might be an apparent slowing in how fast the symptoms are progressing but they tend to be fairly mild and fairly modest benefits. Sometime they are hard to discern without stopping the medicine to see if in fact it's doing something. For medicine like Namenda it's even harder to know whether there helping an individual patient usually there isn't a marked improvement but there might be evidence clinically that the patient's progression has slowed down.

From the point of view of the psychiatric medications the strongest example would be to improve the depression the patients have so they might not be as irritable or agitated as they were before maybe they're sleeping better or maybe they're no longer delusional so that's where you can best measure change from those medicines.

JON MERRIL: Can you give us a summary of the different side effects that we can expect with the different medications that are

used to treat Alzheimer's disease?

DR. LYKETSOS: For the cholinesterase inhibitor drugs, the side effects are things like nausea, diarrhea, occasionally vomiting, some muscle cramps, occasionally slowing of the heart rhythm, very rarely a fainting spell. Namenda can cause dizziness, can cause a little agitation, can cause some sleepiness. The antidepressants and the antipsychotics, it really depends on the individual medicine, they each have their own spectrum of side effects they might be leading to motor restlessness in the sense of needing to move or tremors or headaches or GI upset like nausea, diarrhea, vomiting those sort of things or it might be sedation, it might be dry mouth, blurred vision, it might be constipation.

JON MERRIL: It sounds like it would be very important to be able to measure where someone is in their disease course with Alzheimer's disease. Is there a metric or a way of measuring how rapidly and in what stage someone is in their course of Alzheimer's disease? The reason why I'm asking this is that I would imagine this would be important both for new research that's being conducted with medications and figuring out if they are making a difference in treating Alzheimer's disease as well as on an individualized basis, figuring out whether particular medications are effective in treating an individual patient who has Alzheimer's disease. So, can you comment on the best way of measuring and providing these kinds of metrics in Alzheimer's disease?

DR. LYKETSOS: There are good metrics for measuring progression in people who have symptoms. There are no good metrics in measuring progression in people who have very mild symptoms or who have no symptoms at all. We know that the disease is changing the brain for many years if not decades before the first memory symptom happens but we don't know how to measure it in those people yet so we don't know how to test drugs yet.

JON MERRIL: There is a glimmer of hope in the future that we may be able to repair the damage that's caused by Alzheimer's disease. There was an isolated study of a man who had a particular type of damage to his brain. He was in a comma for twenty years and it was shown through imaging studies that some of the cells had regenerated parts that had been damaged. What do you think about the future of new therapeutic options where the brain could actually have enhanced capabilities to repair the damage due to Alzheimer's disease through the use of future medications or techniques?

DR. LYKETSOS: Well there is always promise. That's where people are talking about stem cells. In order to get any kind of tissue to either create new cells or to get damaged cells to function again, you have to understand cellular mechanisms that we don't understand very well yet or you have to introduce new cells and stimulate them to develop and take the place of dead cells. So in an organ that is simple or simpler like the heart actually people are directly injecting stem cells now that hopefully will become functioning heart tissue. And the brain in extraordinarily complicated so it's going to take awhile before we can go down that path in the brain.

JON MERRIL: Does the composition of the treatment team, the team that is treating a particular patient with Alzheimer's disease influence the type of care that is given to the patient, the types of medications or other therapies that are administered to the patient. Does the composition whether the team includes a psychiatrist, a neurologist or is solely based on a family practitioner, does that make a difference in patient care?

DR. LYKETSOS: Well that's a big topic and I don't know of specific data so I will give you my own opinion. The best piece of information I think that would add to your question is that probably 2/3rds of people with Alzheimer's don't get diagnosed. So that means they probably don't get specific therapies that relate to their condition. For the 1/3 who get diagnosed, it's unclear whether they get the full spectrum of what we call dementia care. My experience from patients who get referred to me is that most are not getting it. In fact we have an innovative program now through Hopkins that we're trying to deliver dementia care in home environments. So we're going out into the community, finding people living at home with dementia, and try to figure out how best to deliver to them dementia care at home.

JON MERRIL: Why do some people with Alzheimer's disease fall through the cracks and we don't diagnose them with Alzheimer's disease? What are the reasons for missing the diagnosis of Alzheimer's disease in patients?

DR. LYKETSOS: I don't know that there is a primary reason. There are probably several reasons they have to do with the disease still

being stigmatized, still being a difficulty that the lay public and many clinicians have in differentiating dementia from normal aging. A lot of people still think that memory loss is a usual part of normal aging. The answers is some memory loss is but not this level of severity. And there are colleagues unfortunately of mine who are very nihilistic and as you pointed out will tend to give up and say well why buy this person a few extra years, they're going to die anyway. I don't usually like that comment and I always remind people of the case of downs syndrome patients for who it's been good to expand their life expectancy quite substantially as we've done even though they're tremendously disabled, more disabled than the average Alzheimer's patient. Life is good a good thing.

JON MERRIL: What's the best way to distinguish between normal memory loss that can occur with aging and the memory loss that's associated with Alzheimer's disease?

DR. LYKETSOS: Well the gold standard these days is the comprehensive dementia evaluation which includes taking history from the person in question and from a family member, a careful examination and cognitive testing by a qualified clinician, and some laboratory studies and one then puts together a broader pattern of findings out of that evaluation and compares it to what is expected from age alone, looks also for characteristic signs and symptoms and can yield a diagnosis of whether the change is what we call a dementia which is what is beyond expected from age or whether its age consistent.

JON MERRIL: How frequently do you run in to individuals that can be characterized as the worried well, individuals that are worried that they may have Alzheimer's disease or the beginnings of Alzheimer's disease but they actually are just having some memory loss associated with the circumstances that may be in play in their lives or may have some ordinary memory loss that is associated with advanced age?

DR. LYKETSOS: Oh it's very common actually especially now a days that there is a lot of public awareness. A lot of people especially in their young sixties, where the rates of Alzheimer's are quite low still, are starting to have age related memory symptoms. Many of them might have mild depression or might not be sleeping well or be drinking a lot of coffee or they're having a lot of stress in there lives and they have memory symptoms that worry them and they come in to be checked. A substantial portion are individuals who had a parent or a sibling with Alzheimer's and they talk themselves into the idea they are starting to get it. I spend a fair bit of time assuring people that I don't think they have it for some of my patients.

JON MERRIL: For patients that actually present with Alzheimer's disease does their history of the illness make a difference, in other words, if they appear to be deteriorating more rapidly than another patient will their be a different type of therapy that is given to a patient that is deteriorating more rapidly or less rapidly, is therapy actually individualized on a patient by patient basis?

DR. LYKETSOS: It's individualized to some extent around those factors but I wouldn't say age or speed of progression really change what we do. We try to get whatever guns we have out for everybody regardless of age and regardless of speed of progression.

JON MERRIL: Is there any evidence that keeping your brain more active, if someone has Alzheimer's disease and they play chess or mahjong or crossword puzzles or other things that were traditionally associated with stimulating the brain, do these activities influence the course and slow down the progression of Alzheimer's disease.

DR. LYKETSOS: There's not evidence that intellectual evidence helps people who have dementia the point where the disease is fairly progressed. Now that's partly because there haven't been terribly good studies to evaluate that. But its very similar to having had a heart attack by the time you have a lot of tissue loss either in the brain or the heart its not terribly easy through functional means to grow tissue, so you wouldn't take a heart attack victim and make them walk more to grow more heart muscle, you'd do a little bit of that but there are limits to it so again you can do some of that with brain loss but not much. Where this might be valuable is in people who have either very mild symptoms or before the disease has lead to symptoms it may be that mental exercises do function to preserve the development of symptoms or the worsening of symptoms and that's under extensive and fairly aggressive investigation right now.

JON MERRIL: There have been a number of articles in the scientific literature as well as in the general press that have spoken about the relationships between diet and exercise and Alzheimer's disease as well as chronic medical conditions such as diabetes and high cholesterol levels as predictors for Alzheimer's disease. Can you comment on the relationship between these disease states and lifestyle

decisions that people are making and the probability that they will develop Alzheimer's disease?

DR. LYKETSOS: So focusing on diabetes. Diabetes affects blood vessels all over the body and specifically in the brain and we know that vascular sufficiency, healthy blood vessels in the brain, are really critical to not getting Alzheimer's. So it's probably the case that diabetes is a risk factor for Alzheimer's because of that. But there are a couple of other mechanisms that have been proposed. People who have diabetes actually tend to have less insulin in their brains. A little known fact in the lay public is that the brain makes its own insulin, it doesn't just freely cross out of the periphery so when you have high sugar peripherally and high insulin or low insulin or general insulin perturbation, the brain seems to make less insulin and that might result in less efficient feeding of the brain nerve cells. It might also result in less availability of a brain enzyme called insulin-degrading enzyme. When you have less insulin you have less need for this insulin- degrading enzyme. An insulin-degrading enzyme is one of the enzymes in the brain that breaks down amyloid so if you have less insulin in the brain and less insulin degrading enzyme, you have less functional ability to break down amyloid. So those are other ways through which diabetes might lead to Alzheimer's people are looking at.

From the point of view of diet and exercise it does seem to be the case that people who exercise more and have certain diets seem a bit less likely to get Alzheimer's. Now whether because they exercise or because they are dieting properly or because people who are less prone to Alzheimer's tend to have a healthier lifestyle, that's an open question still most think that there's something about diet and activity that is relevant to Alzheimer's. So I typically advise people who are at risk either by virtue of age or having a relative with the disease that they take seriously opportunities they have about having a healthy lifestyle in general and a particularly active lifestyle in general because I do think they're going to be better off from the Alzheimer's point of view. I should add that one of our studies published about a year and a half ago did suggest that it's not just the amount of exercise that you do but it's the variety of exercise so if you are expending a certain amount of calories per day exercising, you are going to be better off doing it in three or four activities. So instead of just all swimming, do swimming, a little running, and some gardening. The variety itself is probably relevant to the brain remaining active in several areas where as if you are just doing one type of activity like swimming it's a more limited amount of brain that you are exercising if you will. Whereas with a more variable set of activities you're exercising a broader range of the brain and that probably is protective against brain decline.

JON MERRIL: That's fascinating. It reminds me of the studies the classic studies where people that have lost their vision later on in life they were found to have had more of the brain focused on tactile sensation or touch than individuals who have had sight throughout their lives and this really had shown that the brain can change over time in response to challenges. Can you comment on how the brain can adapt to Alzheimer's disease in positive ways?

DR. LYKETSOS: The brain is plastic. I guess that's not a great lay term but it has the ability to reconnect it self and so you can use diet and activity and social engagement to maintain those connections.

JON MERRIL: Is there evidence that particular types of diet protect us from Alzheimer's disease?

DR. LYKETSOS: So you're offering me the opportunity to the Greek always seeks which is to remind the world that it all started with the Greeks and the Mediterranean diet. The probably most developed diet is what people call the Mediterranean diet; high in olive oil, substantial amount of fruits, vegetables and fish so that's one package if you will that's pretty good. On the other hand a diet similar what to the department of agriculture recommends is also very effective especially if you maintain your weight in a good range, a good healthy range for you height.

JON MERRIL: And what about exercise? Is there a particular exercise regime that may be optimal for those that are trying to stave off Alzheimer's disease or those that actually have it?

DR. LYKETSOS: Yeah so I do suggest that people try and do several hours a week in split increments maybe four to five hours every week in split increments of a ranch of physical activities. Walking is a very good one, a group sport or for an older person doing swimming, aerobics , sit-ercise, those sort of things as part of a group or playing a group sport like softball, baseball, soccer, something along those lines and then also perhaps engaging in some heavy house cleaning or house work or gardening along the same time. So you try to get your single thing like walking, a group thing like a group sport or group exercise and then a higher level of a typical house hold thing like gardening or household activity.

JON MERRIL: What factors do you look at to predict Alzheimer's disease? Are there elements of the family history that you look at? And also with the advent, the discovery of the human genome, are there genetic tests that are accurate in predicting Alzheimer's disease?

DR. LYKETSOS: The major risk factors are age and we don't quite know why that is the case. The older you are the higher your risk. We know that sixty to seventy percent of Alzheimer's is inherited and that does suggest one or more genes and in fact we know that there are two types of inheritance, one that involves a limited number of single genes so that if you inherit one of these genes and we know of three of them. There probably are more and you live old enough you are destined to get the disease. But most people it's what we call a polygenic inheritance, one that involves several genes and probably a few critical environmental factors so a certain combination of genes and certain combination of environmental factors would lead to the development of the disease at a given age. What are the other genes probably the one that is what we call the risk gene something called APOE4. So APOE is a gene you can get variety number two, number three or number four the more copies of number four you have the greater the likelihood you'll get Alzheimer's at a younger age. On the other had there are people who have two copies of E4 who are in their nineties with no signs of Alzheimer's. So having that kind of a gene like APOE4 is not deterministically get you the disease like the other types of genetic risk factors do. We don't quite know why that is with APOE, whether other genes are might be protective or whether its more of a timing gene its still not clear and it maybe that APOE needs to be combined with other environmental risk factors like head injury which is another established risk factor. Now other risk factors in the environment, depression is a risk factor, head injury is a risk factor, education is a risk factor. Brain vascular disease so having strokes or diabetes are also risk factors themselves, having high blood pressure also is a risk factor.

JON MERRIL: Can you clarify the role of education as a risk factor for Alzheimer's disease? What does it mean that education is a risk factor?

DR. LYKETSOS: People who have less formal education are at greater risk for Alzheimer's. There is some evidence from some our own work that the cutoff is somewhere around grade school that the risk attenuates when you go from a grade school education to more than a grade school education but doesn't attenuate much if you go say from high school to college or through college or professional school. So the fact that you and I have been through medical school is probably not much more protective than having gone through high school but someone who's been through high school is probably much more protected than someone who's finished grade school.

JON MERRIL: Looking at the crystal ball, could you predict what would be possible in the future in terms of home healthcare and being able to monitor disease progression in the home? Do you think that there will be any technologies in the future that will enable us to predict disease progression remotely?

DR. LYKETSOS: I'm not sure that we'll be ever to the point where Alzheimer's progression can be monitored with out the involvement of a medical professional, because I suspect the monitoring would either be on clinical grounds which therefore requires a medical professional to make clinical judgments and ratings or some imaging or blood test. Would those potentially be deliverable at home? I guess if we have a single test. We're sort of looking at some blood tests in some of our laboratories. Do we think that you can do the blood test at home? Maybe in the very distant future, but I'll tell you I always worry about complex medical diagnostic testing used in the home base because it's very hard to convey in that context to the individual who is using the diagnostic test all the complexities around testing and errors in testing. So maybe we'll go there someday but not any day soon and even then I would be worried about whether it's the right thing to do.

JON MERRIL: We're seeing more and more sophistication in home healthcare kits with genetic tests that are becoming more and more advanced over time. How valuable are these tests in predicting Alzheimer's disease? For example you had mentioned APOE. How valuable is that test?

DR. LYKETSOS: People could be tested for APOE tomorrow. It's a test available as a company that has it patented so they charge I think a few hundreds dollars to get it done. But I guess the question is what you would do with that information if you were consumer.

JON MERRIL: And they could potentially go in to depression unnecessarily.

DR. LYKETSOS: Or kill yourself.

JON MERRIL: And I would imagine that the depression and stress could put them at more risk for Alzheimer's disease.

DR. LYKETSOS: Or lose insurance. So biology is bringing us a lot of power but boy a lot of complications as well.

JON MERRIL: Well this has been fascinating. We really appreciate the opportunity to speak to you today. Can you give us some final thoughts about Alzheimer's disease that we can end this program on?

DR. LYKETSOS: My main message these days to the general lay public is that we're at a point where we can treat Alzheimer's. Even though we can't cure it we can definitely treat it. So I encourage people who have symptoms, not people before symptoms, I encourage people in the age of risk, so typically over the age of sixty five or seventy to be evaluated because now a days it's better to know and be diagnosed than not to.

JON MERRIL: Well thanks. We really appreciate the opportunity to have spoken to you today.

DR. LYKETSOS: Thank you. Okay, bye-bye all.