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ABBY NOYCE: OK so we're going to talk about Alzheimer's disease. Who here knows somebody who has or had Alzheimer's disease? Anyone with family members? No.

[BACKGROUND CONVERSATION]

Yeah, I'm lucky nobody in my family has it. Anyway, so Alzheimer's disease is part of a group of mental disorders known as dementias. So dementias are a group of disorders, diseases that are characterized by cognitive and behavioral deficits. So people's ability to think, remember, learn as well as they used to declines. This also is depending on which dementia we're discussing, people's ability, for example, to take care of themselves, to generally participate in their daily life declines.

Dementias are usually characterized by gradual onset. So they start off with just a little bit of decline and get worse over time. They're chronic. They're permanent. This isn't something that you have and then get rid of. Dementias are lifelong once you develop one.

In the clinical world, you make this distinction between dementias which are these slow onset chronic disorders and what are called deliriums. So a delirium is acute. It happens it's a quick change in cognitive ability. Working with an older adult population, you'll usually see delirium brought on by sometimes by trauma, sometimes by a medication or a medication interaction.

And all of these are things that cause older adults to end up in the ER for some reason. Somebody looks up and says, Grandma is acting weird. Today something changed. Take her, put Grandma in the car, bring her to the emergency room. First thing the ER doc says, is have Grandma's medications change recently? This is a big cause of a lot of short term changes in older adults.

But dementias are different. Dementias are usually caused by a bunch of things. They can be caused by a progressive disease. They can be caused by trauma. They can be caused by a stroke. And overall, different categories of these affect about 4 million people in this country. And that's almost all people over age 65.

AUDIENCE: What could be a trauma?

ABBY NOYCE: Trauma can be like a head injury or a stroke, something that's kind of-- it's not so much a

disease as something has caused sudden death of some sort to cell in brain. So Alzheimer's is a particular subset of dementia. It's by far the most common one.

It was first described in 1907 Alois Alzheimer. He was talking about a patient he'd been working with for about six years at that point who had a strange form of senile dementia. And it's been known kind of casually for a long time and more specifically more recently that as people get older, in general just in normal aging, your cognitive abilities decline.

Older adults do poorer on a lot of memory tasks. They're slower at a lot of reflex reaction time tasks. In general, your cognitive abilities slow down as people pass into their 50s, 60s, and beyond. Alzheimer's is different.

It's more than anything, it's these same deficits taken to an extreme. And we'll talk a little bit about exactly what kinds of changes you'll see in patients who have Alzheimer's. Alzheimer's accounts for, depending on whose estimate you ask, between 50% and 70% of all dementias.

Because it correlates with lifespan so well as people get older, your chances of getting Alzheimer's increase, it's more common in countries with longer lifespans. So it's much more common in places like the US and Western Europe than it is, for example, in like central Africa just because we've got so many more adults who make it into their 60s, 70s, 80s-- these periods where the incidence starts going way up.

All right, so how do you diagnose this? So in order to get a definitive diagnosis of Alzheimer's disease, this can only be done by autopsy. But there's a bunch of criteria for making what's called a clinical diagnosis-- a diagnosis you can make while people are still alive and say that you have Alzheimer's disease. Why would you want to do this? Why isn't it just good enough to say you have some kind of dementia?

Well, one of the biggest reasons is that the progression of different forms of dementia is different. So the time span that you are likely to have, how fast the decline is likely to be varies across different kinds of dimensions. And being able to say which one someone has helps them and their families kind of figure out what's going on, what happens with this. And in a clinical care setting, that's really important.

So the clinical criteria for Alzheimer's disease, and these are kind of in flux. But this is the American Psychological Association's current round of diagnostic criteria. And so to be diagnosed with Alzheimer's disease, patients have to have multiple cognitive deficits. They

have to have memory impairment, which is kind of the classic thing that everybody knows about for Alzheimer's disease. Alzheimer's disease, if you lose your memory, you lose your ability to learn new information in particular.

Patients also have to have at least one of the second group of cognitive deficits. So remember aphasia is a group of disorders in which people have a hard time with language, with understanding or producing language. Apraxia refers to a difficulty in making smooth movements and motor coordination and control. Agnosia-- go back a couple of weeks the agnosias are our class of disorders which people have difficulty recognizing visually presented objects and describing or interacting with visually presented stimuli in various ways-- or difficulties in executive function.

What kinds of activities is executive function refer to? That's stuff like goal directed behavior, planning cause and effect reasoning-- all of this comes under this executive control heading. And so you also see patients who have difficulty with this.

One of classic examples of this is-- there's some classic research working with babies, like six-month-old babies where you show them an object like a brightly colored little puppet or something-- something that the kid would be interested in and attracted to. And you show the kid this. Then they'll reach and then you put it into a box.

And they'll reach for the box that they saw you put the puppet in. And even if you then show the experimenter picking up the thing and moving it to a different box so there's like two boxes in front of the kid, they'll keep reaching towards the original one, the one that they saw go into first. They don't seem to have the ability to take the information about how the thing moved from place one to place two and translate that into a change in how they want to direct their motor abilities.

They don't have the ability to kind of take the reach for this box instruction and transform it into a reach for that box over there because the doll got moved instruction. So little six-month-old babies make this mistake. Patients with Alzheimer's will also make this mistake.

So patients with moderately advanced Alzheimer's will make similar errors in-- probably not in brightly colored puppets but in a look for this, see it move, and then have to transition your search tasks to a new area. They seem to have a hard time with it. So that's an example of an executive control function that's hindered, that's impaired in patients with Alzheimer's.

The other big criteria for anything like this is that the way the DSM, the Diagnostic and Statistical Manual, works is that in order to qualify as having a disorder of any kind, you've got to have impairment. If you are finding that your memory is declining and yet it is not messing up your daily life at all, DSM will say you don't have a disorder. You are working just fine. You are not having a disorder.

So one of these criteria is a impairment in function compared to the previous level of function. So this is going to vary for different people depending on how high their cognitive abilities were before the onset of symptoms. And the other requirement is that this is, like we said, a gradual impairment. This is not an acute sudden change in cognitive ability. It's gradual, and it's progressive. It gets worse over time.

So what does this progressiveness look like? So most people break Alzheimer's into four main stages. The first of which is what's called pre-dementia. And in pre-dementia stage, most people aren't diagnosed at this stage. It's hard to tell the difference between cognitive decline that's due to Alzheimer's disease from what kind of your normal aging cognitive decline that you're going to see in just about all adults in their 60s and 70s.

But on the other hand, if you have people take, for example, an IQ test every year starting at 65 on. And when they're 80 they become diagnosed with Alzheimer's, you can go back and look at their older tests. And you can see evidence that there was cognitive decline over the preceding five to seven years. But it's not strong enough for it to really be diagnosed as being a dementia of any kind.

So the next stage after the dementia is what's called early dementia. And this is usually when it gets noticed, when it gets diagnosed. You'll see that people's impairments for memory and for learning new information are severe enough that they'll go, they'll talk to their doctor. They'll say, hey, I'm concerned about this.

And they're specifically bad about it learning new information. Childhood memories aren't impaired at this point. Semantic knowledge, knowledge about the world is not usually impaired.

This is the where did I put my keys stage of Alzheimer's disease. It's a new piece of information. It's something from earlier today. But it's just not there. They can't pull this up

Next step is moderate dementia. And at this stage, this is where you start seeing severe speech and language impairment. People can't pull out the knowledge about which words.

They want to use their vocabulary effectively shrinks a lot more obscure words they just can't access anymore.

You see deterioration in motor control. People have a hard time making smooth, coordinated movements. People have serious impairment. They start losing long term memory. They start not being able to remember things from when they were young.

They start not being able to remember facts about the world. They start not recognizing family members, which is kind of another classic Alzheimer's symptom that people have a hard time dealing with. This is the stage where usually people start having a really hard time taking care of themselves.

Usually in that early dementia state, you'll see individuals with Alzheimer's usually moving in with a family member. They're pretty much OK. They can get around. They can handle their stuff. But often, family doesn't want them to live alone.

And in this modern dementia state, that starts being really hard all around. These are patients who are having a hard time, for example, cooking and feeding themselves. They might have start having a hard time tying their shoes. They might say they're having a hard time taking a shower. All of these are things which the people who they're living with have to help them with.

So Alzheimer's is probably the biggest reason for adults to be in a caregiver relationship with another adult not counting like raising children. But when you find people taking care of a sibling or a parent or grandparent, it's usually due to what some kind of dementia.

The other thing that tends to happen in Alzheimer's that's really distressing for family members is that in this moderate stage dementia that you start seeing affective changes. You start seeing mood and personality changes in these patients. So people will start to become aggressive, angry, loud, violent towards family members. They'll push, they'll shove, they'll holler. They'll say things that are completely inappropriate.

And as you might imagine, for somebody who's giving up like all of their free time and a good chunk of their general sanity in the world to take care of this family member, this can be really distressing all around. So it's usually in this moderate stage that you see families really considering moving somebody with Alzheimer's from live-in caregiver family situation into an assisted living sort of nursing home situation, because the stress and the distress of handling all of this just being too much for ordinary people.

And then it progresses into what's called advanced dementia. And at this point, all of this just kind of gets worse. Patients lose motor coordination and muscle tone, eventually to the point where they are bedridden. They usually need help feeding themselves. They usually need help with all kinds of personal care tasks-- bathing, going to the bathroom, all of this.

They often lose pretty much all linguistic ability at this point. And eventually, these patients just lose physical condition to the extent that any old infection that comes along will take them out. And that's usually what people actually die from who have Alzheimer's. It's not the disease itself. It's that the disease leads to this deterioration that then makes it makes them much more vulnerable to other kinds of infections.

How long does this take? Remember it's usually diagnosed that early dementia phase when you first start seeing significant impairment in learning and memory. The mean time for survival after diagnosis is about seven years. So that's the arithmetical average-- add up all the times and divides them. And very few patients, like 3% of patients alive longer than 14 years after diagnosis. So this isn't like immediate. But it's a reasonably quick decline, fade, death kind of story.

So as you might imagine, lots of people were trying to figure out what exactly is going on with Alzheimer's disease. So what we've known for a while is that there's, macro scale, pretty substantial differences between normal patients brains' and the brains of patients with Alzheimer's. The biggest thing that happens is that in the temporal and frontal lobes, you get a lot of cerebral cortex cell death.

Neurons, for one reason or another, retreat from their synapses with other neurons and eventually die. And so what you'll see is that these brains just have a lot less volume than they do in other-- so here's a normal patient. And here's somebody with Alzheimer's disease. And so you can see the way both the cortex and all of these subcortical structures have shrunk.

You can see that the ventricle-- which are the fluid filled spaces that are normally inside your brain-- have enlarged. Again, that's the brain itself is taking up less space. So the cerebral spinal fluid spaces expand. The hippocampus-- which should be this fit right in here where it's folded around-- in a normal patient that would be all the way out to here. So it's dramatically smaller.

This kind of macro scale, hey look, a lot of cells are dying. You might imagine, OK, a lot of cells

are dying. It's no wonder that we're seeing this kind of serious cognitive deficits.

So what's happening on a smaller scale? Why are cells dying? So there's two really characteristic changes that happen at a cellular level in patients who have Alzheimer's disease. One of them is what's called these senile plaques, these beta amyloid plaques. So what happens is that amyloid precursor protein-- so this is a neuron. Here is the cell membrane, here's the interior.

Amyoloid precursor protein is a transmembrane protein. So it has parts that stick out both into the cell and out into the extracellular fluid. We're not entirely sure what it does. It seems to be important in helping neurons to grow and to repair themselves after any kind of damage that might happen to them.

But what happens is that enzymes like there's one called presenilin. There's another one who I didn't write down, that was dumb. But there's a couple of different kinds of enzymes that, in Alzheimer's patients, seem to go a little bit out of control.

So they come along, they break up this amyloid precursor protein into several pieces. And the piece that's relevant is this bit that's right here sticking out along the transmembrane part of it. This part is called beta-amyloid. And these beta-amyloid fragments, when the proteins get snipped up by these enzymes, float out here in the extracellular fluid. And they all clump together. They form these really characteristic senile plaques or beta-amyloid plaques.

Here's an actual histological slide photo, micrograph. So you can see in here and here and there, all of these are places where you've got one of those senile plaques going on where outside of the cell bodies there are just all of these bits of beta-amyloid clumped up on top of each other.

And one theory about what causes the decline we see in Alzheimer's disease is that these senile plaques all glom up on top, causing dysfunction of cellular operation. But we'll come back to that. Questions? Beta-amyloid plaques?

The other big neurological change that you see is what's called neurofibrillary tangles. Plaques and tangles, you guys might have heard about these when you're reading about Alzheimer's or seeing it discussed. It's pretty well established at this point.

So what happens here is that these proteins are part of the cytoskeleton of the neurons. So you guys probably remember from learning about cells in bio that cells have a cytoskeleton,

which does a couple of things. It gives structure to the cell, it helps hold its shape.

But there's also a particular part of the cytoskeleton called microtubules. And microtubules act kind of like train tracks going out to different parts of the cell. They're involved in transporting proteins and vesicles of neurotransmitter and other things that the cell needs to move from one region to another, it moves along these microtubules. And one of the things that's involved in keeping these microtubules stable is these tau proteins.

So diagram moment, so here's our neuron's axon. And it's got lots of microtubules reaching down, which are how the cell brings things from its nucleus out to the axon tips. And normally, these tau proteins have a phosphate group on them, they're phosphorylated. And at that point, the presence of a phosphate group causes them to fold in such a shape that they stabilize the microtubule. They help hold it all together.

And what happens in patients with Alzheimer's disease is that these tau proteins that should be holding the microtubule together become hyper-phosphorylated. They get extra phosphate groups stuck onto them--

--That makes them unstable--

--which makes them unstable. It causes them to change shape because proteins are made up of amino acids. and they want to fold up in such a manner that the electric charges are all attracted and pushing apart in the right way. And so as you start adding phosphate groups onto them, we talked about how phospholating receptors-- we talked two weeks ago about this-- causes them to change their behavior.

Again, it's a subtle change in shape that makes this happen. So in this case when you stick to any phosphate groups on a tau protein, it shifts. It no longer manages to hold the microtubule together. And so what happens is that this microtubule starts to fall apart. And the tau proteins, again, all clump together and wrap around each other in these neurofibrillary tangles.

AUDIENCE: Can you go back one?

ABBY NOYCE: Maybe, yes.

AUDIENCE: So the two cellular level sequences that we looked at, are these causes of the cell deaths?

ABBY NOYCE: Nobody is entirely sure how that works. There's hypotheses that say that these are the causes of the cell deaths. What we know is that they're distinct. They happen in normal aging too, but they happen much more in Alzheimer's patients and in different parts of the brain.

And so it's traditionally looking at these particular cellular level changes has been how that definitive Alzheimer's diagnosis is made. You say, OK, you've got all the clinical symptoms. And after somebody dies, you do an autopsy.

You take a slice of their brain, and you look at it under a microscope for the tangles and for the plaques. They're starting to be some better ways of doing this and some better ways of on non-autopsy required diagnoses. But so we've got--

AUDIENCE: Does that mean Alzheimer's can only be diagnosed after death?

ABBY NOYCE: Definitively, yes. That is likely to change in the next five or 10 years, I suspect. Or at least our non-death requiring diagnosis methods will get better. So one of the things that happens with Alzheimer's is you see tissue loss and distinctive parts of the brain.

You see it in the hippocampus. You see it in the prefrontal lobes. You see it in particular regions of the temporal lobes. You see it along the cingulate gyrus, which is that part of the frontal lobes where they nudge up against each other in the middle. And you can pick out some of that on an on neuroimaging system like an MRI as the resolution on MRI gets better.

There's a staining technique-- well, not quite a staining technique, an imaging technique that works like PET. Remember in classic PET scans where you're looking at what parts of the brain are active, people would drink this radioactive glucose. And then you'd scan where the radioactivity was emitted from because it would get picked up in the blood. And then it would be sent to the parts of the brain that were working the hardest.

Somebody has done a modification of that where you have patients drink a substance that has a radioactive molecule that will bind to, not to the tau proteins, but to the flax, to these beta-amyloid fragments. And so if you have a molecule that will bind specifically to that and then you can stick a radioactive tracer onto that molecule and you have this then bind to these plaques, you can see how much of it is in somebody's brain.

You can measure the level of it which sticks. And you can look at the distribution of these plaques. And there are people working to figure out what the exact criteria for a diagnosis using this would be. So like I said, there's better diagnosis tools kind of in the pipeline right

now.

But you know, some people don't want to know. That's the other half of it is some people will say no, I'm not going to get tested for this. I'm not going to get screened for it. If I'm going to die in seven years, I don't want to know about it.

AUDIENCE: Why?

ABBY NOYCE: Many people-- this is something that keeps coming up, especially-- Yeah, some people want to know. And some people don't. So there's a lot of things like I don't know if you guys have heard of Huntington's disease, which is a neurodegenerative disease that usually first kicks in around age 45. It's also heritable.

So one of the things that tends to happen is people happily have kids in their 20s and 30s. And then they hit 45 and find out that they have Huntington's and then realize that they have probably passed it to their children go, oh no, I didn't know that, whatever. And so Huntington's is one of the easy to find, easy to genetically test for diseases.

It's a mutation on one gene, on one chromosome. There is one very small chance that we can look at and say this is the thing that causes Huntington's. So now you can get tested for it. You can give a drop of blood through the lab, and they'll run a screen and they'll test for it.

And some people want to know. And some people absolutely don't. They know they have a parent who had it so they have a 50% chance of having it. And they do not want to know yes or no for sure. And you can't require them to get tested or anything. But this sort of testing starts bringing up all sorts of issues.

As we get and as we get more and more ideas about what the genetic bases of different kinds of diseases are, we're going to see these issues come up more and more. I don't know. I was listening to NPR this afternoon in the car. And they were talking about HIV testing and again the same thing.

Lots of people don't want to know. They don't want to get tested. They don't want to know for an assortment of reasons. It's an interesting question. It's a difficult question And some of those cases where you might know for sure what the answer for you is but it's very hard to say that the answer for everybody should be this or that.

So we that these two kinds of cellular molecular changes that you see in the brains of patients

who have Alzheimer's. So here's again a micrograph of a neurofibrillary tangles you can see the different strands in here that are all wrapped around each other. They make this kind of characteristic flame shape that you can see in different kinds of staining.

AUDIENCE: It always looks like that?

ABBY NOYCE: It's not always quite that pretty. But I mean, if you look at this photo micrograph. So this photo micrograph claims to only be showing the senile plaques. But all of these shapes in here-- see these? I am not a trained cyto-histological person in identifying Alzheimer's disease characteristics. But those look very similar to me, in my untrained state, to photo micrograph I've seen of what these neurofibrillary tangles look like that discussed that characteristic flame shape.

So I looked at this and said, you're not telling me that's what's there. But I wonder if these are what they are. So I don't know. But they do tend to always have this very characteristic shape where they are narrow on one end and kind of rounder on the other.

AUDIENCE: And that's just how they form?

ABBY NOYCE: That's just how they form. remember this is caused by proteins wrapping around each other in a certain way. So there's going to be characteristics of how the charge is on different parts of them are what's attracted and what's repelled that causes particular deformations.

So like I said, these are things that you see in patients with normal aging. But there's more of them in Alzheimer's patients. They're distributed differently. There's kind of an ongoing theoretical argument about whether Alzheimer's is just normal aging happening worse in some patients or if it's actually something that is qualitatively different than normal aging.

And oh hey, terminology moment. So Alzheimer's is a proteopathy-- which is a word I hadn't heard before actually-- which refers to diseases that happen because of a protein misfolding. Issue. So proteins fold up into a particular shape. And it's that shape which gives them their function.

Think again about ion channels in the cell, they've got to have those different subcomponents lined up in a little cylinder in order to ions in and out. Of shape is important for proteins. When proteins go wrong, they can't do their job anymore.

So what causes this? There's a couple of hypotheses about what the underlying causes are of

Alzheimer's disease. One of the things we know is that early stage Alzheimer's tends to involve particularly the damage to the basal forebrain cholingeric system. So you guys all remember this is subcortical mostly kind of towards the frontal lobe subcortical structures where most of the acetylcholine in your brain comes from, its cells who have their cell bodies in this area and then project them through almost all of cortex. And one thing we know is that these are one of the first cells to deteriorate and start to die in Alzheimer's disease.

And one of the oldest hypotheses is that this reduced synthesis of acetylcholine is the thing that causes Alzheimer's. There are four medications for Alzheimer's on the market right now That are approved by the FDA and so on. Three of them all work on acetylcholine. They all are acetylcholinesterase inhibitors.

Acetylcholinesterase is the enzyme that cleans up acetylcholine out of the synapse after it's been released by a pre-synpatic cell. So if you inhibit acetylcholinesterase then what's going to happen is that every time acetylcholine is released into the synapse, it's going to hang around for longer. It's not to get cleaned up so quickly. And so at least to some extent, this can make up for a reduced amount of it being released. Because it gets to stay around longer, it evens out

It's kind of the same logic as SSRIs selective serotonin reuptake inhibitors as antidepressants. If we inhibit the re-uptake of serotonin, let it sit in the synapse longer, than it'll make up for a decreased amount of serotonin being released. So in this case, we're looking at acetylcholine from this basal forebrain cholingeric system. So these acetylcholinesterase inhibitors work reasonably well. They definitely have an effect on the symptoms of early stage Alzheimer's.

They help people who are having memory impairment. They'll improve that. They'll improve cognitive function. It's not huge, but it's definitely an improvement. That's why they're on the market. But they don't stop it from getting worse. It's like this is a Band-Aid sort of solution.

It also really doesn't seem to make any difference as the dementia progresses as it gets worse. They stop having really any measurable effect at all. So this is an early stage treatment. It treats the symptoms, doesn't stop things from getting worse.

The other medication that's on the market right now is based on a different idea. You guys remember we talked about glutamate when we were talking about long term potentiation in learning and memory? So one of the things that happens that glutamatergic cells have to watch out for is that if a cell takes up too much glutamate, it actually will die.

It's called excitotoxicity. If there's too much glutamate release into a certain region of the brain, it will actually kill those cells. Not sure exactly how this happens. We're not sure exactly how this happens. It may have to do with too much calcium coming in through those NMDA receptors that can let in calcium. And then the calcium triggers apoptosis which is that and then the cell basically commit suicide.

The cell says, oops, something is very wrong. I'm going to kill myself now, shut down, disintegrate. So apoptosis-- you guys probably remember from bio-- is that programmed cell death. Cell death where they get some kind of signal from his surroundings that it is no longer needed, and it should wrap up its business as nearly as possible and disintegrate.

So the other Alzheimer's disease medication is trying to combat this excitotoxicity problem by working on NMDA receptors. It's an antagonist for NMDA receptors. So it sticks to the same spot that glutamate does. It reacts to the glutamate binding site on the NMDA receptor.

But instead of opening the receptor channel the way glutamate does, it just kind of sits there and blocks it. So it's not the right shape to trigger it to open. And it's in the way so the glutamate can't come in and trigger it to open either. So again, this medication reduces that excitotoxocity, but much like these cholinergic medications, doesn't seem to stop long term prediction of the disease. It treats symptoms, and treat symptoms later then the cholinergic drugs do.

The cholingeric drugs treat early dementia. The glutamateric drugs seems to reduce symptoms of mid to late stage dementia. But again, it doesn't stop the progression.

AUDIENCE: So what effect does that have on the person if they don't have glutamate getting into their system?

ABBY NOYCE: So it's not going to block all of the glutamate. And it's only going to work on the NMDA receptors. Actually, the side effects for this one are moderately mild. The side effects are things like slight dizziness and headaches. Whereas the acetylcholinesterase drugs actually have some really nasty side effects or they can.

They're kind of rare, because they see the calling is also the neurotransmitter that's used at the neuromuscular junction. So if you mess up acetylcholinesterase, you're also messing up what happens everywhere your nervous system tells a muscle to do something, which is your

entire body. And you can get some really weird side effects going on with those.

A lot of these drugs can have weird side effects because they aren't as precisely targeted as one might like, especially for something like Alzheimer's, which affects, especially in its later stages, pretty much the entire brain. So this is the cholinergic hypothesis. This has pretty much gone out of favor, because you can fix the amount of acetylcholine that's in the brain, at least for early stages. But it doesn't actually change how the disease progresses.

So at this point, the reduced amount of acetylcholine seems to be a symptom of the disease but not a cause of the disease itself. So the disease is eating the basal forebrain cholinergic cells, which then causes acetylcholine to be reduced. All right.

So the other is kind of two main causes that are discussed is that it's either these tau proteins or these amyloid protein masses that are causing some amount of cell toxicity. So the tau hypothesis says that what's happening is that these tau proteins, for whatever reason, become hyper-phosphorylated. They change shape. The microtubules that they were holding together fall apart. And when the cell can no longer transport things down the microtubules to the tips of its axons, then its ability to communicate with other cells fails.

So first of all, you're seeing these decreases in cognition that can just be explained by synapses breaking, down by cells no longer being able to communicate across synapses. And over time as the cytoskeleton disintegrates further, you're going to get apoptosis and programmed cell death. So there's just one theory.

There are some researchers who think that this is what's going on. There is research being done into it. But most researchers who are studying this stuff think that's what's going on is in this amyloid stuff. And there's a couple of good theories for this.

So one hypothesis is that these amyloid plaques, by breaking up the amyloid precursor proteins, that transmembrane proteins and forming these amyloid plaques in the extracellular fluid, then this in turn messes up the calcium balance in the cell. So the cells have to have a precise amount of calcium. If they have too little, bad stuff happens. If they have too much, bad stuff happens.

And it's the presence of these plaques that causes these cells that have too much calcium inside. Their calcium homeostasis mechanisms get broken. Too much calcium, as we discussed a minute ago with toxicity, can then lead to apoptosis, to this programmed cell death

idea. These are explanations in particular not just for the symptoms of Alzheimer's disease, but for the very specific dramatic cell death that you see as this disease progresses.

One of the most interesting pieces of evidence in favor of this amyloid hypothesis is that that amyloid precursor protein-- remember that's the big transmembrane protein that gets broken up to form the amyloid beta that then forms the senile plaques. So this amyloid precursor protein is on chromosome 21. And as you guys probably know, trisomy, if you have three copies of chromosome 21, you get down syndrome.

Anyone here know anyone with Down syndrome? There was a kid in my class at school who had down syndrome. So down syndrome patients have a really characteristic facial shape. They tend to have poor vision, poor hearing, low IQs, all of that. And the thing about down syndrome is that down syndrome patients almost always exhibit symptoms that are very much like those of Alzheimer's disease.

And they get this early. They don't get this at 65 or 75 or 85. Down syndrome patients get this in their late 30s. They start showing impaired learning, impaired memory, not just relative to normal IQ people, but relative to where they were previously. And it follows pretty much all of the same progression patterns as Alzheimer's disease does.

And the fact that the chromosome that's involved down syndrome is the chromosome that has the gene for this hypothesized cause is a kind of promising piece of evidence. And it makes some amount of sense. These things seem to be related. Another piece of evidence in favor of the amyloid hypothesis is that Alzheimer's disease is, at least to some extent, a heritable disease. There's a genetic component to it.

And there's a couple of different heritable types of Alzheimer's that have been traced to a couple of different genes. One is a mutation on the gene that produces this amyloid precursor protein. There's also a couple of what are called these presenilins, these enzymes that break up the amyloid precursor protein to form the beta plaques, the amyloid-beta plaques. And mutations for a different form of presenilins are another heritable form of Alzheimer's, another place where it's been traced to a particular gene.

So both of these pieces have a genetic basis for the disease are based around this amyloid beta process. So also really interesting, so somebody said, OK, so what if this is what's going on? What if we could manage to vaccinate people against Alzheimer's disease? What if we could manage to immunize them with something that removes these amyloid plaques?

And I couldn't get the full copy of this, but I read the abstract. So these guys-- and this is a brand spanking new paper. This is in like the July 2008 issue of this journal. These guys were doing a clinical trial of this idea. So state 1 clinical trial, you do it on a small group of patients. I think they had 80 patients.

And you kind of want to do it on patients who have nothing to lose, patients who have been unresponsive to other medications, patients who have a terminal disease of some sort. State 1 of clinical trials is the first time you try this drug on human beings. You've tried it on your animal models. It hasn't caused your rats to go into spasms or die or anything. We think it's safe, we think it's beneficial, let's move it to humans.

And so what this immunization does is they have developed a protein that will kind of bond to the beta-amyloid fragments that make up these senile plaques and will remove them from the system. So it will actually go through and clean up all of these amyloid plaques. It will remove plaques. And so if the plaques themselves are what's causing Alzheimer's disease, then removing them should be beneficial.

And so what they found is that the plaques were between OK and great, is that the immunization was between OK and great and for patients at removing these plaque. So compared to a control group who did not get the immunization, the patients who did, the experimental group, it removed somewhere-- for some patients, it was like less than half of the plaques. For some patients it was almost all of them.

So there was definitely it's having some effect in decreasing the number of these beta-amyloid plaques in these patients' brains. But it did not improve either survival rates, either length of time from diagnosis to death for either group of patients. There was no difference. And it didn't change the rate at which the dementia progressed, the rate at which it got worse.

So what this is implying is that is that whatever is going on with the amyloid protein process, and it still seems to be the best candidate for where the cause of this is, it's not simply the presence of the plaques in patients' brains that's causing this decline. The plaques also seem to be a secondary symptom rather than an immediate cause of Alzheimer's. All right, questions?