Why is this happening, number one? Let's think about it. Let's look at these patients. And the obvious thing that pops up in our mind is T3. It must be T3, because we were giving T3 with the extract before. And now, we are no longer giving T3. Maybe we are taking for granted that those deiodinases are so powerful, so adaptive that they will produce the T3 that was being produced by the thyroid.

So the question is, how are T3 levels in patients treated with monotherapy, levothyroxine? Remember, we didn't care about T3 for the diagnosis of hypothyroidism. However, to follow up patients on levothyroxine, we also don't care, but maybe we should care. Now, when we look very carefully-- and let me just make a parenthesis-- I'm not recommending to measure T3 for patients on levothyroxine. I'm just saying that from a research point of view, we should care.

Now, when people looked at T3 levels, again, this is an area of controversy. Levothyroxine, the first paper published on a relatively large cohort of patients was by Jack Oppenheimer in *The New England Journal of Medicine* 1974. That cohort of patients on levothyroxine had low levels of T3, meaning that as an average, they have lower levels of T3 than a control group that didn't have hypothyroidism, meaning that, well, when we are giving levothyroxine, we are normalizing TSH.

But we might not be normalizing serum T3 levels. And why is that important? Because T3 is the biologically active thyroid hormone. Therefore, immediately people thought, well, those low T3 levels might explain these symptoms that patients have. Then, over the 30 years that follow after Jack Oppenheimer's paper, a lot of studies looked at that question. And I have to say, most patients confirmed that serum T3 levels are below-- are not what they should be compared to a control population. But some studies did show that T3 is normal.

When I went to medical school, and I was in my training endocrinology, I was told T3 levels are normal. You just give levothyroxine. Don't even care about T3, because it's going to be normal. Deiodinase will fix it. It's not. They don't. And the reason we know this, there are two large studies, one involving about 2,000 patients, thyroidectomized patients, that were treated with levothyroxine. This study was done in Italy.

And it's clear that for every level of TSH, T3 levels are lower than you would expect from a control population. And we looked at NHANES data. We looked at about 500 patients on levothyroxine. And we matched those patients on levothyroxine with 500 other patients from NHANES as well that were not on levothyroxine. And we matched them for sex, for age, and for TSH levels. And we saw that patients on levothyroxine have about 10% lower serum T3 levels in the circulation.

So this sets the stage for the idea that giving T3 for patients might be helpful. Or let me step back a little bit. It sets the stage for the fact that the lower T3 levels that patients on levothyroxine have might explain those residual symptoms that they have. Now, let me add something else. There are other things that could be explained as well. And for example, menopausal syndrome, many patients with hyperthyroidism are middle aged women that are perimenopausal, or they're undergoing menopausal syndrome.

And those symptoms are very similar to symptoms of hypothyroidism-- low energy, memory doesn't work, gaining weight. So the physician, before they label a patient within that group that T4 or thyroxine was not helpful in the treatment of hypothyroidism, we need to exclude other conditions, because other conditions could result in the same symptoms and signs that we find in these patients. The menopausal syndrome is a typical example.

Maybe you should step back even further and say, does this patient really have hypothyroidism? I always ask my patients, do you have a TSH that's elevated? Bring it to me. I want to see how high it was. And you start asking and start asking. And for many patients-- and I'm not overestimating-- I figured once that between 10% and 15%, maybe 20% of the patients in that category of levothyroxine not being helpful, in my practice, they actually did not have hypothyroidism to start with. But my practice is very biased. I deal with these patients. I don't think that this number reflects the overall situation of hypothyroidism in the United States or in the world.

But my practice was biased. So I spent a lot of time taking patients off levothyroxine also, because I helped. Of course, patients don't want to hear it. They get absolutely mad. They walk away when you tell them you don't have hypothyroidism. You should not be on levothyroxine. Your TSH was never elevated. That patient was victim of a doctor that rushed to a diagnosis and prescribed levothyroxine. And then we have a problem. Of course, levothyroxine doesn't work for the symptoms, because the patient didn't have hypothyroidism.

So physicians need to look from a research point of view. There's data showing that patients with Hashimoto's thyroiditis might develop autoantibodies to other parts of the body. For example, the brain. So about 20%, 30% of Hashimoto's patients will have antibodies against different antigens in the brain. For example, anemia, pernicious anemia, the patients have atrophic mucosa, gastric mucosa, caused by an autoimmune disease as well.

So before we say, oh, yes, I don't think levothyroxine is working for you, we should try to find a good explanation. And there are good explanations that we should be looking for. I don't think we should be looking for antibodies anti-brain, because that's not there. But anemia, yes. Menopausal syndrome, yes. Heart failure, yes.

We should look for things that will drain energy from a patient and worsen cognition. And if all of that failed-- and we should discuss with the patients-- if everything fails, then you say, well, maybe those T3 levels that are low that are supposed to be low or we know are low that maybe we can help here.