The therapy with levothyroxine is based on the principle that T4, which is thyroxine, it's converted to T3 in our body. T3 is the biologically active thyroid hormone. So there's studies showing that T4 might have a minor effect. That's true. It's probably true. However, the most important recognized effects of thyroid secretion today are mediated through T3 levels.

Therefore, the principle of therapy with levothyroxine is that T4 is converted to T3, and that reaction is called deiodination, and it's catalyzed by a couple of enzymes known as deiodinases. So these deiodinases, there are two major pathways that will activate T4 to T3 in our body.

So why we don't give the T3, if T3 is the biologically active hormone, or a combination of T4 and T3, well, let's look at the thyroid. What does the thyroid make? The thyroid makes mostly T4, mostly thyroxine, and it's just a little bit of T3 that's produced directly from the thyroid secretion.

And these deiodinases are very effective enzymes, so that in the '70s when there was a discovery that humans could convert T4 to T3, and subsequent studies calculated how much T3 the thyroid produced, they figured, well, probably these deiodinases are so good at adjusting and adapting themselves that they will convert T4 to T3 at their pace, which will probably account for that small amount of T3 that's produced by the thyroid.

So we calculate that the thyroid gland of an adult human will produce about five micrograms of T3 on a daily basis. And we know that the overall production of the T3 in our body is 30 micrograms, so that the thyroid produces five, and the deiodinases will produce 25. So most likely, they thought, by giving levothyroxine, the deiodinases will make up for that five that's coming directly from the thyroid.

Now, that's not what was happening before the 70s. Since 1880 until the 1970s, what we were giving patients with hypothyroidism was just animal thyroid, desiccated thyroid extract, which contains both T4 and T3. Now, containing T3 in the therapy, it's both a blessing and a curse.

And why is it a blessing? Well, because you're giving, you're trying to mimic what the thyroid makes. The thyroid gives a little bit of T3 to the circulation. So in a sense, you're mimicking what the thyroid does, and also you're giving a hormone that's already biologically active. It doesn't require conversion of T4 into T3.

At the same time, the curse is that T3 is really rapidly absorbed. T3 is really active, and so it can go up in the circulation after patients take a tablet that contains T3. And it could be T3 alone or T3 in combination with the levothyroxine or T3 contained in the thyroid extract, It's T3. T3 is going to be rapidly absorbed, going to go into the circulation, and is going to disappear fast as well.

So the half-life of T3 is very rapid, very short as compared to levothyroxine. So it's really a work to give T3 to patients, because we are exposing these patients to potentially slightly elevated levels of T3 right after they took the tablet and then slightly decreased levels of T3 several hours after they took the tablet.

So all of this went through people's mind in the '70s, and they decided that levothyroxine was going to be the therapy of choice. Number one, powerful enzymes that convert T4 to T3. Number two, long half-life of levothyroxine, about eight days.

So you can easily feed that pool of thyroxine in patient's body without major changes, major fluctuations, because the half-life is so long. And the wisdom of the body that can convert T4 to T3 when needed, at the time that's needed, how much is needed. So that's what favored the choice of levothyroxine as the therapy of choice for hypothyroidism.