

Adjourning Alzheimer's

Synopsis - Potential Therapies In Alzheimer's (Day 78)

We will be recruiting for The Alzheimer's Dietary Study soon! Before we do, let's do **one last recap** for all the potential therapies in Alzheimer's that we have covered.

(1) The Edge

Neurons are altered by new, challenging experiences. For optimal growth, the experiences should exist in the region between that which is overly familiar and that which is utterly confusing; this is **the edge**. We each contain a **fixed genetic code**, but much of it remains locked in life, the genes never expressed. However, by changing what we do, **we can alter how the code is read**, blocking some genes from being expressed and unblocking others that are suppressed; that's **epigenetics**. Thus, rather than say we are the sum of our genes, it is more accurate to say **we are the sum of genes that we express**. If we can find a therapy that is difficult but doable, one that results in optimal neuron health by awakening the right genes against Alzheimer's, maybe we can change the course of the disorder.

(2) Caregiving

Caregiving remains the **most effective, gold-standard therapy** for Alzheimer's. However, caregivers are susceptible to **caregiver burden**, a combination of physical, psychological, emotional, and financial stress as experienced through the eyes of the caregiver, the most burdensome aspects of which include the energy required to be a caregiver, a desire for the supported person to get better, insufficient time for one's own interests, and sadness over the fate of the supported person. Left untreated, caregiver burden can lead to **caregiver burnout**, and that's not good. It is important that caregiver burden be identified early, for there are many **interventions targeting caregivers** that can help them maintain their own health, including arranging "time for self," joining a support group, receiving education and training for challenging behaviours, seeking counselling, and treating mood disorders. If needed, these should be applied.

(3) Medical Therapies

Medications are often used in Alzheimer's, the "big four" being donepezil, rivastigmine, galantamine, and memantine. It is not unreasonable for someone with Alzheimer's to try one, for on average there will be a **4% improvement in cognition at 6 months**; however, after one year or so most people are "back to where they started." Thus, the improvements are **small, and temporary**. After decades of research, proposed future medical therapies - immunotherapies (including vaccines), growth factors, and cell transplant therapies (including stem cells) - remain largely ineffective. The common theme with all these medical therapies is that they are trying to take short-cuts; **none of them take you to the edge**, the place where you challenge yourself. Thus, they cannot help you reawaken the silenced genes you need to tackle Alzheimer's. They cannot help you reclaim your epigenetic power.

(4) Exercise

Exercise is also often recommended in Alzheimer's. Both aerobic and resistance exercise are backed by evidence, but aerobic exercise is backed by more. Several randomized controlled studies have shown that aerobic exercise **probably enhances brain volume and cognition by 1-2% per year**. These gains are **small**, but given that neuron loss in Alzheimer's produces hippocampal and cerebral cortex atrophy, it is tempting to conclude that exercise might impact the Alzheimer's pathological process by slowing down neuron loss and brain atrophy. Exercise **takes you part-way to the edge**, reawakening some of your epigenetic power, but since its effects are small, exercise alone is probably not enough.

(5) Dietary Modification

Dietary modification can **apply multi-targeted epigenetic pressure over a sustained period of time** to the pathological process that is Alzheimer's. In theory, the right diet can tackle Alzheimer's from multiple angles, including epigenetically reawakening long-silenced genes involved in cell energy conservation, survival, and autophagy through master regulatory enzymes such as AMPK. Moreover, the right diet can do this for months or even years since most of the difficulties involved in starting a modified diet occur during the first few weeks of the diet; once the body has a chance to adapt, adverse effects tend to dissipate. Unfortunately, **we still don't know what the "right" diet is for Alzheimer's**. On one hand, a number of large observational studies support high-carbohydrate, low-fat diets, but they only prove correlation. On the other hand, two randomized controlled studies support high-fat, low-carbohydrate ketogenic diets, but they were small and contained several methodological weaknesses. Thus, despite the promise of dietary modification, we have no idea which diet might truly impact Alzheimer's the most. Yet with the right randomized controlled study, we can find out, and it is important that we do find out. It is not always easy to commence a modified diet, but I believe it is achievable by nearly anyone. Moreover, the challenge of sticking to a modified diet is actually the point - success at doing so **takes you right to the edge**, to a place that is difficult yet doable, a place where you might reclaim a substantial amount of your epigenetic power.

(6) Multidomain Interventions

Multidomain interventions herald substantial theoretical benefits in Alzheimer's as they may **apply even more epigenetic pressure over time** than even dietary modification. The two multidomain interventions backed by the most evidence (and interest) are FINGER and ReCODE - **FINGER** involves four single-domain interventions, whereas **ReCODE** is a personalized program that involves as many as 30-40 single-domain interventions. However, multidomain interventions face several major difficulties. They are often time-consuming and costly, involve interventions that may not be doing anything at all, and in the case of ReCODE are highly prone to placebo effect and other potential sources of bias. If these difficulties could be addressed, then multidomain interventions, which potentially can incorporate all the potential therapies we have discussed plus more, **could become more achievable** and used by many people to impact the Alzheimer's pathological process. For the time being, multidomain interventions **take most people too far past the edge**. Yet we have a chance to improve the evidence for them right now. Given that both FINGER and ReCODE contain a dietary modification, each of which is very similar to the one we will use in **The Alzheimer's Dietary Study**, I sincerely hope you will consider joining us for an exciting second half of 2019.

Over the last several weeks, we have covered **several promising therapies for Alzheimer's**; however, I hope you have noticed that **none of them are "magic bullet" approaches** that claim an easy cure without hard work on the part of the person with Alzheimer's. Every so often, we hear about the next big cure for Alzheimer's in the media, yet the prevalence of Alzheimer's continues to climb. Currently, there are about 40 million people in the world with Alzheimer's; many epidemiologists project that the number will exceed 100 million people by the year 2050.

Rather than get overly-excited about the next new therapy that offers a quick and easy path to a cure for Alzheimer's, perhaps it is better to consider the disorder in its entirety, then apply that knowledge through action. Alzheimer's is a complex chain of pathological events that evolves over decades; if we are to slow, halt, or reverse it, then maybe we need a therapy that can apply multi-targeted pressure over a sustained period of time. A therapy that takes us **right to the edge**, the place where you challenge yourself. Importantly, the therapy cannot fall short of the edge, for then it is not epigenetically effective, but nor can it take us past the edge, for then it is not feasible for most people with Alzheimer's. Perhaps the best therapy is the one that **self-empowers and places a person somewhere between routine and impossibility** - a place that is difficult, but doable.

Out of all the therapies we have covered, there is but one with the right theoretical tools to tackle Alzheimer's, one that can take us right to the edge - **dietary modification**, a therapy that is difficult, but doable. However, we do not know which diet is best for Alzheimer's; there is a major disagreement in the literature, and we have the power over the next several months to resolve it. For people with Alzheimer's the world over, we must resolve it - at least, we must try.



Dietary modification can take us right to the edge; we will walk it together.

My friends, we have finally arrived at the end of the Adjourning Alzheimer's email series, the end of our discourse into one of the most complex disorders in existence. Yet for some of you - I sincerely hope, many of you - this is not the end of our discussion. Nor is it the beginning of the end. Rather, **it is the end of the beginning**. Let's see if a diet intervention makes a difference in Alzheimer's.

Matt (Neurologist, Waikato Hospital).