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**To:** "Noam Sobel" <[REDACTED]>  
**Subject:** Ideas - Confidential please  
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Noam – thanks for the opportunity. Am sending from my UW email so I don't get mixed up with the foundation interests (notably not in the neurosciences).

Over the next 12-18 months I would like to lay the groundwork for redefining the role and function of the Autonomic Nervous System. At the end of this document are some options as to how we might proceed together.

For some of the ideas I can think of how to do the experiments and the practical relevance – for others it is more about the recognition of an opportunity without a clear roadmap of how to find an answer. I think together we can.

Please don't share these beyond you for now as they represent a bunch of years of thinking about these things and I really want to pursue them as original ideas that I can contribute to scientifically.

- **Changing our understanding of breathing**

Equal weight is given to nasal and oral breathing – and in fact, mechanically ventilated patients tend to bypass both. Focus has always been given to structural delivery of air to the lungs and little attention has been paid to the various pathways that feed into the neural process of breathing.

Practitioners of yoga, athletes and even some small scale studies have asserted that nasal breathing slows heart rate and blood pressure. Alternatively, sleep experts and other scientists have shown that *mouth breathers* tend to be hypertensive and suffer from various co-morbidities [REDACTED] as sleep apnea and obesity. This suggests that nasal breathing stimulates the parasympathetic nervous system and minimizes sympathetic tone while the converse is true for oropharyngeal respiration.

If this is true, mechanically ventilated patients might always be in acute distress (from the perspective of the nervous system) unless a new type of mechanical ventilation can be created – or current ones adapted – that would engage the parasympathetic system.

To figure this out, one would need to identify the parasympathetic fibers of the nasopharyngeal surface and learn about whether their activation involves mechanical (directional flow) or chemical stimuli. Simple baseline studies of nasal and oral breathing in various exercise and rests states would first need to be contrasted. At that point, oral breathing with mechanical or chemical stimuli to the nasopharynx could be tested to see if there are similar rate and pressure responses within the cardiovascular system.

- **What is sympathetic storming?**

I've written a paper or two on the topic and plenty of others have too. In critically ill, neurologically devastated or even terminally ill patients, something goes terribly (but periodically) wrong causing a "storm" of sympathetic activity. Terms used to describe this phenomenon in published reports include dysautonomia, paroxysmal autonomic instability with dystonia, paroxysmal sympathetic storms, autonomic dysfunction syndrome, and diencephalic seizures. Multiple medications have been used to treat [REDACTED] episodes, although no definitive treatment exists and no one is sure of the mechanism.

Signs and symptoms of sympathetic storming include posturing, dystonia, hypertension, tachycardia, pupillary dilatation, diaphoresis, hyperthermia, and tachypnea. The episodes appear unprovoked and can last for hours or end abruptly. Sympathetic storming often occurs after discontinuation of administration of sedatives and narcotics in the ventilated patients within the intensive care unit (ICU).

I believe it is unchecked sympathetic activity that could be balanced by applying a strong central parasympathetic stimulus (and not a medication or selective tone mediating agent). The nasal or nasopharyngeal afferents / efferents haven't been

clearly elucidated but fixing this might be as simple as a nasal spray. What if all we needed to do was rub some ultrasound jelly (lubricant) onto the turbinates? That would be amazing.

- **Parasympathetic pathology as the etiology of paroxysmal atrial fibrillation**

Stroke is a major health problem; and as the population ages, its significance will grow. Worldwide, stroke is the 2nd leading cause of death. Atrial fibrillation is a significant risk factor for stroke and indeed the treatment is anticoagulation which carries significant morbidity and mortality risk as well. While there are many potential causes for atrial fibrillation (including prior infarct) – I want to focus on a specific subtype called paroxysmal atrial fibrillation which I believe is due to reactivation of HSV (not sure if type 1 or 2) somewhere within the purview of the vagus nerve which results in flawed efferent activity and disordered electrical stimuli to the heart. No one understands why paroxysmal atrial fibrillation comes and goes but it is still managed in the same way as chronic atrial fibrillation. I believe that if we can identify the pathophysiology of this reactivation we can radically transform the way the condition is treated. Instead of miserable anticoagulation, the treatment would shift to acyclovir which is relatively harmless and would radically transform the way we view stroke treatment. It would also be a paradigm shift in cardiac or neuro-cardiac disease similar to the way in which bacteria were discovered as the source of stomach ulcers many years ago.

I've got about 100 papers in hard copy, each with a small piece of the puzzle. What I don't know is how to test this. We know HSV is in ganglia, we know the innervation of the heart, etc etc. Putting it all together is the challenge. We would save a lot of lives and transform stroke prevention as we know it.

- **Sore throat**

I don't believe that sore throats are benign in the sense that they are just a manifestation of post-nasal drip or something that simple. I think it represents neuralgia of CN IX and X – mostly X. It might or might not be difficult to prove but if the afferents (=pain) also represent an "in" for pathologic invaders that is a sure path into the cranial nerves and eventually the CNS.

It just doesn't make sense to me that pathogens have to invade bloodstream or GI mucosa before they become immunologically relevant. Could nerves (especially those in the nasopharynx) be the portal of entry for bad stuff? And could that bad stuff mess things up in the short term and long term – ■■■ that Parkinson and Alzheimer diseases aren't really degenerative but neuroinfectious sequelae?

If you think about it – the primary neurotransmitter (Ach) of the autonomic nervous system is also the one a mess in Alzheimer. I think we are way too distracted by the lipoproteins. Also, strangely enough, Ach is the neurotransmitter for sweat glands (it is an odd one because it is the only Ach-mediated post-ganglionic sympathetic path to not use NA). What if Parkinson was actually an autonomic nervous system disease originating in sweat glands? Parkinson disease patients in late stages and early stages of many subtypes (so, all patients eventually) have dysautonomia and seborrheic keratosis. I think that's why.

It all starts with figuring out how to get "in" to the ANS and I think the answer lies in the vagus nerve.

- **Coma**

I've become quite fascinated by the management of coma patients and in addition to keeping a database of comatose patients (>1,000) I've also continued to wonder about consciousness in general. I am sure you remember when Dr. Crick used to come by the Bower lab – and in his final days working at Caltech I would spend a lot of time talking to him about what he believed to be the neural substrate for consciousness. I always disagreed with him because he felt like it was a complex, networked process.

I believe if we can find the anatomic link between that what we know as the "central nervous system" and the "autonomic nervous system" we will discover the on/off switch for consciousness. I have some ideas but this might mean roping in neurochemists and pathologists to answer a few questions first. The answer for this connection is knowable. Whether or not it is a consciousness switch I can't be sure but even if it isn't, there is something extremely powerful about this interface. Powerful and exploitable – since it is also likely to be a place where the blood-brain barrier is not as relevant. This might be the Holy Grail. 😊

Anyway – there are a lot more ideas. I think that each of the ideas above grows from the previous one, but to some degree can work in parallel as we learn. The first two have (breathing and storming) have immediate clinical relevance. Paroxysmal afib treatment could revolutionize stroke care. Figuring out the sore throat might turn the idea of

degenerative disease on its head – and give us some clues about how to immunize differently...Maybe not with shots into the bloodstream but with strong physical barriers to pathogens along CN X – more like Fort Vagus and less like antibody warriors. And of course – consciousness is everyone’s dream.

I think these are do-able and the nasopharynx might just be the key.

If you think this sounds interesting and would be willing to help me figure these out, let’s try. You’d have to guide me on what your institute would consider appropriate. If Visiting Professor is an option, I’d say let’s do it for a year. I propose to spend up to 4 weeks in residence there and then once or twice weekly (or whatever is needed) videoconferencing. I’ve spoken to a philanthropist who is keen to support emerging science and he is interested in funding this type of work. I would need to put a price on the administrative costs for your institution, graduate student time, and my travel time but I would propose a 12-18 month “pilot” of this work to him and start there.

What do you think?

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