

shake-up of lake water could have released carbon dioxide gas in the enormous amount required to overwhelm the valley.

Oxygen deprivation is extremely dangerous. Oxygen is the most physiologically important gas in air due to its role in cellular respiration. Electrons are harvested from nutrient molecules (sugars, fats, amino acids) by the oxidation reactions of the Krebs cycle. These electrons are then passed through the electron transport chain in order to generate the energy necessary to establish a hydrogen ion (proton) gradient. The energy of the proton gradient provides ATP synthase with the necessary power to make ATP ( $\text{ADP} + \text{Phosphate} \rightarrow \text{ATP}$ ) in the same fashion that a water wheel harnesses the power of a waterfall to make electricity.

Much like a highway, the electron transport chain is all about flow. Electrons have to enter and electrons have to leave. As long as things are flowing everything is fine. Oxygen accepts electrons at the end of the chain and allows them to leave, just like an exit ramp allows you to leave a highway. Without oxygen, electrons continue to enter the transport chain but do not leave leading to saturation or an “electron jam”. The rate of ATP production grinds to a rapid halt without oxygen to accept electrons from the electron transport chain. Insufficient production of ATP prevents cells from doing work that is essential to maintaining order. Once order is lost the cells will die rapidly. Imagine a highway where cars continued to get on and none ever left. In time the whole highway would fill up with cars and all traffic would stop. Oxygen is essential to removing electrons from the transport chain so new electrons can enter and lead to a high ATP production rate.

↪ **Take Home Message** ◀

**Oxygen is an essential component of cellular respiration. A constant supply of oxygen is essential to produce enough ATP to keep you alive.**

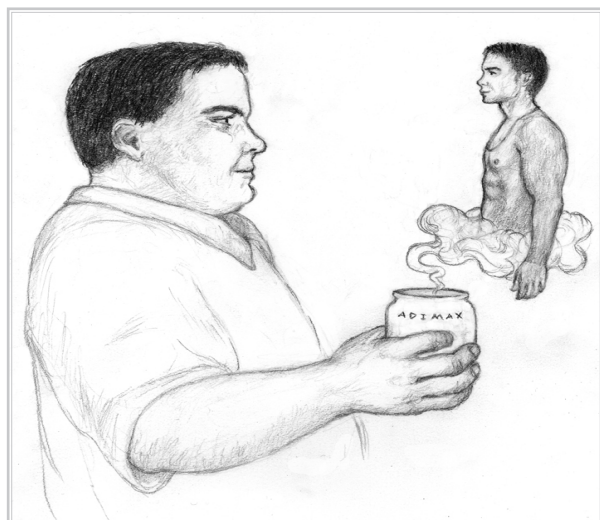


## The Hydrogen Ion Gradient

### DNP DIET DISASTER

Daniel Johnson is a 24-year-old accountant who is significantly overweight. He is looking to vacation at the Jersey Shore this summer, and he wants to be a big hit on the club scene and attract a lot of women. Daniel believes that unless he gets a set of abs like his idols on the “Jersey Shore” his chances of getting any attention from the ladies are slim to none. He figures that he has to lose at least 30 pounds in 2 months to achieve this physical goal. While surfing the internet one night Daniel sees an ad for diet pills called “ADIMAX”. The drug is being marketed as “too extreme” for the FDA and is only to be used by people who are “serious about losing weight fast”. Daniel ends up ordering several boxes of ADIMAX. It takes a few weeks for the pills to get imported from Russia but as soon as they arrive at his apartment he tears the packaging open like a kid on Christmas morning.

He notices that there is no recommended dosage information or anything about active ingredients. The only thing on the cover of the bottle besides the word ADIMAX are pictures of people with ripped abdominal muscles. Daniel is not sure how many pills to take at one time, but he figures that he is serious about losing weight so he should take at least ten because that seems like a nice round number. He maintains this regimen for a few days and begins to lose weight. One day his co-worker, Craig, notices that Daniel’s shirt is so soaked with sweat that it is transparent. Daniel seems to be breathing much faster than normal and he is clutching his chest like a person might do if their heart were racing. Daniel tells Craig that he feels like the blood is boiling inside of his body. When Craig touches Daniel’s skin it is hot to the touch. Craig knows that this is not natural and takes Daniel to the emergency room where it is determined that his body temperature is 104°F (normal 98.6°F).



### Scientific Connection

This is just one example of the many risks associated with idolizing cast members of the Jersey Shore. Going up to strange women, pulling up your shirt, and showing off your abs will lead to more restraining orders than phone numbers. Unregulated dietary supplements exist in a spectrum between useless and deadly. The best way to lose weight is to adopt a philosophy of healthy living that includes modifications to your diet and increases in exercise. The internet is a breeding ground for dangerous “quick fix” products that use “modern science” to yield impossible results. These products often do not list things like “ingredients”, though the buyer is often assured that the components are “all natural” (as we’ve seen, cyanide is also natural—and deadly). In this case, the fictional product ADIMAX contains a drug known as dinitrophenol, which was used in diet pills in the 1930s. Dinitrophenol acts as an uncoupler of mitochondrial oxidative phosphorylation and is banned in the United States for use as either a dieting aid or a pesticide. The scientific rationale behind its use as a diet aid is logical, but the benefits are greatly outweighed by its potential for danger.

Uncoupling agents target the mitochondria, the organelle responsible for ATP production by oxidative phosphorylation. In the mitochondria’s innermost region, the matrix, electrons are harvested from nutrient molecules by the sequential oxidation reactions of the Krebs cycle. Electron carriers (NADH, FADH<sub>2</sub>) taxi electrons to the electron transport chain, which they flow through until they are accepted by oxygen. The passage of electrons through the transport chain provides the energy for hydrogen ions to be pumped into the space between the inner and outer mitochondrial membranes, resulting in the formation of a hydrogen ion gradient. The hydrogen ions really want to make their way back into the mitochondrial matrix but they only have one passageway that lets them do this: the pore of the protein ATP synthase. ATP synthase is like a little revolving door: as hydrogen ions make their way through it part of the protein spins. The force of this turning motion provides the energy for the crucial reaction that makes ATP (ADP + Phosphate → ATP). The formation of the hydrogen ion gradient is essential to the spinning of ATP synthase and the production of ATP. The more ATP synthase spins, the more ATP gets made.

An uncoupling agent like dinitrophenol interferes with the formation of the proton gradient. Electrons are still passed down the electron transport chain and accepted by oxygen; unfortunately, the hydrogen ions leak out of the intramembranous space as quickly as they are pumped into it. In order to increase the amount of protons pumped into the intramembranous space, more electrons are passed through the transport chain, which ironically leads to increased oxygen consumption but decreased ATP production.

How does all of this result in weight loss? The electrons used to generate the hydrogen ion gradient are harvested from nutrients like fat

inside of the mitochondria. The uncoupling action of dinitrophenol requires more nutrients to be burned to make the same amount of ATP, which indeed would lead to weight loss. Unfortunately the increased flux of electrons through the electron transport chain leads to the deadly side effect of dinitrophenol: elevated body temperature.

Your average body temperature is 98.6°F, but where does this heat come from? Why are living people warm and dead people cold? The answer lies in the mitochondrial production of ATP. The process of passing electrons down the electron transport chain generates most of the heat that warms your body. When your body dies you stop producing ATP, which means that you stop producing heat as well. With no heat production the body cools to room temperature. In the case of poisoning with dinitrophenol, there is increased flux of electrons through the electron transport chain. More electrons being passed through the chain means more heat is being produced and the body temperature will rise so high that it can be life threatening. In order to meet the increased demands for oxygen and nutrients the heart beats faster to deliver more blood to the tissues. Breathing rate is also increased to acquire more oxygen from the outside world.

### ↪ *Take Home Message* ◀

**The hydrogen ion gradient is the force that powers ATP synthase and the generation of ATP. It is created by the passage of electrons down the electron transport chain which also generates heat. Uncoupling agents interfere with the formation of the hydrogen ion gradient and can cause both decreases in ATP production and extremely high body temperatures.**