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## A Chat with Dr. Paul Taylor

### CURRENT KENNEDY'S DISEASE RESEARCH

**Below is a portion of a chat with J. Paul Taylor, MD, PhD, of St. Jude Children's Research Hospital. He does an excellent job of explaining some of the Kennedy's Disease research taking place today.**

"At that meeting, I described the direction of our research and how we are focusing on a particular aspect of androgen receptor (AR) function. Two papers were recently published indicating that other scientists are finding the same thing. Specifically, that the mutant form of AR is altering the ways genes are turned on.

... There are different approaches to (potential) therapy and let me address them one at a time. First, autophagy. Yes, I think this is a promising avenue for KD, but not in the immediate future. Several different autophagy inducers are in development but there are no clinical trials underway yet. Autophagy is a cell process for degrading things inside the cell that are unwanted, like clumps of toxic AR for example. It is a natural process, but the idea is to boost it with an autophagy inducer. This has been shown to work for a number of diseases using animal models (including KD).

The second approach mentioned is stem cells. There will be a big boost in stem cell research now that the ban on federal funding

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## Laryngospasm

### DRY DROWNING

Many of us with Kennedy's Disease have experienced the phenomenon of 'Dry Drowning'. It is a frightening experience for all involved including the spouse, children and caregiver. Below is some information from the Voice Dr. (<http://www.voicedoctor.net/therapy/laryngospasm.html>) on the subject.

**Spasm** - A spasm is any involuntary contraction of a muscle. The throat area has a number of muscles all of which have the potential to spasm. If laryngospasm is your condition, then the following should apply. Please be sure a physician verifies that this is your condition.

**Symptoms** - The symptoms are very characteristic.

- Abrupt, sudden onset
- May occur anytime, but often noticeable when eating and talking simultaneously and something feels like it went down the wrong way
- May be awakened in the middle of the night unable to breathe.
- Feels like you are going to die or never breathe again
- Yet typically, it lasts less than 30 or 60 seconds.
- Very noisy and difficult "breathing in"
- Rather easy breathing out, still able to cough.
- Faster "breathing in" makes it worse.

**Causes** - This syndrome results from a spasm in the adductor muscles - the muscles closing or bringing the vocal folds together. As soon as your voice box or the area of the windpipe below the voice box detect the entry of water or other substance, the vocal folds spasm shut. Evolutionarily speaking, this works very well to keep water out of the lungs - if you start to drown or a bug flies down your throat while you were starting to inhale, or you inhale that glass of water, then the vocal cords very immediately and very effectively close.

That closure is a benefit to protect the airway, but it makes "breathing in", very difficult. It can happen even when only the sensation is present of something other than air entering the windpipe.

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has been lifted; and I anticipate that we will begin seeing application of stem cell therapy for some diseases (like diabetes and hemophilia) in the near future. We dream of treating neurological diseases with stem cells, and some investigators have successfully turned stem cells into neurons, even motor neurons, but delivering them to the right location is the difficult part. There is active work on this, but I see that as a tough obstacle.

The first generation of autophagy inducers were all based on a single target (called TOR, by the way) and in animals autophagy can be successfully induced without adverse effects that we are aware of. But there are theoretical concerns, specifically that these drugs also produce immune suppression. This is not a problem in animal trials in the short term because they are on the drug for about 6 months. The concern is that humans with KD or similar disease would need long term therapy so a second generation of drugs has been developed that work differently. Use of the second generation drugs in animals is limited so far. My colleagues at Penn applied to perform a clinical trial of an autophagy inducer (first gen) in humans with Parkinson disease, but were turned down because it was felt that there was not enough animal data yet.

The third approach is targeting AR directly and specifically. This would only apply to KD. That is the idea behind the dutasteride and lupron trials. I will say that I believe that the most promising approach will be targeting AR directly. And this is supported by the two papers just published - one by Dr. Kato in Japan and another by Diane Merry at Jefferson. We will have a paper on this soon too.

Many of you know that we use a fruit fly model of KD. We have used this model to examine over a dozen different parts of the AR protein to find out which ones are responsible for driving neurodegeneration. We have taken over a dozen different forms of AR (each with a targeted mutation that we introduced) and made transgenic flies.

In all of these diseases, the final common pathway appears to be the way the disease protein influences the process by which genes are turned on and off - called transcription. So...we believe that we have found a critical target and to prove it we are now testing this in a mouse model.

A human trial is a very big deal. Let me tell you why we approach this with caution... First, you need to have a promising therapy, meaning preclinical evidence that it will probably work and also evidence that it will probably not be toxic to the subjects. There are risks involved. Beyond the obvious concern about risk to the subjects (e.g. dangerous side effects), there are risks that a poorly run trial can kill a promising therapy. There are also opportunity risks to a clinical trial since it is only practical to run so many and we must make the most of these limited chances."

**The entire transcript can be found on the KDA web site:**  
[http://www.kennedysdisease.org/disc\\_transcripts.html](http://www.kennedysdisease.org/disc_transcripts.html)

**Physiology 101** - Laryngospasm is a normal response to prevent drowning or keeping fluid out of the lungs. If you truly were drowning, this is a great reflex to have functioning. That clamping shut of the vocal cords may save your lungs from a bath or long enough for you to get back to the surface. At other times though, it can be quite a nuisance.

It is an extremely common condition in patients who have had nerves on both sides of their voice box injured or paralyzed. Actually paralyzed vocal cords are not really paralyzed. The nerve almost always regrows, and often crosses or mixes up connections and the vocal cord ends up with a rather permanent tension. Usually after a paralyzing injury, the vocal cords are actually closer together, spasm easily and can still close tightly.

Almost all cases of frequent, recurrent laryngospasm (more than one a month), are due to an injury of the nerve supplying the muscles that close the vocal cords. With a close enough inspection, some sign of that injury will be identified and many of the injuries to the nerve that trigger frequent laryngospasms can be treated.

Each individual laryngospasm episode is a self limiting disorder that will resolve on its own. However, the condition of being susceptible to frequent laryngospasms may go on for some time or a lifetime.

### **A management program –**

- 1- Knowing what the condition is and its short duration helps patients deal with the episodes more confidently.
- 2- The Bernoulli principle - the one you may have learned about in high school physics that keeps airplanes in the air - is the reason laryngospasm worsens with stronger attempts at breathing in. The faster the air flow through a narrow area, the lower the pressure. The voice box is the narrowest part of the windpipe so it has the lowest pressure during rapid breathing. And, in fact, laryngospasm might not be a spasm at all. It may be an inhibition or lack of ability for the opening muscles of the voice box to operate momentarily. Then, the rapid airflow through the voice box, in effect, more easily sucks the vocal folds tighter together.
- 3- With the Bernoulli principle in mind, one can see that slower breathing in will effectively get more air into the lungs than rapid breathing in. In fact, we spend most of our life breathing out, as in talking, then we take a quick breath in and spend more time talking. When one has an episode of laryngospasm, one can reverse this usual trend and take most of your time to breath in slowly and then a quick breath out can be followed by another slow breath in. This can be repeated until the spasm stops.
- 4- An observation was made by a person with the condition that if they tilted their head backwards during an episode, it made the slow breathing in easier. By stretching the neck, it effectively lowers the voice box in the neck and that may prevent some of the clamping down by the vocal cord muscles.

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## The Need for Greater Education and Awareness

### THE NEED TO EDUCATE OTHERS

The KDA normally receives several email inquiries a week. Many of the inquiries are from spouses or caregivers needing additional information to help their loved one that has Kennedy's Disease (KD). Occasionally, we receive an email from a facility that is caring for a person with KD. We are most appreciative of these caregivers because they are taking the time to research KD and understand what a person is going through that has the defective gene.

Recently we received such an email. A caregiver in a nursing home asked a series of questions about how KD impacts a person. We exchanged several emails. Her final email was interesting because she commented that many of the staff felt the person with KD was 'faking it' (my term) and were frustrated with the patient. After reading my responses and looking through the KDA web site, she now better understood the physical and emotional issues a person with KD goes through. Two specific areas that frustrated many of the caregivers were: (1) the almost daily comments from the patient concerning muscle pain (constant aching or cramping), and (2) the frustration the patient exhibited with not being able to perform simple tasks. The caregivers could not understand why the patient would continually try to do something that he just couldn't do. One example was walking and as a result falling.

Fortunately, the caregiver took the time to do some research and also contacted the KDA to help her understand more about the symptoms and emotional frustrations associated with the disease. She now was taking on the task of educating the rest of the staff about KD.

This incident makes me wonder about others with KD that might be in a nursing home or facility where the staff is unaware of the effects of KD on the patient. It once again expressed the need to constantly educate others concerning Kennedy's Disease ... especially those in charge of your care (in a hospital, nursing home, and even your doctor's staff).

*Laryngospasm -continued from page 2*

### Medication

- I have injected botulinum toxin into the adductor or closing muscles of the voice box and this has diminished both the severity and frequency of episodes in some people - particularly patients with bilateral recurrent laryngeal nerve injuries. It has also helped in a few cases of unilateral recurrent laryngeal nerve paresis where there has been recovery and the paralyzed side is now hyperactive.
- There may be a medication that would reduce the "tickle" sensation that triggers the episodes. Amitriptylline has sometimes been helpful in reducing throat tickles.
- If reflux is the presumed culprit, taking steps to eliminate it might be helpful.

## Not Every Health Issue is KD Related

### IS IT REALLY A KD SYMPTOM?

We have to always be careful that we don't associate every unusual symptom or health issue with KD. If it isn't listed in the common symptoms for KD, make certain you check with your GP or neurologist. Just because we have KD doesn't mean we are immune to all other health disorders. It is better to play it safe and discuss anything unusual with your doctor.

**Examples:** An associate complained about chest pain and related it to KD, but later found out he had a heart condition. Another continually had neck pain and finally discussed it with his doctor. He had a pinched nerve.

## America Online

### RECENT UPDATE TO THEIR BROWSER

Recently we had two people that use AOL call with the same problem. After they had AOL do an update, they no longer could reach our site using the AOL Web Browser. When they used Internet Explorer, they were able to reach us just fine. We are not sure what AOL changed with their update but for some reason AOL is stopping people from getting to us when they use the AOL web browser. If you have Internet Explorer give that a try and let us know if it works for you. We would also recommend that you contact AOL tech support and ask how you can regain access to our web site.

## The Future (Robotics)

### NEARER THAN WE THINK

There are some neat devices out there that could really help those of us with a handicap. Check out these two links for examples of what is going to become available:

**Honda Robo-Leg:** <http://blog.wired.com/cars/200...honda-announces.html> From this link, at the bottom of the page that opens, the You Tube video is interesting.

**HAL (Hybrid Assistance Limb) Exoskeleton:** <http://www.cyberdyne.jp/englis...otsuithal/index.html> This device is going on the market for \$4,200. I can almost see the expression on the face of the Walmart Greeter as one of us walked into the store with this suit on.

They both have a battery life of about two hours, but that should improve over time.

## KDA Forum

### *“Have you visited the forum recently?”*

The KDA forum is alive and well. There are many topics posted covering a variety of subjects. The benefits of this forum service include no advertising, and email notification of message replies. Visit the forum on our web site.

[http://www.kennedysdisease.org/disc\\_forums.html](http://www.kennedysdisease.org/disc_forums.html)

## Spinal Anaesthesia in a patient with Kennedy's Disease

### A RECENT REPORT

**AN EXCERPT:** Reported by: Lee JY, Choi YR.

**CONCLUSION:** Kennedy's disease typically presents as muscular atrophy, weakness, and fasciculation predominantly of bulbar, facial, and proximal muscles of the extremities. When a patient with Kennedy's disease is scheduled to undergo a procedure requiring anaesthesia, anaesthesiologists should carefully assess patient preoperative status, respiratory function, and inquire about swallowing difficulties or a history of intolerance to any general or local anaesthetic agent. Considerations for general anaesthesia concern possible prolonged neuromuscular blockade and consequent postoperative muscle weakness and a compromised baseline pulmonary function.

1. Many inhalation agents have been reported to be well tolerated by the patients with lower motor neuron disease.
2. However, it is not clear whether neuromuscular blocking agents prolong neuromuscular blockage. Depolarizing muscle relaxants, such as, succinylcholine, are not recommended. Moreover the possibility of hyperkalemia and of resultant ventricular arrhythmia or fibrillation has been reported in patients with neuromuscular and lower motor neuron diseases by several investigators.

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## KDA e-Xpress

A publication of the  
Kennedy's Disease Association.

Editor: Bruce Gaughran

Comments, suggestions, and questions should be sent to:  
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## The Objectives of the Kennedy's Disease Association

- Sharing information about Kennedy's Disease with those who seek it
- Creating a support system for those living with Kennedy's Disease
- Increasing public awareness of Kennedy's Disease and its effect upon families
- Increasing awareness of Kennedy's Disease in the medical community
- Raising funds, with an aggressive target to earmark at least 70% of every dollar donated to be used for Kennedy's Disease research

## An Amazing Soup

### CREAM OF CHICKEN WITH WILD RICE

1 1/3 Wild Rice	2 tbsp. Chicken bouillon
1 (3 lbs.) Whole chicken, Cut into pieces	3/4 tsp. ground white pepper
7 cups water	1/2 tsp. salt
1 cup chopped onion	1/2 cup margarine
1 cup chopped celery	3/4 cup all purpose- flour
2 tbsp. vegetable oil	4 cups milk
1 cup diced mushrooms	3/4 cup white wine

Cook the wild rice according to the package directions, but remove from heat about fifteen (15) minutes before it's done. Drain the excess liquid and set the rice aside.

In a stock pot over high heat, combine the chicken and the water. Bring to a boil, and then reduce the heat to low. Simmer for forty (40) minutes, or until chicken is cooked and tender. Remove the chicken from the pot, and allow to cool. Strain the broth from the pot, and reserve for later. When the chicken has cooled, remove the meat from the bones, cut into bite size pieces, and reserve. Discard the fat and bones.

In the same stock pot, over medium heat, sauté the celery and onion in the oil for five (5) minutes. Add the mushrooms, and cover. Cook for five (5) to ten (10) minutes, stirring occasionally, until everything is tender. Return the broth to the stock pot, and add the partially cooked wild rice. Stir in the bouillon, white pepper and salt; simmer, uncovered, for fifteen (15) minutes.

Meanwhile, melt the margarine in a medium saucepan over medium heat. Stir in the flour, and mix until smooth. Whisk in the milk until it's bubbly and thick. Add some of the broth mixture to the milk mixture continuing to stir constantly. Then stir all of the milk mixture into the broth mixture. Mix in the reserved chicken meat and the white wine. Allow to heat through for fifteen (15) minutes, and then serve.

*Forest Updike (USA)*  
page 135 *KDA Cookbook – Recipes from Around the World*

### Spinal Anesthesia -continued from page 4

3. If muscle relaxation is required, non-depolarizing neuromuscular blocking agents should be considered, and neuromuscular transmission should be monitored closely.

There is additional important information on this subject as well as specific recommendations at:  
[http://www.kennedysdisease.org/disc\\_surgery.html](http://www.kennedysdisease.org/disc_surgery.html).

Review and, if needed, print the information provided for further discussion with your physician before any surgery.

## COOKBOOKS

For more great Recipes, including the one in this newsletter, you can purchase the wonderful KDA cookbook "**Recipes from around the World**". It contains 300 recipes including many contributed from KDA Associates. The books are \$12.00 when shipped within the US. If the books are to be shipped outside the US, please email the KDA for possible additional costs.

