Connecticut Parkinson's Working Group Newsletter

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The articles chosen this issue were carefully selected to bring out points I believe need to be made, at least to us, the great unwashed (non-M.D.'s): There is exciting research going on that is looking for a cure. Sometimes, in looking to develop a palliative drug, pharmaceutical companies come across results that would put them out of business. If you are looking for a cure, don't let levodopa cloud your thinking. Good research often takes an infuriating amount of time.

I know that some of the articles are a bit hard to read. I also believe that the readers of this newsletter seek a deeper understanding of what are often issues with complex overtones, but which are simplified by the print media. Even so, I usually cut out some of the over-the-top inclusions. This is the latest published research, and it holds out hope for all of us. We owe it to ourselves to keep informed, knowledgably informed.

Comment on the following article: For those of you who have not been following this story on growth factors (following article), let me try to fill you in: I became interested in GDNF in 1990 when I read an article in SCIENCE (the AAAS journal) about monkeys that had had their substantia nigra blasted with MPTP to produce the symptoms of PD. MPTP kills dopamine producing neurons. They were given GDNF, I believe orally, and were back to their rambunctious selves in no time. Since then I have been following the trials in humans, none of which have produced any significant results. I believe this is because GDNF in humans must be delivered more precisely to the spot where it is needed. The only people who seem to have made a dent in the problem up until now were those at Amgen. I went so far as to inquire about participating in some of the GDNF studies but, on good advice, rejected the trials. I was in the final phases of consideration for the Cere-120 Phase Two trial [see following article]; due to personal matters, I also bowed out there.

The reason I was excited about Cere-120 is that it is in the same family as GDNF and essentially acts as GDNF would, if Ceregene could use it, but Amgen has a patent (!!!) on it. So Ceregene developed NTN. They are able to deliver it precisely to the putamen, the spot in the brain where it is needed most to reverse some of the symptoms of PD. Let me point out: this is not a potential cure, since it ostensibly addresses palliative measures rather than curative ones. (See the article in the last newsletter on how the whole brain is affected with gene therapy.) However, I think most of us would be ecstatic if we could get rid of our motor control symptoms. This is great news. **Stan**

CEREGENE PRESENTS LONG-TERM FOLLOW-UP OF PHASE 1 TRIAL OF CERE-120 IN PD

[From CNN]

December 12, 2007 Ceregene, Inc. today presented long-term follow-up data from a Phase 1 clinical trial of CERE-120 in 12 patients with advanced PD. CERE-120 uses gene therapy to deliver the neural growth factor neurturin to the major area of neuron degeneration that occurs in the brains of PD patients. Long-term follow up assessments at 18 and 24 months post treatment, suggest a sustained reduction in PD's symptoms. It was previously reported that an average of 36% reduction in PD symptoms was seen 12 months after CERE-120 administration. Of the 12 subjects treated, nine had shown a clinically meaningful reduction in symptoms at 12 months, and the mean improvement of these responders' at 12 months was 46%. Today it was reported that the eight evaluable responders exhibited a persistent mean improvement in symptoms of 52% at their longest time

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of follow-up (24 months for low-dose cohort* and 18 months for high-dose cohort). More specifically, there was a statistically significant improvement in the primary endpoint compared to baseline defined as the reduction in PD symptoms as measured by the Unified PD Rating Scale (UPDRS) motor "off" score ("motor off" meaning patients were off PD medication at evaluation time). CERE-120 continues to appear safe and well-tolerated, with no treatment-related or surgically-related serious adverse events reported for any of these patients. These data were presented today at the World Congress of PD by Raymond T. Bartus, Ph.D., Ceregene's executive vice president of clinical and preclinical R&D, and COO.

The Phase 1 trial was an open-label study conducted in 12 patients with advanced PD at two clinical trial sites—University of California, San Francisco and Rush University Medical Center in Chicago. William J. Marks Jr., M.D., associate professor of neurology at UCSF, was the principal investigator on the trial. All 12 patients enrolled in the study underwent stereotactic** neurosurgery to deliver one of two dose levels of CERE-120 into their putamen—a region of the brain affected by the degeneration of neurons in PD. Several validated secondary motor endpoints, i.e., timed walking test and Purdue pegboard, which also suggested improvement at 12 months, continued to show improvement at 18 and 24 months.

"We are pleased to see that the improvement in motor symptoms seen in the PD patients 12 months after CERE-120 treatment appears to be persisting over longer time," stated Jeffrey M. Ostrove, Ph.D., president and CEO of Ceregene. "These positive clinical data offer further support for our recently enrolled multicenter Phase 2 trial for CERE-120 in the US as well as our plans to initiate another Phase 2 trial that will begin in the third quarter of 2008 which will be conducted in several European countries in collaboration with Genzyme."

"I am encouraged that PD patients continue to respond well to CERE-120, over longer periods of time," stated Dr. Bartus. "Not only have we seen no treatment related serious adverse events at up to two years post dosing, but the apparent improvement seen at 12 months seems to continue as well. We, therefore, look forward to analyzing the results of our ongoing controlled Phase 2 trial of CERE-120 near the end of 2008 to determine whether they confirm the possibility that CERE-120 might significantly and persistently improve the symptoms of advanced PD patients."

This Phase 1 clinical trial was partially supported by a grant from The Michael J. Fox Foundation for PD Research. Based on the encouraging results of the Phase 1 study, the Foundation awarded another $1.9 million grant, which is providing partial funding for Ceregene's ongoing Phase 2 trial.

*Cohort – A group of individuals having a statistical factor (such as age or class membership) in common in a research study.

** Stereotactic – Precise positioning in three-dimensional space.

ABOUT PHASE 2 TRIAL OF CERE-120 CURRENTLY UNDERWAY

A double-blind, controlled Phase 2 clinical trial completed enrollment last month of 58 patients with advanced PD at nine medical centers in the US, with two thirds of the patients being enrolled in the active treatment group and one third in a control group. Patients received CERE-120 via stereotactic neurosurgery to deliver the drug into the putamen region of the brain and are being followed for 12 months for safety and efficacy. Clinical data from this trial are expected to be available in late 2008, and if the data are positive, a Phase 3 trial is expected to commence in 2009.

ABOUT CERE-120

CERE-120 is composed of an adeno-associated virus (AAV) vector carrying the gene for neurturin (NTN), a naturally occurring protein known to repair damaged and dying dopamine-secreting neurons, keeping them alive and functioning normally. NTN is a member of the same protein family as glial cell-derived neurotrophic factor (GDNF). The two molecules have similar pharmacological properties, and both have been shown to benefit the midbrain dopamine neurons that degenerate in PD and are responsible for the major motor impairments. CERE-120 is delivered by stereotactic injection to the affected area of the brain, providing stable, long-lasting expression of NTN in a highly targeted fashion. Genzyme Corporation has licensed the ex-North American rights for the development and commercialization of CERE-120 from Ceregene, a deal which was announced in June 2007.

Comment on the following article: The following is another example of results that reveal different factors for success than were anticipated. In the gene therapy article, it was growth factor in place of levodopa, here it is adenosine in place of electrodes.

> **Surgery for PD was developed decades before the advent of any of the effective medications that we use today. For most of the past century, innovative surgeons worked to refine surgical treatments for PD. During the 1940s and 1950s, these procedures consisted of surgically-created lesions in deep parts of the brain to control symptoms of tremor and rigidity. In one frequently-performed procedure, the pallidotomy, a surgeon created a tiny lesion in an area of the brain known as the globus pallidus. When levodopa was introduced as a treatment for PD in the late 1960s, interest in surgical approaches waned dramatically. For the next 30 years, medications dominated the treatment of PD.** (Text is taken from PDF publication edited by Blair Ford, M.D. Assoc Prof, Dept of Neurology Columbia University Medical Center)

This is me again: I have personal experience with a relative of mine who was a subject of early surgical trials; she was permanently and seriously affected, in a negative way, by bilateral application of techniques of the 1950s.

This article indicates another potentially significant breakthrough in treatment of motor symptoms. It also requires that something be delivered to a precise location in the brain, that is, where adenosine is produced. These two articles should make us consider the road to a cure as something other than supplying dopamine (through levodopa) to dopamine-poor neurons. **Stan**

SLEEP CHEMICAL CENTRAL TO EFFECTIVENESS OF DEEP BRAIN STIMULATION

Article adapted by *Medical News Today* from original press release. 24 Dec 2007

A brain chemical that makes us sleepy also appears to play a central role in the success of deep brain stimulation (DBS) to ease symptoms in patients with PD. The surprising finding is outlined in a paper published online Dec. 23 in Nature Medicine.

The work shows that adenosine, a brain chemical most widely known as the cause of drowsiness, is central to the effect of DBS. The technique is used to treat people affected by PD and who have severe tremor, and it's also being tested in people who have severe depression or obsessive-compulsive disorder.

Patients are typically equipped with a "brain pacemaker," a small implanted device that delivers carefully choreographed electrical signals to a very precise point in the patient's brain. The procedure disrupts abnormal nerve signals and alleviates symptoms, but doctors have long debated exactly how the procedure works.

The new research, by a team of neuroscientists and neurosurgeons at the University of Rochester Medical Center, gives an unexpected nod to a role for adenosine and to cells called astrocytes that were long overlooked by neuroscientists.

"Certainly the electrical effect of the stimulation on neurons is central to the effect of DBS," said Maiken Nedergaard, M.D., Ph.D., the neuroscientist and professor in the Department of Neurosurgery who led the research team. "But we also found a very important role for adenosine, which is surprising."

Adenosine in the brain is largely a byproduct of the chemical ATP, the source of energy for all our cells. Adenosine levels in the brain normally build as the day wears on, and ultimately it plays a huge role in making us sleepy—it's the brain's way of telling us that it's been a long day, we've expended a lot of energy, and it's time to go to bed.

The scientists say the role of adenosine in DBS has not been realized before. Even though scientists have recognized its ability to inhibit brain cell signaling, they did not suspect any role as part of DBS's effect of squelching abnormal brain signaling.

"There are at least a dozen theories of what is happening in the brain when DBS is applied, but the fact is that no one has really understood the process completely," said Robert Bakos, M.D., a neurosurgeon at the University of Rochester and a co-author of the paper, who has performed more than 100 DBS surgeries in the last decade. "We've all been focused on what is happening to the nerve cells in the brain, but it may be that we've been looking at the wrong cell type."

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Nedergaard's team showed that the electrical pulses that are at the heart of DBS evoke those other cells—astrocytes—in the area immediately around the surgery to release ATP, which is then broken down into adenosine. The extra adenosine reduces abnormal signaling among the brain's neurons.

The team also showed that in mice, an infusion of adenosine itself, without any DBS, reduced abnormal brain signaling. They also demonstrated that in mice whose adenosine receptors had been blocked, DBS did not work; and they showed that a drug like caffeine that blocks adenosine receptors (the reason why caffeine helps keep us awake) also diminishes the effectiveness of DBS.

"It may be possible to enhance the effectiveness of DBS by taking advantage of the role of agents that modulate the pathways initiated by adenosine," said Nedergaard. "Or, it's possible that one could develop another type of procedure, perhaps using local targeting of adenosine pathways in a way that does not involve a surgical procedure."

The latest work continues Nedergaard's line of research showing that brain cells other than neurons play a role in a host of human diseases. ATP in the brain is produced mainly by astrocytes, which are much more plentiful in the brain than neurons. Astrocytes were long thought of as simple support cells, but in recent years, Nedergaard and colleagues have shown that they play an important role in a host of diseases, including epilepsy, spinal cord disease, migraine headaches, and Alzheimer's disease.

The research on DBS came about as a result of a presentation Nedergaard made to colleagues about her research on astrocytes. Bakos linked her detailed description of astrocyte activity to what he sees happening in the brain when DBS is applied. Based on Bakos' experience in the operating room and with funding from the National Institute of Neurological Disorders and Stroke, Nedergaard went back to the laboratory and analyzed the effects of DBS in a way that no one had ever before considered.

"The correlation between what we see in the clinic and [what] Dr. Nedergaard has found in the laboratory is really quite startling," said Bakos. "All the credit goes to her and her team. This has been a nice interchange of information between the clinic and the laboratory, to speed a discovery that really could have an impact on patients."

Authors: The lead authors on the paper are post-doctoral research associate Lane Bekar, Ph.D., and neurosurgeon Witold Libionka, M.D. The Rochester team is based both in the Department of Neurosurgery and the Center for Translational Medicine. In addition other authors from Rochester include research assistant professors Guo F. Tian and Takahiro Takano; graduate students Arnulfo Torres and Ditte Lovatt; technical associate Qiwu Xu; former post-doctoral research associate Xiaohai Wang; and Erika Williams, a Fairport native and an undergraduate student at Williams College. Jurgen Schnermann of the NIH also contributed.

Source: Tom Rickey, University of Rochester Medical Center

SOME OBSERVATIONS ABOUT DBS AND LIFE

by John Longhi

DEEP BRAIN STIMULATION SURGERY INVOLVED TWO OPERATIONS: the first to implant electrodes in my brain, the second to connect them with wires to neurostimulators in my chest. The purpose of this system is to deliver a carefully controlled amount of electronic white noise to specific areas of the brain (the subthalmic nucleus, in my case). The electronic noise interferes with the misbehaving cells affected by Parkinson Disease cells and thus reduces many PD symptoms. Immediately after the first operation, even though they hadn't installed the stimulators, let alone turned them on, I felt much better than I did before I went in. Apparently, the 2 electrodes that they inserted into my brain damaged enough misbehaving cells to make a difference. However, the PD-afflicted brain cells must have healed in the week following the first operation because my symptoms gradually returned and I had to resume my PD medication

The second operation was uncomfortable, but I have only dim memories of the pain and nausea, much of which was idiosyncratic. If my stomach could have tolerated the anesthesia and pain-killers after the second operation, recovery would have been easier. As it was, the discomfort lasted only 18 hours. After the first

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operation I felt better because only local anesthesia was used. There were only 2 hours of bad headache before the Tylenol took over. A week after the second operation, I was delighted to watch the tremors in my right hand disappear as a nurse adjusted the neurostimulator settings.

As dramatic as the effects of the neurostimulator adjustment were, however, after 6 months, I still needed most of my PD medication. Weaning myself off the meds has not been easy. It has also been disappointing, since I did not need the meds immediately after the operation. In other words, the electronic noise hasn't yet proven to be as effective as simply damaging selective parts of the brain. Nonetheless, I doubt that I would have opted for an irreversible operation, and on the plus side, I feel better than before the operations: tremors, freezing, and dyskinesias are greatly diminished, and I am sleeping better. The only physical downside is that I tire more easily and occasionally need a brief afternoon nap. After 2 years there is also a substantial upside to the operation in terms of reducing medications. With the help of daily diaries and the realization that it sometimes takes 10 days to 2 weeks for my body to adjust to a lower dose, I've made the following changes slowly: eliminated Mirapex (4.5 mg/day) and Comtan (800 mg/day) completely; reduced Sinemet from 600 mg/day to 200, and reduced Sinemet CR from 400 to 300 mg/day.

SOME SUBVERSIVE IMPRESSIONS: The only negative after the first operation was my appearance. Instead of shaving my whole head, for which I was prepared, they shaved 2 rectangular areas in the front which became the site of L-shaped rows of surgical staples. To compound the esthetic deficit, the vast amounts of Novocain, injected into my forehead to counter the effects of the screws that held the steel halo in place, dripped to my eyebrows, creating a Neanderthalish bulge, and on into my lids which sagged with Lecterish menace. But mentally I was fine—just an occasional craving for fava beans and chianti.

There were several memorable situations at the hospital at the time of my first operation that made it hard not to put a humorous spin on some otherwise straightforward statements (e.g.: **"Don't drink the tap water"** signs in the hospital, warning of bacterial infections, set the tone). For starters: At 8:00 PM—"you'll be admitted as soon as a room clears", becomes "someone is bound to die soon" and "we're waiting until they clean up the operating room" becomes "the last group made such a mess that they're having to hose it down". Some specifics: the intern who took me for a pre-op CAT scan called for an elevator before and after the scan; ***the scan was on the same floor that we started from***. But he was focused when we got to the scan room: he had an enthusiastic squeeze and hip bounce for an appreciative and comely technician. Prior to the scan they attached the steel halo to my head, which did not hurt because of the copious Novocain. All those years of HS football prepared me well for the next embellishment, which was a flexible plastic piece that looked like a segmented lampshade and fit over the steel halo. As we waited in pre-op, which was like an open-air market with 50 stalls and a constant flux of people and gurneys, I noticed people glancing sideways at me. Apparently, the sight was grotesque enough so that someone finally pulled the curtains, so I would not frighten the other patients (I enjoyed watching the crush of humanity and made occasional eye-contact with discomforting effect on the object of my glance).

Eventually, an attractive anesthesiologist came by; unfortunately, she went to the comatose patient in the next bay and was confused when she could not get a coherent response from "Mr. Longhi". When Terry finally convinced her that the real "Mr. Longhi" was next door, she cheerfully told us that I would be asleep during the operation and would not feel a thing. *Wait a minute!* ***I was supposed to be awake during parts of the procedure to twiddle my fingers on cue. Nevermind!***

An hour into the operation, the electronic pattern recognition equipment, used to tell which part of the brain the tip of the electrodes had penetrated, failed. The surgeon —a dynamic fellow worthy of the title "brain surgeon"—was able to work around the loss, but needed to get Terry's permission. So he called to the waiting area where she and Sarah were and ***said that he was coming up to talk to them***. When he found them ashen-faced and shivering, he apologized profusely for not explaining the situation.

I awakened in the recovery room with a killer headache that eventually abated with some Tylenol. Despite not having had any medication for ten hours, I did not notice any Parkinson symptoms—a sure sign that the operation was having a positive effect.

The next day we waited until mid afternoon for "transportation" to the MRI that would confirm the position of the electrodes and allow us to go home. When Transport finally came, I was delivered to an ante-room where I again waited. While there, I had a ringside seat to the way the MRI team worked. It was

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truly surprising that they managed to fit in the scans at all, between personal calls and stray conversations. The real sense of precariousness came after the MRI, as I was waiting an unreasonably long time for transport back to my room and was beginning to wonder if I should just jump off the gurney, grab my file, and make a break for it. Then they wheeled in a semi-conscious poor soul who just had a heart transplant and proceeded to subject the guy to a "Who's on first?" interrogation.

What's your name? [mumble]
What kind of operation did you have? [mumble]
Did they leave any wires inside? [mumble?!]
We can't do the scan, if they left any wires inside. [mumble, mumble!!].

To be fair, the nurses on the floor were attentive; they insisted that I call them for escort to the bathroom at night, and sure enough, they came within a minute on at least 10 occasions of my pushing the call button.

SOME RECOMMENDATIONS: In large hospitals your life could depend upon having an alert and caring partner/friend at your bedside. Don't try to go it alone. PD patients should get a written order from their physician and/or surgeon allowing them to keep their medications at their bedside. However, to avoid conflicts, the pills should be in their original pharmacy bottles. Also, don't take all of your pills to the hospital, because they may get lost. And don't let anyone take your pills to the pharmacy if you can avoid it, because then they surely will get lost.

If some thing hurts, squawk. Every person's response to a procedure is different. Sometimes a recovery nurse is waiting for you to complain to insure that you are awake and alert before administering medication. There is nothing noble about enduring pain, especially unnecessarily.

COMMENT ON THE FOLLOWING ARTICLE: Here is another piece in the puzzle that addresses activities going on in the cell. In a nutshell, dopamine reacts with alpha-synuclein (sin NUKE-lee-in) causing it to mutate. Now, being defective, it is carried to the cell's trash bin, where it would ordinarily be digested and out of the way. The new form sticks to the trash bin and won't get digested. Eventually it gets in the way of emptying any trash, which triggers cell death. These mutant cells occur in 5%-10% of PWP. Now, the real thing. **Stan**

RESEARCHERS DISCOVER POSSIBLE CLUE TO THE CAUSE OF PD

January 3, 2008 A glitch in the mechanism by which cells recycle damaged components may trigger PD, according to a study by scientists at the Albert Einstein College of Medicine of Yeshiva University. The research, which appears in the January 2, 2008 advance online issue of The Journal of Clinical Investigation, could lead to new strategies for treating PD and other neurodegenerative diseases.

All cells depend on a surveillance system known as ***autophagy*** (which literally means "self eating") to digest and recycle the damaged molecules that arise as cells age. In autophagy, defective proteins and other molecules are transported to membrane-bound sacs called lysosomes. After attaching to the lysosomal membrane, the molecules enter the lysosome, where they are digested by enzymes. This cleanup process may be particularly important for nerve cells, which generate defective molecules more rapidly than most other types of cells. When autophagy is impaired, toxic compounds can accumulate and cause cell death.

"It is widely suspected that accumulation of a particular protein, known as alpha-synuclein, within affected nerve cells of PD patients contributes to the death of these cells," says Dr. Ana Maria Cuervo, senior author of the article and associate professor of anatomy and structural biology at Einstein. Dr. Cuervo previously showed that mutant forms of alpha-synuclein—found in the five to 10 percent of patients who have familial PD—are poorly digested via autophagy and also block the breakdown of other substances. While these alpha-synuclein mutations are rare, other modifications of alpha-synuclein can be found in the brains of all PD patients.

In this study, Dr. Cuervo and her colleagues looked at how several different modified forms of alpha-synuclein affected autophagy in vitro and in tissue culture. One particular modification of alpha-synuclein was found to interfere with autophagy: the compound created by the interaction of alpha-synuclein with dopamine, the main neurotransmitter produced by the nerve cells damaged in PD.

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"Alpha-synuclein molecules modified by dopamine bound tightly to the lysosomal membrane, but they got stuck there and weren't effectively transported into the lysosome," says Dr. Cuervo. As a result, the alpha-synuclein molecules altered by dopamine were poorly degraded, and the presence of these molecules on the lysosomal membranes interfered with autophagic digestion of other compounds as well. "We propose that inhibition of autophagy caused by dopamine's alteration of alpha-synuclein could explain the selective death of dopamine-producing nerve cells in PD," says Dr. Cuervo, who notes that interference with autophagy has also been implicated in other neurodegenerative diseases including Alzheimer's. "By devising strategies for boosting autophagy in nerve cells or suppressing the chemical reactions that interfere with the autophagy—by lowering alpha synuclein expression, for example—we may be able to treat patients afflicted with these conditions," she says.

GOLF?

There are some members of CPWG who are avid golfers—many of them were frustrated because they could not play regularly. One member of this group is Tom Sullivan; he is the kind of guy who, if he sees something is broken, regardless of who owns it, he will seek ways to fix it. My guess is that he saw the problem, was a member of the group of people who wanted to play, and decided to do something. The result is a regular weekly golf game during the golf season. I have played (??) with the group once, on the hottest day of the year, in Portland, on a course which accommodates the regulation game players as well as those wanting to play par-three and even only nine holes. The whole (pun tried for and missed) experience cost me about $30 for greens fees, a golf cart, and lunch at their cafe.

We started around 10 a.m., everyone in a cart with or without a partner. The first thing I found out at the first hole is that these guys were good. This group consisted of: Tom Sullivan, Steve Holahan, Dick Montross, Jeff Lincoln, Ray Przygocki, and Bob McGinnis. I hadn't played the game in decades, but they treated me like an equal, which set me at ease and allowed me to enjoy the time. They were not only good, they were aware, a trait one doesn't encounter as often as one should. We stopped after nine holes (I may have actually "stopped" somewhat earlier due to the heat even though my body went the whole nine.) at about 1 p.m. and gathered in the cafe for cool air, cool drinks and lunch. I had a good time and hope I get the chance to join the group again this year. They play at different courses throughout the season to give as many people as possible a chance to play.

I wasn't the only person who thought the group was something special: They were written up, with several photos, in the local press. If you want to know more, call Tom (860.343.8278); he will put you on their email list and you will be informed of the schedule as it evolves.

NANCY JENSEN

We never got to know Nancy Jensen as she would have liked us to know her. She passed away early Friday, 29 February 2008 in Mystic at the Pendleton recovery facility. She got involved in PD issues to the maximum of her ability, which was considerable, tempered by PD and other ailments, which were, unfortunately, also considerable. Those of us who knew her will miss her presence, with her positive attitude and her available ear.

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Articles in this newsletter are for information only.
Any questions of treatment should be discussed with your physician.

Write your Representatives in Congress!

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