PXE Awareness

National Association for Pseudoxanthoma Elasticum (NAPE, Inc.)

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Holiday Greetings

From NAPE

National Association for Pseudoxanthoma Elasticum (NAPE, Inc.)

8760 Manchester Road, St. Louis, MO 63144-2724
Voice & Fax: 314-962-0100
Email: napestlouis@sbcglobal.net Web: www.napxe.org

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Board of Directors

Board of Medical Advisors

Table of Contents

President's Message

Dear NAPE Friends,

2007 was fast-paced and exciting in NAPE's office as we served more PXE patients than in any previous year, and we were busy trying to keep up with scientific and medical discovery announcements. Our Board voted to review with the physicians most closely associated with NAPE the question of dietary calcium intake. The scientific literature is limited on this topic, which led us to focus on the advice of practicing physicians who are aware of the great increase in information about the role of calcium in the body. Please see the article on calcium in this issue.

Board member Sally Dawoud has worked closely with Dr. Leanne Dahlgren and her associates on the issue of pregnancy for women with PXE. Dr. Dahlgren continues to be quite interested in working with women who are pregnant or who have delivered a child. We have agreed to provide contact information for a questionnaire which is available on Dr. Dahlgren's website. We hope that many women will take advantage of the opportunity to help Dr. Dahlgren build a database about the impact of PXE and safety issues during this vital phase of a woman's life. See the item by Dr. Dahlgren in this issue.

We were delighted with this year's Nobel Prize in Medicine which has benefited PXE patients quite directly. Dr. Struk's proposed research, approved by our Board, takes advantage of the knowledge that won these scientists the Nobel. See Linda Austin's article in this issue.

Our NAPE Board also approved research proposed by Dr. Kattesh V. Katti which will study improved diagnostic and treatment protocols for PXE vision loss using nanomedicine. The next issue of *PXE Awareness* will carry an article about his work. Please note in this issue the brief item about his latest discovery of a method to make nanomedicine safe for transporting medications to specific disease sites in the body.

Over the past year we have rejoiced with PXE patients who describe their treatment with Avastin as a miracle sight-saver. We have been grateful for Genentech's ground-breaking success in understanding VEGF and developing inhibitor drugs, including Avastin and Lucentis. We were stunned when Genentech informed retina specialists that it would make Avastin less available and encourage greater use of Lucentis for vision loss treatment. Genentech has now decided to reconsider as retina specialists around the nation reacted strongly against Genentech's decision. A final decision will be made early in 2008. Details are available in an article in this issue. Please discuss this with your retina specialist and thank him/her for the quick vigorous response of the medical

profession on our behalf. NAPE's Board is reviewing this with the intent to inform Genentech and the NIH of the concerns of PXE patients.

Dr. Chris Bergstrom's Atlanta conference talk focused on VEGF inhibitor drug development. The good news is that many labs have joined the search to improve on Avastin/Lucentis in vision loss. The bad news is that these projects are far from completion with the possible exception of VEGF Trap now in a promising large third phase trial. In the meantime, we must rely on Genentech's Avastin or Lucentis. We must work with Genentech in the best interests of PXE and AMD patients.

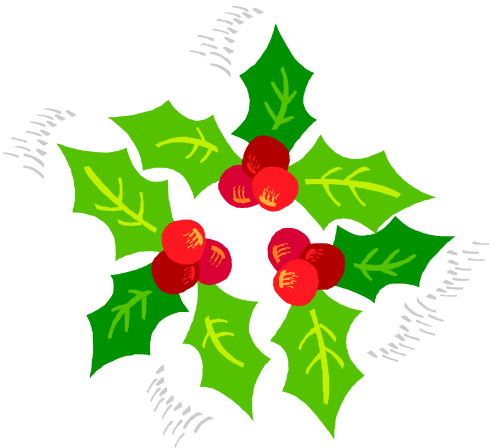
The Atlanta conference in late September demonstrated the great contribution of the medical profession to our lives. We were informed at a remarkable level by Drs. Struk, Katti and Bergstrom on vital issues. Dr. Ken Neldner, now in his 80th year, kicked off the conference, and Dr. Rashmin Gandhi, eye surgeon, brought greetings from Sankara Nethralaya, the largest eye care center in the world. These men's work schedules are daunting, yet they made time to fully participate in our conference, making themselves available for presentations as well as private conversations. We are grateful recipients of their generous care. Thank you. Thank you.

In January, Dr. Katti, Dr. Struk, Board member Heidi Kevelin and I will go to India to visit Sankara Nethralaya. Thanks to Dr. Katti, we will have the

opportunity to collaborate with the scientists and physicians of this institution on the inheritance of PXE, its diagnosis and treatment. Earlier in 2007, Dr. Katti visited with Dr. Struk in Berlin. Later this coming spring, Dr. Struk will visit Dr. Katti's labs in Missouri. These brilliant scientists will work together to better understand, treat and over time to cure PXE. We are deeply grateful to them. They have made 2007 very special—and we believe 2008 will be even better.

We at NAPE hope you enjoy a wonderful holiday season. Stay tuned for the next issue of *PXE Awareness* as we bring you up-to-date on the world of PXE.

Fran Benham



Calcium in PXE Diets

By Fran Benham

Calcium is a mineral necessary to life. It is the basic ingredient of our bones and teeth. Perhaps less widely known are its other roles vital to a healthy life. A small portion of our calcium is found throughout our bodies in blood, muscle and in bodily fluids. It is necessary for blood vessel contraction and expansion, for muscle contraction, hormone and enzyme secretion and for sending messages through the nervous system. A constant level of calcium is necessary to maintain efficient functioning of our bodies. Even our bones require a supply of calcium as they constantly reform and rebuild. The need for calcium intake varies as we age, starting with prenatal development to the end of life.

Robert P. Heaney, MD, states that until relatively recently many physicians recommended that patients with various disorders limit dietary calcium intake. Today with greater scientific understanding of the roles of calcium in the development and maintenance of healthy bodies, such advice is unusual. Indeed, all actively practicing physicians best known to NAPE patients encourage their patients to consume the recommended dietary allowance developed by the Institute of Medicine of the National Academy of Sciences. When asked, most indicated that patients should obtain dietary calcium from a variety of foods, limiting the amount obtained from dairy products, which while high in

calcium also are high in saturated fats. PXE patients, prone to cardiology problems, should limit intake of such fats. A list of calcium sources is provided to help us review and improve our own calcium consumption. Our physicians noted that PXE patients should not consume more than the recommended dietary allowance of calcium.

The literature about calcium reveals it to be quite complicated. Not only must we consume an adequate amount for our age and gender, but we must be concerned about its absorption by our bodies. The older we are, the greater that concern. The body uses vitamin D, obtained from food and from skin exposure to sunshine, to assist calcium absorption. PXE patients need to be careful to avoid great sun exposure, but as little as fifteen minutes of such exposure creates substantial vitamin D. We also are informed that weight-bearing exercise such as walking, running and dancing improves calcium absorption, which also can be adversely impacted by high levels of dietary sodium, potassium, protein and alcohol.

Finally, with guidance from trusted medical advisors, the NAPE Board of Directors has voted to update NAPE literature to encourage those diagnosed with PXE to consume the recommended dietary allowance of calcium. As always, NAPE urges patients to discuss medical matters, such as this, with their physicians. Following is the National Academy of Sciences Institute of Medicine recommendations with lists of calcium and vitamin

D food sources. At the end of the article are excellent sources of information from which this article was prepared and which provide much additional valuable information.

Recommended Daily Dietary Calcium Intake

Age, Male and Female	Calcium (mg/day)
0-6 months	210
7-12 months	270
1-3 years	500
4-8 years	800
9-13 years	1300
14-18 years	1300
19-50 years	1000
50+ years	1200

Food Sources of Calcium

Food	Calcium (mg)
Yogurt, plain, low fat, 8oz	415
Collards, boiled, 1 cup	358
Orange juice, calcium fortified, 1 cup	350
Oatmeal, instant, 2 packets	326
Yogurt, fruit, low fat, 8oz	245-384
Sardines, canned in oil, with bones, 3oz	324

Cheddar cheese, 1 ½ oz, shredded	306
Milk, non-fat, 8 fl oz	302
Milk, reduced fat (2% milk fat), 8 fl oz	297
Milk, whole (3.25% milk fat), 8 fl oz	291
Milk, buttermilk, 8 fl oz	285
Milk, lactose reduced, 8 fl oz	285-302
Mozzarella, part skim, 1 ½ oz	275
Figs, dried, 10 medium	269
Spinach, boiled, 1 cup	244
Tofu, firm, made w/calcium sulfate, ½ cup*	204
Orange juice, calcium fortified, 6 fl oz	200-260
Salmon, pink, canned, solids with bone, 3oz	181
Soybeans, boiled, 1 cup	175
White beans, boiled, 1 cup	161
Pudding, chocolate, instant, made with 2% milk, ½ cup	153
Mustard greens, boiled, 1 cup	150
Cottage cheese, 1% milk fat, 1 cup unpacked	138
Tofu, soft, made w/calcium sulfate, ½ cup*	138
Cornbread, one 2-oz piece	133
Vegetarian baked beans, 1 cup	128
Navy beans, boiled, 1 cup	128
Great northern beans, boiled, 1 cup	121

Spinach, cooked, ½ cup	120
Instant breakfast drink, various, powder, prepared with water, 8 fl oz	105-250
Frozen yogurt, vanilla, soft serve, ½ cup	103
Black turtle beans, boiled, 1 cup	103
Swiss chard, boiled, 1 cup	102
Ready to eat cereal, calcium fortified, 1 cup	100-1000
Turnip greens, boiled, ½ cup	99
Broccoli, boiled, 1 cup	94
Kale, cooked, 1 cup	94
English muffin	92
Kale, raw, 1 cup	90
Ice cream, vanilla, ½ cup	85
Pinto beans, boiled, 1 cup	82
Soy beverage, calcium fortified, 8 fl oz	80-500
Butternut squash, boiled, 1 cup	84
Chickpeas, canned, 1 cup	80
Chinese cabbage, raw, 1 cup	74
Sweet potato, boiled, 1 cup	70
Green beans, boiled, 1 cup	58
Barley, 1 cup	57
Brussel sprouts, 8 sprouts	56
Navel orange, 1 medium	56
Raisins, 2/3 cup	53
Tortilla, corn, ready to bake/fry, 1 medium	42
Tortilla, flour, ready to bake/fry, 1 at 6” diameter	37

Sour cream, reduced fat, cultured, 2 tbsp	32
Bread, white, 1 oz	31
Broccoli, raw, ½ cup	21
Bread, whole wheat, 1 slice	20
Cheese, cream, regular, 1 tbsp	12

*tofu processed with a non-calcium salt will not contain significant amounts of calcium

Recommended Daily Dietary Vitamin D Intake

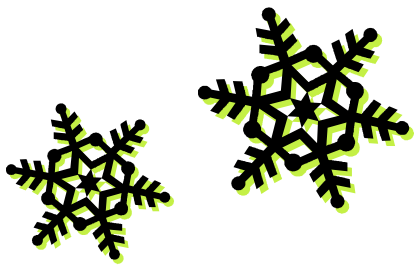
Age, Male and Female	Vitamin D (IU/s per day)
0-13 years	200
14-18 years	200
19-50 years	200
51-70 years	400
71+ years	600

Food Sources of Vitamin D

Food	International Units (IU) per serving
Cod liver oil, 1 tbsp	1360
Salmon, cooked, 3 ½ oz	360
Mackerel, cooked, 3 ½ oz	345

Tuna fish, canned in oil, 3 oz	200
Sardines, canned in oil, drained, 1 ¾ oz	250
Milk, nonfat, reduced fat, whole, vitamin D fortified, 1 cup	98
Margarine, fortified, 1 tbsp	60
Pudding, from mix and made with vitamin D fortified milk, ½ cup	50
Ready-to-eat cereals fortified with 10% of the DV (daily value) for vitamin D, ¾ cup to 1 cup serving	40
Egg, 1 whole (vitamin D is in egg yolk)	20
Liver, beef, cooked, 3 ½ oz	15
Cheese, Swiss, 1 oz	12

Information for this article has been taken from personal correspondence, from *Eat, Drink, and Be Healthy*, Chapter Nine, by Walter Willet (Simon & Schuster, 2001), and from the NIH Office of Dietary Supplements fact sheets at http://dietary-supplements.info.nih.gov/factsheets/calcium.asp and http://ods.od.nih.gov/factsheets/vitamind.asp .



Genentech: Avastin or Lucentis?

By Fran Benham

Genentech, founded in 1976, has enjoyed phenomenal success in creating blockbuster biotech medications. Avastin was created to inhibit VEGF (vascular endothelial growth factor) induced blood vessels from nourishing tumors. Genentech chemist Napoleone Ferrara followed his remarkable invention with the discovery that blood vessel growth in age-related macular degeneration (AMD) also occurred in the presence of high levels of VEGF. He began six years of research to modify Avastin for use in the eye, creating Lucentis which in Phase II and Phase III trials demonstrates almost miraculous sight saving ability. While Ferrara was busy with this effort, others were speculating that Avastin might help the large number of patients losing vision due to AMD. Dr. Philip Rosenfeld of the Palmer Eye Institute of the University of Miami treated patients in the process of losing vision with a fragment of Avastin with remarkable results. Word spread quickly among physicians and patients. Patients losing vision due to PXE also enjoyed a positive outcome and today many retain vision thanks to Avastin.

Genentech took Lucentis through the FDA approval process, but not Avastin, which earlier was approved for colorectal cancer. The approval process was expensive as was the transition of Avastin into Lucentis. So why are doctors and

patients, happy with Avastin, resisting the switch to Lucentis? Money! An injection of Avastin costs from $50 to $75 and is repeated every six to eight weeks. Lucentis, injected monthly, costs $2000 per shot.

The NIH wants a comparison study of the two drugs, but Genentech has refused to participate. Recently Genentech informed physicians that Avastin would be made less available for vision treatment, but quickly withdrew the decision in the face of protests from physicians. Genentech is reviewing its options with a decision expected in the near future. Lucentis has been approved for Medicare coverage, but most PXE patients begin vision loss in their 40's, with some in the 30's, and a few in their 20's or 60's. Medicare does not help the majority of PXE patients whose vision loss in prime earning years is shock enough, when most are diagnosed with PXE.

NAPE's Board of Directors is discussing this with the intention to inform Genentech and the NIH of PXE's particular issues in the decision process. We have been thrilled and grateful for the miracle of Avastin, and we are deeply grateful for Genentech's role in this miracle. Many of us lose our ability to pursue chosen careers with vision loss. Avastin has made it possible for many to continue to work and provide vital family support. We need medication we can afford. The cost of Lucentis may cause some to have no choice but to accept blindness just when we dared to be hopeful.

There must be a solution fair to Genentech which also allows us to retain sight. Talk about this with your retina specialist. Let him/her know of our gratitude for physician support of patients in this matter and of your concern about Genentech's final decision.

Sources for this article came from *Forbes.com*, "Genentech's Avastin May Limit Lucentis' Potential" by Peter Kang; *The New York Times*, "Genentech in Competition With Itself on Eye Drug" by Andrew Pollack; *The Wall Street Journal*, "How Genentech Wins at Blockbuster Drugs" by Marilyn Chase; *VentureBeat.com*, Life Sciences, "The Temptation of the Dark Side: Genentech, Avastin and Macular Degeneration" by David P. Hamilton.

PXE and the 2007 Nobel Prize for Medicine

By Linda Austin

Alfred Nobel was a scientist, inventor and entrepreneur with factories and laboratories in over 90 locations in 20 countries as well as 355 patents in his name. Although he is known for inventing a method of turning highly volatile nitroglycerine into the more stable dynamite, perhaps his most famous contribution was establishment of the Nobel Foundation. This organization awards annual prizes for outstanding work in physics, chemistry, medicine/physiology, literature and for peace.

The 2007 Nobel winners were announced in October. Of particular interest to NAPE was the award for medicine/physiology given to Martin Evans of Cardiff University in Wales, Mario Capecchi of the University of Utah and Oliver Smithies of the University of North Carolina at Chapel Hill. Their work was chosen over new research in cancer and aging and over the discovery of genetic fingerprinting. The Nobel Committee stated that the work of these men “has revolutionized life science and plays a key role in the development of medical therapy.”

Martin Evans, considered the “father of embryonic stem cell research,” isolated stem cells from mouse embryos so that the genetic material could be modified with the help of viruses and used as a

vehicle to introduce new genes that would be inherited by offspring. Mario Capecchi and Oliver Smithies, meanwhile, had each separately determined that introducing specific corrective DNA into a cell with a defective gene could result in a "repair" of the defective gene. But, in order for this repair to be inherited, a certain type of cell—the embryonic stem cell—had to be used. These scientists developed methods to deactivate (knock out) specific genes within an organism or to replace them with altered forms. This is called "gene targeting." And, only gene manipulations using embryonic stem cells could be passed down to descendants of the organism.

And what does this Nobel prize have to do with PXE? Being able to "knock out" the functioning of a specific gene within a mouse allows researchers to study that gene in great detail. Mice that have been genetically altered to exhibit characteristics of a certain disorder, such as PXE, and which can produce offspring with the same genetic alteration, provide opportunity to gain understanding with the potential to test treatments…an exciting development indeed for researchers and patients!

Since the 1980's when the first results of this type of research were reported, over five hundred different knockout mouse models of human disorders have been created for medical studies, including two mouse models developed to study the PXE ABCC6 gene. NAPE will now fund the design of another highly specialized, genetically altered

mouse for PXE research proposed by Dr. Berthold Struk. Struk, whose early genetic research led to the identification of the PXE ABCC6 gene, has continued to study the genetics of PXE and believes this ABCC6 mouse model will move us closer to inhibiting the effects of this aberrant gene. The 2007 Nobel Prize for medicine/physiology should be recognized by PXE patients for its real world potential for improving our lives.

Readers wishing additional information will find it in the following sources used for this article: “Who’s on Nobel List?” *St. Louis Post Dispatch*, October 8, 2007; “Three Share Nobel Prize for ‘Designer Mice’ Research,” *St. Louis Post Dispatch*, October 9, 2007; “The Nobel Prize in Physiology or Medicine 2007,” Press Release and Advanced Information, *Nobelprize.org* website.

Nano Greening

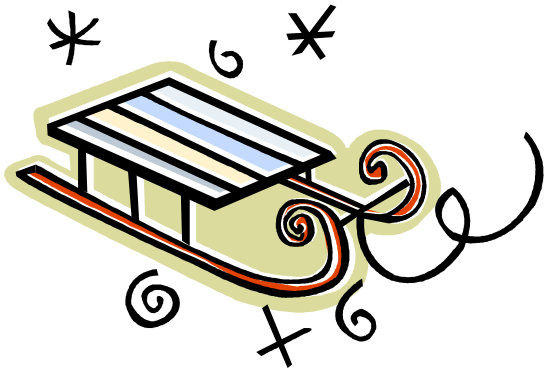
By Frances Benham

The University of Missouri-Columbia has announced a significant advance in nanomedicine —the use of soy coated nanoparticles for the delivery of medications. Soy, grown world-wide and relatively cheap, makes it possible to deliver medicine to specifically targeted cells and tissue safely without toxic side effects. Toxic side effects have been a basic concern about the use of nanoparticles which are built on a foundation of gold. Gold does not create heat or react chemically with medicinal chemicals as do other metals which thereby destroy the intended medical benefit. Gold nanoparticles coated with soy deliver medicine as targeted, then are excreted by the body without harm. This discovery by Dr. Kattesh V. Katti and his colleagues opens the door for many medical applications. It has been greeted by scientists around the world as a major breakthrough in the field of nanotechnology.

An example of the potential use of green nanoparticles follows. Avastin, which is protecting vision in PXE patients with active neovascularization, is injected directly into the eye. Much care is taken to protect the eye from infection. The procedures have been highly successful with excellent results for patients. The use of green nanoparticles coated with Avastin would allow intravenous injection with very small amounts of the medicine targeted to attach and treat specific

injured cells and tissue. Less medicine would be needed for a treatment which should result in fewer side effects. Treatment could be administered by a medical technician rather than the retina specialist who currently injects Avastin into the eye. It is expected that this procedure could lower treatment costs while using less medication with the potential for fewer possible side effects. As treatment with Avastin must be repeated a number of times (the number not yet determined), this approach should prove effective and attractive to patients.

NAPE's Board of Directors has voted to work with Dr. Katti, who is committed to the development of new treatments and diagnostic tools for use in PXE. NAPE will provide funding to support work now underway in Dr. Katti's lab. *PXE Awareness* will report regularly on progress as developments occur. For more detailed information about gold nanoparticles, please refer to Dr. Katti's article, "Nanomedicine: Should NAPE Be Interested?" in *PXE Awareness*, November 2006—also on the NAPE website www.napxe.org.



PREGNANCY AND PXE

By Leanne Dahlgren, MD

My colleagues and I are very interested in helping women who have PXE obtain the best care possible during pregnancy. We invite women who have PXE and have experienced pregnancy to read the abstract provided below and to tap into the website address provided at the end. Please complete the questionnaire in the knowledge that this is a protected website and that your responses will be confidential. We hope to obtain enough information about pregnancy among women with PXE to advise physicians through medical literature about what to look for and how to protect such women. Thank you for participating in this study.

Background: Pseudoxanthoma elasticum (PXE) is a rare hereditary disorder characterized by systemic degeneration of elastic tissue. It affects the skin, eye, cardiovascular system and gastrointestinal system. Most women have normal pregnancies, but gastrointestinal bleeding, ruptured aneurysm, and hypertension have been reported. Damage to the pelvic floor is theorized.

Case: We report a case of a 27 year-old primi-gravida with PXE. Pregnancy was uncomplicated. A term primary elective caesarean delivery was performed to protect the pelvic floor and reduce the chance of retinal hemorrhage. As well, an apronectomy was performed to improve cosmetic results of abdominal skin healing.

Conclusion: Primary elective caesarean delivery should be considered. Further studies are warranted to establish the effects of pregnancy and delivery on the pelvic floor in women with PXE.

We would like to determine if women with PXE are at higher risk of different complications of skin and tissue healing as a result of pregnancy. You will be helping women with PXE everywhere if you agree to fill out our short survey (5 minutes). Your responses remain anonymous. We hope to learn more about the effects of pregnancy on PXE and determine the optimal management of pregnancy in women with PXE. Thank you for your time.

Please copy or type this address into the address bar on your internet home page. It will link you to the web based survey.

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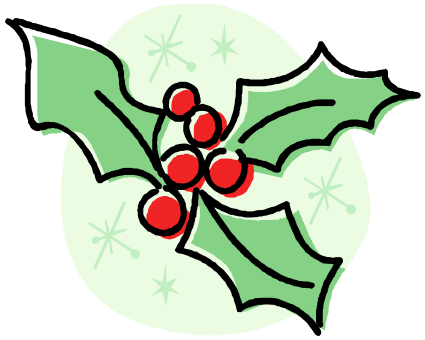

How We Live With PXE – A Survey

By Frances Benham

Karolyn Kells, PhD, RN, was NAPE's first Denver Office Manager. Karolyn lives with PXE and wants to educate America's nurses about the disorder and how it impacts life. As Professor of Nursing, Karolyn has been granted a year-long sabbatical during which she will survey PXE patients to determine how it impacts our lives and how we cope.

Patients at the Atlanta conference were invited to take part in a pre-survey evaluation of Karolyn's planned questionnaire. Many volunteered and Karolyn is in the process of contacting some of them to review those things she and they believe are important for understanding among medical practitioners—especially nurses.

NAPE's Board has authorized Karolyn to contact by telephone, at her own expense, NAPE members to invite them to take part in a telephone interview. Results will be made available to nursing journals. Karolyn will present her findings at next September's annual conference which will begin on Friday evening with her report. We believe her findings will stimulate much discussion among members, physicians and scientists present. Should Karolyn telephone you, the NAPE Board hopes that you will respond to her questions, knowing that she understands and shares your concerns about living with PXE