Smart Life Forum

John D. Furber

Clioquinol & Alzheimer's Disease

Cubberly Community Center
4000 Middlefield Road, Room H1, Palo Alto, California

August 14, 2003 at 7:00 pm

Meet John D. Furber, M.S. Biological Sciences

This will be Mr. Furber's third talk before the SLF. He previously spoke at the December 2001 and June 2002 meetings. John D. Furber is an entrepreneur and scientist who has been studying the biology of aging and regeneration for 20 years. He earned a Master of Science degree in Biological Sciences from the University of California at Irvine (1990), and a Bachelor of Arts degree in Physics and Mathematics from the University of California at Santa Cruz (1975). Between degrees, he served the United States Congress as a Technology Policy Analyst in the Congressional Office of Technology Assessment. Mr. Furber was a principal in starting five companies during the 1980s and 90s. Currently, he is running a biotechnology company, Legendary Pharmaceuticals, which is developing pharmaceutical drugs and gene therapies to repair and reverse progressive damage to mitochondria and lysosomes, in order to prevent and treat serious, late-onset diseases commonly associated with aging.John is a frequent contributor at scientific meetings related to the study of aging. He is on the Board of Directors of the American Aging Association. He is also a member of the Gerontological Society of America, and the Society for Free Radical Biology & Medicine.John has several web pages which provide useful information and links for

researchers and the lay
public interested in Aging, Nutrition, Bioinformatics, Genomics, and Molecular Biology. For further details please see: http://www.legendarypharma.com/ & http://members.aol.com/johnfurber

Mr. Furber will be giving a two part talk on August 14. First, he will present a news summary from the recent annual meeting of the American Aging Association, held in Baltimore, June 6 - 9. Following this, he will update the group on what he has learned about the drug, clioquinol, as a potential treatment or preventative for Alzheimer's and Parkinson's diseases.

I. Report on the American Aging Association meeting

The American Aging Association was founded in 1970 as a non-profit, tax-exempt national organization of lay and scientific members dedicated to promoting biomedical aging studies directed toward slowing down the aging processes.Their annual scientific symposium was held June 6 - 9 in Baltimore. The theme this year was "NUTRITIONAL MODULATION of AGING and AGE-RELATED DISEASES."

The meeting organizer was Dr. James Joseph of Tufts University. Dr. Joseph is co-author of "The Color Code."
This excellent bookdescribes how the phytochemicals which give fruits and vegetables their bright colors are the samephytochemicals which give them antioxidant, anticancer, and cardiovascular-protective properties. The meeting program and abstracts of all the talks and posters from the meeting are on the Web at http://www.americanaging.org/past_meetings/AGE03/Program.htm
Especially interesting were several talks on Alzheimer's dementia and other neurodegenerative diseases, and on preservation of cognitive functioning with fruits and vegetables.

II. Clioquinol for Alzheimer's and Parkinson's diseases

We do not yet have the whole story on Alzheimer's disease, but there are some treatments which are showing promise. Alzheimer's has been characterized by aggregated deposits of amyloid beta protein among brain cells, selective killing of specific brain cells, and tangles of Tau protein within brain cells. This damage occurs in characteristic localities of the brain. For several years, the widely held belief has been that the amyloid beta deposits and tau tangles are killing the brain cells around them. However, a recent controverial hypothesis suggests that, quite the opposite, amyloid

beta and tau are actually antioxidant defenses protecting the brain cells from the oxidative stress which is killing them. It is interesting to note that everybody has amyloid beta (A-beta) deposits in their brain, which accumulate with age. However, most (but not all) Alzheimer's patients accumulate A-beta deposits faster than most normal people. It has been suggested that without treatment, everybody would develop Alzheimer's by age 150 if they lived that long.

Amyloid-beta aggregates form in a few characteristic locations in the brain, in synapses and cerebrovascular lamina media. This is striking because amyloid beta is expressed everywhere in the brain. But the aggregates form in areas which are particularly high in copper, zinc, and iron ions. These transition metals are well known mediators of free radical production and oxidative stress. Professor Ashley Bush and colleagues at Harvard Medical School discovered that amyloid beta binds to these metals, and in binding, it aggegates into clumps. There is some controversy regarding whether the aggregates keep the metal ions from making so many toxic free radicals, thereby providing some protection to the cells. A recent clinical trial which used antibodies to dissolve the A-beta plaques in Alzheimer's patients resulted in the patients getting worse.On the other hand, the aggregates take up space, and are somewhat toxic to neurons, as well. And because the aggregates are holding so many metal ions, they could be producing some free radicals as well.

Bush and colleagues began experimenting with metal chelators to test their hypothesis that if a drug can safely chelate the metal ions, then toxic free radical production would go down and neurons would be protected. A-beta would longer needed. They discovered that some chelators could extract the metals out of the aggregates. Surprisingly, in so doing, the aggregates themselves dissolved. However, the body and brain have essential uses for trace amounts of these metals, so very strong chelators would cause deficiency diseases. So they determined that the best results would come with a rather weak chelator. Furthermore, the chelator would need to pass through the blood-brain barrier into the brain in order to reach the A-beta plaques of Alzheimer's dementia.

The drug which worked the best and met these requirements was an antibiotic called clioquinol. Unlike more commonly known chelators such as EDTA, clioquinol is hydrophobic, so that it rapidly passes through the blood-brain barrier into the brain. It then is rapidly excreted, so that a single dose of clioquinol is almost completely gone from the brain within three hours. Conventional chelators don't work in the brain because they don't penetrate the blood-brain barrier. Furthermore, they can cause iron deficiency diseases because they are much stronger chelators than clioquinol.

Clioquinol has been around for decades, and it has many names including: Iodochlorhydroxyquin, 5-chloro-8-hydroxy-7-iodoquinoline, 5-chloro-7-iodo-8-quinolinol, Entero-Vioform, Intestopan, Mexaform, Oxychinol, and Sterosan. It was developed by Ciba-Geigy as an oral antibiotic to treat amebic dysentery (traveler's diarrhea). It is also formulated in a petroleum jelly base to form an

antibiotic skin cream. More than 500 million doses of oral clioquinol have been taken, over the years. However, oral clioquinol was pulled off the market after it was implicated as a contributing factor to a mysterious nerve disease called SMON, which affected several thousand Japanese people in postwar Japan.

After analyzing the data, Bush and colleagues concluded that vitamin B-12 deficiency was the link between clioquinol and SMON. Clioquinol interferes with B-12 metabolism. Combine this with several factors peculiar to diet and conditions in postwar Japan, and SMON could result. Consequently, they surmised that with proper B-12 supplementation, clioquinol could be safely used to treat Alzheimer's. Other researchers have also suggested supplementation with vitamin B5, selenium, and zinc would provide additional protection. A company was formed, Prana Biotechnology,** to develop this novel treatment for Alzhemier's. A clinical trial was conducted in Australia, but the results have not yet been published. Business considerations may be playing out here. One problem is that the original clioquinol patent has expired. Clioquinol is now public domain and it carries the SMON stigma as well. Although Prana has use-patents for clioquinol combined with B-12 and selenium as a treatment for Alzheimer's, if Prana (or any company) spends a lot of money to prove the safety and effectiveness of clioquinol for Alzheimer's, they might get FDA approval, but the fruits of their investment could be nibbled away by generic drug companies grabbing their market. Furthermore, Prana is in a dispute with a Greek company over use-patent rights to use clioquinol for Alzheimer's. Prana is thus trying to come up with another drug which works as well or better than clioquinol, so that they can get a strong composition-of-matter patent on it. Bush and Prana are not saying what dosage was used in the clinical trial. But careful reading of the literature gives us an idea of what dosing regimen they probably chose for clioquinol with vitamin B-12.

More recently, Julie Andersen and colleagues at the Buck Institute for Age Research, in Novato began exploring the use of clioquinol as a treatment for Parkinson's disease. Parkinson's disease is characterized by the degeneration of a particular kind of brain cell (dopaminergic neurons) in a particular part of the brain called the substantia nigra. Oxidative stress is suspected as the cause of this dopaminergic neuron death. Histological examination shows that these cells fill up with protein aggregates called Lewy bodies. These neurons also accumulate a black pigment called neuromelanin. Iron accumulates more in the substantia nigra than in other parts of the brain and iron is known to be a major mediator of oxidative stress. In fact, iron binds to neuromelanin and iron binding to alpha-synuclein seems to be cause it to aggregate into Lewy bodies. In mouse experiments, the Andersen group found that oral clioquinol was protective against experimentally induced Parkinson's disease.

Clioquinol has not yet been approved by the FDA for the treatment of Alzheimer's or Parkinson's,

and perhaps never will be. Many scientists and regulators, recalling the Japanese SMON epidemic, are wary of allowing the general public to take it orally for any purpose, unless compelling evidence of safety and efficacy is presented. However, as noted above, for-profit companies are unlikely to invest in clinical trials for a public domain drug. Perhaps this is a job best done by nonprofit institutes, universities, and the National Institutes of Health. Even on a fast track, clinical trials would take a couple of years, perhaps much longer. Older adults experiencing early stage Alzheimer's disease or mild cognitive impairment may not want to wait. But volunteer self-experimenters face several hurdles. They must find a supply of the drug which has not been mixed into a skin cream. The cost would not be covered by insurance. If they obtain the drug in bulk form, they must find a way to accurately measure out doses, suchas capsules or a medicine dropper. It would be very helpful to find a sympathetic neurologist who could advise, test, monitor progress, and watch for signs of SMON or B-12 deficiency.

However, extreme discretion might be needed to protect his reputation and his medical license. Far easier is to drink green and black teas, which contain iron chelators and antioxidants which cross the blood-brain barrier. In addition, other supplements, antioxidants, fruits, and NSAIDs are probably somewhat protective. Although easier to obtain, these have not shown the potency of clioquinol in experiments to date. In conclusion, Bush suggest that clioquinol or "similar compounds may have utility in other degenerative diseases where abnormal metalloprotein biochemistry is implicated such as Parkinson's disease, cataracts, prion diseases, and ALS."