

The Alzheimer's Prevention Program (ADPP)– A fourth year update

The regular quarterly reporting on the ADPP stopped with December 2004's Dutch Study Report X, because it was time to become less obsessive about the program and to settle it down to a long term maintenance level. AD Prevention, if it ever gets to be worthwhile for that part of the population that is distinctly susceptible, will be a long-term prevention therapy. The incubation time, where the Beta Amyloid first starts to aggregate in the brain, and triggers the beginning of unraveling of the axon binding proteins is at least a decade. To head off a cascade of amyloid deposition-tau unraveling, and synapse death will require a systematic application of brain healthy nutrients, anti inflammatory, and antioxidant pharmaceuticals and vitamins, and cardiovascular medications over the last decades of a concerned persons lifetime.

With that perspective my ADPP became more balanced in the last year, guided always by the epidemiology. The disease's complexity at the molecular level is challenging some of the best minds in biochemistry and armed with DNA based analytical chemistry, genetically manipulated laboratory animals, and high resolution imaging technologies these researchers will someday be able to explain the dynamic development of the disease. Long before a consensus on that theory based explanation there will evolve an art, based on empirical evidence, to successfully deal with preventing the disease.

The ADPP Maintenance Year

The agents employed in 2005, my maintenance year, were nearly all a continuation of the evolution reported in the Dutch Study I-X reports. I decided to back down from the highest dosing of Ibuprofen at 800 mg/day to 600mg/day. This was not done because any gastrointestinal or kidney/liver problems but just an attempt at rebalancing the elements of the program. Research by Greg Cole's laboratory at University of California (UCLA) had shown some promise for Curcumin in side-by-side comparisons with Ibuprofen in transgenic mice. At comparatively low dosages the turmeric spice constituent showed equal or better prevention of β amyloid deposition in mice, and it showed a marked effect of disaggregating or depolymerizing deposited plaque, sort of a resolubilizing, making it a candidate for clearance to either the blood flow or into the cerebral spinal fluid (CSF) system. Turmeric spice had been introduced in the program in early 2004, first on the basis of the epidemiology findings that in India, where it is extensively used in cooking, the incidence of AD is 25% of the US. The component of turmeric believed to have medicinal properties is curcumin, present at 2-3% of the spice. Being a strong colorant is a good indication of possessing antioxidant properties.

To match the UCLA study dosages, corrected for the metabolic ratio with mice and men, which used laboratory grade curcumin from Sigma-Aldrich, I eventually employed a concentrate at a reported strength of 95% from Curmax who furnished a Certificate of Analysis from a third party laboratory. The 1000 mg/day dosing equates to 36 grams of whole spice, a very impractical quantity to ingest. Table I below gives the maintenance ADPP program agents along with their respective category(s) and dosage and aliquots.

By way of ADPP increases, the B vitamins, Folic acid and B12 were increased in a major way to the mega dose level, B12 by 950 % to 530 mcg/day and Folic acid by 260% to 2175 (2200 rounded) mcg/day. The effect of this dosing on serum levels of these vitamins and their power in lowering the inflammatory protein Homocysteine was carefully investigated from the base line started in 2000, 285 days before the ADPP began.

Table I Alzheimer's Disease Prevention Program Medicinal & Nutritional Agents

Class of ADPP Agent	Agent	Daily Dosage (total)	Taken in Aliquots	Notes and Purposes
Anti-inflammatory	Ibuprofen	600 mg/day	3	NSAID, Mainstay of Program Multifunctional
	Curcumin	1000 mg.day	2	
Anti-oxidant	Curcumin	1000 mg/day	2	Paired with Folic Acid Paired with E when taken d isomer and γ isomer, natural
	Vitamin C	1000 mg/day	2	
	Vitamin E	1200 IU/day	3	
Cardiovascular:				
-Anti-hypertensive	Atenolol	50 mg/day	1	β blocker, taken in am. Diuretic, taken in am. BBB transiting ACE inhibitor, taken in pm.
	Chlorothio.	25 mg/day	1	
	ramapril	5 mg/day	1	
-Lipid adjusting	Lovastatin	20 mg/day	1	BBB transiting statin; LDL & TG lowering Timed release, HDL elevating
	Niacin	500 mg/day	1	
-Vascular Perfusion	Vitamin B12	530 mcg/day	1	Nerve protection, Homocysteine lowering tHst lower, prevent hippocampal atrophy Temper vascular inflammation, B50 3x wk.
	Folic acid	2175 mcg/day	3	
	Vitamin B6	27 mg/day	1(a)	
Cell Repair & General Nutritional Supplementation	Fish Oil	2000 mg/day	2	DHA 400 mg, EPA 600 mg, capsules DHA 550 mg, EPA 400 mg, liquid
	Cod Liver Oil	4800 mg/day	1	
	Multivitamin	Standard MDR	1	Senior formulation, copy of Centrum As Carbonate, Tums, aggregate D, 800 IU
Calcium	600 mg/day	2		

Alzheimer's Prevention Program Results

The periodic routine (metabolic panels) blood analysis that has been followed since start of the ADPP was continued in 2005 and reported in Table II. Table II starts with the intensification of NSAIDs use following APOE genotyping in October 2003, and when a ϵ -3, ϵ -4 genotype disclosed the expected inherited risk from one parent. Table II starts at ADPP day 720, so in using Table II's time scale; Zero (0) = 720 days, and the last entry at 542 days of intensification is $542 + 720 = 1262$ ADPP days. The Homocysteine assay (tHst) run by Quest (*), in that column, was done 73 days later, or 1335 ADPP days.

Table II Blood Testing in the Intensification and Maintenance Period s

Days ADPP intensification following November 20, 2003

Parameter	0 days	52 days	67 days	90 days	95 days	120 days	150 days	182 days	325 days	542 days
Glucose, mg/dL		138 ¹		101 ²	117			132	118	87
Calcium, mg/dL		9.8			10.6			10.2	9.5	10.1
Blood Urea Nitrogen mg/dL		20			17			14	16	14
Creatinine, mg/dL		1.3			1.3			1.4	1.3	1.4
BUN/Creatinine ratio		15.4			13.1			10	12.3	10
Albumin, g/dL					4.6			4.7	4.3	4.7
Albumin/Globulin ratio					1.4			1.4	1.2	1.5
Total protein, g/dL					8.0			8.1	8.0	7.8
Platelets cells/mL ³	188,000		261,000	217,000		215,000	212,000	210,000/204,000	229,000 ⁴	192,000
Hemoglobin, g/dL	14.2		15.5	13.9		14	14.4	13.8 /15.3	13.6	14.6
White Cell Count, cells/mL	8,900		8,500	6,100		7,100	6,800	6,700/7500	7,900	6,900
HDL, mg/dL				31				22	32	32
LDL, mg/dL								46	23	32
Triglyceride, mg/dL								337	246	148
Total Cholesterol, mg/dL ⁵	125		150	127 ⁶		129	133	131 /135	104 ⁷	94
Bilirubin, mg/dL					0.66			0.6	0.77	0.8
Alkaline Phosphatase, U/L					54			51	53	61
AST, U/L					25			27	24	26
ALT, U/L					35			31	30	27
C- reactive protein, mg/L					1.1				---	ND
Homocysteine, μ mol/L					9.9				8.8	7.9 *
HbA1c %									5.5 ⁸	ND
Test Location	BCNJ	Quest	BCNJ	BCNJ/MMH ⁹	Quest	BCNJ	BCNJ ¹⁰	BCNJ/Accumed ¹¹	Quest	Accumed/Quest *

¹ Meal taken incorrectly just before testing. Was unawares that basic metabolism included glucose.

² 2.0 hours after four cookies and two glasses of apple juice at BCNJ donation site.

³ Three years, nine months of BCNJ donations (31), thru donation 73 with average platelet count of 222,000 \pm 23,000 cells/mL

⁴ Avg. Platelets, Hemoglobin, White Cell Count (immediately below) from BCNJ donations 68,69,70,71 6/19 thru 9/20, 2004

⁵ Four years, of BCNJ donations (29) thru donation No. 67 with average total cholesterol at 131 \pm 7 mg/dL

⁶ Average of two tests, one at each institution, \pm 1.0 mg/dL

⁷ After 130 days of low dose Statins were added to ADPP: 10 mg Simvastatin, then 82 days 20mg Lovastatin.

⁸ This glycolated hemoglobin A1C assay reflects average glucose over prior 8 weeks. < 6% for non diabetics is normal.

⁹ Morristown Memorial Hospital community heart clinic. Piggybacking on wife's appointment after BCNJ No.64

¹⁰ Blood Center of New Jersey platelet donation No. 66

¹¹ Where two values are presented these are from BCNJ/Acuumed Diagnostic Laboratory respectively. BCNJ donation 67

Table III Effect of B Vitamins on Homocysteine

Date m/d/y	ADPP Program Days	Daily Supplementation		Plasma Assay *		Homocysteine μ mol/L
		B12 mcg	Folic Acid mcg	B12 pmol/L	Serum Folate nmol/L	
2/16/2000	- 285	56	800	428	> 20	-----
2/20/2003	445	56	800	406	18.2	-----
2/25/2004	815	56	800	-----	-----	9.9
10/15/04	1045	313	1040	-----	----	8.8
7/28/2005	1335	526	2175	-----	----	7.9
11/23/05	1450	532	2175	642	> 24	-----

* All assays by Quest Diagnostics except for 2/20/2003, which was performed by Cleveland Clinic Foundation (CCF) in connection with peripheral neuropathy studies

The Accumed analysis at 1262 days is part of an annual community cancer screening which included stool and urine analysis which all reported as normal. These screenings adds to the assurances of home testing with toilet bowl test papers that has been employed since ADPP outset, and a colonoscopy at ADPP day 600, that no GI problems have surfaced in four years of the program.

Table III shows how folic acid and B 12 vitamins can drive down Homocysteine. The increased dosing in these B vitamins is reflected in subsequent serum assays. As the serum assays and dosing have increased the Homocysteine assay (tHst) has decreased from an already low value (normal for the age is 11.5) to the lowest quintile of the published studies relating brain atrophy to Homocysteine levels, and the 50% AD associated risk threshold of >14 μ mols/liter.

Homocysteine reduction through a two year clinical trial treatment of a Japanese cohort, with B vitamins has been shown (JAMA March 2, 2005) to lower the incidence of hip fractures amongst stroke victims by 75%. The corresponding decrease in Homocysteine (tHst) was 38% amongst the treated group and an (tHst) increase of 31% experienced amongst those given the placebo. Interestingly the number of falls in the treatment group and the placebo group were the same. Since no difference in bone mineral density or strengthening of the patient's collagen was observed this reader concludes that the swifter mental acuity of the treatment group were able to detect the initiation of the fall and to react to it in a hip protective manner. The treatment levels of B12 were 1500 mcg/day, and Folic acid 5000 mcg/day. These levels are near three times now used in the ADPP.

In 2005 the Veterans Affairs Normative Aging Study (Amer. Jol. Nutrition) revealed how high levels of Homocysteine, and low dietary B vitamins lowered cognitive performance in a predictable fashion, inhibiting spatial copying (drawing figures) ability, verbal memory, and lastly Mini Mental State Examination (MMSE) scores. Folate deficiency alone was seen as having a distinct spatial copying inhibition.

Without knowing much about the power of these B Vitamins, except that B12 could have saved an Uncle who died as a young man of pernicious anemia in 1930, and how folic acid, taken in advance of pregnancy, dramatically cuts the risk of spinal birth defects in newborns, I was encouraged to use a daily Centrum multivitamin at age 55 by my wife, and a B-50 supplement by Michigan friends & the serum assays by Dr. James Tobin of Ishpeming, Michigan at ages 64 & 65 respectively. I may have thusly escaped this disease with a pre ADPP based on folic acid dosing (800mcg/day) alone. In any case the relentless pushing lower of total Homocysteine (tHst) to the lowest quartiles by increasing B vitamin dosing is the most powerful assurance that the program is going to be successful. Conclusion; here are safe and effective, and incredibly inexpensive agents to have in an AD prevention kit.

A year on the move

If you want to give yourself a “maxi-mental states exam” try taking a couple of consulting assignments entailing round-the-world, multi country travel arranged for online, on your own, and taken by yourself with no more than 96 hours of advance preparation. In May I did a technical due diligence (TDD) for the financing of a plant expansion in Thailand. This was supposed to be a two party visit and analysis of a world scale PTA plant. I was very familiar with the plant, (the owners people were friends) having been present at its creation in 1992. The second party never showed up and he was stood-in for by a lovely local financial analyst for his firm. This Thai woman smoothed the travel arrangements in-country but it was a technical assignment after all, with me doing the heavy lifting. For the first time I had the feeling I might not be able to finish the job when I got home with the raw data. Her bulldog pressure on the client, in response to my follow on questions and request for more data, pulled us through for a very good analysis, done on time.

Travel involved the world’s longest flight Newark, NJ to Singapore via Singapore Airlines. 19 hours each way, non-stop. Traveling East over the Atlantic to the arctic circle, over Europe & Asia going to Singapore. For the return traveling east, over Japan, across the Bering Sea, to the arctic circle, over Alaska, & across Canada and back to Newark.

The second assignment in late October was an all western circuit that went first to Brazil, returning to the US at San Francisco, then Seoul and Ulsan, Korea, then on to the United Kingdom, and later home all in 9 days. Chemical plants, planning environmental investments, were inspected in Brazil and Korea and report writing was done in London. This time the heavy lifting of post travel reporting was done by the consulting firm’s manager based in London, while I was along mainly as graybeard window dressing. We both scheduled our own travel, he with British Air, I with three carriers in United’s Star Alliance.

We met all rendezvous’ appointments traveling in opposite directions without the help of cell phones that don’t work anyway in Korea. All told 55 hours in the air, 32,000 miles. In the Mini Mental State Exam (MMSE) they first ask you where you are and what date it is and will you draw a clock of the time of day. In this Maxi-Mental States Exam there is no right answer to any of these questions. There are currency conversions to do constantly, heat and material balances to make in your head, and e-mails to write and read from airport waiting rooms equipped with ‘T’ mobile wireless Internet access.

I did two more TDD assignments this year, one dealing with solar grade silicon manufacturer in the Western US, for a Japanese client, and at a chlor-alkali operation in the Midwest for a prospective plant purchase. In both those assignments I was part of a team and had a lot of top-level help.

I feel pretty good about being able to navigate these assignments at age 70. If AD is in my future it is taking a long vacation, or something may be working in the ADPP.

A year as a patient

An acute attack of an infected prostate (prostatitis) sent me to the emergency room, and catheterization at our local hospital on Christmas Eve 2004. The end result of that episode, after 6 weeks of antibiotics was advice to take Avodart a prostate shrinking 5 alpha reductase inhibitor, generic name dutasteride, which requires some six (6) months to reach a near terminal size reduction. Most of the data on this class of medicine comes from clinical trials of finasteride (Proscar) a early Merck development which has been around for a more than a decade being used to treat benign prostatic hyperplasia (BPH), and grow hair on balding men. (Propecia)

In a mixed result from a eight year clinical prostate cancer prevention trial (PCPT) finasteride showed a certain marginal, but statistically significant reduction in the incidence of prostate cancer but also that the cancers which did occur were significantly more aggressive (higher Gleason grade, when biopsied and tissue examined by pathologists). That mixed blessing set the drug back, substantially unused, until one of the high priests of prostate pathology (there are two, Epstein at John's Hopkins, and Bostwick at the Mayo clinic) pronounced at a medical conference that the biopsies (taken nationally and internationally) and read for the trial by a special team in Texas should have been thrown out because of the nature of 5 alpha reductase inhibitor mechanism is atrophy of the epithelial tissue making up the prostate gland. Such atrophy supposedly corrupted the microscopic examination by the pathologists. This pronouncement by Bostwick, after his retirement from Mayo's, set loose the urology profession to go whole hog and prescribe the latest and greatest 5 alpha reductase drug from Glaxo Smith Kline, namely dutasteride. Mind you dutasteride has almost no experience to match that of finasteride but the FDA approved it for this BPH purpose. Here is yet another clinical trial, this one founded in pathology of tissue, a hard science, where total doubt results from a major effort. Perhaps a bungled effort, perhaps not. The second high priest has been silent.

Being a chemist or rather a bastardized chemist by virtue of two chemical engineering degrees and 48 years practice, I have an overall medical philosophy that chemistry eventually trumps surgery to cure or prevent disease. This is based on sound history; like a few parts per million of iodine preventing goiter tumors, which used to be excised in a bloody operation by the tens of thousands; Zantac, and antibiotics replacing tens of thousands of stomach ulcer operations; the list goes on and on.

I did not like the idea of a drug, which caused atrophy of epithelial tissue. This means the tissue is rendered dead to be slowly removed by macrophages and discarded in body wastes. I asked Glaxo if dutasteride passed the blood brain barrier and they said yes and also the placenta barrier, making it very dangerous for a pregnant female even to touch the pill or its container. All this gestation information is part of the package insert accompanying the free sample shoved at me by the advising urologist who removed the catheter. Also any platelets I might have donated could not be used for six months after using a 5 α RI, because the platelets could be used for a pregnant female and abort her pregnancy or lead to a birth defect. Six months to purge any trace of this drug from your system!

When my CCF urologist of 11 years also joined the dutasteride bandwagon I agreed to use this for six months if he then would do a surgical urethra-reaming job called a TURP on me. I stopped the dutasteride at six months and am waiting until my urologist musters sufficient clinical data to justify the surgical approach.

Meanwhile the plumbing is working but not like it once did. I developed this background to make the point that my model for AD, discussed in DS-X, attributes, causally, the dysfunction of the brain's endothelial cells at the blood brain barrier (BBB), which become tighter, more resistant, with age, to passage (clearance) of the β amyloid proteins out to the waste sinks of the CSF and the venous and arterial blood circuits. Atrophied epithelial prostate and dysfunctional endothelial BBB sound too much alike, to me, to risk my using dutasteride for any length of time. And if your going to search for a cause of supposedly growing autism incidence I would look at 5 α RI's use in premature balding men with this placenta transiting agent working at conception. I would bet on vanity anytime over mercury preservative in childhood vaccinations.

Alzheimer's prevention, the conference, the setback, the delay

The Prevention Conference

The much anticipated Alzheimer's Prevention Conference in Washington DC last July turned out to be quite a disappointment. The evolving program from the AD Forum website indicated possibly interesting panels and their chairmen. I was interested mostly in the Rotterdam Study update at 13 years (1991-2004) and early in 2005 asked Monique Breteler, of Erasmus Medical Center, and a panel chairwoman, if she was going to present this important story. She said that their data analysis process was still in its earliest phases and still compiling data. She said the update would not be ready for this conference.

The rest of the conference looked weak to me so I bowed out of the \$600 registration fee and the four day stay in expensive DC hotels. I was later sent an abstract of all the papers presented at the conference. This was a benefit from attending the 9th International Conference in Philadelphia in 2004, along with a one year subscription of the Alzheimer's Association new journal; Alzheimer's & Dementia. The abstracts proved to be interesting and most revealing in one attempted follow up.

A subset of the National Institute of Health (NIH) that funds most of dementia research is the National Institute of Mental Health (NIMH) in Bethesda, Maryland. A team at Trey Sunderland's laboratory led by Nadeem M. Mirza, and nine other authors including Sunderland presented startling data (abstract O2-02-08) on the effect of ibuprofen and lovastatin on the changes in CSF β amyloid₁₋₄₂ concentration for healthy subjects of nominal 60 year olds who are "at risk of contracting AD" based on their having a first degree relative with AD. All prior work most especially that done in Sweden, showed that CSF amyloid concentrations dropped significantly, well ahead of clinical diagnosis maybe a decade, in concentration, of this aggregating oligimer. The Swedish work I regard as exceptional in an otherwise world of stop and go, hop and jump characteristic of US research in this field, reminiscent of observing a playground of children with attention deficit disorder. The Swedish laboratories have shown that CSF concentrations are refractory to change with two studied statins after a drop in amyloid or a rise in Tau, both of which are among the strongest candidate biomarkers for AD diagnosis.

Well, the NIMH work showed a significant jump in amyloid after 3 months of lovastatin at 40 mg/day, and separately, ibuprofen at 800mg/day. This could mean that the all important clearance problem across the

blood brain barrier was showing some response to a prevention treatment. A scan of Table I would show why I would be interested in that finding. The units for the amyloid assay reported in the abstract were nanograms per milliliter, ng/ml, and all the Swedish work had showed the same range of assay but in pico grams per ml, pg/ml, one thousand times less concentration. These concentrations are ultra important as the Swedes have shown that the build up of trapped amyloid is about 5 milligrams in 30 years. I thought this could easily be cleared up and called NIMH.

This institution should change its name to National Institute of Mental Incompetence (NIMI). Nobody answers his or her phone. I eventually left messages at all the named authors with a request for a call back. None received. I searched the online phone directory of Maryland for Mirza, found that he had left the NIMH team, moved to Portage, Michigan and left a forwarding number. I contacted him and at first he was informative and helpful. He said he would check with NIMH on the anomaly of my units discrepancy and get back to me by e-mail. This he did and insisted that their units' ng/ml were correct. I was so concerned by this obvious error I made a special attempt to reach Sunderland.

I went so far as to ask other AD researchers whether this laboratory was on the up and up. The dialog with Mirza in voice and e-mail had raised in my mind the issue of "dry labing, and graphite analysis" or in laymen's terms, faking data. Attempts again to reach Mirza became fruitless. One had to come to the conclusion he was digging in his heels and refusing to budge. Eventually, Trey Sunderland e-mailed me from Europe and confirmed a mistake in editing had occurred. There was no substantive follow up from him or anybody on the paper's author list to the subject matter and the amazing results disclosed in the abstract. Right now I would give the likely reliability of this work a fat Zero. The lack of commentary from the AD research community on this disclosure leads me to believe we may be looking at yet another bungling bureaucracy on the banks of the Potomac.

Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)

It has been a bad year for this aborted trial. It came to a premature end when the concern over cardiac problems arose with COX II NSAIDs, Vioxx, Celebrex, and Bextra. In its flurry to leave the ADAPT scene the ADAPT team let loose a bundle of half baked interim data, largely since recanted, indicating that Naproxen, the COX I NSAIDs that was being compared with Celebrex for AD prevention, had a higher incidence of heart disturbances amongst their study subjects. Interestingly, the study team on the VIGOR trial (COX II vs. COX I face off over adverse gastrointestinal effects) had asserted (incorrectly) that naproxen had special cardiac prevention benefits that made Vioxx look bad. There will be no worthwhile findings from this three-year trial gone badly. The John Breitner led team of Johns Hopkins trialers, the same bunch that brought us the Cache County Epidemiological Study, which has established simultaneously, everything and nothing, is on to greener pastures. If my friends in Upper Michigan ran a beagle trial as poorly as this Hopkins gang, an English bulldog might win.

The medical community in its scientific branches asserts that the Clinical Trial is the Gold Standard for discovering or verifying the efficacy of medical treatments and devices. My conclusion from reading the final reports of trials on prostate cancer prevention, gastro intestinal responses to pain medications, Alzheimer's prevention and a good deal more; in North America the gold standard may be fools gold. The unexplained and excessive drop out rates alone nullifies any conclusions. I sold our Merck shares yesterday, most reluctantly. When you loose Eric Topol, the best cardiologist in the country, you loose it all. The Merck

funded VIGOR trial fell into the same incompetent management hands as we have seen in the NIH funded trials.

Delay in Rotterdam Update

I have long been waiting for the updated Rotterdam Study to compare the extended 1991-1998 findings from this highly regarded group at the Erasmus Medical Center in the Netherlands. Confirming the EMC's website time table, Dr. Monique Breteler, the chief of epidemiology of that institution, has from time to time given me to believe these results 1999-2004 will be forthcoming in 2005, admittedly later rather than sooner. As of November she has turned silent to requests for when the findings might be released. Suddenly no response. Nada! And I thought my earnest admiration of their work, and her photo, which does not exaggerate her charm, meant we could be friends. Maybe the American taxpayer is not the only public funder who is being scrubbed with Old Dutch Cleanser.

Madrid in July 2006

Next year brings the 10th International Conference on Alzheimer's disease and related Dementias. It will be held in Madrid, Spain. My wife and I will be there and eventually reporting on our findings. We'll go direct from the US to Europe, bypassing the opportunity repeat a maxi mental state exam.

Larry G. Nault

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