The Cognitive Enhancement Recearch Institute's

Down's Syndrome Collection

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About the Contents

The articles, editorials, updates, sidebars and questions-and-answers (Q&As) in this collection were originally published in the pages of *Smart Drug News* (from 1992 through 1997) and *Smart Life News* (from 1997 to the present). They are arranged chronologically. The first article in the collection, a feature article on Down's syndrome written by Ward Dean, M.D. (CERI's Medical Advisor) and Steven Wm. Fowkes (CERI's Executive Director) was published on Valentine's Day in 1994. The latest article was published in 2001.

This collection consists of 44 items drawn from 26 newsletters. Only the newsletter pages with information on Down's syndrome are included. Five of the items are full-length feature articles (typically 4-7 pages each). There are also 28 Q&As (one or two pages each), nine sidebars (one page each), an editorial (one page), a notice of a television show (one page) and an update on a conference (one page). The latter two items are now of historical interest only, but are included anyway, in the interest of completeness. The information in the former items is still as valid and relevant today as when first published.

Navigating the Collection

When using Acrobat Reader to view the Down's Syndrome Collection, you can access each individual page by using the "thumbnails" tab, which will display all the pages in the document by their "collection" page number. The "thumbnails" feature, if not readily apparent, can be accessed using the menu options in your software.

Please note that the collection page numbers *do not appear on the actual pages themselves*. The page numbers on the bottom of each page are those that appeared on the original newsletters. These are based on a volume-issue-and-page numbering system. To help keep these different systems straight, the table of contents (see next page), lists both page-numbering systems — side by side. If you choose to print these pages, you may wish to write the collection page numbers on each page in a brightly colored ink to make it easier to find your way around.

Every page in this collection will have something relating to Down's syndrome on it. However, because these are *whole* pages collected from newsletters, many pages will have lead-in or follow-up text that deals with some other subject covered by CERI. You may ignore this unrelated information, or consider it a bonus, whichever you prefer. If you see something interesting, the volume, issue and date information in the footer on each page will allow you to find and obtain the back issue from which it was collected.

Subscriptions

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Thanks again for downloading our Down's Syndrome Collection.
I hope you have an enlightening reading experience.

Steven Wm. Fowkes
Executive Director

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Smart Drug Update: Part 1

Smart Drugs and Down's Syndrome

by Steven Wm. Fowkes and Ward Dean, M.D.

If you listen to scientists who specialize in academic research into Down's syndrome, or to the Down's Syndrome Association, there is basically nothing a parent can do to prevent the profound mental deficits and impaired growth of a Down's child. But if you listen to Dixie Lawrence, a devoted adoptive mother of one Down's child, or to Dr. Jack Warner, a California pediatrician with a ten-year history of treating Down's children, there is plenty that parents can do. In fact, this small group of motivated parents and dedicated practitioners has succeeded in doing what the authorities have decreed to be impossible — the normalization of Down's children's growth rates and mental abilities. Down's children treated with this new smart-nutrient and/or smart-drug treatment program are now being mainstreamed into public schools on a routine basis. Their growth rates are equivalent to those of normal children, and the IQs of those children started on the program early in life are comparable to normal children. One 5-year old Down's girl even has a documented IQ of 140!

Henry Turkel, M.D.

The pioneering work on a treatment program for Down's syndrome was begun over fifty years ago by the late Henry Turkel, M.D. Dr. Turkel's treatments, which he called his 'U series' medications, consisted of a combination of nutrients and drugs formulated to compensate for some of the metabolic errors which result from the extra 21st chromosome (called *trisomy 21*) which causes Down's syndrome. Turkel's U-series contained vitamins, minerals, fatty acids, digestive enzymes, lipotropic nutrients, an amino acid, and numerous drugs (thyroid hormone, antihistamines, nasal decongestants, and a diuretic). The FDA stopped the interstate distribution of Turkel's U-series medications and refused to issue a New Drug Application for them. Nevertheless, U-series medications were determined to be legal for distribution within the state of Michigan, where over 5,000 patients were treated with some success.

Jack Warner, M.D.

Dr. Turkel's treatment has now been refined by California pediatrician Jack Warner, M.D. Dr. Warner and his wife Charlene run *The Warner House*, a center for the study of trisomy disorders, in Fuller- ton, California. Dr. Warner's approach is to combine a nutritional/metabolic therapy with physical therapy and developmental optometry. He says, "Warner House is probably the only place that has such a comprehensive approach to treating Down's syndrome. We have a developmental optometrist, and absolutely the world's best physical therapist. She sits on the floor and works with these children for almost an hour, and we video tape the session so the parents can take the tape home with them."

Dr. Warner's program not only significantly counteracts some of the cognitive deficits associated with Down's syndrome, but it prevents and reverses some of the physical and developmental abnormalities characteristic of the condition. Most of the Down's syndrome children being treated with the program are developing near-normal to above-average intelligence, without the chronic illnesses typical of Down's syndrome. Many are competing successfully in public schools, and some of the children fortunate enough to be placed on the program early in life do not have the pronounced physical features typical of untreated Down's children.

Dixie Lawrence

Dixie Lawrence is the Director of Adoption Options of Louisiana, an organization

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"This small group of motivated parents and dedicated practitioners has succeeded in doing what the authorities have decreed to be impossible — the normalization of Down's children's growth rates and mental abilities."

"Down's children treated with this new smart-nutrient and/or smart-drug program are now being mainstreamed into public schools on a routine basis."

that places Down's and other children for adoption. She is also the adopted mother of Madison, a Down's child now 4 years old. After seeing a relative's Down's boy being successfully treated by Dr. Turkel's method, Dixie investigated the Turkel and Warner programs and gathered a group of 30 Louisiana families together to bring Dr. Warner's team to Baton Rouge. She has since developed an independent protocol combining elements of both programs with both amino acids and smart drugs. Dixie's daughter and several of the other family's children have gone on Dixie's modified program with spectacular results. A couple of Down's infants have even been treated *in utero*. In one case, the delivering obstetrician refused to believe that the infant was a Down's syndrome baby until presented with a chromosome analysis.

Professional Skepticism

In the 1950s, Dr. Turkel's U-series treatments were met with skepticism and/or hostility by governmental bureaucrats and mainstream researchers who adhered to the then-dominant view that nutrition is at best a trivial influence in such a basic genetic disorder. For every published study that indicates that nutrition can have a positive influence in Down's syndrome, there is at least one that concludes that nutrition is of no benefit. Despite authoritative opinion, parents of Down's children were willing to give Turkel's program a try. Although parents regarded the treatments as successful, they complained about the difficulties in complying with the program and some of the side effects of the drugs employed.

The Warner Program

Dr. Warner's improved program is more convenient than Dr. Turkel's U-series medications. Dr. Warner avoids the regular use of drugs, and, unlike Dr. Turkel, he does not automatically prescribe thyroid supplements to *all* Down's children. Instead, he does a thyroid workup which identifies the majority of Down's children who do need thyroid support, and the specific amount they need.

The basic dietary supplement in Dr. Warner's program are called "Hap Caps." They do not contain any drugs or thyroid. The prescription of thyroid or other drugs is left to the determination of the attending physician with due consideration for the specific medical needs of each patient.

Hap Caps are formulated to counteract specific metabolic disturbances seen in Down's syndrome. Chief among them are disturbances in the antioxidant enzymes catalase (abnormally low levels) and superoxide dismutase (abnormally high levels) [Groner, *et al.*, 1985; Shah, *et al.*, 1989; Lejeune, *et al.*, 1992]. This disturbance responds positively to the high dosages of dietary antioxidants, like vitamins E, A and C, and the minerals zinc, copper, manganese and selenium.

Another metabolic disturbance is the diminished production of digestive enzymes [Abalan, et al., 1990], which is directly counteracted by the addition of supplemental enzymes to the Hap-Cap formula.

A third disturbance is amino acid regulation. Disturbances in the regulation of cysteine, lysine, methionine, phenylalanine, tyrosine, glutamate, GABA, histidine, tryptophan and cystathionine have been reported [Hyanek, *et al.*, 1970; Airaksinen, 1974; Petre-Quadens and De Lee, 1975; Shaposhnikov, 1979; Pueschel, *et al.*, 1980; Reynolds and Warner, 1988; Lejune, *et al.*, 1992]. Some of these disturbances can be counteracted by supplemental amino acids, like tyrosine and tryptophan. Unfortunately for the Down's children, the FDA has banned the tryptophan that they need. For the last several years, they have had to do without. Other amino acid disturbances can be dealt with by supplemental vitamins, like B_6 and B_{12}.

New Practitioners

Karel Mommeyer, M.D. **011-32-11-821767**
Zavelstraat 25, B-3520 Zonhoven, Belgium
Regenerative treatments through cell therapy, ozone therapy, natural therapy (procaine injections), and chiropractic adjustments. FAX: 011-32-11-821909.

Dharma Khalsa, M.D. **602-749-0404**
SuperHealth Ranch, 2545 North Woodland Road, Tucson, AZ 85749
Pain, stress and longevity specialist. Medical Director at health ranch specializing in anti-aging and rejuvenation. Prescribes brain boosters when desired and medically indicated. Founder of the Alzheimer's Prevention Foundation. FAX: 602-749-0407.

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1808 South Pennsylvania Avenue, Suite One, Lansing MI 48910
Internal medicine.

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Homeopathy, nutritional medicine, orthomolecular medicine, thyroid, non-conventional cancer treatments, life extension. Smart drug expert.

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Disturbances in carbohydrate metabolism have also been reported [Turkel, 1981; Raiti, *et al.*, 1974].

Neuroendocrine disturbances are also a feature of Down's syndrome. The frequency of thyroid abnormalities in Down's children is very high compared to normal children [Napolitano, *et al.*, 1990]. In addition, growth abnormalities have been traced to a deficiency of insulin-like growth factor (IGF) type 1 [Anneren, *et al.*, 1986, 1990]. Both IGF-1 and IGF-2 are stimulated by the action of human growth hormone (hGH), but in Down's children, IGF-1 does not rise in infancy. A major amount of research is now being directed towards the use of hGH in treating Down's syndrome children, with some success [Torrado, *et al.*, 1991]. hGH increases IGF-1 levels and growth rates in Down's syndrome children, but it also increases IGF-2 levels. The use of hGH in the treatment of Down's syndrome is still highly controversial.

"The delivering obstetrician refused to believe that the infant was a Down's syndrome baby until presented with a chromosome analysis."

Beyond Supplements

Dr. Warner's program also emphasizes physical therapy and developmental optometry. It is the *combination* of metabolic support, thyroid support, and physical and optometric vision therapies that allows Down's children to overcome their developmental learning disabilities and to compete with normal children in sports, school and social interactions. Many of the children on the Warner program have been successfully integrated into public schools, and a number of them have gone on to participate in such sports as baseball and skiing.

"The use of hGH in the treatment of Down's syndrome is still highly controversial."

Many of these treated Down's children are not easily recognized as such, even by professionals. Three years ago, Dr. Warner's group set up their first presentation booth at the National Perinatal Association meeting. They had photos of four of their Down's children on display. "We had people coming up to us and saying, `Why didn't you put up pictures of Down's syndrome children?'" says Ardith Meyer, physical therapist for the Warner team. "They didn't look like Down's children," she adds. The physical changes in appearance reflect the underlying improvements in the children's metabolism and development.

"If parents and therapists don't see that the child has potential, they'll never try anything."

Dr. Warner has now treated more than 700 Down's children with his program. He regularly refers his Down's patients for physical therapy and developmental optometry.

Counseling and Physical Therapy

Ardith Meyer and Dr. Stephen Meyer are a husband-and-wife team that have been providing physical therapy for Down's children and counseling for their parents. Their center, *A Child's Life*, is located in Diamond Bar, California. Steve Meyer is a clinical psychologist. He counsels the parents about behavior problems with the children and assists with physical therapy evaluations. Ardith Meyer does the physical therapy and provides the parents with a physical-therapy program for use at home.

Steve Meyer states, "Dr. Warner's nutritional program has revolutionized my attitude towards Down's syndrome children. Prior to my experiences at the clinic, I had thought that the retardation was a direct factor of the genetic defect. Now I realize that the retardation is a product of an error in metabolism. When we correct this metabolic problem, their mental potential moves into the normal range. We have seen many children move into the above-average range. These children have potential!"

Ardith Meyer thinks that one of the biggest problems is that many professionals and parents do not see any potential in Down's infants and children. "If parents and therapists don't see that the child has potential, they'll never try anything," states Ardith Meyer. "People lock Down's syndrome children into a `mentally-retarded' label and fail to realize their strengths, their weaknesses, or their interests. Down's children are like everybody else, they gravitate towards what they enjoy, and if you can make the program interesting and fun, they'll do it." The entire team agrees that Down's syndrome is more properly considered a learning disability than retardation. Ardith Meyer says, "Most of the world does not understand that yet."

Without intervention, Down's children have "moderate" to "major" developmental impairment with IQs in the 55 range. With intervention, many move into the "normal" range [85 to 115]. Some remain in the "mild" developmentally impaired range. The effectiveness of the program depends on the age at which treatment begins. "It's clearly, the earlier, the better," states Steve Meyer. "I want to see them at eight days of age," states Ardith Meyer. "I can start showing the parents what to do that will prevent the waddling gait and difficulty in

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running when they are in their teens." In the 7 years that she has been working with Down's children on the Warner program, she has yet to see a single child that has not benefited when started in the first few years of life. A few of the older children with autistic tendencies and severe behavioral problems are the only ones that have not benefited from the program.

"When I first started with Dr. Warner, I was reluctant to talk about the program with the other pediatricians with whom I worked," Ardith Meyer says. "I thought, I'm going to wait and see how this is. Now that I've seen so many children go through the program, I'm proud to talk about it."

"I have observed that Down's syndrome children who have been on the Warner House clinic metabolic program respond better to optometric vision therapy than those not on the program."

Optometric Visual Therapy

Dr. Phil Klingsheim is a behavioral and developmental optometrist who treats the vision problems of Down's children. He says, "Optometric vision therapy can be a great aid to Down's syndrome individuals in assisting them to reach their full potential academically." Vision therapy involves clinical tests and training procedures that correct neurosensory, neuromotor, and neurophysiological visual dysfunctions. Dr. Klingsheim is impressed with the Warner program. He states, "I have observed that Down's syndrome children who have been on the Warner House clinic metabolic program respond better to optometric vision therapy than those not on the program. They seem to be more alert and mentally available to benefit in vision therapy situations."

The A-B-A-B Research Design

Although government and academic researchers expect all therapies to be proven in double-blind studies, this would require that half of the children receive a placebo instead of the treatment formula. The withholding of treatment from the placebo group would be ethically untenable for Dr. Warner's team, who are now completely convinced that the program is beneficial. "Most parents would refuse to take their children off the program," adds Steve Meyer.

"Most parents would refuse to take their children off the program."

Under such situations, researchers resort to the A-B-A-B research model, in which the therapy is purposefully discontinued for an interval, and then restarted. By chance, this has happened for a few children on the Warner program. "The child comes to us in condition A, and goes on the program for phase B," explains Steve Meyer, "then, for some reason (through a family crisis or economic issue), the child temporarily goes off the program. We know which parents are being faithful to the intervention and which ones aren't based on the number of vitamins they order. When the children go off the intervention, we definitely see a decline in their growth, alertness, attentiveness and general health." And when they go back on the Warner program, their growth and learning is restored.

"These serendipitous cases fulfill what is called an N-of-one research model, the A-B-A-B pattern, which is a very useful model commonly used in behavior modification research," asserts Steve Meyer. "Fortunately for the children, most of the parents come to us with a positive expectancy and, after they experience the initial improvement in the child, they comply with the program. When they aren't faithful, there's usually some environmental circumstance that has hindered them, like a divorce or unemployment. In one family, the husband was very reliable with the morning medication and the wife was lax with the afternoon. That's probably the hardest situation to deal with because of the division within the family."

Ardith Meyer describes one A-B-A-B case of a mother who ran out of Hap Caps. And because she couldn't get to the store, she started giving her Down's son regular milk instead of non-dairy products. When she finally brought him in, he was lethargic and sick. "She told me that she didn't think the program was working. I had to say, `Wait a minute. You have to keep him on the program. Look what has happened when you took him off of it.' She put him back on the program and he got healthy and alert again."

A Mother's Experience with Piracetam

Dixie Lawrence has also experienced a few A-B-A-B instances with her daughter Madison. One of the most graphic was when she ran out of piracetam. Right after Madison first went on piracetam (with phosphatidylcholine and vitamin B5), she spontaneously potty-trained herself, started speaking in phrases, and developed an active symbolic immagination. Months later, when Dixie ran out of piracetam for a week, within days of ceasing piracetam,

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Madison broke her potty training and lost her immagination and much of her verbal fluency. Fortunately, when piracetam administration was restored, she regained everything.

After hearing about Madison's achievements, several other families in Louisiana put their Down's children on piracetam, B_5 and phosphatidylcholine with very positive results. Dr. Warner is interested in Dixie's results with amino acids and piracetam and is looking into incorporating both into his program. He states, "One of the wonderful things that Dixie has come up with is the extra amino acids and proteins. There's a Dr. Lejeune in Paris that has been working with this [Lejeune J, 1991; Lejeune, et al., 1992], although I don't think that what he is doing is a complete answer. I think all of these approaches have to be put together,

Dr. Lee-Benner Visits the Warner House Clinic

We asked CERI Medical Editor Lord Lee-Benner, M.D. to drop in on a weekend Down's clinic at the Warner House. This is his report.

I saw eight children, a number of whom were new and just starting Dr. Warner's metabolic program. Some of the children that had been on the program for a while had recent interruptions, so this group may not have been a fair sampling. Their ages varied from 6 weeks to 11 years, most of whom were between 2 and 5 years. I could see mongoloid features in all of the children, even the older ones who were 9 and 11.

Although the features were there, the treated children were doing very well. They were active, outgoing and fairly talkative. They were not dull like the untreated children. The growth pattern scores of the children on the program were in the 50th percentile (on a "normal" growth percentile evaluation chart, not a Down's syndrome growth chart), compared to scores below the 5th percentile for those not on the program. These "normal" growth results are definitely a significant and interesting factor of the Warner program.

Based on the serial photographs, there appears to be some improvement in facial features. Those on the program for a short time were not quite as "Asiatic" looking. The epicanthal folds [vertical folds of skin on each side of the nose which tend to hide the inner corner of the eye, closest to the nose] were hard to see from the photos, and Dr. Warner acknowledged that he had better photos and examples. I did observe that the treated children appeared to have less epicanthal fold than the untreated children.

I talked with the family members who are very positive and supportive. I thought the mothers were especially courageous. The parents are very pleased with the program. They reported that their children were healthier and interacted more with their peers and teachers. Their mental abilities were improved and all of them were in or headed towards regular school programs. That was impressive.

"The growth pattern scores of the children on the program were in the 50th percentile."

All of the new children had nasal or sinus conditions. Those on the program longer had fewer or less symptoms. Several hadn't had colds for a long time.

The children on the Warner program are fortunate to have access to a behavioral optometrist who administers a series of tests to the children to discover subtle visual disorders (relating to tracking, fixation, focus, depth perception, peripheral perception, binocularity, and coordination). The children are then trained to overcome these vision-related difficulties. A lot of school children with behavioral problems — so-called dyslexia and attention deficit disorders — would benefit from this kind of testing and training. *All children* should probably see a behavioral optometrist, preferably before they go to school and develop a bad self-image.

They're treating the children with thyroid supplements and keeping the T_4 level up around 8.6 (high-normal), or as close to that as possible. They don't accept "normal" thyroid function tests as an indication not to treat with thyroid. For those that I saw, all had benefited from thyroid supplementation. They use the Broda Barnes method monthly to follow the children.

"I was impressed with the caring and professionalism of the Warner team."

They also use nutritional supplementation. The zinc question is an issue. I just found a study which demonstrates that zinc supplementation stimulates growth and development in undersize Japanese children. They were using 2mg/kg/day elemental zinc for six months and they measured increased IGF-1 levels without increased hGH levels. They were following *zinc clearances* (which tested abnormal) rather than *zinc levels* (which tested normal). Abnormal zinc clearance may be an indication of a preclinical zinc deficiency.

I was impressed with the caring and professionalism of the Warner team. They are definitely doing God's work. **LLB**

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maybe including the use of Nootropil [piracetam]. I know that Dr. Schmid has been using piracetam in Germany for years, but I didn't know that it was available [by prescription] in the United States until recently."

A Family Affair

At A Child's Life, the children are invited to come to the clinic with their entire family. The physical therapy session is videotaped so the parents can refer to it at home if they have trouble remembering new exercises. Ardith Meyer says, "It's my job to help the parents understand what specific needs the children have and give them very specific things to do." A lot of the parents are eager to learn what they can do to help their child develop, and the video tape makes it easy.

"All of these approaches have to be put together, including the use of Nootropil."

The contribution that family relationships make to the growth and development of Down's children is crucial. One Canadian family with a young Down's boy and three older siblings came to a Seattle clinic held by Dr. Warner's team. Ardith Meyer uses what she calls "motor-planning cards," which have instructions to get into a specific body position. She relates, "I got down on the floor and into the positions with the boy, and the whole family joined us on the floor and did the motions with us. It was so spontaneous, like *this is just what we do for recreation*. The family support was awesome, and the boy was picking it up so quickly."

"In another family, the mother brought her Down's syndrome daughter in to us at 8 days and every two months since then. The girl is fortunate to have four older brothers who love her dearly and who excel at motivating her to do the exercises. She couldn't have a better situation." She adds, "The mother just called me to determine whether it was worth the trouble to drive in to the center through the earthquake-damaged freeway system here in Los Angeles, and one of the brothers told the mother to come in because the daughter `had changed and needed a new program.'"

"The parents desperately want support from medical professionals."

According to Ardith Meyer, the parents desperately want support from medical professionals. "If their doctor doesn't believe that their child can change, they will go find someone who will, even if the advice they get is not appropriate." For decades, Down's children were seen as mentally retarded, not as learning disabled. Because of this attitude among professionals, parents left the mainstream to find someone who would try to help them. "When some parents come to me and talk about some other treatment regime, I usually know what they are going to say because the other programs haven't changed since the 50s."

"But these children do have potential, and I am thrilled to work with them. I show them what to do. It's not me, it's them. I'm just somebody who's paying attention to them. I have learned a great deal about what their needs are over the years, and I've also learned why they need to have a physical therapist working with them. With the Down's child, their needs change. Early on, between birth and three years, their postural muscles, muscle tone and motor skills need a lot of attention. Later, a lot of Down's children are hindered by their lack of *verbal* skills." "You can even see it in the toddlers before they walk," says Ardith Meyer. "They understand everything you are saying but they cannot verbally respond to you." Because of these communication difficulties, Down's children tend to get pegged lower in school. According to Ardith Meyer, one of the hardest thing for Down's children to learn are perceptual-motor activities, like handwriting, spelling and reading words.

School and Play

At A Child's Life, Ardith and Steve Meyer try to incorporate strengthening and coordination exercises into play. "You can't ask a 9-month-old infant to crawl across the room towards nothing, they won't be motivated," argues Ardith Meyer. "You can't ask a ten-year-old to do push-ups. If you want children to do something, you have to incorporate it into a play activity." For example, she has the children load stuff into a wagon and pull it up a hill.

The Teachers Report

Ardith reports that the treated Down's children are just as willing to go out and play at recess as normal children. "The teachers will write to us and say that the treated Down's children are more motivated," states Ardith Meyer. Many teachers have asked the parents, "What are you doing differently?" The teachers report that the treated children are really paying attention in class, they are very interested in climbing on the gym at recess, and they are interacting with their peers. "One mom said that

continued from previous page

the teacher could tell when she ran out of the Hap Caps," says Ardith Meyer. "The child went right back to being lethargic and uninterested." She adds, "If the teachers go to the trouble to report these observations, you know the Hap Caps are making a major difference."

Part two of this article will detail the specific substances and dosages being use to treat Down's children.

"Many teachers have asked the parents, `What are you doing differently?'"

"The teachers report that the treated children are really paying attention in class."

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More references will be provided in Part 2.

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Smart Drugs and Down's Syndrome:

An Interview with Dixie Lawrence

by Steven Wm. Fowkes

Dixie Lawrence is the Director of Adoption Options, a Louisiana-based adoption agency, and a founder of Trisomy 21, Inc., a not-for-profit educational foundation researching treatments for Down's syndrome. Dixie is also the mother of three children, ages 26, 22 and 4. Her 4-year-old adopted daughter Madison has Down's syndrome. For the last 2 years, Madison has been on an extremely successful treatment program which incorporates vitamins, minerals, amino acids and piracetam. Dixie's personal experience with body building allowed her to recognize amino acid deficiencies in her daughter and motivated her to include amino acid therapy in the treatment. Dixie's latest treatment innovation has been the incorporation of piracetam into her daughters program. Madison's results are described in the following interview.

CERI: Can you give our readers a brief and simple explanation of Down's syndrome?

Dixie: Down's syndrome results from complete or partial duplication of chromosome 21, one of the smallest of the human chromosomes. Chromosome 21 contains, among other things, the genetic blueprint for various proteins, enzymes, and other metabolic substances. Normally, a human being has 46 chromosomes, but people with Down's syndrome have 47. The duplicated 21st chromosome, called *trisomy 21*, causes a gene "overdose" that leads to an excess of some gene products and numerous metabolic imbalances.

I could see some of the physical imbalances in my own child. Down's syndrome children, for instance, have dry skin, slow-growing sparse hair, low muscle tone, slow

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Book Review:

Questions and Answers About Prozac

by T. Michael Hardy

Prozac: Questions and Answers for Patients, Family and Physicians, by Ronald R. Fieve, M.D., (ISBN 0-380-77718-5 paperback, 212 pages, $4.99, Avon Books, New York, 1994).

Perhaps a better title for this little book would have been *Everything You Want to Know About Prozac*. Dr. Fieve (pronounced Fee-vee) delivers the information in a refreshingly straightforward manner. Anyone who is taking Prozac, or is giving it consideration, should immediately go out and get this handy little paperback.

Dr. Ronald Fieve is a distinguished psychiatrist who, among other things, pioneered the use of lithium for manic depression. He is also the author of the bestselling *Moodswing*. Dr. Fieve's extensive clinical experience with Prozac provides his readers with a wealth of information about not only Prozac but other medications and conditions relating to mental health.

Dr. Fieve offers his own insight into the reports of "personality transformations" popularly associated with Prozac in the press. He discusses the concept, and points out that the "substantial minority" who are said to have undergone radical personality changes are, in his estimation, really no more than 10% of patients at most. He explains that this seeming contradiction to the observations of Peter Kramer, author of *Listening to Prozac*, is really a matter of definition. As Dr. Fieve writes, "a person who is less depressed becomes, by defini-

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growth and very loose ligaments. All of these symptoms are complications of amino acid, mineral and vitamin deficiencies.

I want to emphasize the importance of amino acids. A French scientist, Dr. LeJeune, showed almost identical amino acid deficiencies in 79 Down's syndrome individuals. Serine levels are particularly deficient. Some people might not think that low serine levels are a serious problem, but Dr. Evan Jones of North Carolina University, an expert in the field of amino acids, has advised us that serine deficiency could indeed contribute significantly to many of the problems associated with Down's syndrome, including mental retardation.

"A French scientist, Dr. LeJeune, showed almost identical amino acid deficiencies in 79 Down's syndrome individuals."

One of the most significant of the metabolic imbalances is probably the overproduction of superoxide dismutase (SOD), an antioxidant enzyme which is encoded on the lower arm of chromosome 21. The increased levels of SOD are associated with decreased catalase levels, increased lipid peroxidation, decreased immune response, and possibly increased risks of leukemia.

"One of the most significant of the metabolic imbalances is probably the overproduction of superoxide dismutase (SOD), an antioxidant enzyme which is encoded on the lower arm of chromosome 21."

CERI: There are many different genetic forms of Down's syndrome. Don't some just have *pieces* of chromosome 21 duplicated.

Dixie: Right. There's *translocation* which occurs when part or all of chromosome 21 is stuck to the end of another chromosome — usually chromosome 14. This form of Down's syndrome is inherited. The most common form is *non-disjunction*, where the genetic material doesn't separate properly during cell division.

CERI: The duplicated chromosomes are supposed to separate, so that one copy goes to each side of the newly divided cell. Without separation...

Dixie: ...both copies of chromosome 21 go to one side. Then you have 45 chromosomes in one cell and 47 in the other. The 45-chromosome cell tends to die, and the 47-chromosome cell continues to reproduce. Non-disjunction probably represents about 85-95% of all cases of Down's syndrome.

When non-disjunction happens *after* the first cell division, you have mosaicism. Mosaics have *two cell lines*, one with the normal 46 chromosomes and one with 47. Depending on the percentage of normal cells, mosaics may be significantly less affected than non-mosaics.

CERI: How old was Madison when you adopted her?

Dixie: She was 12 weeks old. She had skin rashes, constipation and a history of frequent respiratory and ear infections. It seemed apparent that she had certain deficiencies which were affecting her immune response.

I liken Down's syndrome to a cake recipe. If you mix cake batter with too much of some ingredients, it'll bake into something *like* a cake, but it won't be what the recipe intended. With Down's syndrome, there are too many ingredients in the human "recipe." Unlike trisomy 18 and trisomy 13 which alter the recipe so much that the fetus dies or the child lives only a short time, the trisomy 21 recipe is correctable. We can add the "short" ingredients to balance out the "extra" ingredients. In other words, we use nutrition to compensate for the genetic overdose.

I do not believe in vitamin-only therapy because it only corrects part of the problem. I do believe that it helps, but it's like putting a band-aid over a surgical incision.

CERI: Even Dr. Warner uses tyrosine and tryptophan — or at least he used to use tryptophan before the FDA pulled the plug on it.

Dixie: Research studies do suggest that Down's children are tryptophan deficient, and therefore serotonin deficient.

CERI: I wonder if they're melatonin deficient?

Dixie: Probably. The levels of serine seem to be the lowest. When you are working with an amino acid profile, it is the lowest one determines what you have to work with.

CERI: Right. The most deficient amino acid limits the rate of protein synthesis, and that ultimately limits growth.

Dixie: When we supplement the deficient amino acids, we can alter their growth rates. We can't just supplement serine, or tyrosine, or tryptophan, we've got to supplement all of the amino acids that they need, including the ones that may show up in abundance. Now that might not make much sense, but you can think of the serum as a sludge pool for amino acids. What counts are the amino acids which get *inside* the cells.

CERI: And vitamins and minerals are the essential cofactors for protein synthesis.

Dixie: B_6 especially.

We're beginning more and more to recognize the importance of coenzyme Q_{10} in not just immune function, but basic brain function too.

CERI: You started investigating Down's syndrome in 1990 after you adopted Madison?

Dixie: Yes, when she was a small baby.

CERI: Was doctor Turkel still alive then?

Dixie: Turkel had left Michigan and was living in Israel then. I didn't find him until 1991. I first heard about Turkel because of a Louisiana woman whose 9-year-old son Zack kept popping up on the honor roll. I heard that Zack had Down's syndrome because he was my ex-husband's nephew. But after the divorce, I lost track of the family. Years later, I was more than

Smart Drugs and Down's Syndrome: An Interview with Dixie Lawrence

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surprised to see his name on the honor roll. He wasn't on any Special Ed honor roll, it was *the* honor roll. Zack's mother had started the local Down's syndrome group here, so I called her and congratulated her on how lucky she was. I had assumed that Zack was a true Down's mosaic in which some percentage of body cells are normal, because of his exceptional mental function. I was wrong. He was on Dr. Turkel's program. Because of that, Zack is very intelligent. For example, can you spell "elevator" backwards?

"Years later, I was more than surprised to see his name on the honor roll."

CERI: No, I can't. Not quickly.

Dixie: He can, just as quickly backwards as forwards. Immediately. Any word that he knows. Now we're talking about a child with Down's syndrome, a child who's never missed the honor roll.

CERI: When did he start the Turkel program?

Dixie: At nine months of age.

CERI: So he's been on Turkel's program for over ten years?

"I found Dr. Turkel in Jerusalem in the middle of a bombing raid. I could hear the explosions in the background as I was

Dixie: Actually, he was on Turkel's program for three years, until Turkel quit doing his program. Fortunately, his grandmother owned a health food store. His family duplicated the Turkel program as much as they could and he's been on it ever since. Because of his family's dedication, Zack will never need to be dependent on anyone. He is one of the top students in his school. He is essentially a normal kid. He has very few Down's syndrome features. You can tell if you look closely at him and you know what to look for. He's cute, very attractive, and smart as a whip.

CERI: Does he have any of the classic problems like with verbal communication, or did he have any problems as he was developing?

"Can you spell `elevator' backwards?"

Dixie: He has extremely good speech, but he stutters if he gets flustered or tries to talk too fast. The speech centers have not been affected by Turkel's program as well as they could have been. That's where piracetam comes in. Dr. Puchel's work on the neurological aspects of Down's syndrome has shown that areas of the brain do not connect properly, and that the transmission of information between the two hemispheres of the brain is garbled. The combination of piracetam and choline seems to address that. Just having a speech defect does not make one mentally retarded.

CERI: No. It may make people *think* that you're mentally retarded.

"It's very conservative, but you have to understand that he's working within the system. He actually met with the FDA before

Dixie: Absolutely. And having Down's syndrome facial features does not make you mentally retarded. It certainly doesn't help you.

I found Turkel in Jerusalem in the middle of a bombing raid. I could hear the explosions in the background as I was talking to him. He gave me the name of a Canadian biochemist, Kent McCleod, and he gave me the name of Dr. Warner. I called Warner and asked if he was doing the Turkel formula. He said he was doing some- thing similar, and it *is* similar.

Turkel's program contained drugs that were frightening to me. Turkel used a powerful diuretic, and a Ritalin-like stimulant...

CERI: Phenylpropanolamine.

Dixie: Right, which to me was more of an inhibitor and I didn't want that. I think he was working with older children who had a lot of acting-out and attention-deficit problems that he was addressing. It's not so in a baby.

CERI: But if you treat the baby with the physical therapy and optometric therapy like Warner's team does...

Dixie: Yes. His is a whole-body approach. I like it. I like Warner very much because he's open minded to alternative approaches. He understood that I had looked at what he was doing and thought I needed to do more for Madison. His program is far superior to anything else offered to Down's children by the medical profession, but I couldn't ignore the amino acid problems that I saw in Madison.

CERI: In a lot of ways his program is very conservative.

Dixie: It's *very* conservative, but you have to understand that he's working within the system. He actually met with the FDA before he started his program.

CERI: That must have put some serious limits on what he could put in his formula. Dr. Lord Lee-Benner was impressed with Dr. Warner's results, but he was particularly concerned about the low amount of zinc in Hap Caps.

Dixie: Yes, very low zinc. When I put Madison on the Warner program, I added an additional 15 mg zinc and 25 mg B_6 per day.

CERI: Dr. Lee-Benner brought to my attention a study that was done in Japan where they studied zinc's effect on not Down's kids but low-growth kids. On zinc, their growth normalized and their insulin-like growth factor type-1 (IGF-1) normalized. It's the IGF-1 that is deficient in Down's syndrome. They produce normal amounts of IGF-2 in infancy, but never seems to make the transition to IGF-1 in childhood. In this study, zinc acted specifically on IGF1, without altering IGF-2 or growth hormone itself.

Dixie: Madison's diet is not necessarily restricted to anything in particular. I feed her a lot of raw food, raw carrots and raw vegetables, because of the digestive enzymes they contain. I avoid giving her raw legumes and nuts because

Smart Drugs and Down's Syndrome: An Interview with Dixie Lawrence

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they have enzyme inhibitors. Down's kids definitely seem to be deficient in digestive enzymes.

CERI: Do you also supplement her with digestive enzymes?

Dixie: I do, but digestive supplements are so bitter that it's hard to get them down her.

"I feed her a lot of raw food, raw carrots and raw vegetables, because of the digestive enzymes they contain."

CERI: So she's not old enough to take capsules and pills.

Dixie: No. I wouldn't even try. I shake her supplements up in her juice. One thing that we have discovered is that apple pectin is a really good flavor-masking agent.

CERI: What supplements do you favor for Madison?

Dixie: There are two I would use for Madison. One is an over-the-counter product made by TwinLab called MaxiLife plus CoQ_{10}, which we have used with piracetam, choline extra C, B_5, and a liquid amino-acid formula. The second is a complete product that I helped formulate called MSB Plus, available through a Canadian pharmacy.

"How many other families in your area have put their Down's kids on a nutritional program like Madison's?"

CERI: What's her daily regimen?

Dixie: She gets a teaspoon of the MSB Plus formula and 800 mg piracetam in the morning in her juice. When we were using the MaxiLife/liquid amino method, she got one MaxiLife in the morning, a tsp of liquid amino acids, extra vitamin C and B_5 plus phosphatidylcholine and piracetam. I mixed it in apple juice, with apple pectin as a flavor-masking agent.

CERI: Do you have a growth chart of her so far?

Dixie: Yes. She's only in the tenth percentile, but she's supposed to be small — both of her birth parents were tiny. She's not a big kid, but she's a whole lot bigger than she would have been.

"Three weeks into this modified Warner program, Madison stood up and walked — very well I might add."

CERI: How many other families in your area have put their Down's kids on a nutritional program like Madison's?

Dixie: About 50. Zack was the first, and Madison was second. It took me two years to do the research, not only because it was hard to locate Turkel, but because I was concerned about some aspects of his program — the reliance on diuretics and nasal sprays, and the one-formula-fits-all approach.

Just before her second birthday, Madison was diagnosed with nystagmus [constantly twitching eye movements] and moderate to severe nearsightedness by two of the best pediatric ophthalmologists at Children's Hospital. Both specialists said she needed surgery to correct her vision, but I said no. I wanted to try the program first.

CERI: This was about two months before you started the program?

Dixie: Yes. The first thing I did was to pump her full of brewer's yeast. I started using brewer's yeast in her cereal for the B-vitamins, antioxidants, and amino acids she needed. And I started feeding her yogurt every single day.

CERI: Yogurt? Doesn't that cause a mucous problem?

Dixie: No, not if you wait until the expiration date on the container. The yogurt seems to coat the intestines and help with digestion. I also added an extra capsule of milk-free acidophilus culture, avoided any kind of rice cereals, and absolutely avoided uncultured cow's milk. We've kept her healthy. Of course she was also getting vitamin C three times a day and a multi-vitamin.

Both eye doctors said that her eyes were structurally normal, so I figured that the problem must be neurological.

CERI: So were you doing any physical training exercises with her?

Dixie: At that point, yes. But when we started the treatment program at two years, I pulled her out of absolutely everything and started treating her like a normal child. At 22 months of age, even going to physical therapy once a week, she was still nowhere near walking. She could barely crawl. At 26 months, she went on Dr. Warner's program.

I got a group of about 30 families together to bring Dr. Warner from California to Louisiana. I told the parents, "I don't know all of what this man has to offer, but if we all pitch in, we can fly him and his team here." So we did.

When I got home and read his labels, I thought, "He's using taurine and tyrosine, but he's not using other amino acids to maintain a balance." So I did. I balanced the amino acids, and added more vitamin C, more zinc and more vitamin B_6.

CERI: So you were using his basic Hap Cap formula, and adding these other things?

Dixie: Yes. But I had to add to it too much, and it rapidly became a pain in the rear. Three weeks into this modified Warner program, Madison stood up and walked — very well I might add.

Her muscles started changing immediately after starting the program. Within two weeks, I could see a calf muscle that she never had before. Within three to four weeks, the calf muscle was obvious. Her "feel" changed. Holding her was no longer like holding a rag doll.

At 24 months, she couldn't climb one step; six weeks after she went on the modified Warner program, she could climb a flight of stairs, up and down. My mother-in-law asked, "What's happened with Madison? It's like a light bulb went off in her head." My pediatrician brother-in-law

Smart Drugs and Down's Syndrome: An Interview with Dixie Lawrence

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doesn't think I'm crazy anymore. Last Christmas he gave her a 24-piece puzzle designed for six year olds. Although she wasn't even four yet, Madison opened the package, took out the puzzle, popped the pieces out and put it back together in about five seconds, right in front of him. His mouth dropped. Madison is still speech-delayed, but that is the only significant delay still remaining.

"My pediatrician brother-in-law doesn't think I'm crazy anymore. Last Christmas he gave her a 24-piece puzzle designed for six year olds. Although she wasn't even four yet, Madison opened the package, took out the puzzle, popped the pieces out and put it back together in about five seconds, right in front of him."

CERI: Well, that's common in Down's syndrome children.

Dixie: She had almost no speech — except maybe two or three words — until we started her on the piracetam.

CERI: OK, to continue with the program...

Dixie: The modified Warner program was fine, but I kept having to crush the supplements to add it to her food and drinks. Then I found the Maxi-Life formula mentioned in a book on Alzheimer's disease. After calling TwinLab in New York, I had my friend at the local health food store stock it for me. I changed to MaxiLife because of the Coenzyme Q_{10}. There seems to be a CoQ_{10} deficiency involved, and CoQ_{10} deficiency has been linked to lowered immune response.

CERI: That's probably why they have cardio-myopathy more often than often than the average infant.

Dixie: I think so. Madison was lucky to have been born without a heart defect.

The greatest change in her facial features happened during the first three months on the program. Madison went from a flat face, typical of Down's syndrome, to almost normal. It was such a dramatic change that some people who had not seen her in a while did not recognize her. Some looked at her and said, "What did you do?"

"I now deeply regret not starting Madison on a metabolic formula in early infancy."

There was always a cognitive level in Madison from eight months forward that was recognizable, but it was like she was locked inside and couldn't get out. As her mother, I could see it, but a stranger probably wouldn't. She was eight months old before I realized that she really had potential. When I would change her diaper, she would puff her belly up for me to rub her tummy. Then one particular time, I was busy with an especially dirty diaper, she poked her tummy up and I said, "Rub your own tummy." And she did! Later I felt guilty. When I first adopted Madison, I thoroughly expected to raise a seriously handicapped child who would never leave home as an adult. I had done what a lot of parents do, to become complacent in comfortable ignorance.

"One of our children was recently highlighted on a news broadcast that aired in California. She was chosen, quite frankly, because she is nothing like a child with Down's syndrome. Because she started on the metabolic therapy and piracetam in early infancy, almost no evidence of the Down's phenotype remains."

CERI: Yes, but maybe we can change that.

Dixie: I now deeply regret not starting Madison on a metabolic formula in early infancy. Those children started very early in life show few developmental delays, if any, and even fewer physical signs of Down's syndrome. For instance, one of our children was recently highlighted on a news broadcast that aired in California. She was chosen, quite frankly, because she is nothing like a child with Down's syndrome. I know she has Down's because we placed her for adoption. But because she started on the metabolic therapy and piracetam in early infancy, almost no evidence of the Down's phenotype remains. You would have to see her genetic analysis to know she had Down's syndrome.

Despite all the scientific evidence to support what we are doing, the proof is in the pudding. In most ways, Madison functions as a normal four year old. She can operate the television and VCR remote control, she uses the track ball to play simple computer games, she speaks in complete sentences, and she potty trained herself at 33 months of age. Basically, she's a normal kid. Her head circumference, by Down's standards, is quite impressive. A recent study stated that average head circumference for 17 year old Down's syndrome females is 49 to 50 cm. Madison's head circumference is 48.75 cm at 4 years of age. Most Down's children are noticeably microcephalic. Madison, clearly, is not. Neither are any of the other kids who start the metabolic therapy early in life.

CERI: What else have you noticed about the children on the piracetam/nutrition program?

Dixie: Hair growth. Madison's hair grew 10 inches in one year. Ten inches! Madison's hair is now so long she sits on it. This is in comparison to Down's syndrome children who don't even have any hair, or slow-growing straight hair, never curly. Madison's hangs straight to about her waist and then the ends form little ringlets — like Shirley Temple curls.

Untreated Down's syndrome children have an under-development of the nasal bridge and the sinuses, and an under-development of the mandible and maxilla [lower and upper jaw] which really interferes with dentition. They have a flattened upper lip because of under-development of the underlying bone. Before treatment, Madison had all these features. After treatment, her nasal bridge developed, her jaw (mandible *and* maxilla grew to normal, and her crossed teeth straightened out. She didn't have to have braces; she simply had jaw development. Her dentition is now normal. Before treatment, she was missing three teeth buds. The dentist said those teeth would never come in. After treatment, they all did.

Her vision also improved. At 34 months, her eye exam was normal. No nystagmus, no strabismus, no nearsightedness. Perfect vision, without glasses. Glasses had been prescribed for her when she was younger, but she would never wear them.

Normalization of her facial features was extremely quick. In about six months, her appearance changed from a very flat-faced,

Smart Drugs and Down's Syndrome: An Interview with Dixie Lawrence

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weak-eyed, clearly handicapped Down's syndrome child to a child who did not look handicapped. I don't care what any of those "experts" say about this treatment not working.

To give you another example, I used to place six Down's syndrome babies a month. Now I'm lucky to place six *a year*. When the parents see Madison, they pick their kid up and go home. They see that there is something that they can do. They're not scared and lost anymore.

"I used to place six Down's syndrome babies a month. Now I'm lucky to place six a year. When the parents see Madison, they pick their kid up and go home."

CERI: That's the big issue, not knowing what to do, and feeling helpless about the situation. So how did you find out about piracetam?

Dixie: Initially, I was looking for something which would facilitate communication between the two hemispheres of the brain. I found one German reference to piracetam, and ultimately, I read about it in Ross Pelton's book, *Mind Food and Smart Pills*. I then started looking for a source. A good friend of mine was being treated for diabetes in Mexico, so I asked him to scout out the pharmacies for me. He found a good one that I have been working with ever since.

Before I gave the piracetam to Madison, I took it myself. I started with an attack dose of 4800 mg. For a month, I recorded my every reaction in a log book. Then, after consulting with a local doctor who is very supportive of what we are doing, I started Madison on 400 mg a day.

CERI: How old was she then?

Dixie: That was about one year ago. She was around 33 months old. Until that point, she was in diapers. Although we had tried to potty-train her, she didn't seemed to have any understanding of what we wanted her to do. Potty training begins when a child recognizes that urine is something which comes from their own body. Madison just didn't understand this, so we didn't push the potty training. She was doing well in other areas, but her higher intellectual and verbal skills were still quite delayed. At this time, she was on the metabolic program including amino acids, but not yet on piracetam.

"Madison potty trained herself. She took her own diaper off, went to the bathroom, took the potty seat apart, put the lid on the big potty seat, turned the base of the potty seat upside down as a stool, climbed up on the toilet by herself and pee-pee'd in the potty. My husband said, `If she does that again, I'll be impressed.'"

CERI: What happened after you put her on piracetam?

Dixie: Five days after starting piracetam with choline and B_5, Madison potty trained herself. She took her own diaper off, went to the bathroom, took the potty seat apart, put the lid on the big potty seat, turned the base of the potty seat upside down as a stool, climbed up on the toilet by herself and pee-pee'd in the potty. She was ignoring us, but my husband and I were watching her while she did all this. He said, "If she does that again, I'll be impressed." About 45 minutes later she headed back to the bathroom and did the same thing again. She's been completely potty trained ever since. She finally understood.

CERI: She must have learned the process from your earlier instructions...

Dixie: I'm sure she watched the other kids in her nursery school use the potty. Children with Down's syndrome seem to understand far more than they can verbalize and physically express.

CERI: Did you see her verbal abilities change?

Dixie: About the fifth or sixth day she started saying things. She had a few words, she could say "cookie" and "outside," then she started saying, "Wanna go outside." And I asked, "You wanna do what?" She repeated, "Wanna go outside."

CERI: And how much piracetam were you giving her?

Dixie: At that time I was giving her a low dosage of 800 mg a day, split in two 400 mg doses. For a while I reduced it to 200 mg twice a day to see if it had any effect. It did not. She did not revert. Now she's back up to 800 mg a day of the liquid piracetam.

CERI: What else have you noticed?

Dixie: She's doing some amazing things. She wasn't *just* potty trained, she went to her dresser, took out her underwear, put both feet through the holes, and pulled them up and on. This is highly unusual for a three-year-old Down's child.

The most amazing thing she did was to develop an imagination, an unheard of development in Down's syndrome children of that age. She likes to play ball. She overhand pitches, and she's got a strong and accurate arm. She can knock your head off clear across the room. About a week after starting piracetam, she came in and said, "I wanna play roll ball." We looked all over and couldn't find the little basketball that she usually plays with, so she sat down on the floor and she told me, "Sit down." I sat down and she pretended to pick up her roll ball and throw it at me. I looked at her like she was nuts, but I pretended to catch it and threw it back to her. She pretended that it hit her in the head. She ducked her head and she goes, "Oh, boo-boo." This might just be cute for another child, but for a Down's syndrome child we're talking about an extremely important development.

Her imagination has continued to grow. She now "flies" with Peter Pan whenever she sees the puppets on the screen, and sometimes when it's not on.

CERI: Wonderful! Thank you for this very interesting interview. I'm sure we'll have you back for more in a future issue.

Q&A Questions & Answers:

(continued from previous page)

the complete address of the addressee. In other words, wrap the cash with your order-letter and seal it into a standard #10 business envelope. Address that envelope and then seal it into a Tyvek® envelope (a fiber-reinforced, "un-tearable" brand of envelope). Address that envelope and put it into a cardboard UPS or FedEx envelope. With this procedure, accidental shredding of the outer envelope by processing machines (it does happen!) will not spew your cash on the floor. **SWF**

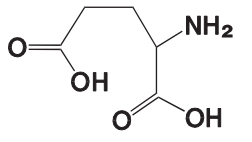
"Can users of deprenyl `crash and burn' if they stop suddenly?"

Question: *Yesterday I signed up for a one-year subscription to your newsletter. I have read both smart-drug books, but have yet to receive my first newsletter.*

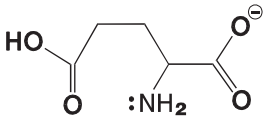
I have been using deprenyl since November 1993. I found this substance to be the ***most*** *beneficial and positive supplement I have ever used. I have been using vitamins, amino acids, Hydergine, piracetam, etc. for 17 years (not all at the same time) in search of cognitive enhancement and health maintenance. Many of these materials have provided profound and satisfying results. But deprenyl* ***hit the spot****.*

Between my own testimony and the facts presented in the deprenyl literature, I have a dozen and growing number of friends who are taking deprenyl with very positive results. The nagging question about deprenyl that haunts us is: what happens when you stop taking deprenyl? Moreover, since deprenyl selectively inhibits MAO-B enzyme activity, is there a rebound effect caused by this inhibition? Does the brain produce more MAO-B to make up for the "inactivated" MAO-B? Is there a feedback loop in operation similar to Inderal and the beta-receptor site overgrowth that happens with high-dose and long-term propranolol use? From what I have seen in the literature, this does not seem to be a problem. Can users of deprenyl "crash and burn" if they stop suddenly? Two of my friends (who were getting major anti-depressant relief from deprenyl) stopped taking it for a week and slowly sank back to where they were in their depression (before deprenyl) and had a subjective feeling that they were even more depressed than before. I'm not sure what to make of this. My first thought is that the relatively sudden contrast between the deprenyl state and the depressed state magnified their sense of "lowness." Or, they really might have been more depressed after deprenyl. I am concerned that MAO-B synthesis is working overtime to keep up with deprenyl-induced MAO-B inactivation. When deprenyl is discontinued, will a person be overwhelmed for a while with excessive MAO-B production, until MAO-B production returns to pre-deprenyl levels? **RRJ**

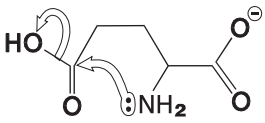
Figure 2:
A Proposed Glutamate Cyclization Mechanism



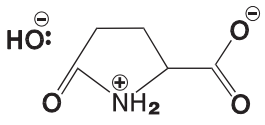
glutamic acid



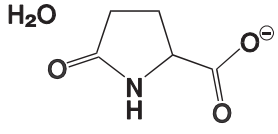
partially ionized glutamate



cyclization



pyroglutamate intermediate



pyroglutamate

Answer: You aptly pointed out the big problem with trying to assess degrees of depression: the subjective nature of the condition. Sudden depression is always more strongly felt, or more strongly noticed. In fact, many people who slowly slide into depression over years do not even notice that they are depressed. Because of this difficulty, your friend's subjective evaluations are not very useful measures of what is or is not happening with enzyme levels and feedback loops.

Based on the numerous anecdotal reports we have received about deprenyl, a rebound effect is possible but not obvious. If it exists at all, it is probably very subtle, showing up only in certain people or after years of use. Such an effect would be diffi- cult to measure, given the normal metabolic changes associated with aging. In other words, how could we determine that the measured before-and-after differences were from the cessation of deprenyl as opposed to the myriad of other influences that occur in free-living humans?

One possible rebound effect that you do not mention is the tyramine re-uptake inhibition property of deprenyl. Deprenyl's inhibition of tyramine re-uptake is responsible for deprenyl's lack of a "cheese reaction" (a hypertensive episode) that is otherwise typical of both MAO-A and MAO-B inhibitors. If the tyramine-reuptake inhibition property of deprenyl wears off faster than the MAO-B inhibition, there could be a "cheese effect window." As far as I know, this has not been scientifically inves- tigated nor clinically observed. We have heard of occasional headaches with deprenyl discontinuation, which might have to do with blood pressure changes, or it might not. We wish we had more information about these possibilities, but these concerns aren't stopping us from taking deprenyl. **WD & SWF**

Question: *Thank you so much for the wonderful interview with Dixie Lawrence. I have several children in my medical practice who were started on the regimen described in Dr. Turkel's book, many years into Down's syndrome, and they have all improved mark-*

Q&A Questions & Answers:

(continued from previous page)

"If you can help me learn more about Dr. Warner's modern, up-to-date nutritional program for Down's syndrome, I and my patients would be very appreciative."

edly in intelligence and personality. I have read your article several times and cannot find any summary of Dr. Warner's program for the Down's child, nor any suggestion of how to contact Dr. Warner. If you can help me learn more about the modern, up-to-date nutri- tional program for Down's syndrome, I and my patients would be very appreciative. **HW**

Answer: Dr. Warner's referral listing appeared in the issue *following* the first article on Down's syndrome. You can write or call him at: The Warner House, 1023 E. Chapman Avenue, Fullerton, CA 92631, 714-441-2600 (Fax: 714-441-2522). He will be happy to send you information on the dietary supplement nutrient formula that he uses. **SWF**

Report: *Hi guys. Thanks for the good information that keeps pouring out from Menlo Park.*

"We are sorry to have to announce that* The Neuroendocrine Theory of Aging *is now out of print."

Last week I was on vacation in California from New York and decided to drive to Tijuana to see if I could get some of the drugs I wanted to try but hadn't yet made the connection through the mail. I parked in a lot on the US side and walked across the border with a day pack on my shoulder. I walked to the right after the border point and found numerous farmacias (as they call their drug stores down there). I was interested in Dilantin and piracetam. Everyone spoke English and were very willing to sell me any amount that I could afford. Prices were almost all the same. I purchased six boxes of piracetam (Nootropil, 30 tablets, 800 mg) and five boxes of Dilantin (Epamin, 50 capsules, 100 mg). I then walked back across the border. I reminded myself that FDA policy permitted the purchase of a 3-month supply, so I felt comfortable in the event that I would be questioned. All packages were scanned as we passed through the border. The American border guards noticed my supplies and asked if I had any prescription drugs. I acknowl- edged that I did and opened up my pack to show them the contents. I was asked if I had a prescription. I said no. I was informed that I really should have one. I them mentioned my understanding of the FDA personal-use drug-importation policy. The guard was familiar with the policy. He looked me in the eye, looking for furtiveness or uncertainty. Finding none, he informed me that the reason for the prescription requirement was that I might sell the drugs in the US at a profit and return the next day for more. I expressed that I didn't think there *was* enough money or demand for the drugs I was carrying. He said that in any case, I should have a prescription because otherwise all they would have to determine my integrity was an honest face. So I said, looking him right in the eye, "How's my face?" He laughed and said, "Get out of here." Their's is not an easy job and I've always found that if I remember that they are human and deserving of respect, I never have a problem. I'm happy to report a successful outcome. I don't know if that's the way it goes for everyone else. For me it was fun, and happily I now have a good supply of smart drugs for the next few months.

Love and kisses, from New York. **Anon**

"The American border guards noticed my supplies and asked if I had any prescription drugs."

Question: *Thanks to Mr. Hardy for the book review and the last copy of* The Neuroendocrine Theory of Aging and Degenerative Disease. *Keep the reviews coming.* **KM**

Answer: You are very welcome. We are sorry to have to announce that *The Neuroendocrine Theory of Aging* is now out of print and unavailable. Dr. Dean informs us that he is hard at work on a revision, but it will probably be more than a year before it is republished. **TMH**

Comment: *Thank you for the interview with Mrs. Dixie Lawrence. It was fascinating reading. It is almost incredible what dedicated people who think for themselves can achieve.* **KM**

Comment: *The comments about long-term* storage of powders, capsules, etc., prompted me to write you about a helpful device I'm using, particularly for hygroscopic substances like DMAE powder. It's called a Pump'N'Seal, from USA Direct (they have an 800 number, but I don't have it). This device is one of those things that you see in late-night infomercials. Strangely, the damn thing works. Using it, I can partially evacuate (with attendant moisture) a container and its contents. I like the jars that have a soft-seal lid, such as those used for cocktail sauce and jellies, but I can even use plastic bags (with a little oil added at the sealing edges). **LEB**

"Do you have any ideas why Durk Pearson said that he woke up from a violent dream swinging his arms and legs while using GHB?"

Question: *I enjoyed John Morgenthaler and Dan Joy's article on GHB. Do you have any ideas why Durk Pearson said that he woke up from a violent dream swinging his arms and legs while using GHB?*

If GABA doesn't cross the blood brain

Q&A Questions & Answers:

(continued from previous page)

"What mail-order houses sell progesterone in the United States?"

progesterone in the US? Where are they getting it, from Europe? **SL**

Answer: The term "micronized" refers to finely ground powders which are better absorbed orally. Progesterone can be micronized to enhance oral absorption (*i.e.*, from capsules), but it can also be effectively administered topically (in skin creams). Absorption through the skin is excellent, and progesterone is absorbed into the subcutaneous fat layer where it is slowly released into the blood stream. And since the blood supply from the skin goes into general circulation before passing through the liver, less progesterone is removed from circulation by the liver than with oral dosing. The blood supply from the stomach and intestines passes through the liver before entering general circulation.

Progesterone creams are available in the US both with and without a prescription. Compounding pharmacies make them, with and without estrogen (estradiol or estriol) and/or small amounts of testosterone. Natural medicine outlets also sell progesterone creams, even though they may be obscurely labeled as containing "yam extracts" for legal reasons having to do with the FDA. I have been getting progesterone cream from the Withers Mill Company in Missouri (1-800-223-0858). Their product was recommended to me by Dr. Lee, author of *Natural Progesterone*. **SWF**

Correspondence

Please send your questions to: CERI Q&A, P. O. Box 4029, Menlo Park, CA 94026-4029. You may also FAX them to CERI Q&A at 415-323-3864, or phone them to us at 415-321-CERI and leave a message.

Note: Initials of the subscriber/author follow each question (OTP refers to an over-the-phone question, and Anon refers to a question asked by a reader requesting anonymity). If you want us to use your full name, or if you want us to omit your initials, please state so in your correspondence. Initials following answers refer to the individual editors listed on the masthead on page 1.

Political Update: Pending Congressional Reform of the FDA

(continued from page 1)

that, it should be specified by law. Bottom line: the FDA should be prohibited from interfering with any legitimate medical treatment being supervised by a licensed physician.

Second, medical devices should *not* include 1) exercise and sports equipment, 2) sound and light machines, 3) classical music tapes/CDs, and 4) other recreational devices that may "alter the structure or function of the human body." The structure-and-function definition of "drug" and "medical device" is absurdly broad and should be scrapped in favor of a new, narrow definition. Bottom line: the FDA should be prohibited from seizing any consumer device which they cannot prove to be hazardous.

Thirdly, the FDA must be forced to detail all charges against any individual or company against whom they take enforcement action. If the FDA cannot explain the law and regulations to affected parties, they have no business enforcing it. Bottom line: the FDA should be prohibited from keeping charges secret after enforcement is initiated.

Lastly, FDA censorship powers need to be abolished. The truthful-and-not-misleading claims provision of last year's Hatch/Richardson bills was blocked by Rep. Waxman and associates. With new Congressional leadership, this provision should now be passed. Bottom line: The FDA should not be permitted to prohibit truthful information of any kind.

Please let your Congressional Representatives and Senators know how you feel about FDA powers and what you think they should do about it. Hopefully, pending momentum for FDA reforms will be channeled into constructive changes which will be more than superficial. **SWF**

New Sources

NutriGuard Research **1-800-433-2404**
P. O. Box 865, Encinitas, CA 92023
NutriGuard carries arginine pyroglutamate, phosphatidyl choline, Staminex, glucosamine, and numerous other multi-nutrient formulas. From outside US and Canada call 619-942-3223.

ASTAK **813-973-7902**
29949 S.R. 54 West, Wesley Chapel, FL 33543
ASTAK distributes the liquid DHEA product developed by Discovery Experimental & Development, Inc.

Day One Segment Scheduled for January

An ABC TV production crew recently visited CERI and filmed Executive Director Steven Wm. Fowkes for a multi-part feature on smart drugs. We hear that one of these parts will focus on the Down's syndrome story that we have been reporting. Look for it when *Day One* returns to the air in January with Diane Sawyer as co-anchorperson with Forest Sawyer.

Fowkes

Editorial:

Dealing with Your Doctor

by Steven Wm. Fowkes

"Medical licenses are attached to extensive state regulations governing the conduct of physicians."

"Although orthodox medical rhetoric states that there is a direct connection between generally accepted medical practices and patient welfare, such an argument does not stand up to scrutiny."

"Such `investigations' are quite common and are often defined by a conspicuous absence of patient complaints and a lack of specific allegations of harm or endangerment."

"Support pending legislation in your state to protect alternative practitioners. With such legislation, doctors may be able to afford to practice their best medicine."

For many of us lucky enough to find an enlightened physician willing to prescribe FDA-approved drugs for unapproved uses, the temptation to ask for prescriptions for unapproved drugs may seem a natural thing to do. Although this may be perfectly legal according to federal regulations, the *practice* of medicine is regulated at the state level. Medical licenses are attached to extensive state regulations governing the conduct of physicians, which includes the prescription of drugs. Unfortunately for consumers, these regulations are modeled after an anti-competitive medieval institution — the guild.

In the Middle Ages, guilds were set up by practitioners to protect the secrets of their trade in exchange for compulsory (*i.e.*, restricted) membership. To become a member of the guild, you had to have connections, and you probably had to endure a long, poverty-level apprenticeship to learn your trade.

In our modern day and age, it may seem anachronistic that medicine would be regulated by this same social institution. Modern doctors must endure a long (and somewhat cruel) apprenticeship (medical school and residency) to learn to be a doctor. Doctors' conduct is regulated by somewhat-vague references to "generally accepted" medical practices, in other words, whatever *other* doctors think should or should not be done. As you might imagine, this system rewards orthodoxy and victimizes innovation.

Although orthodox medical rhetoric states that there is a direct connection between generally accepted medical practices and patient welfare, such an argument does not stand up to scrutiny. Some innovations may put patients at greater risk, but others are more likely to provide added benefits. To determine the relative risks and benefits, one might think that a risk-benefit analysis would be the standard of judgment, but it isn't. A bene- ficial treatment is automatically condemned just because it is not yet recognized by other doctors.

Regulation of doctors by the generally-accepted-practices standard not only ends up denying patients effective treatments, it is often used to persecute unorthodox doctors. Such politically and economically motivated "investigations" are quite common and are often defined by a conspicuous absence of patient complaints and/or a lack of specific allegations of harm or endangerment. Medical regulators would like us to believe that these actions are for the patients' benefit, but they are more often based on anti-competitive motives. In other words, the initial complaint was motivated by the desire to eliminate a popular, more effective, less toxic, and/or less expensive medical alternative to a standard practice. In addition, some doctor's file complaints to stop the flight of their patients from their practices to another doctor who is better able to help their patients. These ego-motivations are not recognized or acknowledged because the complainant's identity is rarely disclosed. The accused never gets to face the accuser. No cross-examination or impeachment is possible.

Other motivations include the defense of ideological positions (expert opinions) taken by authorities. Good examples of this include investigations for 1) the prescription of vitamins instead of drugs, 2) the prescription of drugs for unapproved uses, 3) failing to use an approved therapy (*i.e.*, chemotherapy or vaccinations), and 4) prescription of drugs that the FDA has not yet determined to be safe or effective (even if they are completely safe and effective). This is "political correctness" applied to medicine.

So before you expect your doctor to prescribe piracetam to you, or before you get upset that your doctor won't do it, recognize that they are effectively caught between a rock and a hard place. Consider the wisdom of obtaining the drugs without a prescription and ask your doctor for medical supervision. This minimizes the likelihood that your doctor will get disciplined and/or lose his or her license for providing you with the innovative medical services you want.

In the meanwhile, support pending legislation in your state to protect alternative practitioners from this kind of harassment. With such legislation, doctors may be able to afford to practice their best medicine. ¤

Dixie and Madison

"Scientists from the United States, Canada and France will gather in San Diego, California to attend a three-day symposium"

"At this time, it is estimated that more than 5,000 US patients are on MSBP, with an equal number scattered among some 14 other countries."

"Best results are obtained by modifying the formula to each child's individual metabolic needs as identified through blood and urine analysis."

Trisomy 21 News Update:

Down's Syndrome Symposium

by Dixie Lawrence

Scientists from the United States, Canada and France who are involved in researching Down's syndrome will gather in San Diego, California to attend a three-day symposium November 7-9. This symposium will be attended by researchers and biochemists involved in metabolic studies of Down syndrome, including Marie Peeters of the Institut De Progense — founded by Jerome Lejuene, the scientist who originally discovered that trisomy 21 is caused by the presence of an extra 21st chromosome. Marie Peeters and I will be addressing the conference on Thursday, November 9th, and a panel discussion will follow at 6PM. Panel participants will include Steven Fowkes (CERI), Dr. Paul Spurlock (Tulane University), Dr. Alex Bralley and/or Dr. Richard Lord (MetaMetrix Medical Testing Laboratory), Kent McLeod (NutriChem Laboratory), Dr. Charles Thomas (Pantox Laboratory), and Dr. Marie Peeters.

News Update

National media exposure over the past year has enabled Trisomy 21 Research, Inc. to provide thousands of parents and physicians with information regarding the potential manipulation of gene over-expression as a viable therapeutic approach to managing Down's syndrome. A standard formula is now available (called MSBP) from NutriChem Labs in Ottawa, Ontario, Canada, however, best results are obtained by modifying the formula to each child's individual metabolic needs as identified through blood and urine analysis.

Growing acceptance in the medical community has prompted even persons who were initially skeptical to take a second look at this approach to improving the lives of persons with Down's syndrome. At this time, it is estimated that more than 5,000 US patients are on MSBP, with an equal number scattered among some 14 other countries including Great Britain, Saudi Arabia, Australia, New Zealand and South Africa. Well-designed, double-blind studies are now in progress in several countries including the US and New Zealand.

Trisomy 21 supplies parents with pertinent documentation and abstracts for their physician's information and review. Generally, once a physician has ordered and reviewed metabolic profiling of both blood and urine, they have little difficulty assisting parents with this protocol. Results of tests consistently show dangerous low levels of antioxidants and certain amino acids necessary for neurotransmission, among other metabolic abnormalities.

As of this time, the National Down Syndrome Associations have not addressed the merits of the MSBP program, other than to advise their readers to disregard it. While this is the official line, it is interesting that persons involved with the management of various parent groups have placed their own children on the protocol.

We hope that the upcoming symposium in San Diego will add to the momentum of our efforts and will move us closer to the day when caring for the diverse nutritional needs of patients with Down's syndrome and the use of nootropics to enhance memory and learning will become a standard of care for our children. ¤

New Source

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Coming to a Theater Near You

We will be covering the proceedings of the **Down's syndrome symposium** in the next few issues of Smart Drug News.

We will have a feature article on **intelligence** by David Bezanson, Ph.D.

All the **wild speculation** in the national media about the absence of the Q&A in this issue are merely rumors. ;-) Pay them no heed. It will return.

And, yes, Virginia, we are in the process of reviewing another melatonin book.

Nutrition Arts: The Art of Nutritional Therapeutics

continued from previous page

"The concept of a secondary nutritional deficiency of tryptophan as a public health risk has not been adequately advanced in the medical literature."

cantly enhanced in diseases which involve immunological responses [for an in-depth discussion of these relationships, see *Forefront* 7(2): 1-6, July 1992].

In such cases, diminished serotonin levels and depression could be viewed as a natural consequence of excessive catabolism of the essential nutrient tryptophan. From the standpoint of nutritional biochemistry, the concept of serotoninergic-related depression as a symptom of primary or secondary deficiencies of tryptophan seems hard to assail. It is a general principle of nutritional science that the restoration of a nutrient-dependent function by the administration of a nutrient is *prima facie* evidence of nutritional deficiency.

Restoration of brain serotonin levels can be achieved through drug intervention or by correcting the primary or secondary tryptophan deficiency. A future *SDN* article will describe newer diagnostic approaches to identify causes of secondary tryptophan deficiency.

To our knowledge, the concept of a secondary nutritional deficiency of tryptophan as a public health risk has not been adequately advanced in the medical literature. Perhaps this is related to the medico-pharmaceutical paradigm that would have us rely upon patentable and profitable drug treatments rather than nutritionally oriented self-care. And perhaps we should also acknowledge that the average physician probably doesn't have the time, diagnostic technology and economic incentive to unravel the complex array of lifestyle and metabolic factors which induce secondary deficiencies of tryptophan, low serotonin states and depression. ¤

"Doctors were discussing a theoretical problem with piracetam and possible calcium metabolism problems in the brain. Have you heard anything about this?"

Question: *I was recently privy to a conversation between several doctors who were discussing a theoretical problem with piracetam and possible calcium metabolism problems in the brain. Have you heard anything about this? My 6-year-old daughter has Down's syndrome and has been taking piracetam for two years. She is doing very well on it, but now I'm a little worried about long-term piracetam use.* **OTP**

Answer: See next question and answer.

Question: *Hello Steve! I am the mom of a 26-month-old boy with Down syndrome (DS). He has been taking MSP Plus with piracetam for the past eight months and we are impressed with the results. During an on-line DS chat session, one father announced that he had taken his child off piracetam because a doctor at the National Down Syndrome Congress convention had mentioned that piracetam has been linked to exacerbating calcification of the brain in persons with DS. When I pressed him for the information the doctor used to draw this conclusion, I got no clear response. Obviously, if there is any truth to this statement at all, which at this point I seriously doubt, then it would behoove me to be certain that I am giving my son the proper amount of piracetam. I suspect that his intake of dairy products would be more of a concern (as it relates to calcification of the cells) than his intake of piracetam. I would appreciate your comments greatly. Thanks in advance!* **TR**

Answer: There is no credible evidence that this is a significant concern. The calcium buildup that everybody is talking about results from excitotoxicity, a technical term for the overstimulation of excitatory neurons. The best example of an excitotoxin is *glutamate* (better known as monosodium glutamate, or MSG). Glutamate is also a natural excitatory neurotransmitter. In normal amounts, it is used by neurons to transmit messages from one part of the brain to another. In higher amounts, it causes marked stimulation (an increased flux or flow of calcium into the cells). In even higher amounts, it causes overstimulation (excitotoxicity) which results in too much calcium entering the cells and extreme cellular stress from trying to pump out all the excess calcium. If the cell cannot keep up with the influx of calcium by pumping it out, it can die.

Glutamate (also called glutamic acid) and its related amino acid cousin asparate (aspartic acid) are common components of the protein found in our food. Other dietary substances are also known to stimulate excitatory receptors, but to a lesser degree. These include glutamine, aspartame, pyroglutamate and piracetam. Pyroglutamate is much weaker than aspartame, and glutamine and piracetam are much weaker than pyroglutamate.

Given the prevalence of powerful excitatory substances like glutamate and aspartate in our natural diets and in commercially processed foods (which contain MSG,

Q& Questions & Answers:

(continued from previous page)

"Given the known benefits of piracetam in the treatment of various neurological conditions, it would seem inappropriate to avoid it for that reason."

"Can I get Parkinson's or some other disorder by getting used to deprenyl and then ceasing its use?"

protein hydrolysates and soup broths — all high in free glutamate), and the ready availability of glutamine, aspartame (NutraSweet), and pyroglutamate (one of the primary natural skin humectants [moisturizers] of the human body), it is highly doubtful that piracetam poses a significant excitatory risk to the central nervous system of free-living human beings.

I'd also like to point out the susceptibility to excitotoxicity is increased in infants, children, the elderly, people who've suffered head traumas, and individuals exposed to certain toxins (through food poisoning and bacterial/fungal infections). In the large number of clinical studies of piracetam in the elderly, excitotoxicity and calcium-channel side effects have not been reported. When I last reviewed the literature, there were no reports of piracetam antagonizing the activity of calcium-channel blocking drugs, which are now popularly prescribed for elderly individuals. And piracetam seems to provide substantial clinical benefit in the post-trauma recovery phase following head injuries.

Although the above discussion does present a theoretical basis for activation of calcium channels by piracetam, the evidence for would seem to indicate that it is not clinically significant. Given the known benefits of piracetam in the treatment of various neurological conditions, it would seen inappropriate to avoid it for that reason.

I wouldn't worry about dietary calcium from food (*i.e.*, dairy products) as a risk factor either. It is excessive neurologic activity or hormone imbalances, not excessive calcium, which is the primary cause of calcium overload in neurons. Unless there is a magnesium deficiency (which is needed to balance calcium), dietary calcium is not likely to pose special risks for DS children.

I think that DS kids have a harder time with dairy products than kids without DS due to excessivbe mucous formation that provides a growth media for respiratory and inner-ear infections. But if the reports I've received are any indication, MSB+ [a nutritional formula developed specifically for DS children] treatment seems to normalize immune function and resolve the chronic infections which plague untreated DS children. In that case, the risks from consumption of dairy products should be similar to kids without DS. **SWF**

Question: *I have tried a few small doses (1/8 to 1/4 of a 5 mg tablet once a week) of deprenyl and have noticed useful effects similar to those described in your book* Smart Drugs II. *However, I am concerned about possible detrimental long-term effects. For example, since deprenyl inhibits the degradation of neurotransmitters and boosts the release of dopamine, I am curious if any studies have been done to determine if the brain can acquire a dependence on the deprenyl for generating dopamine or for other aspects of neurotransmitter activity. More bluntly, can I get Parkinson's or some other disorder by getting used to deprenyl and then ceasing its use? If so, what is the minimum period of time necessary to establish a dependence?*

Have there been other kinds of studies on the long-term effects of deprenyl use? If so, what were the results? If such studies were carried out on an elderly population or on groups with Parkinson's, what inferences can reasonably be made regarding possible effects on healthy persons from such studies?

I would like to continue to use deprenyl now that I have settled on a comfortable dosage (1 mg every 5 days with about 150 mg dl-phenylalanine). However, I am considering delaying further use until I can get reliable data on long-term effects. I would greatly appreciate any relevant information which may help me make this decision. **HAP**

Answer: We *all* suffer from slight degradation of the substantia nigra of the brain as we get older (severe degradation results in Parkinson's disease). One prominent neuroscientist told me that "if we lived long enough, we'd *all* suffer from Parkinson's disease." No long-term studies that I know of have been conducted using *normal* human subjects — as with most potential life-extending agents — nor are any studies likely to be performed. If we wait for long-term human studies to be conducted before we attempt anti-aging intervention, the information gained will be of no use to those of us now living. The best we can do is to

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Smart Drugs & Down's Syndrome: Part 2

Antioxidant Intervention in Down's Syndrome

by Steven Wm. Fowkes

Two years ago, we published our first article about smart drugs and Down's syndrome which focused primarily on clinical approaches. This article will begin an extensive discussion of metabolic and biochemical mechanisms underlying Down's syndrome — and proposed nutritional interventions which may mitigate these metabolic disturbances.

Genetic Over-Expression

Unlike most other genetic conditions which are characterized by a deficiency (deletion) or change (mutation) of the genetic material, Down's syndrome is characterized by a *duplication* of all or part of the 21st chromosome. Normally, each cell in the body is supposed to have *two* 21st chromosomes (one derived from the mother's egg and the other from the father's sperm). Every time a cell divides, each of the 46 chromosomes must be duplicated and separated, one copy of each chromosome ending up in each daughter cell. Sometimes the process of pulling apart the duplicated chromosomes malfunctions, and both copies of one of the 21st chromosomes end up in the same daughter cell. In other words, one cell has *only one* 21st chromosome (which fails to replicate) and the other has *three* 21st chromosomes. This is why Down's syndrome is referred to as trisomy 21 (tri means *three*, somy refers to chromo*some*).

This extra genetic material causes overexpression of the duplicated genes. In other words, genes make both enzymes and proteins, and too many genes lead to

continued on next page

Melatonin Update:

Is Melatonin a Sex-Enhancing Hormone?

by Steven Wm. Fowkes

Since the recent publication of *The Melatonin Miracle: Nature's Age-Reversing, Disease-Fighting, Sex-Enhancing Hormone*, written by Drs. Walter Pierpaoli and William Regelson, interest in melatonin's sex-enhancing properties has become a media issue. In their chapter on "Melatonin and Sex," Pierpaoli and Regelson argue that the age-associated decline in sex drive may be ameliorated by melatonin supplementation. In mice experiments, they observed that melatonin "had a profoundly rejuvenating effect" on aged mice. "Their coats grew thick and lustrous, their eyes remained clear and cataract-free, their digestion improved, and their strength and muscle tone was enhanced." Regarding sex, they state, "Both males and females displayed [...] the sexual fortitude of much younger mice, and they appeared to preserve interest in sex throughout their entire extended lifetimes."

Although the mechanism of this pro-sexual effect in mice is not clear, Pierpaoli and Regelson suggest that this may be partly due to the ability of melatonin to preserve ovaries and testes against age-associated shrinkage. They state, "We believe that there is a direct connection between the youthful state of the sex organs and the level of sexual activity." They suggest that this may be extrapolatable to humans, and that melatonin supplementation may enhance fertility, delay menopause, enhance erotic dreams and sexual pleasure, boost libido and encourage intimacy.

The appeal of such claims is obvious. But are these effects real in humans?

At the Fourth Annual Antiaging and

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Smart Drugs & Down's Syndrome: Antioxidant Intervention in Down's Syndrome

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too many enzymes and proteins. This, in turn, distorts normal metabolism and development.

Nutritional Intervention

The key concept underlying nutritional intervention in Down's syndrome is *metabolic correction of genetic overexpression*. Although the extent of the metabolic disturbances in trisomy 21 is not fully known, several of the more significant disturbances are now becoming well characterized. Effective metabolic management of these disturbances offers the hope of ameliorating the disability typically associated with untreated Down's syndrome. The degree of amelioration must depend on 1) the metabolic effectiveness of the intervention, and 2) the age at which it was begun. Early clinical reports by physicians and anecdotal reports by parents utilizing some of the approaches that will be discussed in this article suggest that *functional normalization of growth rate and cognitive development* is likely if intervention is begun early in life. This possibility is at complete odds with the orthodox view that Down's syndrome infants are born retarded and that treatment is fundamentally futile.

Several of the major metabolic pathways known to be disturbed in trisomy 21 are directly attributable to genetic overexpression. Perhaps the most important example of this is *destabilization of the antioxidant defense system* by overexpression of the enzyme *superoxide dismutase* (SOD), which is located on the 21st chromosome. Overexpression of the enzyme *cystathionine* β*-synthase* seems to be significantly responsible for the metabolic disruption of "active" methylation pathways (the SAM cycle). And connective tissue problems appear to be directly attributable to overexpression of collagen genes on the 21st chromosome.

Other metabolic disturbances have not

Figure 1:
H_2O_2 Flow Diagram

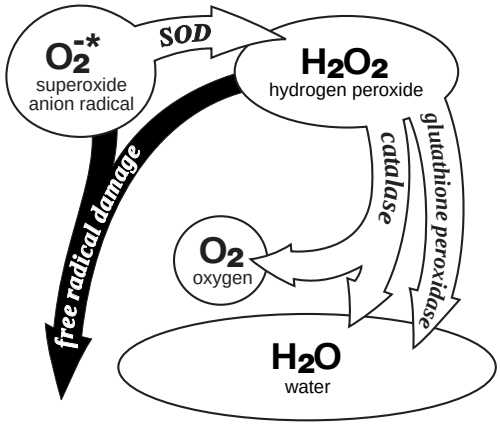
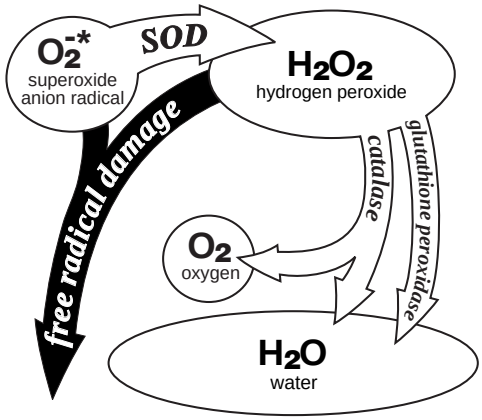


Figure 2:
H_2O_2 Flow in Down's Syndrome



What are Free Radicals?

Molecules are composed of atoms bonded together. This bonding process is accomplished by the sharing of electrons. When two atoms come together and their electrons pair up, a bond is created.

It is a general principle of quantum chemistry that only two electrons can exist in one bond. Specifically, each electron must have opposite "spin" from the other. Like male and female animals, "up" electrons pair up with "down" electrons, and bonds are created. Paired electrons are quite stable; almost 100% of all electrons in the human body exist in a paired state.

When a bond is broken (by radiation, for example), the electrons can stay together (*i.e.*, both go to one of the atoms and the other atom gets none) or they can split up (one electron goes to each atom). If they stay together, the molecular fragments are called *ions*, and they are electrically charged (the atom with the electrons is negatively charged and the one without the electrons is positively charged). A good example of this is sodium chloride (salt) which splits up into a chloride anion (Cl^-) and a sodium cation (Na^+).

If the electrons split up, the atoms are *free radicals* (molecules with an unpaired electron). The unpaired electrons are *highly energetic* and seek out other electrons with which to pair—and stealing them in the process. This electron "rip off" is what makes free radicals both useful and dangerous.

Since most electrons exist in a paired state, free radicals often end up reacting with paired electrons. When they do so, one of the electrons pairs with the (former) free radical and the "odd electron out" becomes another free radical (odd plus even equals odd). Only when a free radical pairs up with another free radical is the free radical terminated (odd plus odd equals even).

Antioxidants (also known as free radical scavengers) function by offering easy electron targets for free radicals. In absorbing a free radical, antioxidants "trap" (de-energize or stabilize) the lone free-radical electron and make it stable enough to be transported to an enzyme which combines two stabilized free radicals together to neutralize both. **SWF**

Smart Drugs & Down's Syndrome: Antioxidant Intervention in Down's Syndrome

(continued from previous page)

been tied to specific genes. As examples, tryptophan deficiency and ammonia accumulation are common features of Down's syndrome. Fortunately, these metabolic disturbances are just as amenable to nutritional intervention as those tied to genes. The remainder of this article will be devoted to discussing the antioxidant disturbances associated with overexpression of SOD. The rest of the examples will be discussed in the following article.

Superoxide Dismutase

Superoxide dismutase (SOD) is a vital free-radical scavenger. Its job is to "mop up" stray superoxide ion radicals (O_2^-) and convert them to hydrogen peroxide (see Figure 1). Hydrogen peroxide is then detoxified by other enzymes (catalase and glutathione peroxidase). Normally, SOD is in balance with catalase and glutathione peroxidase. But in Down's syndrome, there are *three* copies of the SOD gene instead of the normal two. With overproduction of SOD, catalase and glutathione peroxidase are challenged to keep up with the accelerated production of hydrogen peroxide. When they don't, excess hydrogen peroxide accumulates in the cells and tissues (see Figure 2) causing increased oxidative stress, free-radical proliferation and accelerated aging.

When endogenous (internally manufactured) antioxidant enzymes (catalase and glutathione peroxidase) are overwhelmed with hydrogen peroxide, exogenous (dietary) antioxidants are forced to take up the slack. This greater-than-normal burden on exogenous antioxidants is evidenced by depleted levels of vitamins A, E and/or C, zinc, selenium, and/or glutathione in untreated Down's syndrome individuals.

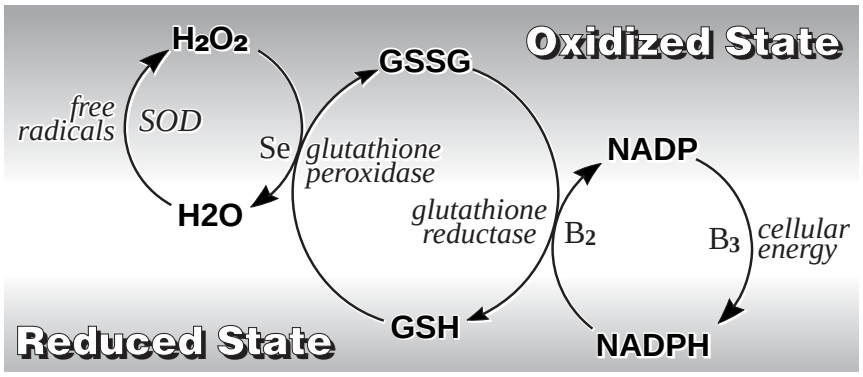
Glutathione

Glutathione (GSH) is a central player in the antioxidant defense system (see Figure 3). It is a tripeptide (3-amino-acid protein) made from glutamate, cysteine and glycine. The active site on the glutathione molecule is the sulfhydryl (SH) group on the cysteine part of the glutathione (which is where the "SH" comes from in the "GSH" abbreviation for glutathione). The sulfhydryl group (sometimes called a *thiol* group) interacts with a free radical to form a glut*athi*one radical, which dimerizes (pairs up with another glutathione radical) to form oxidized glutathione (GSSG) (see Figure 3). Oxidized glutathione is then recycled (reduced) back to glutathione for reuse.

The maintenance of reduced glutathione appears to be especially critical for overall health maintenance; Down's syndrome children appear to be more susceptible to infection when glutathione levels are low, even when other deficiencies are milder than expected [MacLeod, 1996]. Down's syndrome children with high glutathione levels appear to be more healthy, even if they are suffering from additional deficiencies that are quantitatively more severe than usual.

Although glutathione levels do tend to increase when other antioxidant deficiencies are corrected, they generally do not fully normalize. We do not know why. Given that cysteine is a component of glutathione, it is somewhat paradoxical that Down's syndrome is characterized by

Figure 3: The Recycling of Glutathione



Reduced (anti-oxidized) glutathione (GSH) is used by glutathione peroxidase (a selenium-dependent enzyme) to detoxify hydrogen peroxide (H_2O_2). In this process, the oxidation power of hydrogen peroxide is transferred to oxidized glutathione (GSSG). In other words, H_2O_2 moves down while GSH moves up. While GSSG still has oxidizing power, it is significantly less than that of H_2O_2. GSSG is recycled by glutathione reductase using NADPH. In the process, NADPH is converted into $NADP^+$ (the oxidized form of NADPH). The regenerated GSH is then ready to detoxify more hydrogen peroxide.

When the antioxidant defense system is functioning properly, most of it's components are present in their reduced form (H_2O, GSH, and NAHPH). If there is a malfunction, then the oxidized components (H_2O_2, GSSG and/or NADP) tend to accumulate — with adverse effects. The entire process is driven by energy production at the cellular level, which involves proper thyroid hormone levels, healthy mitochondrial function, and an active pentose-phosphate metabolic pathway. The pentose-phosphate pathway is especially important for providing NADPH for red blood cells and hepatocytes (liver cells). In some populations, one of the key enzymes in the pentose-phosphate pathway (glucose-6-phosphate dehydrogenase, or G6PD) is frequently deficient due to mutations. Over 300 variants of G6PD have been identified! With diminished G6PD activity, the supply of NADPH is impaired, GSSG levels tend to accumulate, and control of hydrogen peroxide (and superoxide) is impaired. This results in formation of methemoglobin (an oxidized and inactive form of hemoglobin), and if severe enough, hemolytic anemia (wholesale destruction of red blood cells). **SWF**

(continued from previous page)

"Functional normalization of growth rate and cognitive development is a reasonable expectation if intervention is begun early in life."

abun- dant cysteine *and* deficient glutathione. The dynamics of this relationship are not yet fully understood, but it may be wholly or partly the direct result of oxidative stress.

Glutathione Peroxidase

Glutathione peroxidase (GSHpx) is a endogenous antioxidant enzyme that detoxifies hydrogen peroxide (H_2O_2, or HOOH) and fatty acid hydroperoxides (fatty-OOH). It is constructed from four identical subunits, each of which contains one atom of *selenium* (Se), a fairly rare element in the oxygen and sulfur family. Glutathione peroxidase uses reduced glutathione to detoxify peroxides, releasing oxidized glutathione in the process. Oxidized glutathione is recycled by *glutathione reductase* back to reduced glutathione (see Figure 3) using riboflavin (vitamin B_2) as a cofactor and NADPH as a reducing agent (an anti-oxidizing substance, like vitamin C).

The central role of selenium in glutathione peroxidase activity provides a focus for intervention. Selenium supplementation may be able to up-regulate glutathione peroxidase activity to restore some degree of balance with the over-expressed SOD. In areas of the world where selenium deficiency is severe (*i.e.*, New Zealand and China), selenium supplementation has been found to readily reverse selenium-deficiency diseases in animals (*e.g.*, white-muscle disease in sheep) and man (Keshan's disease).

Food sources of selenium can be problematic. Selenium is not an essential nutrient in plants as it is in animals. Wheat grown in selenium-rich soil (*i.e.*, South Dakota) contains respectable levels of selenium, but wheat grown in selenium-poor soil (*i.e.*, Oregon) does not. Does anybody really know where their wheat was grown?

In one trial of Down's syndrome individuals, selenium supplementation was found to increase the levels of glutathione peroxidase. Thus, selenium supplementation appears to be a viable strategy for compensating for SOD overexpression.

The Antioxidant Defense System

The control of free radicals and oxidizing agents is central to the life process. While the atmosphere is dominated by oxygen (20%) and free radicals (billions per cubic foot), the chemical environment within our cells is reduced (the opposite of oxidized). A good way to think of oxidation and reduction (redox for short) is in terms of electrons. The atmosphere and oxidizing agents (like bleach) are poor in electrons, and the reduced chemicals of cellular metabolism (fatty acids, carbohydrates and amino acids) are rich in electrons. We tap into the electron tug-of-war between oxidants and reductants to drive our biochemical machinery, much like how a battery drives an electric motor. By carefully transporting oxygen (safely bound to hemoglobin) to the cells where it can be combined with carbohydrate (acetate) under enzymatically controlled conditions, a host of electron-rich chemicals essential to life can be generated (NADH, NADPH, $FADH_2$, and ATP).

The fundamental antagonism between the oxidized atmosphere and reduced living systems makes control of oxidation (and oxidizing free radicals) essential. The gasoline-air explosion in a car engine or a raging forest fire are graphic examples of the power of oxidation in action. By comparison, the bio-oxidation of fats and

FDA Retaliation Getting Noticed

We've been suggesting that the FDA is a vindictive agency for years, but now Congress and the media are beginning to ask questions. With the Republican takeover of key Congressional committees last year, some corrageous industry insiders have testified that fear of FDA retaliation keeps industry personnel from making honest criticisms of the agency. Although FDA spokespersons have denied that retaliation exists, several egregious examples have prompted several key committee members to notify FDA Commissioner David kessler in writing that any intimidation of committee witnesses would not be tolerated. Although the issue has not received much media attention, a November 1995 survey of health care business executives conducted by Citizens for a Sound Economy (CSE) found that 46% of the 500 executives surveyed believe that the FDA has retaliated against companies that have criticised the FDA by "slowing down the approval process or more closely scrutinizing the companies' records and factories." Almost two-thirds of the executives thought "the FDA has become more concerned with expanding its jurisdiction and power than with facilitating approval of new drugs and medical products."

The extent of FDA retaliation may never be fully appreciated due to the fundamentally subjective nature of the drug-approval process [see "The Efficacy Standard Reconsidered" in *SDN* v4n8p1]. However, the CSE survey did report that 4 of 10 companies stated that "they did not pursue new product development because of FDA regulations and the approval process."

Citizens for a Sound Economy Foundation, Washington, DC, 202-783-3870.
Special thanks to John Hammell, Political Coordinator for the Life Extension Foundation, for bringing this survey to our attention.

Smart Drugs & Down's Syndrome: Antioxidant Intervention in Down's Syndrome

(continued from previous page)

carbohydrates is a severely constrained process. Even so, significant quantities of oxidizing free radicals (several percent of the total energy flux) escape from biological control. The antioxidant defense system is necessary to "mop up" these stray free radicals to maintain the reduced conditions necessary for life.

Loss of control of oxidation and free radicals has been implicated in such diverse conditions as bruising, cataracts, sunburn, radiation poisoning, cancer, heart disease, and sudden infant death syndrome.

Antioxidant Assessment

In the last decade, several new testing technologies have been developed for assessing antioxidant requirements. The use of these testing systems offers the potential of identifying both oxidative stresses and antioxidant deficiencies. The most well established approach is direct quantitative measurement of antioxidants in blood. These might include vitamin C, vitamin A, vitamin E (varied tocopherols), coenzyme Q10, b-carotene (and other carotenoids), glutathione, uric acid and bilirubin, Quantitative measurement of blood is currently expanding to include measurements of oxidants and oxidation by-products, like iron, lipoprotein cholesterol, triglycerides, and lipid peroxides. One company is even measuring oxidative damage to DNA. These assessments will undoubtedly get much more sophisticated in the near future.

"Loss of control of oxidation and free radicals has been implicated in such diverse conditions as bruising, cataracts, sunburn, radiation poisoning, cancer, heart disease, and sudden infant death syndrome."

While quantitative assessment of antioxidants measures the pieces and parts of the antioxidant defense system, there is an oxidative stress test which measures the ability of living blood cells to resist an oxidative challenge. Although this approach is relatively new, it promises to provide information about how well the parts of the antioxidant defense system operate in concert.

Although vitamin and trace-mineral assessments will be discussed in more detail in the next article, it is important to mention that vitamins B2, B3, B6, B12 and folic acid, and the minerals copper, zinc, manganese, iron and selenium, play a vital role in the antioxidant defense system. Furthermore, heavy metals have a deleterious effect on antioxidant defenses which must be taken into account. All of this will be discussed in the next issue.

Although these tests require considerable sophistication for interpretation, they are powerful tools for identifying nutritional status and guiding antioxidant intervention.

GATT (and the World Trade Organization) vs Vitamin Supplements

Although GATT and NAFTA were promoted as free-trade agreements, they do *far more* than attempt to lower trade barriers. In order to determine which laws are fair and which are anti-competitive trade barriers, there must be a "standard" with which to make a comparison. Many standards are currently being established by international committees set uyp by these agreements, and all countries are bound to conform — or else. Through the Wold Trade Organization (WTO), the "or else" can include sanctions and heavy fines, which continue until the "problems" (local laws) are corrected (repealed).

Under the GATT/WTO agreement, the status of dietary supplements is under review by the *Codex Alimentarious Commission*. In response to a proposal from the German delegation, the commission is now considering international GATT/WTO standards that would: 1) prevent any supplements from being sold for preventive or therapeutic use, 2) prevent supplements from having potencies higher than amounts set by Codex, 3) prevent any country from developing alternative standards regarding supplements, and 4) require all new dietary supplements to obtain some kind of Codex approval before they could be marketed. In other words, the Codex proposals will force the US to accept regulations fundamentally identical to those proposed by the FDA and repeatedly rejected by Congress.

Congressional acceptance of the GATT agreement has made CODEX regulations binding on the US economy. In other words, Congress has *already surrendered US sovereignty on this issue* to the CODEX Commission. If the German CODEX proposal is approved as it stands, US voters will have three tough options to consider: 1) vote every Senator and Representative out of office that voted for GATT (and see that their replacements repeal it), 2) accept international criticism and financial penalties, or 3) accept decimation of the nutritional industry in accordance with the wishes of some international special interests.

Although free trade is the Washington buzz word about GATT, it appears that no country will be allowed to have freer trade than that sanctioned by GATT/WTO. Since the US has the freest supplement industry in the world, it appears that our freedom is to be sacrificed in the interests of "international harmony" and a "kinder, gentler" new world order. ¤

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Additional Metabolic Issues

Part 3 of this series will continue in the next issue with discussion of metabolic disturbances relating to methylation metabolism, collagen synthesis, tryptophan metabolism and ammonia detoxification.

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"Too many of the questions require a doctorate in chemistry in order to understand what they are about."

"Would you please give me the conversion factor to go from your chart to theirs so that I may compare the DHEA charts."

Question: *I am renewing my subscription one more time. I am very frustrated when I read your answers. To many of the questions require a doctorate in chemistry in order to understand what it is all about. Is it possible to simplify the answers so it is clear to us non-PhDs?* **EF**

Answer: Thanks for renewing. I am sorry that answers are too technical or obscure. I, for one, would be happy to work harder to make them easier to understand. I enjoy getting simple, basic questions for the Q&A column. We get so few, I give them a high priority.

Can I suggest that when you are reading the next issue of *Smart Drug News* that you keep a pen and piece of paper handy to write down questions as you are reading? I'd appreciate the help, and a lot of other subscribers would probably thank you as well. **SWF**

Question: *I contacted two of the non-US suppliers on your list for GHB. They both had "sodium 4-HB" which, from the suggested doses, is much weaker than the GHB I read about in* Better Sex Through Chemistry. *This makes their prices seem rather expensive. What different kinds/strengths of GHB are there, and do you know who supplies "pure" GHB?* **(net)**

Answer: Almost all the available GHB is sodium GHB (NaGHB). The free acid is liquid, quite acidic, and somewhat unstable; I don't know anybody who sells it. It's difficult to ship and would be *much* more likely to be discovered by Customs when imported.

NaGHB and GHB are used interchangeably. NaGHB is about 18% sodium and 82% hydroxybutyrate. NaGHB typically varies from 99% to 99.9% purity. Get only the 99.9% purity.

Some companies produce a GHB version of cough syrup by dissolving NaGHB in sugar water. Although this is frequently referred to as liquid GHB, it is not the same thing as free-acid GHB.

GHB can be called γ-hydroxybutyrate, γ-hydroxybutyric acid, sodium γ-hydroxybutyrate, 4-hydroxybutyric acid, 4-hydroxybutyrate, and sodium 4-hydroxybutyrate. Hopefully, somebody will eventually figure out that it is a bright idea to make potassium GHB (KGHB), or other mineral salts of GHB (MgGHB or CaGHB). **SWF**

Question: *On page 96 of* Smart Drugs & Nutrients*, there is a chart showing typical DHEA levels for men of various ages. The chart is presented in ng/ml units. I have recently received a lab report that stated my level as 700 ug/dl (I am a 72-year-old male). Could you please convert this to the units used in your chart.*

As page 2 of this fax, I am sending a chart of the same type which was sent to me by the Life Extension Foundation. The units are mcg/dl. Would you please give me the conversion factor to go from your chart to theirs so that I may compare the two charts. **RHG**

Answer: The "ug" units are probably micrograms (which should be abbreviated as µg or mcg by convention). But I guess ug looks enough like µg....

There are 1000 ug in 1 mg, and 1000 mg in 1 g. The "ng" units are nanograms. There are 1000 ng in 1 ug (mcg). So to convert nanograms (ng) to micrograms (ug), divide by 1000. To convert micrograms to nanograms, multiply by 1000.

The "dl" units are deciliters (one tenth

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Smart Drugs & Down's Syndrome: Part 3

Nutritional Intervention in Down's Syndrome

by Steven Wm. Fowkes

The previous article of this series (Part 2) discussed genetic overexpression and the antioxidant disturbances associated with the superoxide dismutase (SOD) gene. This article will cover additional metabolic disturbances, and nutritional interventions targeted to ameliorate those disturbances.

Methylation Pathways

Down's syndrome individuals exhibit significant disturbances in methylation pathways (see Figure 1, page 2). The overexpression of cystathionine β-synthase (located on the 21st chromosome) causes homocysteine to be converted into cysteine (reaction 2) at an accelerated rate [Chadefaux, 1985]. This conversion requires serine. One of the signs of increased cystathionine β-synthase enzyme activity is a systemic depletion of serine reserves. Indeed, the vast majority of untreated Down's individuals show serum serine levels at the low end or below the low end of the normal range.

Serine is also used to fuel the folic acid cycle (Figure 1, cycle B). The shortage of serine impairs the production of methyl tetrahydrofolate (Me-THF), which is required to recycle homocysteine to methionine (reaction 1). With an insufficiency of Me-THF, more homocysteine goes down the cystathionine pathway to be converted into cysteine instead of being recycled into methionine. This undercuts methylation metabolism.

Methionine is required for the production of S-adenosylmethionine (SAM), the "active methyl donor" that is a vital part of countless metabolic reactions throughout

continued on next page

Smart Drug Update:

Recent Developments with Deprenyl

by Ward Dean, M.D., and Steven Wm. Fowkes

Over the last year, we have been investigating several controversial matters concerning L-deprenyl (selegiline), one of which is creating a mini-controversy on the Internet. The question being discussed on the Internet arose from last year's publication of a long-term study of Parkinson's disease which evaluated three therapeutic regimens: 1) L-dopa; 2) L-dopa plus deprenyl; and 3) Parlodel (bromocriptine). The results of the study raised some serious concerns about the use of deprenyl/dopa combination therapy for Parkinson's disease, and some have questioned the value of deprenyl alone for Parkinson's disease and, of broader concern to many readers of *Smart Drug News*, it's use as a potential life-extending, anti-aging and cognition-enhancing substance in normal, healthy people.

This article should be considered an interim report, pending a more comprehensive evaluation that is being prepared. We had intended to incorporate personal communications from the authors of the study in question, as well as from other prominent Parkinson/deprenyl researchers and clinicians. However, because of the furor being generated on the Internet, we believed that this preliminary (and necessarily incomplete) report should be made at this time.

Dopa/Deprenyl Combination Therapy

The focus of the controversy regards the long-term findings of the Parkinson's Disease Research Group (PDRG) of the United Kingdom [Lees *et al.*, 1995]. The results of this study indicated that the combination of deprenyl plus L-dopa (also known as levodopa, or just dopa for short) resulted in a increased incidence of mortality

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"This experience should encourage moderation when supplementing methyl donors and methylation co-factors."

the body. The under-activity of the folate cycle coupled with overactivity of the cystathionine pathway diverts the homocysteine from the SAM cycle (see Figure 2, page 3). In other words, the almost-closed cycle is opened and homocysteine drains into the cysteine pool.

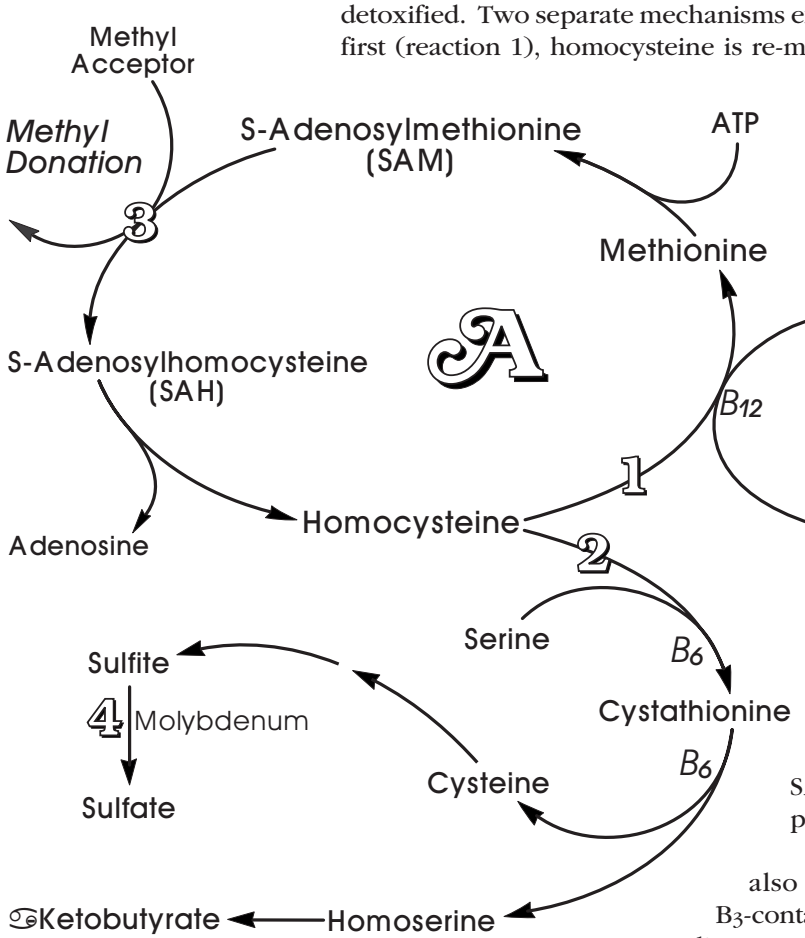
Many parents have reported cognitive and behavioral improvements after supplementation with methyl donors (DMAE, choline, DMG and betaine) and methylation catalysts (folic acid and vitamins B_6 and B_{12}). SAM itself has also been used to treat children with attention-deficit disorder.

Although methylation pathways are usually deficient in Down's syndrome, some degree of moderation is required not to overdrive the folic acid cycle (Figure 1, Cycle B). In Dr. Peters study of folic acid in Down's syndrome, approximately ten percent of the children exhibited excessive hyperactivity and/or irritability when given 20 mg folic acid (50 times the adult RDA). In a recent version of MSB Plus compounded by Nutrichem Pharmacy (which normally includes 45 mg vitamin B_6, 45 mcg B_{12}, 1 mg folic acid, 200 mg serine, 75 mg methionine and 75 mg cysteine), an increase of folate to 3 mg (7.5 times RDA) and methionine to 275 mg (approximately the RDA) resulted in a substantial number of children exhibiting extreme irritability and hyperactivity behaviors. The symptoms reversed in days with discontinuation of the additional folate and methionine, but this experience should encourage moderation when supplementing methyl donors and methylation co-factors.

It is not known whether the disturbances in serine, folate and methylation metabolism are fundamentally due to cystathionine β-synthase overactivity or whether they may also be due to impaired digestion and mal-

Figure 1: The SAM Cycle

One of the essential metabolic functions of the body is *active* methyl donation (cycle A). The active methylation donor is S-adenosylmethionine (SAM), which is produced from methionine by the addition of ATP (adenosine triphosphate). After the methyl group has been donated (reaction 3), homocysteine remains. Because homocysteine has pro-oxidant properties (elevated levels are associated with cardiovascular disease), it must be detoxified. Two separate mechanisms exist — both of which are serine dependent. In the first (reaction 1), homocysteine is re-methylated by methyltetrahydrofolate (Me-THF, or "activated" folic acid) back to methionine, and the SAM cycle is closed. Under most circumstances, this should be the dominant pathway. In the second mechanism (reaction 2), homocysteine is combined with serine to form cystathionine which is split back apart (slightly differently) to yield cysteine and homoserine. This reaction depends on the enzyme cystathionine β-synthase which opens up the SAM cycle and results in loss of methionine (and accumulation of cysteine).



The restoration of the SAM cycle is not solely dependent on increasing serine levels. The folate cycle (cycle B) is essential to close the SAM cycle and keep methionine available for producing SAM.

The folate cycle not only requires folic acid, but also vitamins B_6 and B_{12}, and NADH (a vitamin B_3-containing reducing agent). NADH is now available as a dietary supplement in the US.

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absorption of associated vitamins, minerals and amino acids. An experiment is being designed using trisomy-16 mice to investigate the influence of digestive stimulation on metabolic imbalances that might give us some clues.

Collagen Expression

Collagen is a major constituent of connective tissue, skin, cartilage, tendon and bone. It comprises approximately 30% of all the protein in the human body. Collagen proteins are fibrous (linear, or branched) and they are responsible for the "toughness" of tissues. Without collagen, tissue would have the consistency of Jell-O.

Collagen proteins have an unusual amino acid profile. They are 1) devoid of tryptophan and cysteine, and 2) rich in glycine, lysine, proline, hydroxyproline and hydroxylysine. The latter two are rare amino acids.

"The collagen connection to Down's syndrome is fairly obvious. Newborn infants and children exhibit extreme joint laxity. In addition, structural defects in the formation of the heart affect roughly half of all Down's syndrome individuals."

The collagen connection to Down's syndrome is fairly obvious. Newborn infants and children exhibit extreme joint laxity. In addition, structural defects in the formation of the heart affect roughly half of all Down's syndrome individuals. Of the dozen-plus collagen genes that have been discovered, two of them reside near the tip of the 21st chromosome.

Collagen synthesis is extremely complicated. Collagen is initially made as a *pre*procollagen, which is transported and converted to *pro*collagen, which is then hydroxylated, glycosylated, wound into a helix and transported again, after which it is clipped into collagen molecules, assembled into collagen fibers, and cross-linked into final form. Each of these steps could be impaired by a host of conditions. For example, the hydroxylation of collagen is dependent on vitamin C, which also serves as an antioxidant. Also, the final cross-linking of collagen depends on the enzyme *lysyl oxidase*, which uses copper as a co-factor. Copper is also a component of the over-expressed superoxide dismutase. It is not known to what degree collagen mis-metabolism may be due to induced deficiencies (*e.g.*, vitamin C), or the direct over-expression of the two collagen genes on the 21st chromosome.

These two mechanisms may not be easily separable. The competitive effects between overactive and underactive collagen pathways may induce secondary proline or vitamin C deficiencies. In other words, the overactive collagen pathways may squander scarce resources leaving the underactive pathways starved for raw materials.

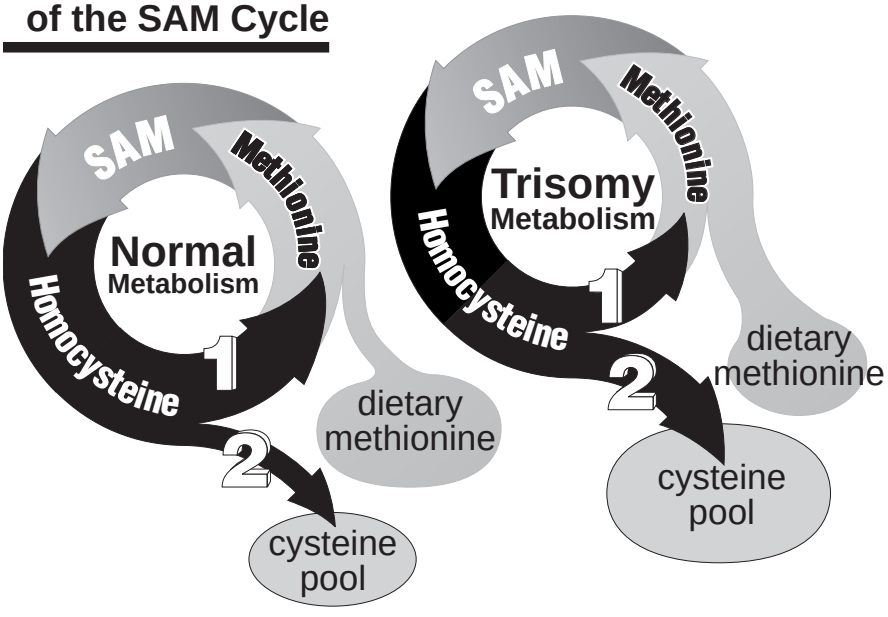
It is this latter observation that led Dixie Tafoya to try feeding the collagen pathways as a nutritional intervention strategy for her daughter. When she added vitamin C, bioflavonoids, α-ketoglutarate and proline, her daughter's connective tissue and ligaments improved markedly. This strategy appears to be universally successful.

Tryptophan, Serotonin, Melatonin

Down's syndrome individuals frequently show low serum tryptophan levels. Whether this deficiency is primary (poor tryptophan absorption) or secondary (increased tryptophan catabolism) is not known. Regardless of the cause, low tryptophan levels impair protein synthesis (tryptophan is usually a rate-limiting amino acid) and decrease serotonin levels (tryptophan is the precursor to serotonin). Serotonin is the brain neurotransmitter that not only regulates emotional control and sleep quality, but helps influence carbohydrate feeding behavior. People with low serotonin levels tend to have carbohydrate cravings.

Serotonin is also the precursor for melatonin, an important neurohormone that plays a role in the synchronization of circadian (daily) biorhythms, the regulation of aspects of immune function, and protection from hydroxyl radicals (an especially dangerous kind of free radical that can be easily produced from hydrogen peroxide). Although newborn infants produce minimal melatonin, production dramatically increases during the first two years of life. Melatonin peaks in early childhood, and begins a steep decline just before puberty.

Figure 2: Flow Diagrams of the SAM Cycle



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"Zinc deficiency may have serious manifestations in Down's syndrome infants. Zinc is not only a component of SOD, it is required for proper growth, healing and immune function."

Ammonia Detoxification

Ammonia is a byproduct of many metabolic reactions. When protein is burned for energy, ammonia is released (from the *amino* part of amino acids). Ammonia is absorbed by key molecules and transported through the body to be dumped in urine in the form of urea (an ammonia-rich chemical).

Glutamine and Arginine

One of the key ammonia-carrying molecules in the brain is glutamine, an amino acid which tends to accumulate in Down's syndrome. Glutamine is made from glutamate (glutamic acid) by the addition of one ammonia molecule, and from α-ketoglutarate by the addition of two ammonia molecules. Due to the general overabundance of ammonia in Down's syndrome, α-ketoglutarate is the ideal precursor to supplement the glutamate/glutamine pathways without increasing the ammonia burden.

The primary urea-carrying molecule in the body is the amino acid arginine. When arginine reaches the kidneys, it is split into urea and ornithine by the enzyme *arginase*. The urea is dumped in the urine and ornithine is recycled to pick up more urea. Due to the over-abundance of ammonia, ornithine is the preferred supplement to increase urea-carrying capacity in Down's syndrome.

Arginine and ornithine are also used clinically to increase the release of growth hormone. Typically, relatively large doses are required to produce this effect. However, there might be some degree of growth-hormone effect from smaller doses in children who are slower growing and/or metabolically challenged in varying ways. More research will be needed to determine whether this effect is significant in Down's syndrome.

Testing and Customization

Although antioxidant disturbances, and serine and tryptophan deficiencies, are almost universal concomitants of Down's syndrome, there are other metabolic problems that commonly show up. Zinc deficiency, for example, may have serious manifestations in Down's syndrome infants. Zinc is not only a component of superoxide dismutase, it is required for proper growth, healing and immune function. Perhaps more importantly, zinc is required to produce insulin-like growth factor type 1 (IGF-1), which is specifically deficient in Down's syndrome children after about one year of age. Zinc supplementation has been shown to significantly increases IGF-1 levels in non-Down's syndrome children. In an earlier Down's syndrome study, 15 of 22 individuals receiving zinc sulfate experienced increased growth [Napolitano *et al.*, 1990]. This suggests that zinc deficiency may be a common problem in Down's syndrome.

Another problem that has been reported to be somewhat common is *hypothyroidism*, which is usually treated with thyroid supplements. Although overexpression of SOD may be directly responsible for the diminished levels of rT3 [Lejeune, 1990], this hormone has minimal biological activity and this mechanism cannot account for lowered T3 or T4. Some other nutritional factors may directly influence thyroid hormone regulation. Iodine is necessary for the production of thyroxine (T4), and selenium is a component of the enzyme that converts T4 into T3, the most potent and active form of thyroid hormone.

Some doctors suggest that thyroid should be in the top half of the "normal" range for best health, but many doctors unfamiliar with hypothyroidism and Down's syndrome de-emphasize thyroid medications because of a widespread professional prejudice against supplementing thyroid when blood tests indicate that thyroid hormones are in the "low-normal" range.

New Practitioners

Randy V. Smith, M.D. 770-991-0933
Smith Psychiatric Clinic; 1631 Phoenix Blvd., Suite 8; Atlanta, GA 30349
Psychiatrist with focus on AAMI, Alzheimer's disease, ADD, and associated affective or depressive components.

Julian M. Whitaker, M.D. 714-851-1550
Whitaker Wellness Institute
4321 Birch Street, Suite 100; Newport Beach, CA 92660
General practice and preventive medicine, with emphasis on nutrition, supplementation, hormone replacement and IV therapies, including EDTA chelation. The institute also offers week-long residence programs (medical testing, treatment and education) for heart disease, diabetes, arthritis and other degenerative diseases.

Eric R. Braverman, M.D. 609-921-1842
PATH, 212 Commons Way, Building 2; Princeton, NJ 08540
Dr. Braverman is the Director of Princeton Associates for Total Health and has expertise in "DHEA and all of the smart drugs and nutritional therapies." He is an instructor at New York University Medical School and has authored more than sixty medical research papers. PATH services include: brain electrical activity mapping, cranial electrical stimulation, ultrasound vascular screening, and computerized neurological and psychometric assessment. Fax: 609-921-6092.

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"In the last decade, several new testing technologies have been developed for assessing nutritional requirements."

"Although all these tests require considerble sophistication for meaningful interpretation, they are powerful tools for identifying metabolic problems and guiding nutritional (and pharmacological) intervention."

Nutritional Assessment

In the last decade, several new testing technologies have been developed for assessing nutritional requirements. The use of these testing systems offers the potential of identifying the specific nutritional deficiencies of each individual — whether they have Down's syndrome or not. Red-blood-cell mineral analysis is good for determining nutritional trace mineral deficiencies (and excesses) for less than $200. Hair mineral analysis of trace minerals is also a valuable nutritional assessment, but it is especially valuable for testing heavy metals (lead, mercury, cadmium, bismuth, arsenic, etc.). Although it may be more difficult to interpret, it costs only about $50.

Two different kinds of antioxidant tests are now available. An *antioxidant profile* measures the levels of specific antioxidants (ascorbate, carotenoids, tocopherols, bilirubin, ubiquinone, urate, etc.) and oxidants (iron, TIBC, ferritin, etc.). This is probably one of the most useful tests for nutritional assessment in Down's syndrome. The *oxidant stress test* measures the ability of living cells to resist oxidative stress in an *ex vivo* assay. The latter test is an exciting new develop- ment.

Organic acid testing measures the many chemicals that are found in urine. This test may be one of the most useful tests for fine-tuning a nutritional program. By quantifying the waste acids in urine, signs of over-active or underactive enzyme systems can be identified.

Although all these tests require considerable sophistication for meaningful interpretation, they are powerful tools for identifying metabolic problems and guiding nutritional (and pharmacological) intervention. These tests are in no way limited to individuals with Down's syndrome. They can be used to identify nutritional deficiencies in anybody and everybody. We will describe these testing systems in more detail in future articles.

New Source

International Nutrition, Inc. **1-800-899-3413**
9510 Hallhurst Road, Baltimore, MD 21236.
International Nutrition has recently introduced Nutrivene-D, a high quality nutritional formula designed for metabolic management of Down's syndrome. It has received an endorsement by Trisomy 21 Research Inc. Nutrivene-D does not require a prescription. International Nutrition's compounding pharmacists can add piracetam to the formula with a doctor's prescription. Additional compounding services are available. Local phone: 410-581-8042. Fax: 410-581-8070.

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Q&A Questions & Answers

(continued from previous page)

Not everybody gets identical antidepressant effect from tryptophan that they do from Prozac and other SSRIs. **SWF**

Report: *This report is more anecdotal verification of what you already know, that deprenyl, piracetam and Hydergine exhibit synergy. The satisfactory level of the aforementioned for me is: 1.25 mg deprenyl (sublingual, 2X daily), 1.25 mg Hydergine (sublingual, 2X daily), 266 mg piracetam (oral, 3X daily), 250 mg choline (oral, 3X daily, with B_5 as needed). The 266 mg doses are an 800 mg piracetam tablet chopped into thirds. Very simply, much less is better. Coffee is* not *recommended.* **DRH**

"Will piracetam negatively affect my daughter's lipid metabolism?"

Question: *Thanks for your e-mail message about Down's syndrome. I suppose one of my questions which you will not be able to answer is whether or not piracetam would negatively affect my daughter's lipid metabolism.* **KM**

Answer: Piracetam does require a functional steroid hormone system (sex and adrenals) for it to provide benefits, but I am unaware of *any* effect of piracetam in *altering* steroid metabolism. I do not know of any effect of piracetam on triglycerides or cholesterol lipoproteins either. Personally, I doubt that piracetam influences lipids in any gross, obvious way. The only subtle effects that I might speculate as being possible is prostaglandin production, which piracetam might possibly lessen. **SWF**

"Is there any particular area in which you think you have seen cognitive improvements from piracetam?"

Question: *How much cognitive improvement have you personally experienced from piracetam? Are there are any side-effects (such as insomnia or personality changes) in children with Down's syndrome? Mostly I'm worried about a personality change for the worse as my daughter Megan, despite her extensive disabilities, is a happy and charming child.* **KM**

Answer: Improvements from piracetam can vary from subtle to dramatic. The degree of impairment seems to be the most significant variable. Those with severe impairment tend to get the more dramatic benefits and "normal, healthy" individuals tend to get more subtle benefits. This has been true for me.

I don't think personality changes from piracetam have been carefully researched. The only anecdote that I've heard is a reduction in my *own* irritability at being interrupted when I'm engrossed in an editing job on my computer, which was related to me by my wife and co-workers. Such effects are quite subtle and I think that scientists would have a degree of difficulty in quantifying the effect so that they could measure and study it. Furthermore, I kind of doubt that this is the kind of personality changes that you are worried about. Compared to the kind of personality changes that might be experienced with use of deprenyl, Prozac, Buspar, etc., piracetam isn't in the same league.

In my opinion, children with Down's syndrome may show much bigger personality changes from the nutrient part of their program than piracetam. Untreated, they tend to be gregarious and beneficient. Treated, they tend to be like every other kid on the planet. Unfortunately, that can mean stubbornness, acting out, rebelion, disobedience, and all the other behaviors that are the bane of parenthood. But that might also include independence, curiosity, assertiveness, intellect, self directedness, and other qualities for which parents hope dearly. The good with the bad; it's a mixed blessing.

At very high doses, piracetam can cause overstimulation. But insomnia and fussiness are not so much personality changes as they are *reactions*. The symptoms reverse quickly with reduction of dose or discontinuation of the piracetam. Personality can definitely be altered by changes in serotonin or dopamine levels, but piracetam has minimal effects on those neurotransmitter systems. Piracetam is more likely to influence general level of attentiveness or verbal expression. I don't necessarily think of those as personality issues. **SWF**

Question: *Is there any particular area in which you think you have seen cognitive improvements from piracetam?* **KM**

Answer: Organizational skills, verbal and speech skills, memory, motor and coordination abilities, and cognitive integration. In Down's syndrome, the improvement seem to be quite similar, except that verbalization and speech gains are conspicuous and exceptional. **SWF**

Question: *As a* Smart Drug News *subscriber and Life Enhancement products purchaser, I hope you can respond to this inquiry. I e-mailed it to Will Block back in February, but received no response and on 3/18 I sent the following message to you and also got no response. The last message to you was*

Editorial and Opinion: The Biological Evolution of Energy Systems

(continued from previous page)

"Oxidative phosphorylation was as great an advance as photosynthesis. It allowed the subsequent development of all animal life forms, including man."

extinct. Those that survived were relegated to minor anaerobic niches like bogs and mid-ocean hydrothermal vents.

As reduced-carbon chemicals (methane, ethane, "natural" gas) became scarce, plants had to develop better carbon-scavenging abilities. Eventually they were nearly depleted and carbon dioxide became the only appreciable carbon source. Plants became quite efficient at absorbing it. The modern atmosphere contains only about a third of a percent CO2. Much of the carbon that is not buried in rock or dissolved in the ocean has been incorporated into living structures.

Adaptation to Crisis

As the atmosphere became increasingly oxidized, living systems adapted. They developed antioxidants and ways of directly harnessing the oxidizing power of the atmosphere to drive metabolic reactions. Organisms developed ways of recycling antioxidants to better keep oxidizing free radicals under control.

One of these emerging life forms developed a way to use atmospheric oxygen for the direct production of chemical energy. This process is now called *respiration* (derived from "breathing" oxygen from the air). Technically, it's referred to as *oxidative phosphorylation*, which means oxygen-driven attachment of phosphate to produce ATP (adenosine *tri*phosphate). Oxidative phosphorylation was as great an advance as photosynthesis. It allowed the subsequent development of all *animal* life forms, including man.

The increased quantity and efficiency of energy production allowed animals to be more active, to run faster, jump higher and heal faster than their predecessors. They even had enough energy to "waste" on maintaining an elevated body temperature, and warm blooded animals began to dominate the earth.

The relative wealth of energy could also be devoted to increased neural processing of information. Central nervous systems became more complex and brains got bigger. Ever increasing neural complexity has led to consciousness, an emergent property of mind that has extended the anti-entropic nature of life into a new realm.

Scientific Myths to Live By

Through our understanding of the underlying mechanisms of life, we are now able to more finely tune our minds to the business of living and surviving as anti-entropic beings in an entropic universe.

"How do I know which improvements relate to Nutrivene and which to piracetam?"

"What do you think about attack doses of piracetam for children?"

Question: *I just received 400 mg piracetam capsules from England yesterday. My daughter with Down's syndrome is 2.5 years, 24.5 lbs and I will begin dosing at 30 mg/kg/day. That works out to about 3/4 of one capsule per day, which I will split it into 3 doses of 1/4 cap at a time. She has been on Nutrivene for one week. Already her speech and signing have improved significantly. How do I know which improvements relate to Nutrivene and which to piracetam? What do you think about attack doses for children? Do you think that piracetam would be any help to a 12-year-old boy diagnosed with ADD? I took one cap myself and didn't notice much difference except I was much faster and more coordinated on the keyboard.* **PS**

Answer: When you make two changes at the same time, you can't know which is responsible for any observed effect, or if it is the *combination* that is responsible. But if you allow one intervention to stabilize before making the second, you can separate the effects. But even then there is room for doubt. The best method for establishing cause and effect in a single individual is the A-B-A-B process. In other words, if adding something (A) causes an effect and withdrawing it (B) causes the effect to go away, and then adding it back (A) causes the effect to return and withdrawing it again (B) causes it to disappear again, then you can be relatively assured that the effect is caused by the intervention. Is this knowledge worth putting your daughter through the A-B-A-B process? If not, then you may be forced to accept the fact that you may never know for sure.

I do *not* recommend standard loading doses for children, especially when they cannot effectively communicate their subjective internal state. But an escalating dose regimen that gradually ramps up the dose over time (*i.e.*, 10 mg/kg, 20 mg/kg, 30 mg/kg, 40 mg/kg — or 15 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, etc.) will allow you to titrate the piracetam dose to your child's needs and tolerance without risking acute overstimulation. But now that your daughter is already on 30 mg/kg, you

Q&A Questions & Answers

(continued from previous page)

could try increasing the dose to 35 or 40 mg/kg and see if she does any better. If not, then cut back to 30 mg/kg and try 20 or 25 mg/kg at a later time.

When I first tried piracetam, I started at 5 mg/kg for a week, then increased to 10 mg/kg and 15 mg/kg before I ran out. I never noticed anything. The second time, I got a much larger supply and started a loading dose of 70 mg/kg. I got beneficial effects the first day. After a week at 70 mg/kg, it was starting to get to be too much. After 9 days, I cut back to 50 mg/kg, and then a few days later, to 35 mg/kg (my present regular daily dose). On special occasions (TV appearances, oral presentations, etc.) I will up my dose to 50 mg/kg for the day. I know a few people who get good results with 15 and 20 mg/kg, and two large men who take close to 100 mg/kg (when they can afford it!). So you can see that there is a broad range of potential doses to consider.

"When would be a good age to start children on piracetam?"

Piracetam might easily help a 12-year-old boy with ADD. There may not be many studies of piracetam in Down's syndrome, but there are plenty of piracetam studies of attention deficit/hyperactivity syndromes. It is also true that the testing procedures used to assess the nutritional status of Down's children are equally applicable to ADD, ADHD or NDA kids (not diagnosed with anything). Exposure to toxic heavy metals (lead, cadmium, mercury, etc.) is a known risk factor for hyperactivity and learning disabilities. Nutritional deficiencies are also known to impair cognitive abilities, intellectual development, non-verbal intelligence and academic performance. A hair mineral analysis, red blood cell mineral analysis, and a urine organic acid analysis costs about $500.

Piracetam is a subtle drug. It is not subjectively intrusive like amphetamine, Ritalin or caffeine. It is easy to seamlessly integrate it into one's "normal" reality and not notice beneficial effects. Improved typing skills is probably only the tip of the iceberg. If you take a higher dose for a longer period of time, I wonder if you or anybody else in your life would notice other benefits. My co-workers here at CERI noticed that I was more interruptible when taking piracetam. I don't think that I would have noticed that by myself. **SWF**

Question: *Hello Steve. Thanks for talking with Jacquelin from Homelink down in San Diego about our request for piracetam. She was quite concerned about our giving it to a baby. Nice lady.*

We have looked on the Internet re research papers on piracetam. The places that mentioned it didn't come through on our network. Anyway, has CERI done an article on it before? We would like to know more about it. Also, has there been any thought with regards to other drugs similar to piracetam and what their affect might be to Down syndrome children? **N**

Answer: Piracetam is one of the most popular smart drugs. Annual international sales exceed a billion dollars. We've covered it extensively in the newsletter, and both smart-drug books contain chapters on piracetam. There are a half-dozen piracetam analogs that might be usable, but no controlled testing in DS has been completed yet. Piracetam has the largest amount of research, especially with children subjects.

Question: *Have you heard anything as to when would be a good age to start children on piracetam? As you know, ours is four months old and so far he acts quite normal and has even surpassed normal children. We are wondering whether we should wait until we notice problems, or, go ahead before the crucial first six month brain cell building time is over. Any thoughts?*

Answer: The brain does not stop building in six months. It is a long gradual process

New Sources

Key Pharmacy & Home Health Care **1-800-878-1322**
Puget Sound Drug Corp.; 23422 Pacific Highway South; Kent, WA 98032
They carry DHEA, natural estrogens, progesterone, testosterone, piracetam, L-tryptophan and 5-hydroxytryptophan, and formulate on a dye- and preservative-free basis. They support natural and alternative medical philosophies and carry a large selection of vitamins, minerals and botanicals. Local phone: 206-878-3900.

Tierra Marketing International (TMI) **1-800-736-6253**
223 N. Guadalupe, Suite 285; Santa Fe, NM 87501
TMI is a world-wide source for original-formula, procaine-based Gerovital (GH3). They are the only US-based wholesale/retail supplier of true GH3 that we know. They also carry 5-hydroxy-L-tryptophan, NADH, pregnenolone, and DHEA. Visa, MC, Amex accepted. Contact Tierra for prices, as well as details of their 1994 court victory defending GH3 against the FDA. Fax: 505-982-0698. E-mail: VitaMan@rt66.com. Web: www.rt66.com/vitaman/.

Quality Health, Inc. **Fax: 011-44-171-580-2043**
401 Langham House; 29-30 Margaret Street; London W1N 7LB, ENGLAND
Quality Health offers most of the popular smart drugs, including piracetam, hydergine, vasopressin and deprenyl (Jumex). They accept Visa and MasterCard and claim a 3-week delivery time. Faster delivery is available. Web: www.qhi.co.uk.

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that continues through childhood. The metabolic toxicity of untreated DS adversely affects brain development to such an extent that by two years it is conspicuous. The nutrient part of the therapy controls that toxicity to a significant degree, but it is probably never too early to start. There are a few reported cases where *in utero* nutrition and/or piracetam therapy was started after amniocentesis-based diagnosis of Down's syndrome. Although only a few cases, they appeared to be quite successful.

We do not have much data on what piracetam specifically does to brain development. The absence of adverse reports in animals and humans does not indicate that there are no effects. Several anecdotal reports suggest that piracetam may enhance brain development, but we do not know for sure. Treatment of infants with myoclonic seizure disorders does not provide quality information about piracetam's effect in healthy DS babies. It does not appear to offer any significant risks, and dozens of DS infants have been started on piracetam before three months of age (including "Rosebud" Spurlock, the youngest daughter of Beverly and Paul Spurlock).

In general, I recommend that you start the nutrition formula first to establish tolerance, dosage and benefits before adding piracetam. That way you can assess the added effect of the piracetam independently of the effects of the nutrients and titrate the piracetam to your child's individual needs. **SWF**

"I started him on additional supplements right away and people have already noticed a big difference. The doctors now want all the kids with mitochondrial disorders to get the Pantox antioxidant profile."

Report: *Dear Steve: I spoke to you over 2 months ago about my son who has Leigh's Disease, a mitochondrial disorder. Anyway, I took a month Family Leave to spend with my son and I am very very happy to report that he is doing wonderfully*

A big 'thank you' for your help and information. Marc got the Pantox antioxidant profile and it was good that he did. Although most of his values were good (I have been giving him all those vitamins), the carotenoids (α-carotene, β-carotene and lycopene) were practically zero. He was under oxidative stress because of this. I started him on additional supplements right away and people have already noticed a big difference. As a matter of fact, the doctors now want all the kids with mitochondrial disorders to get the Pantox profile. Thank you again! **JM**

Comment from Internet: *The ketogenic diet is a diet in which 80 to 90% of all calories are derived from fat instead of carbohydrates and proteins. This forces the body to convert to a fat-burning pathway, creating ketone bodies as a by-product. The ketone bodies act as anti-convulsants; how is not known. The diet is used on children who do not respond to usual drug therapy for seizure control. And the diet is terrible. Poor little guy can't have cookies, pancakes, bread, pasta, etc...* **LL**

Response: The factor that is responsible for inducing the fat-burning pathways is *carbohydrate restriction*, not fat consumption per se. Diets high in protein, moderate in fat, and low in carbohydrate will also induce ketosis.

Carbohydrate restriction in children is not only unnatural for them (they usually burn sugar fuels like gangbusters), but it may have other systemic stresses as well. The process by which individual cells differentiate into specific functions appears to be associated with a decrease in cellular glucose utilization. In other words, the growth and maturation process is characterized by a shift from carbohydrate metabolism to fat metabolism. The effect of carbohydrate restriction on children is largely unstudied. But then again, the same can be said of carbohydrate restriction in adults.

In pregnant women, the placenta produces hormones that increase maternal insulin resistance (decreasing maternal

Calendar of Upcoming Events

Sept 14 Steven Fowkes, Dixie Tafoya & Dr. Paul Spurlock will be speaking at a Down's syndrome parent conference in Pittsburgh, Pennsylvania. Call Sandy Prince at 412-531-1733 for more information.

Sept 28 Steven Fowkes, Dixie Tafoya, Paul Spurlock and Julee Bramson will be speaking at a Down's syndrome parent conference in Huntsville, Utah (near Ogden). Call Janet Hoffman at 801-745-1339 or Julee Bramson at 801-472-8778 for registration info.

Oct 12-13 Steven Fowkes, Dixie Tafoya and Paul Spurlock will be speaking at a Down's syndrome parent conference in Windsor, Canada on the 12th and South Bend, Indiana on the 13th. Several members of the Trisomy 21 scientific advisory board will be joining them in South Bend. Call Tamera Ragan at 616-684-2349 for more information.

Oct 27 Steven Fowkes will be speaking about "Nutrition for Healthy Kids" at Health 2000, an all-day fund-raising event in support of California medical freedom sponsored by California Citizens for Health, Hiatt Rickeys, Palo Alto. Call Cathleen Springer 415-367-6763 for additional information.

1996-1997 The MindPOWER Adventure Series featuring speakers Ward Dean, Michael Hutchison, Ray Sahelian and Win Wenger will be taking place throughout 1996 and 1997 at locations across the country.

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glucose utilization). This results in a major diversion of maternal blood glucose to the fetus which sustains it's phenomenal growth rate. Fats are primarily used for structural purposes (construction of membranes), not for energy.

"Although it may seem counter-intuitive, high-carbohydrate diets (even high-complex carbohydrate diets) promote fat accumulation and obesity in anybody that does not exercise sufficiently."

In adults, carbohydrate restriction diets may actually be preferred. Such diets tend to reduce insulin resistance (a major problem in middle-aged and older individuals) that turns on fat neogenesis (the conversion of carbohydrate into fat) which makes people obese (despite eating a low-fat diet). Interestingly, the paleolithic diet (what our ancestors supposedly ate) is low in carbohydrate, except during the summer and fall (exactly when we want to put on *fat* for the coming winter season). Although it may be counter-intuitive, high-carbohydrate diets (even high-complex carbohydrate diets) promote fat accumulation and obesity in anybody that does not exercise sufficiently. Carbohydrate-restriction causes weight loss without any need for exercise.

"Interestingly, the paleolithic diet (what our ancestors supposedly ate) is low in carbohydrate, except during the summer and fall (exactly when we want to put on fat for the coming winter season)."

There is another mechanism that may be responsible for the anti-epileptic properties of ketogenic diets — increased production of ATP (the energy "currency" of the cell) and reducing power (resistance to oxidation). More than 90% of the energy consumed by our cells is produced in tiny organelles called mitochondria, which are like little blast furnaces or mini-power plants. The efficiency of these mitochondria is dependent on many factors, nutritional and enzymatic. Nutritional factors include lipoic acid, NADH, coenzyme Q, and carnitine, all of which are available in foods or supplements. One of the most essential enzymatic factors is the function of the citric acid cycle, which can be fed by carbohydrate fuels (glucose, acetate, etc.) or fat fuels (fatty acids, ketones, etc.). Dependence on glucose alone may not allow the citric acid cycle to function adequately. The induction of ketosis provides an additional energy-fuel input into the citric acid cycle which may compensate for impairment of glucose utilization. With up-regulation of the citric acid cycle comes increased mitochondrial efficiency, increased energy production in the form of ATP, and increased reducing power (NADH) for fighting oxidative stress.

"A few days ago, I found that melatonin doubled the glutathione peroxidase levels in mice brains. What do you think of that?"

The over-expression of superoxide dismutase (SOD) in Down's syndrome results in increased conversion of superoxide anion radicals into hydrogen peroxide, a powerful oxidizing agent. Hydrogen peroxide can form numerous free radicals which end up being scavenged by vitamin C, vitamin E, vitamin A, glutathione, and many other antioxidants. These antioxidants become oxidized when they detoxify free radicals, and it is the reducing power produced by the mitochondria which recycle them back to their reduced (active) forms so that they can be used again and again. These antioxidants are depleted in Down's syndrome.

Mitochondrial ATP (the major chemical energy-transfer molecule) is also responsible for powering the electrical potential of the nervous system. Is it possible that seizures are more likely in a state of depleted ATP? But that's another question, and this is long enough already. I think I'd better stop here. ;-) **SWF**

Question: *I am a friend of Dixie's and have a 3 year old with Down's syndrome. I am a premed student and spend a lot of time researching this condition.*

In 1978, LeJeune found a 0.58 correlation between serum glutathione peroxidase levels and IQ in Down's kids. I have done Medline searches like a year ago looking for glutathione peroxidase stimulants, and only found aloe vera juice. A few days ago, I found that melatonin doubled the glutathione peroxidase levels in mice brains. What do you think of that? Do you know what neurotransmitters melatonin is involved in? We bought the slow release tablets. Any idea of its half life? **KW**

Answer: Since melatonin in present in very small amounts in childhood, I would be very careful about supplementing it. Melatonin is made from serotonin, a brain neurotransmitter involved in sleep and emotional control which is made from the essential amino acid tryptophan. Both melatonin and tryptophan are deficient in Down's syndrome. I presume that serotonin is as well. I think that tryptophan supplementation is probably safer, and then the body can make melatonin the way it is supposed to. In other words, I think that it is premature to consider melatonin deficiency *before* correcting a known tryptophan deficiency.

Glutathione peroxidase production requires selenium (four atoms per enzyme). Selenium is often depleted under conditions of high oxidative stress. Make sure you assess the status of this critical micronutrient.

Glutathione (the substrate for glutathione peroxidase) also tends to be low in Down's individuals. Glutathione can be supplemented directly (both MSBplus and

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Nutrivene have it). Although the precursor (cysteine) and related N-acetylcysteine (NAC) can increase glutathione production a little bit under some circumstances, these should probably *not* be supplemented in Down's syndrome. Due to over-expression of cystathionine β-synthase, which is coded on the 21st chromosome, cysteine levels tend to be well above normal.

Ray Sahelian and I discussed melatonin half-lives in "A Consumers Guide to Using Melatonin" [*SDN* v4n9p1]. If you or any other parents of children with Down's syndrome try melatonin with them, please report your experiences to us. **SWF**

"I am new on line and have no idea what you are talking about when you say visit your web site."

Question: *Dixie Tafoya told me to contact you regarding the proper dosage of piracetam for my 5-month-old daughter. I have finally received (after 2 months of trying) 300 ml of piracetam liquid. There were no dosage instructions. She weighs about 12-15 lbs. Could you please recommend her dosage.* **R**

Answer: At the standard 12-15 mg of piracetam per pound of body weight, her dosage calculates to be 144-225 mg per day, or 50-75 mg three times per day.

The liquid piracetam *must* have the concentration listed on the label. It would say some number of *milligrams per milliliter* (mg/ml), or some such equivalent in the labeling. Or it would state the total amount (weight) of piracetam in the entire bottle, which you could divide by 300 ml to get the mg/ml figure.

Conversion Equations
(mgs to teaspoons)

$$\frac{\text{dosage in mg}}{? \frac{\text{mg}}{\text{ml}} \times 5 \frac{\text{ml}}{\text{tsp}}} = \text{dosage in tsp}$$

$$\frac{50 \text{ mg}}{20 \frac{\text{mg}}{\text{ml}} \times 5 \frac{\text{ml}}{\text{tsp}}} = {}^1/_2 \text{ tsp}$$

The top formula in the margin is a general formula for converting a mg dosage into a teaspoon (tsp) equivalent. The Glaxo-brand liquid piracetam sold in Mexico (Nootropil) has a concentration of 20 mg/ml, which calculates (see the bottom equation) to a half-teaspoon daily dose (one-sixth teaspoon three times per day) at a 50 mg dosage. In a small child, the volume of liquid piracetam may be so small as to require an *eighth*-teaspoon to measure the dose sufficiently accurately.

One last comment: liquid medications sometimes contain antifungal preservatives (like methylparaben and/or propylparaben) to protect the product from molding (especially alcohol-free formulas). Some children do not tolerate these chemicals well. If your daughter has a bad reaction to the liquid piracetam, you might want to try piracetam tablets or capsules at a later time before abandoning piracetam therapy altogether. It is probably also a good idea to read the labels on other liquid pediatric medications (cough syrups, antibiotics, etc.) and watch for similar adverse reactions. **SWF**

Question from Internet: *I am new on line and have no idea what you are talking about when you say "visit the web site at signature below." What the heck are you talking about?* **DK@AOL**

Answer: Your internet vendor (America On Line) has a service that you can access that will allow you to "surf the web" all over the world. The web (short for the World Wide Web) is a collection of electronic documents in a specific format (HTML) that is highly compact for efficient transport over phone lines. The files can exist anywhere in the world on any computer that is connected to the Internet. Once these HTML (hypertext markup language) files get to your computer, your AOL software (or any other web-browser program) will expand them to be presented to you on your screen with different size fonts and color pictures.

There are also "search engines" that are provided by various companies that allow you to browse their indexes of web materials. So if you search for "smart drugs," they will likely send you to us.

Since I am not familiar with AOL's interface, I cannot tell you how to access their web browser. You will have to look it up in your manual, or ask their on-line help. They are heavily promoting this service, so it should be easy to find.

Every web site has an internet address code, called a URL (universal resource locator). These codes begin with

http://

(which specifies the use of hypertext transfer protocol) and end with an internet location like

http://www.ceri.com

The "www" means it is a world-wide-web site, "ceri" is our registered internet domain name, and "com" means we are a commercial company (just like AOL.com refers to America On Line). There are many other categories that you might run into in a URL: "edu" means an educational organization, "org" refers to a non-profit organization, "gov" means a governmental agency, "ca" means Canada, "fl" means Florida, "net" means internet service, etc.). The "." (periods) separate all the items of the internet address from each other.

URL codes can also have additional

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"Should I receive the shipment at my home (since it is for personal use) or would my work (at a downtown physical rehabilitation clinic) be better?"

"One of the things that the FDA likes to do is jump to the conclusion that anything and everything being imported is intended for commercial use, regardless of whether or not you have stated otherwise."

"Under administrative law the burden of proof lies with you to establish that you were not using the imported items for commercial purposes. In other words, you are considered guilty until you prove yourself innocent. Medical licensure is part of administrative law."

was thinking the personal-use issue might come up since my work is part of the medical care system. **anon**

EuroCare has ceased business, and ALP is closing down. IAS, InHome and Era-Bond (newly listed in this issue) carry GHB and tryptophan. Although InHome is on import alert and IAS and Era-Bond are not (as far as I know), I don't think that import alert really makes that much difference regarding Customs detentions. Both GHB and tryptophan are politically hot (*i.e.*, on the government's "hit list"), so if you are unlucky enough to have your shipment detained, your chances of a hassle are high regardless of which company ships it to you. Basically, it's 99.44% politics and 0.56% content. **SWF**

IAS has told me that they will not ship controlled drugs to states in which their use is restricted. They will probably be adding GHB to their controlled-drug list soon. **WD**

One of the things that the FDA likes to do is jump to the conclusion that anything and everything being imported *is intended for commercial use*, regardless of whether or not you have stated otherwise. This is part of their standard detention form letter. If your shipment is being delivered to a work address, they might be more inclined to get stuck on that assumption. Maybe, maybe not. So much depends on the individual that you end up dealing with, and which side of the bed they got out of that morning.

As far as legal consequences are concerned, there are two ways to look at your risks. In *criminal* court, there would be a burden of proof placed on the prosecution to establish that you were, in fact, using the imported items commercially (*i.e.*, within your professional practice with your clients). You would be considered innocent until proven guilty. Since you are not using the imported items for anything but your personal use, it would be near-to-impossible for a prosecutor to make any charges stick (solicitation of perjury would be the only way). However, under *administrative* law the burden of proof lies with you to establish that you were *not* using the imported items for commercial purposes. In other words, you are considered guilty until you prove yourself innocent. Medical licensure is part of administrative law.

It is highly unlikely that personal use of imported smart drugs would lead to a court case under any circumstances, but it would depend on whether or not anybody had something to gain by your demise. If you are important enough to be a special target, then you might want to consider these issues carefully. If you are an "anonymous" practitioner with no particular political visibility, then you may not. When I edited *STOP the FDA: Save Your Health Freedom*, I stopped practicing as a nutritional consultant, even though it was an unlicensed profession. I figured that the book would give me political visibility with people who might be inclined to want to hassle me. So far, nothing has happened (other than some undercover surveillance and possibly some phone tapping). Many of my smart-drug shipments have come directly to my office. I have yet to experience a single detention. **SWF**

Down with Down's?

I have been reading your Smart Drug News *newsletter with much intrest, as my granddaughter has Down syndrome. Perhaps your newsletter should refer to Down syndrome instead of Down's syndrome, as this is the proper name for the syndrome. I think it would add validity to your newsletter by using the proper name.* **LC**

Down's syndrome *is* the proper name, with a capital D and a small s. Some people are pushing to have the possessive dropped, but there is hardly a consensus on the change. I've heard the arguments about the inappropriateness of diseases being possessive, but I'm not impressed with the reasoning. Since Professor John Langden Down did the seminal work in characterizing Down's syndrome, it was his "academic contribution" or "intellectual property." That makes it possessive. Therefore, it is both grammatically correct and traditional to call it Down's syndrome.

When we name something after somebody as a memorial, we do not use the posessive. For example, if somebody were to breed a new variety of cherry whose tree trunk had horizontal striations which looked like hatchet chops, it would be appropriate to name it a George Washington cherry tree. But if one is referring to the actual mythical tree that George Washington cut down, then it would have to be called George Washington's cherry tree. Chopping down a cherry tree imparts possession, having a tree named after one's self does not.

So the bottom line, for me, is whether or not professor Down's relationship to the syndrome is more possessive or more honorarial — especially since the good doctor is no longer with us. Since this evaluation is significantly subjective in nature, I accept both uses as valid.

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One reason I prefer Down's syndrome is that it mitigates the pejorative confusion with down (the direction). Down has a negative connotation with earthiness, baseness, depression and purgatory, as opposed to up's connotation of liveliness, inspiration, morality and heaven. I think saying "he's Down's" or "I am Down's" or "she is using TNI for her Down's" makes a subtle distinction that diffuses some of this connotation.

In situations where there is some ambiguity about English, popular use usually establishes the convention. Of seven books that I currently have on my desk that mention Down's syndrome (including both a regular and medical dictionary) *not one* refers to it as "Down syndrome." *All seven* use Down's syndrome exclusively. **SWF**

Codex in Canada? US next?

There's a rumor on the Internet that Canada has banned DHEA and is in the process of reclassifying all herbs as drugs in accordance with pending Codex regulations. Is this true? **(net)**

According to Internet reports, both items are already fact.

We were able to confirm that Canada has classified DHEA as an anabolic steroid and a controlled substance. One Canadian pharmacist told us that it has even been banned from any prescription medical use. Another source stated that DHEA remains available through "some compounding pharmacists." Two sources told us that DHEA is obtainable by doctor's prescription through the government's Emergency Drug Release Program in Ottawa—if you've got the stamina to fill out all the requisite paperwork and the time to waste waiting for approval!

Verifying the herbal matter turned out not to be so easy. According to Keith Stelling, a member of the Board of Directors of the Ontario Herbalists Association, Canada now classifies therapeutic herbs as drugs. He was quoted as saying, "Effective 1 January 1997, most herbalists and many naturopaths, health food store proprietors and their staff, importers, growers and even restaurant owners are now liable to conviction for *drug trafficking* [italics ours]. In a sudden about-turn in policy, the [Health Protection Branch] has reclassified a whole list of traditional herbal medicines as drugs because they have a pharmacological effect." However, according to Micheline Ho, the only representative of the Health Protection Branch that seemed to know anything about herbs or government regulations about herbs, there has been *no* change in the legal status of herbs. She was quite emphatic that herbs were still legal in the over-the-counter market.

The herbs that were supposedly affected include: bayberry, betel nut, boldo, rhamnus, calamus, capsicum/cayenne pepper, cascara, chaparral, coltsfoot, comfrey, ephedra, eyebright, feverfew, gelsemium, germander, ginkgo, goldenseal, gotu cola, hawthorn, horsetail, kava kava, lily of the valley, lobelia, poke root, psyllium seed, black radish seed, blood root, senna, squill, pau d'arco (taheebo), tea tree oil and valerian.

Although they may not *yet* be banned in Canada, these herbs *are* being targetted by new Codex regulations that are being formed under the auspices of the World Trade Organization, sanctioned by the NAFTA and GATT agreements. These "free trade" agreements (see *SDN* v4n10p5) will classify herbs (and many nutrient-based dietary supplements) as drugs and force signatory nations (*e.g.*, the US and Canada) to remove them from the over-the-counter market. In this case, NAFTA and GATT have nothing to do with free trade and everything to do with *restraint of trade* by vested interests (*i.e.*, pharmaceutical companies) who will profit handsomely from decreased competition. Although the proposed Codex regulations are not finalized, when they are, *they will directly conflict with the US Constitution and existing health-freedom laws*. The US Constitution reserves unenumerated powers to the individual States and people (the Ninth and Tenth Amendments), and Federal law currently prohibits the FDA from removing herbs and nutrients from the over-the-counter market for reasons other than public health, and then only with specified rule-making procedures (*i.e.*, public hearings, open testimony, public comment, published proceedings, etc.). Whether these international agreements (NAFTA and GATT) will prevail, or the US Constitution and law will prevail, nobody knows. But given the power and influence that was exercised by well-placed special interests to 1) misrepresent the NAFTA and GATT agreements to the public, and 2) jam NAFTA and GATT through Congress with minimal debate in the face of serious questions, I am deeply concerned.

I believe that the only workable solution to the Codex problem is for the US to abandon its involvement in the "new world order" and repeal NAFTA and GATT. These international agreements do not include any guarantees of personal freedom or human

"There's a rumor on the Internet that Canada has banned DHEA and is in the process of reclassifying all herbs as drugs in accordance with pending Codex regulations."

Communicate your thoughts and suggestions about Codex to:

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continued from previous page

rights. They are designed only to further the economic interests of their sponsors. The *US Constitution* and *Bill of Rights* are an inconvenient impediment to their plans.

"The economic interests being served by Codex are clearly those of the multinational drug and chemical corporations."

The economic interests being served by Codex are clearly those of the multinational drug and chemical corporations. These companies will profit from 1) removal of *local* government-imposed trade barriers (the free-trade side of NAFTA and GATT), and 2) establishment of international trade barriers (anti-competitive regulations) against non-patentable, generic health technologies (the restraint-of-trade side of NAFTA and GATT). While consumers may be likely to benefit from removal of *local* trade barriers, they are going to pay dearly for loss of affordable, over-the-counter nutrients and herbs. Only the international pharmaceutical companies will profit handsomely from both. It shouldn't come as a surprise that Codex delegates are primarily pharmaceutical company representatives and governmental regulators of the pharmaceutical industries.

"I find it telling that the new governing bodies of the new world order are unaccountable to either voters or consumers."

I find it telling that the new governing bodies of the new world order are unaccountable to either voters or consumers. It's a neatly efficient piece of work, indeed. **SWF**

Piracetam and Seizures?

Are there any precautions that should be taken in administering piracetam to a child with seizures? **TR**

"Are there any precautions that should be taken in administering piracetam to a child with seizures?"

One should watch closely when giving *anything* to a child with seizures! This may include piracetam, although there are no special contraindications with piracetam and seizures. In fact, piracetam is considered a *treatment of choice* for myoclonic seizures in many parts of the world. In clinical tests, piracetam was found *not* to interfere with any of the anti-epileptic medications tested, yet it *was* effective in ameliorating the cognitive dysfunction side effects of the medications. This was reviewed in *Smart Drugs II* (page 110).

I think that the concerns being expressed about piracetam and seizures is based on theoretical issues that have no basis in clinical data. Since piracetam has been reported to increase cellular calcium influx in tissue culture (an effect which is common to excitotoxins like glutamate (MSG), aspartate, pyroglutamate, and aspartame (NutraSweet) and glutamine), and excitotoxins can aggravate seizure disorders, somebody has reasoned that piracetam should not be given to people with seizure disorders. Despite this hypothetical caution, piracetam has not been found to exhibit any significant excitotoxic activity, and is clinically used to *decrease* seizure incidence. We discussed some of these issues in a previous answer, which is posted on our DS-only web site: http://www.win.net/ceri.

There are significant disagreements about what mechanisms underly seizure disorders. One of them has to do with deficient energy (ATP) production at the cellular level by mitochondria (tiny energy powerplants within cells). ATP energy from mitochondria is required to pump ions across nerve cell membranes. Sodium, potassium and calcium flow across these membranse when they fire electrically. Excitotoxins cause extra calcium to flow into the cells. This burdens the ion-pumping system and drains ATP energy reserves. The possible involvement of this mechanism is supported by the efficacy of ketogenic diets which not only induce fat-burning enzymes in the mitochondria but also control seizures. Furthermore, genetic mitochondrial disorders and syndromes are often associated with seizure activity. **SWF**

Down's Syndrome Surgery and Nutritional Therapy (TNI)

I am a pediatrician caring for a 3-months-old boy who may soon be starting targeted nutritional therapy for Down's syndrome. He is currently taking digoxin and hydrochlorothiazide. He also may be undergoing heart surgery with its attendant anesthesia etc. in the next few months. I was wondering if there is any information available about potential drug interactions between these compounds. **DZ**

Nutritional therapy is intended to normalize biological functions which are disturbed by the overexpression of genes on the extra 21st chromosome. There may be many functions normalized that we do not even know were disturbed, including effects on blood clotting (which is sensitive to oxidative stress), vascular diameter (which is influenced by prostaglandins), healing rate (which we know is influenced by zinc and vitamin A), and susceptibility to anesthesia (which may be influenced by higher-than-normal levels of nitric oxide). I do know that DS children are more easily anesthesized than non-DS children and that most anesthesiologists are generally unaware of this problem (one DS child in southern California died from minor elective surgery last year).

In my opinion, the biggest concern is the risk from the surgery itself, which is

continued from previous page

aggravated by the chronic oxidative stress of untreated DS and ameliorated by nutrient-and-antioxidant therapy. More than two decades ago, pre-operative use of vitamin E was shown to decrease surgical mortality in adults. I think this applies in spades to DS individuals who may have abnormally low levels of vitamin E, vitamin A, glutathione, selenium, zinc, and/or S-adenosylmethionine. Although you did not specifically mention piracetam, it has a marked ability to mitigate hypoxia. This provides a mechanistic justification for it's use *prior to surgery* (to compensate for reduced blood oxygenation due to blood flow between sides of the heart) and *during surgery* (to diminish possible brain damage from ischemic complications from the surgery).

"Although you did not specifically mention piracetam, it has a marked ability to mitigate hypoxia. This provides a mechanistic justification for it's use prior to surgery (to compensate for reduced blood oxygenation) and during surgery (to diminish ischemic complications)."

The lack of statistical data make any decision to start, continue or stop TNI therapy in the face of specific conditions or complications problematic. However, biochemically speaking, ceasing therapy has no specific theoretical justification.

As with any drug treatment of a condition, one should be ready to lower the dosage of medication or cease it altogether when one addresses the biochemical causes of the condition. In other words, the use of drugs is usually compensatory, and when the condition requiring compensation is eliminated, so is the need for the drug. **SWF**

Titrating GHB Dosage?

I plan on purchasing GHB in the powdered form. In order to titrate the dosage, I would like to know if it is soluble in water or alcohol? **SB**

"I am puzzled by the recent touting of dietary 5-hydroxytryptophan as an alternative to typtophan."

GHB is very soluble in water and somewhat soluble in alcohol. This makes water the ideal vehicle for dosing and alcohol a good solvent for recrystalization. The thing you have to be careful about with water is that GHB solutions are a growth media for fungi and bacteria. It helps if you can keep the concentration of GHB as high as possible, or only mix what you are going to use in a short period of time. Another approach is to freeze the GHB solution to prevent the growth of microorganisms. If you dilute 10 grams of GHB in a pint of water and fill two trays of ice cubs (20 cubes), then each frozen ice cube will contain 500 mg of GHB. It's very convenient. **SWF**

Splitting Piracetam Capsules?

I have 800 mg capsules of piracetam from a compounding pharmacy. How can I accurately measure a 600 mg dose of piracetam? **OTP**

"I have 800 mg capsules of piracetam. How can I accurately measure a 600 mg dose?"

The ice cube method will work great. To get 600 mg (3/4 of a capsule), dissolve 3 capsules of piracetam into approximately 2 ounces of water and pour into 4 wells of a plactic ice cube tray. Take care to fill each well to the same level (use a dropper to redistribute liquid from overfilled wells to underfilled wells). Freeze. Each ice cube will have 600 mg of piracetam. If you want a 500 mg dose (5/8ths of a capsule), you can use 5 capsules to make 8 ice cubes. If you want a 700 mg dosage (7/8ths of a capsule), use 7 capsules to make 8 cubes. The exact amount of water is not critical. It should be enough to dissolve the piracetam but not so much as to overfill the requisite number of ice cube wells.

If you are using tablets, there will be a residual powder in the water that will not dissolve (i.e., it will be milky white instead of clear). This cloudiness in the solution is from the binders in the tablets, not undissolved piracetam. You can ignore it.

For measuring much smaller dosages, use the same process. Just use fewer capsules or tablets and more water. If you want to measure 133 mg doses (approximately 1/6th of a capsule) dissolve 1 capsule in water and fill 6 ice cube wells. If you want to measure 25 mg doses (1/32nd of a capsule), dissolve 1 capsule and make 32 ice cubes.

If the milligram dose does not come out to an even fraction of a capsule, use more than 1 capsule at a time (as we did in the first example) or leave the last ice cube only partially filled. In other words, if the desired dosage comes out to 3.5 doses per capsule, you can either fill three cube wells to full and a fourth to halfway, or use 2 capsules to make 7 cubes. **SWF**

5-HTP and Carbohydrate

I am puzzled by the recent touting of dietary 5-hydroxytryptophan (5-HTP) as an alternative to typtophan, with no apparent mention of the Wurtman's Rule requiring a high-carbohydrate meal. Is this simply because the carbohydrate meal is required for typtophan transport across the blood-brain barrier, but not 5-HTP? **PVS**

Tryptophan and 5-HTP use the same amino acid transport enzyme to get through the blood-brain barrier. Transport of both are inhibited by competing large, neutral amino acids. High-carbohydrate meals lower competing amino acids and therefore enhance both tryptophan and 5-HTP transport into the brain. The carbohydrate-

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The adaptogen article on Eleutherococcus senticosus, by Gavin Lee, was still being peer reviewed at deadline. It will appear next issue.

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Smart Drug Update:

The Case for Piracetam in Down's Syndrome

by Steven Wm. Fowkes

One of the current focal points for the emergence of smart drugs into popular consciousness and mainstream use is the application of piracetam to Down's syndrome (DS). This application has generated lots of controversy within DS circles for several reasons: 1) piracetam is not FDA approved, 2) US physicians are generally unfamiliar with its use, and 3) major establishment DS organizations have a policy that DS is fundamentally untreatable.

US physicians and scientists associated with these DS organizations are actively discouraging piracetam's use. Allegations of elevated seizure risks and possible long-term side effects from piractam are being made. However, the complete lack of such effects during more than two decades of worldwide clinical experience with piracetam suggest that political and ideological considerations are the sole basis of these anti-piracetam policy positions. Indeed, the increasing use of piracetam and *targetted nutritional intervention* (TNI) is putting these matters to the test. This article will specifically focus on the use of piracetam in DS-related conditions [see v2n10, v3n4, v4n10, v5n1 for previous articles].

A Brief History

Piracetam's earliest use in Down's syndrome (DS) was in Spain and Portugal in 1974 in a comparative study (using historic case controls) of *Dromia* (a 5-hydroxytryptophan-containing product) and *Noostan* (a brand of piracetam) in 26 children from age 3 months to 12 years of age [Fialmo, 1976]. This study was obscurely published, not

continued at top of next page

Book Review:

Brain Longevity

review by Anne M. Fowkes

Brain Longevity: The Breakthrough Medical Program that Improves Your Mind and Memory, by Dharma Singh Khalsa, M.D. with Cameron Stauth (ISBN: 0-446-52067-5).

I see *Brain Longevity* as a quintessential book of the 90s. It blends many disparate elements of our current culture, such as Eastern and Western medical traditions, into a program that is somewhat mysterious yet eminently practical. It is touched by the wisdom of the ages, sculpted with double-blind placebo-controlled studies, and tempered by Dr. Khalsa's own clinical experience.

It is in some ways a romance — a tale of a maverick young doctor scouring many paths to find the answers to questions that were raised during his work as an anesthesiologist, questions about why the stress surrounding surgery seemed to take a heavy toll on patients' cognitive abilities. His discourse is often couched in seduction, luring the reader to join the quest, to lay aside the messages of allopathic disinterest and institutional complacency, and to reclaim the mystic "old age" which meant wisdom and power rather than an inexorable slide into the pre-death death of will and consciousness.

The evil genie in this story is cortisol, the product of a primitive stress response run amoc. Cortisol and adrenaline (also called norepinephrine) are major adrenal hormones of the fight-or-flight syndrome, which evolved to allow us to escape danger. Ordinarily, surges of cortisol are followed by periods of calmness, during which we can recover. However, the chronic stress of our current lives keeps us constantly in an activated state, in which cortisol is spewed out in quantities our bodies were never designed to handle.

Dr. Khalsa presents a compelling picture of just what all that unabated cortisol does to

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indexed in any computer database, and remained largely unknown in the US.

In the early 90s, Dixie Tafoya, the mother of a child with DS, read *Smart Drugs & Nutrients* and realized that piracetam's beneficial effects on various learning disabilities might address some of her daughter's developmental problems [see *SDN* v3n4]. Piracetam's almost complete lack of toxicity [Reynolds, 1996; Dukes, 1996] coupled with its ability to 1) enhance the higher (telencephalic) functions of the brain, 2) enhance interhemispheric communication through the corpus calosum, 3) enhance memory and learning in both animals and humans, and 4) prevent memory loss and learning difficulties induced by drugs, stress and trauma [reviewed by Vernon and Sorkin, 1991] made it seem an ideal prospect for DS therapy. Her daughter responded dramatically, and piracetam use has been spreading through the DS community ever since.

"Gains in speech were especially dramatic."

In 1995, Dr. Fialmo's study of Dromia and piracetam was rediscovered in the US. It showed universal benefits in motor development, mental development, speech, affectivesocial (emotional) development, scholastic achievement, and EEG changes indicating improved hemispheric synchronization (see Figure 1). The gains in speech were especially dramatic.

Toxicity and Pharmacology

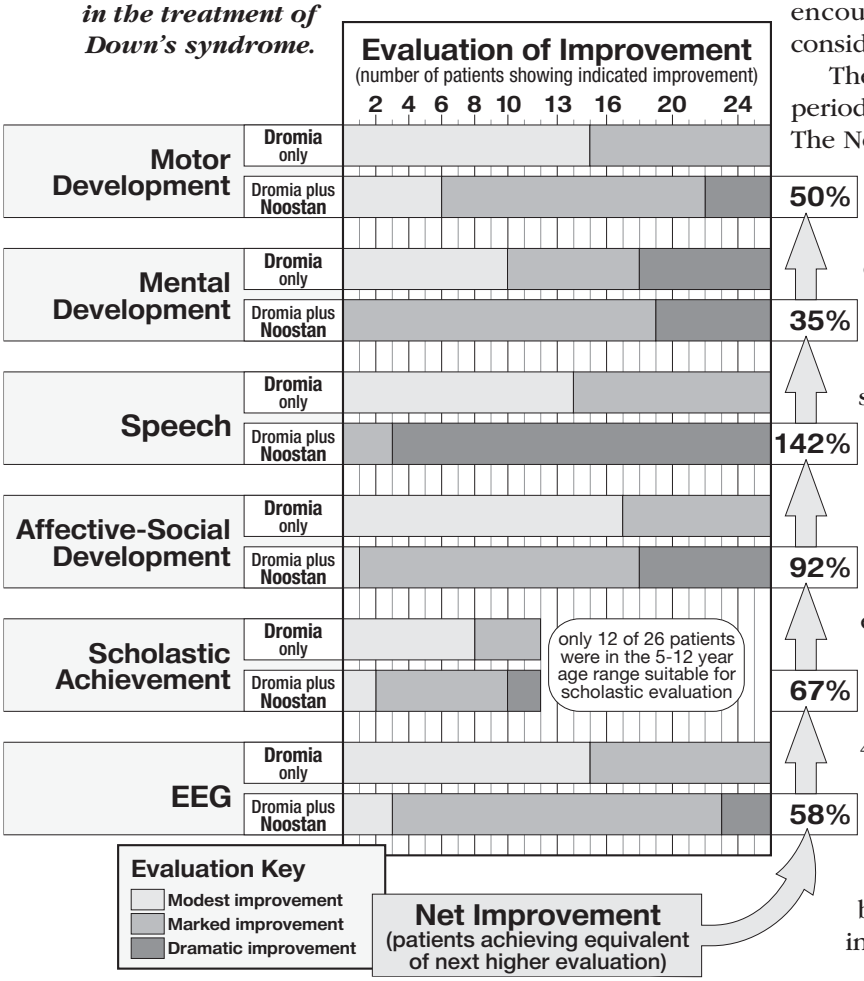
One of piracetam's most unique and conspicuous features is its *extremely low toxicity*. The classical measure of drug toxicity, the LD_{50} (the dose causing death for 50% of test animals), is not applicable; standard dosing methods (oral, intravenous injection, intraperitoneal injection) cannot deliver enough piracetam to kill laboratory animals. Doses of greater than 20 g/day have been given to people suffering from myoclonic seizure disorders, without serious side

Figure 1:

The Fiona Study

Piracetam and 5-hydroxytryptophan in the treatment of Down's syndrome.

The Fiona study compared two groups of 26 children between the ages of 3 months and 12 years. The first group received only Dromia (5-hydroxytryptophan plus "pyriglutine") during a two year period between 1972 and 1974. The second group received Dromia plus Noostan (a brand of piracetam) for a two year period between 1974 and 1976. There was no no-treatment group, presumably because the Dromia-only therapy (described as "very encouraging" and a "considerable success") was considered a standard of care by the clinical team.



The Dromia was administered at 1 mg/kg/day for periods of 3 months, with breaks between periods. The Noostan was administered at 30 mg/kg/day on a continuous basis.

Improvement in all subjects was evaluated as modest (light gray), marked (medium gray), or dramatic (dark gray) in each of 6 categories. Scholastic evaluation was possible only in the 12 patients older than 5 years of age.

Net Improvement was calculated by scoring 1 for modest, 2 for marked and 3 for dramatic improvement, subtracting the Dromia-only total from the Dromia-plus-Noostan total in each category, and then dividing by the number of subjects. A Net Improvement score of 100% is equivalent to all children advancing to the next better evaluation (*i.e.*, from modest to marked, or marked to dramatic). The Speech Net Improvement score of 142% indicates the equivalent of 100% jumping one level of improvement plus 42% jumping two levels.

A positive Net Improvement score does not imply that all children achieved that positive improvement. It means that children with less-than-indicated improvement would be balanced by children with greater-than-indicated improvement. SWF

Smart Drug Update: The Case for Piracetam in Down's Syndrome

(continued from previous page)

"One of piracetam's most unique and conspicuous features is its extremely low toxicity."

effects [Karacostas *et al.*, 1993]. The recommended dose of piracetam for infants with myoclonic seizures is 10-20 g/day (approximately 1-2 rounded tablespoons), a phenomenally high dose by normal drug standards.

Piracetam is absorbed rapidly and completely following oral intake, and it is excreted predominantly unchanged in the urine. Peak plasma levels are reached in less than an hour. However, brain concentrations rise more slowly. It may take days for piracetam to reach peak levels in the brain, and days for it to fall after discontinuation. Additional information about piracetam can be obtained by reading the *Smart Drug Update* on piracetam [see *SDN* v1n10] and the piracetam chapters in *Smart Drugs & Nutrients* and *Smart Drugs II*.

Piracetam and Seizures

"Of 21 patients with disabling myoclonus due to various causes, 10 had to be rescued from the placebo phase of the study due to severe exacerbations of their myoclonus."

Allegations of increased seizure risk from piracetam have been made by a few US physicians associated with establishment DS organizations. This is of special concern due to a higher-than-normal incidence of seizures in DS individuals. The basis of these allegations of seizure risk is enhanced cellular calcium influx from piracetam, an *in vitro* (test-tube) finding whose applicability to real life must be seriously questioned in the face of decades of clinical experience to the contrary [see *SDN* v5n8p10]. In fact, piracetam has mild anti-seizure activity, and it protects against memory and cognitive deficits caused by seizures.

Piracetam is used as an adjunctive therapy for epilepsy. Although its effects on epilepsy are not considered sufficiently substantive when used alone, piracetam does potentiate the antiepileptic activity of other drugs. Some newer "racetam" analog drugs appear to have stronger anticonvulsant activity.

"Piracetam is recognized throughout most of the world as a treatment of choice for myoclonus, a seizure-like condition characterized by uncontrolled muscle twitching or jerking."

Piracetam is recognized throughout most of the world as a treatment of choice for *myoclonus*, a seizure-like condition characterized by uncontrolled muscle twitching or jerking. This application of piracetam has been thoroughly researched from a clinical perspective. Piracetam has orphan drug status in the US for treatment of myoclonus.

In a recent study of 60 patients, piracetam was found to be "effective in myoclonus, especially that of cortical origin" when used either singly and with other drugs [Ikeda *et al.*, 1996]. Although this study was open-label, a blinded video inspection was employed. Piracetam was of positive benefit to handwriting, feeding, sleep, attention deficit, depression, gait ataxia (incoordination), and convulsions, but not to dysarthria (articulation difficulty). This latter finding is somewhat paradoxical, given that enhancement of speech and language skills is generally the rule rather than the exception. There was also "no positive correlation between clinical and electrophysiological [EEG] improvement," suggesting that piracetam works through a different mechanism than standard anticonvulsant drugs.

In an earlier study, myoclonic patients with positive clinical responses to piracetam (2.4 to 16.8 g/day) were studied in a placebo-controlled, double-blind, two-week, crossover trial. Of 21 patients with "disabling spontaneous, reflex or action myoclonus due to various causes," 10 had to be rescued from the placebo phase of the study due to severe exacerbations of their myoclonus [Brown *et al.*, 1993]. No patients required rescuing from the piracetam arm. Piracetam improved motor function scores, writing ability, functional disability scores, global assessment scores, and visual tests. The authors concluded, "Piracetam, usually in combination with other antimyoclonic drugs, is a useful treatment for myoclonus of cortical origin."

The dose of piracetam may be quite large in some circumstances and still be well tolerated. In one case of accidental electrocution, spastic tetraparesis (limb paralysis) and spontaneous myoclonus (muscle twitching) in both arms were successfully controlled by 24 g/day piracetam, administered intravenously [Karacostas *et al.*, 1993]. The myoclonic movements returned three days after the piracetam was discontinued six weeks into therapy, and were almost abolished when the piracetam was resumed.

A review of the treatment of myoclonus with piracetam covering "62 case reports, 3 open trials and 2 double-blind trials, covering 171 patients" has been published [Van Vleymen and Van Zandijcke, 1996]. A clinical review of the symptoms and diagnosis of myoclonus, progressive myoclonus epilepsy and other epilepsies, and the use of piracetam and 5-hydroxytryptophan in recent clinical trials, has also been published in *Nurse Practitioner* [Tate, 1995].

Membrane Fluidization

One of the effects common to many antiseizure medications and therapies is *fluidization of brain membranes*. Membrane fluidity is influenced by many factors, some of which are cholesterol content, fatty acid

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profile, and degree of lipid peroxidation. The higher the cholesterol content, the more rigid and impermeable membranes become. The more polyunsaturated the fatty acid profile, the more fluid they become. And peroxidization, a potential risk factor in DS, decreases membrane fluidity.

Brain membranes may be especially sensitive to changes in membrane fluidity. They have an especially high degree of polyunsaturation, containing high levels of EPA (*eicosapentaenoic acid*) and DHA (*docosahexaenoic acid*), which have 5 and 6 double bonds respectively. These highly unsaturated fatty acids increase the fluidity of brain membranes, but they also make them especially sensitive to free radicals and oxidative stress, a putative risk factor resulting from overexpression of *superoxide dismutase* (SOD), an antioxidant enzyme which is encoded on the 21st chromosome. The overexpression of SOD increases production of hydrogen peroxide {see *SDN* v4n10].

"Piracetam may have special application to Down's syndrome due to developmental delays in the closing of the heart muscle wall between the right and left sides of the heart."

The latter fatty acid, DHA, is found in relatively high levels in human breast milk, but not in soy or cow's milk. Infant formulas manufactured in the US do not contain DHA, but many in other parts of the world do. The lack of DHA in early infancy, and/or its peroxidation, may have deleterious effects on cognitive development. The higher-than-normal incidence of nursing difficulties in DS infants may make them more at risk from this problem.

Piracetam mitigates oxidative stress and fluidizes brain membranes. The membrane fluidizing effects of piracetam have been reported in both rodents and man. The age-related decrease in brain fluidity seen in aged rats is partially corrected by administration of piracetam. However, in young rats, piracetam caused no measurable fluidization [Mueller *et al.*, 1997]. This suggests that piracetam has a normalizing or self-limiting effect on brain membrane fluidity. In other words, if fluidity is normal, nothing happens, if fluidity is abnormal, it is normalized. This finding may be of particular interest in DS due to the possibility of abnormal fluidity changes in early infancy and childhood. Although this has yet to be measured directly, various signs of decreased membrane fluidity are evident (seizure risks are high in infants, and they have been observed to increase over time).

Piracetam and Hypoxia

Hypoxia is a condition of low oxygen levels in the tissues. Hypoxia can be caused by lack of oxygen in the air (hypobaric or high-altitude conditions), decreased oxygen-carrying capacity of the blood (anemia or carbon monoxide toxicity), by impaired circulation (ischemia, heart attacks, blood clots, etc.), or other causes.

For decades, piracetam has been studied as an anti-hypoxia agent. This may have special application to DS due to developmental delays in the closing of the heart muscle wall between the right and left sides of the heart. This results in the mixing of blood from the right side of the heart (which pumps oxygen-depleted blood to the lungs) with blood on the left (which pumps oxygenated blood to the rest of the body). This effectively diminishes oxygen delivery capacity and exposes affected individuals to some degree of chronic hypoxia.

Hypoxia has an adverse effect on cognitive functioning, which piracetam effectively prevents [see *SDN* v1n10]. Hypoxia is also associated with increased lipid peroxidation, which is inhibited by piracetam and antioxidants [Nagornev *et al.*, 1996]. This effectively increases human resistance to high altitude. In aged patients with ischemic heart disease, the combination of piracetam and tocopherol acetate (vitamin E) provides better control of angina pain, increases exercise tolerance, and positively influences hemodynamic measurements [Pimenov *et al.*, 1997]. These

Senility Prescription Practices

Clinical prescription practices may vary dramatically between countries. Regional differences in practice often reflect political and regulatory issues. In a recent survey of family physicians and neuropsychiatrists in Lower Saxony, Germany, physicians were asked what they would prescribe based on a written case description of a 70-year-old widow with moderate dementia and vascular risk factors. The doctors were randomly assigned one of two different case descriptions, one whose history was typical of *vascular dementia*, and the other which was typical of *senile dementia of the Alzheimer's type* (SDAT). The following top responses were received:

Drug	Vascular dementia	Alzheimer's (SDAT)
Piracetam	25.6%	30.9%
Ginkgo biloba	24.4%	28.4%
Nimodipine	14.1%	25.9%
Aspirin	29.5%	17.3%

Overall, there were only minor treatment differences based on the type of dementia or the medical specialty. The exceptions were co-dergocrine (ergoloid mesylates, or generic Hydergine), which was favored for SDAT over vascular dementia, and ginkgo, which was favored by family physicians over co-dercrine and nimodepine (which may reflect an emphasis of family physicians on cost and safety factors).

Stoppe G, Sandholzer H, Staedt J *et al.* Prescribing practice with cognition enhancers in outpatient care: Are there differences regarding type of dementia? Results of a representative survey in Lower Saxony, Germany. *Pharmacopsychiatry* 29(4): 150-55, 1996.

(continued from previous page)

observations confirmed earlier work [Pimenov *et al.*, 1992].

Hypobaric hypoxia of pregnant rats causes memory impairment and learning delays (in both passive and active tasks) in newborn pups. Postnatal piracetam (200 mg/kg/day) in the second and third weeks of life partially corrected behavioral disturbances and physical development, but not adaptive behavior, caused by this prenatal hypoxia [Trofimov *et al.*, 1993].

"Postnatal piracetam in the second and third weeks of life partially corrected behavioral disturbances and physical development caused by prenatal hypoxia in rats."

The adverse role that oxidative stress can play in cognitive functioning can also be blocked by piracetam. Craniocerebral trauma in rabbits causes 1) increased free radical activity, 2) decreased antioxidant function, and 3) increased lipid peroxidation throughout the brain. These effects are prevented by piracetam or amphetamine (which are stimulants), but not by phenobarbitol (a CNS depressant) [Promyslov and Demchuk, 1995]. The lack of any direct antioxidant effect of piracetam or amphetamine in an *in vitro* model suggests that the antioxidant effect is entirely mediated by secondary metabolic effects of these compounds.

Piracetam and Heart Disease

Although piracetam has obvious theoretical applications to the hypoxic conditions typical of heart disease, Russian doctors and scientists appear to be the only researchers pursuing this application.

In 1995, Dasaeva published the results of a study of hypertensive subjects under job-related stress (*i.e.*, "nervous and emotional stress" in their work environment). Piracetam "appeared to improve psychic state, mental performance and the occupationally important function of memory" without any adverse effect on attention. A follow-up report on the use of piracetam with reserpine (an antihypertensive medication that is also used as an antipsychotic agent) found that piracetam reversed the adverse effects of reserpine on activity, memory and cognitive function [Dasaeva and Vermel, 1996]. The authors stated that the combination of piracetam and reserpine "is thought effective for inpatient treatment of hypertensive subjects exposed to psychoemotional stress."

"These clinical improvements were statistically significant and continued for several months after discontinuation of the piracetam."

In elderly patients with stable effort angina, piracetam (2.4-5.2 g/day) improved several metabolic and hormonal indices. Low-density lipoprotein cholesterol in serum decreased, as did triglycerides. There were also improvements in glucose tolerance (reduced hyperglycemia and hyperinsulinemia) [Pimenov *et al.*, 1995].

Piracetam's hypoxia-protective effects may be maximized under more extreme conditions. In a rat study of experimentally induced heart attacks, piracetam (400 mg/kg) and sodium oxybutyrate (GHB) (200 mg/kg) normalized aortic blood flow acceleration during exercise and increased overall survivability [Tsorin *et al.*, 1993]. Yet neither piracetam nor GHB had any significant effect on cardiac contractility at rest.

Piracetam may also be of benefit to other hypoxia-related conditions. In a Russian clinical study of 155 patients with destructive pulmonary tuberculosis, the effectiveness of conventional antibacterial therapy (isoniazid, rifampicin, streptomycin) was enhanced by the addition of chemotherapeutic drugs (pirazinamid or ethambutol) and vitamin therapy. There was additional enhancement of efficacy from the addition of antioxidant therapy (tocopherol acetate or galascorbin) with anti-hypoxants (piracetam, calcium pangamate and piriditol) [Savula *et al.*, 1993].

Piracetam and Inflammation

The regulation of biological responses to oxygen free radicals, whether due to low or high oxygen levels, is mediated by tissue hormones called *prostaglandins*. These powerful hormones are created by the interaction of oxygen free radicals and polyunsaturated fatty acids (PUFAs). In a series of complicated metabolic transformations, the oxidized PUFAs are converted stepwise into various prostaglandins which mediate such injury-related biological responses as platelet aggregation (to maximize clotting in bleeding areas and minimize it in others), vasoconstriction (to minimize blood loss), immune cell activation (to absorb necrotized tissue and prevent infection), vasorelaxation (to maximize blood flow during repair) and blood pressure. The proper coordination of these events is necessary for proper response to traumatic injury and for effective healing.

"The prostaglandin cascade often results in collateral damage to otherwise healthy tissues immediately adjacent to damaged tissue. Piracetam moderates this damage."

The prostaglandin cascade often results in collateral damage to otherwise healthy tissues immediately adjacent to damaged tissue. Piracetam has been shown to moderate this damage. In a study of animal burn wounds, piracetam (200 mg/kg IM) or hyperbaric oxygen were both found to protect the basal epidermal cells (the "living" skin layer) from necrosis (death) [Germonpre *et al.*, 1996].

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"The anti-hypoxic, neuroprotective and anti-inflammatory effects of piracetam would seem to offer potential benefits to persons facing surgical trauma."

Piracetam and Heart Surgery

The high incidence of heart defects in DS infants has raised questions about how concurrent piracetam use may affect surgical risks. The standard response of US cardiovascular surgeons (and hospitals) is to insist that piracetam be discontinued prior to surgery. There are obvious legal and liability justifications for this policy, but are there medical reasons for this recommendation? In other words, would piracetam increase or decrease survivability in open heart surgery?

The anti-hypoxic, neuroprotective and anti-inflammatory effects of piracetam would seem to offer significant potential benefits to persons facing surgical trauma, especially when it is heart surgery which might entail periods of interruption of blood flow to the brain. Several research teams across the world have been investigating aspects of this issue.

In a randomized study of patients with severe or recurrent venous thrombosis, piracetam has shown a beneficial potentiating antithrombotic effect when administered with anticoagulants (heparin or vitamin K antagonist) [Moriau *et al.*, 1995]. This effect is partially attributed to an anti-platelet effect characterized by 1) inhibition of thromboxane (a prostaglandin), and 2) reduction in fibrinogen and plasma factor VIII (von Willebrand's factor) [Moriau *et al.* 1993]. It was also attributed to various rheological (blood flow) effects due to increased deformability of cell membranes (red cell, white cell and platelet). Increased deformability allows red blood cells to better squeeze through through microcapilaries throughout the tissues of the body.

In healthy adults, these rheological effects are observed at single doses of 9.6 g and 4.8 g, but not at 3.2 g and 1.6 g. Since the standard dose of piracetam is 0.8 to 1.6 g three times daily, standard use may be below a rheological threshold. These effects peak about 1-4 hours after dosage and gradually disappear over 8-12 hours [Moriau *et al.* 1993]. This suggests that frequent dosing (at least three times daily) is a requirement for high-dose piracetam use. It is appropriate to reiterate that additional caution may be warranted with any combination of high-dose piracetam with anticoagulants (*i.e.*, warfarin) [Pan and Ng, 1983], high-dose anti-myoclonic drugs [Ikeda *et al.*, 1996], or blood-thinning agents (PUFA-rich fish oils, BHT food preservative, aspirin, etc.).

Piracetam (400 mg/kg) has also been reported to have beneficial effects on the maturation of blood cells in rats [Nyagolov *et al.*, 1993]. Increased iron incorporation into newly formed red blood cells, increased reticulocytes (a red cell precursor), and increased maturation of erythroblasts (a red cell progenitor cell line located in bone marrow) were all indications of piracetam-induced erythropoiesis (the generation of new red blood cells). A similar pro-maturation effect was seen in white blood cells (small lymphocytes and granulocytes).

Learning Disabilities

Piracetam's ability to enhance learning abilities may be directly related to its effect on membrane fluidity. In rat studies, 300 mg/kg of piracetam administered once daily enhanced brain fluidity and active avoidance learning *only in old animals* [Mueller *et al.*, 1997]. There was no measurable effect on either parameter in young animals.

Piracetam is quite effective in reducing memory loss and learning deficits in rats caused by *kindling* (induction of epileptic-like seizures by toxic chemicals). Kindled rats show decreased active avoidance

Piracetam and Sickle Cell Anemia

Piracetam's fundamental lack of toxicity has prompted numerous pediatric uses over more than two decades of clinical use. One of the latest appears to be sickle cell anemia and β-thalassemia. Piracetam shows a strong anti-sickling influence *in vitro* and *in vivo*, and a Saudi Arabian double-blinded clinical study found a significant reduction in "the clinical severity of the disease, the number of crises, the extent of hospitalization and the blood transfusion requirements" in children in the 3-12-year age range [El-Hazmi *et al.*, 1996]. Although these clinical improvements were highly statistically significant ($P<0.001$) and continued for several months after discontinuation of the piracetam, there were no corresponding changes in haematological or biochemical parameters associated with sickle cell disease.

El-Hazmi MAF, Warsy AS, Al-Fawaz I *et al.* Piracetam is useful in the treatment of children with sickle cell disease. *Acta Haematologica* (Basel) 96(4): 221-26, 1996.

Piracetam in Angelman Syndrome

Angelman syndrome is a genetic condition characterized by a deletion of part of maternal chromosome 15 (15q11-13), which is associated with severe mental retardation, ataxic (uncoordinated) gait, tremulousness, and jerky movements. Although not yet fully studied, the critical region of the 15th chromosome contains several genes that code for GABA-A receptor subunits. The GABA-A receptor is the most common GABA receptor in the brain. GABA-A receptors regulate the flow of chloride ions (Cl^-) across neuron membranes, which decreases neuron excitability. In Angelman syndrome, the lack of adequate GABA-A influence increases neuronal (CNS) excitability and results in myoclonic (muscle twitching) activity, which was reported to be significantly reduced in 5 patients by treatment with piracetam [Guerrini *et al.*, 1966].

Guerrini R, De Lorey TM, Bonanni P *et al.* Cortical myoclonus in Angelman syndrome. *Annals of Neurology* 40(1): 39-48, 1996.

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"Learning deficits in rats caused by prenatal alcohol exposure are partially corrected by post-natal piracetam administration."

"Only piracetam was effective in preventing kindling-induced learning deficits regardless of the timing of administration."

"Early intervention is a form of training which can augment environmental influences on development and enhance cognitive potential."

learning. Of vinpocetine (0.1 and 1.0 mg/kg), methylclucamine orotate (225 and 450 mg/kg), meclofenoxate [centrophenoxine] (100 mg/kg) and piracetam (100 mg/kg), only piracetam was effective in preventing kindling-induced learning deficits regardless of the timing of administration (*i.e.*, either before or after kindling) [Becker and Grecksch, 1995]. None of these drugs had any significant effect on the *severity* of induced seizures. Piracetam also prevents *amnesia* in kindled rats [Genkova-Papazova and Lazarova-Bakarova, 1996].

Learning deficits in rats caused by prenatal alcohol exposure are partially corrected by post-natal piracetam administration [Trofimov *et al.*, 1996].

The possibility of synergy between biologically based therapies (*i.e.*, nutrition and/or drugs) and cognitive therapies (*e.g.*, training, physiotherapy, speech therapy, memory exercises, etc.) deserves close consideration. The standard early intervention therapy for DS children is a form of educational training which can augment environmental influences on development and enhance cognitive potential. Synergy between *Ginkgo biloba* and memory training [see *SDN* v1n10p7] has now been confirmed with ginkgo (160 mg/day) and piracetam (2.4 or 4.8 g/day) [Deberdt, 1994]. These studies suggest that nootropic drugs and memory training enhance *different* cognitive functions and act complementarily. Deberdt writes, "This potentiation is very clear in the treatment of dyslexic children." While the dyslexic placebo group achieved only half the normal progress in reading accuracy and comprehension during a normal school year, the piracetam group (3.3 g/day) achieved a full year of progress.

Piracetam and Language Skills

Piracetam has a specific language-enhancing effect. This effect has been observed in studies of adults and children with learning disabilities, and it has recently been confirmed in a double-blind, placebo-controlled study of aphasic infants and young children (of up to three years of age) [Huber *et al.*, 1997]. Aphasia involves impairment of communication skills (speech, written or signing) due to neurological dysfunction in the dominant speech centers of the brain. Huber and colleagues studied the effect of piracetam and placebo on 6 weeks of intensive language therapy and found statistically significant enhancement of language reaquisition in the piracetam group.

In a 12-week, randomized, double-blind, placebo-controlled pilot study of 158 adult stroke patients undergoing rehabilitation, recovery was significantly enhanced by piracetam. Recovery in a subset of aphasic individuals was also significantly enhanced (P=0.02) [Enderby *et al.*, 1994].

Summary

Piracetam offers the potential of addressing a host of DS-related conditions without imposing any significant toxicity. It has been demonstrated to augment cognitive, learning and memory abilities, to decrease oxidative and hypoxic stress, and to stabilize cells in the blood and central nervous system. The degree to which these benefits may accrue to DS individuals needs to be thoroughly investigated.

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Smart Drug Update:

The Case for Piracetam in Down's Syndrome

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"Piracetam offers the potential of addressing a host of Down's syndrome-related conditions without imposing any significant toxicity."

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Rumors about GHB?

As a European physician, I was dismayed to read an article (I do not know its source) which made ludicrous, alarmist statements about GHB. Do you know anything about these terrorist allegations about comas, deaths, date rapes, respiratory shut downs, etc.? GHB is approved here as a prescription medication. We are having no problems with it at all! **anon, M.D.**

"As a European physician, I was dismayed to read an article which made ludicrous, alarmist statements about GHB."

As you may have just read in our recent editorial, elements in the US government have decided that GHB is the new demon drug to be prohibited at all costs. It may be a coincidence, and it may not, that the governmental myths about marijuana (which is Schedule I; no allowed medical uses) are unraveling as several states are attempting to decriminalize its medical use. I prepared a 17-page report to the California Legislature (which is now posted on our web site: http://www.ceri.com) in an attempt to counteract the anti-GHB propaganda, and I made arrangements to have Dr. Ward Dean fly out to California to testify before the California Senate Committee on Criminal Procedures. But for some undisclosed reason, the hearing was moved up a week without notice to me, and Dr. Dean's testimony concerning the safety of GHB and the inaccuracy of alleged GHB-related deaths was never heard. Despite my overt testimony that the "facts" being offered in support of the bill were highly questionable, the committee was not interested in hearing anything more than token opposition to the bill. It passed overwhelmingly.

Interestingly, the California Senate (SB#) and Assembly (AB6) bills to criminalize GHB were temporarily derailed, not because they would be bad social policy, but because they would cost money. California law now requires that the fiscal costs of all bills be considered in an appropriations committee before they are moved to the floor for final vote. The authors had asserted that the bills would have negligible fiscal impact (i.e., less than $150,000 per year), but the appropriations committees found that arrest and incarceration of only 6 persons on GHB charges based on the bill would result in exceeding that limit.

"In May, three bills were introduced into the House of Representatives that would control GHB at the Federal level."

The Senate bill (SB3) has now passed the Senate Appropriations Committee and will probably pass on the floor of the Senate as this issue goes to press. It now looks like possession of GHB is about to become a felony crime in California. The law will become effective immediately; *there will be no grace period.* **SWF**

Attempts are now underway to criminalize GHB nationally. In May, three bills were introduced into the House of Representatives that would control GHB at

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Consumer's Guide to Using Melatonin" in *SDN* v4n9p1-4). In general, if you go to bed late, you might want to use a quick release melatonin product (sublingual liquid, sublingual tablet, or capsule). If you go to bed early, you might want to use a timed-release product. Most timed-release tablets are put together in layers and consequently do not function in a timed-release manner when broken into pieces for purposes of reducing the dosage. Timed-release tablets require use "as is." **SWF**

"We'd be interested in hearing a report from you about your experiences with melatonin and meditation."

We'd be interested in hearing a report from you about your experiences with melatonin and meditation. Please consider writing them up for us. **WD & SWF**

QHI Gets Vote

I would just like to report that I received very good service from Quality Health, Inc., and would recommend them. Products arrived 10 days from faxing order, and came with all original packaging and inserts. **DA**

Down's Syndrome and Doctors

I have an almost-5-year-old daughter with Down's syndrome and have been reading with interest the information on TNI and piracetam provided by both you and Dr. Paul Spurlock on your respective web sites. Without medication, my daughter has tested low normal in IQ, but her expressive speech is still significantly delayed (although her speech teacher recently told me that she is ahead of most Down's children her age). It sounds to me like piracetam may be just what she needs. **BH**

"Speech enhancement is one reason why piracetam is being used so frequently with Down's syndrome."

You may be right. Speech enhancement is one reason why piracetam is being used so frequently with Down's syndrome. It specifically addresses a significant prenatal element (diminished corpus callosal development) that is common in Down's children (and to males in general). It can act as a specific enhancer of linguistic skills that depend on *interhemispheric coordination* for effective function. See "The Case for Piracetam in Down's Syndrome" in the last issue. **SWF**

I have discussed the use of TNI and piracetam with our pediatrician, but he is invoking the "first do no harm" rule. **BH**

"I have discussed the use of TNI and piracetam with our pediatrician, but he is invoking the 'first do no harm' rule."

What does that have to do with piracetam? Piracetam is essentially non-toxic and no reports of permanent damage have *ever* been made, unlike many drugs that your pediatrician has probably already prescribed to your daughter. The primary harm that may result is 1) your disappointment in the face of high expectations, 2) financial loss (piracetam costs from 25 cents to several dollars per day depending on age and dosage), and 3) rare temporary symptoms of headache, nausea, diarrhea, constipation, irritability, hyperactivity, spaciness, or other symptoms which may happen when you give anything to anybody. **SWF**

He has agreed to prescribe the testing, but only after we visit a geneticist. However, he is reluctant to allow any supplementation beyond the USRDAs. **BH**

Find a new physician!! **WD**

I have to agree with Dr. Dean. The US RDAs are *minimal* levels of nutrition that are designed only to prevent deficiency conditions (a gross sign of unmet need) in the average "normal" person, which also means that they are *not* designed to supply the total nutrition needs of the majority of people. The safe level is usually 2-10 times higher for minerals, 5-30 times higher for fat-soluble vitamins, and 100-1000 times higher for water-soluble vitamins. The toxic level is higher still. Your physician's prejudice lacks scientific justification.

A typical physician regularly prescribes drugs with safety margins of less than 10 (*i.e.*, ten times more than the prescribed dose will cause serious adverse side effects). Medical opinions about megavitamins have arisen from anticompetitive rhetoric against orthomolecular physicians who use nutrients (and drugs when necessary) to restore the proper molecular functioning of the body, as advocated by the late Nobel laureate Dr. Linus Pauling. But Professor Pauling had the unpardonable gall to tell physicians things that they knew to be false, namely 1) that vitamin C was effective against the common cold, 2) that the RDA for vitamin C should be 200 mg, and 3) that 2000-10,000 mg daily was probably healthier still. It was pure heresy! But recently, Dr. Mark Levine and colleagues at NIH have scientifically verified the correct RDA of vitamin C in a detailed, painstaking study of young healthy men in a totally controlled environment [see *SDN* v5n2p1]. You guessed it, it's 200 mg daily! Pauling was right on target. But like Cassandra, he had to be persecuted for his prescience.

The sad thing is that the levels of nutrients in TNI formulas for DS are tens to hundreds of times lower than over-the-counter supplements in widespread use within the US. Check out the labels on *MSB-plus* and *Nutrivene-D* and see for yourself. Your physician probably hasn't even examined either

Q&A Questions + Answers

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formula to see if there are any real long-term risks from high levels of nutrients. There aren't. The risks of using the formula are far less than those of *not* using it. And the risks are probably far less than an agile adult crossing a street during rush hour to buy groceries at the local market. **SWF**

"If your doctor is unwilling to provide medical supervision, then you really need to find another physician!"

My physician said that regardless of what the geneticist says, he will not support piracetam, due to the lack of research in the use of piracetam specifically in Down's patients. **BH**

Does he prescribed antibiotics to your daughter? If so, ask him if he knows of any studies testing that antibiotic in DS patients. Most have not been tested specifically in DS populations. If he then falls back to "years of general clinical experience" with antibiotics in DS, ask why 20+ years of general clinical experience with piracetam is insufficient.

I think they call such double standards *hypocrisy* outside of the medical profession.

Fortunately for you and your daughter, you do not need a prescription to obtain and use piracetam. The FDA's personal-use import policy specifies that importation of piracetam is allowed for the treatment of debilitating or life-threatening conditions. Untreated DS is definitely debilitating, so you are covered. The personal-use import policy also specifies that patients must be under "medical supervision" for the imported item(s). This *does* require your daughter's physician's participation. If he's unwilling to provide medical supervision, then you *really need to find another physician!* **SWF**

Correspondence

Please mail your questions to: CERI Q&A, P. O. Box 4029, Menlo Park, CA 94026. Or you can fax your questions to 415-323-3864, or e-mail them to questions@ceri.win.net. Initials of the author follow each question. If you want us to use your full name, or if you want us to omit your initials, please state so in your correspondence.

Nutrition Update: Designer Brain

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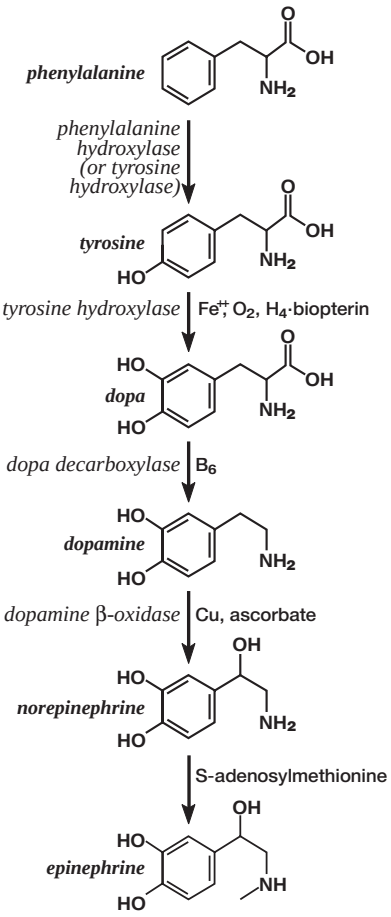
Dopamine Biosynthesis



aspects of our relationship to the external environment, including emotional tone and motivational level.

While the cerebral cortex is a recent evolutionary adaptation of higher mammals, the brain's limbic structures are an age-old system common to mammals, reptiles, birds and amphibians. This has led to the limbic system being described as the "reptilian" brain. However, this term may be more a reflection of a general cultural prejudice against "primitive" emotions and "animalistic" motivations by researchers interested in compartmentalizing (and denigrating) our less-than-spiritual characteristics. As we will see later in this article, the limbic system is a necessary and essential aspect of being human.

Two of the dominant neurotransmitters of the limbic system are serotonin and dopamine. Serotonin promotes calmness, emotional stability, and passivity, while dopamine promotes arousal, emotional volatility and activity. These opposing actions can be considered complementary regulators of our behavioral responses.

This emotional and motivational regulation is enhanced by active interaction with environmental influences. Serotonin levels are readily influenced by dietary composition, while dopamine levels are not. Thus, the active dynamic between these two neurotransmitters allows for the central nervous system to adapt quite effectively to basic external conditions.

One of the simplest ways to investigate the balance between serotonin and dopamine is through *selective neurotransmitter precursor loading*. This approach is based on feeding the metabolic pathways that produce the different neurotransmitters.

Dopamine Biosynthesis

The catecholamine neurotransmitters (dopamine, norepinephrine and epinephrine) are synthesized from phenylalanine, tyrosine or dopa (see margin illustration). The rate-limiting step in this pathway is the conversion of tyrosine to dopa by *tyrosine hydroxylase* (which can also convert phenylalanine to tyrosine).

There are fairly large differences in how the choice of precursors affects dopamine synthesis. The most obvious one is that dopa is the only precursor which bypasses the rate limiting step in the pathway. Indeed, dopa supplementation raises dopamine synthesis to a much larger degree than phenylalanine or tyrosine. There is also a major difference in the degree to which different precursors enhance the different catecholamine neurotransmitters. I have observed that phenylalanine and tyrosine enhance norepinephrine more than dopamine, and dopa enhances dopamine more than norepinephrine.

Epinephrine, also known as adrenaline, is normally only found in trace amounts in the brain. It is primarily a peripheral (body) neurotransmitter produced by the adrenal gland for the "fight or flight" response to stressful (*i.e.*, "emergency") situations.

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significantly increasing it. Tryptophan and 5-HTP appear to offer the potential for better therapeutic results, decreased side effects, and lowered health-care costs. ¤

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"Our pediatrician's main concern is that we don't know what is going to show up five to seven years from now; his example was L-tryptophan and the problems that it ended up causing."

Down's Syndrome and Doctors

My physician said that he will not support piracetam due to the lack of research in the use of piracetam specifically in Down's patients. **BH**

The Barcelona study (conducted by Dr. Fiona and associates) tested piracetam with and without 5-hydroxytryptophan in a DS population [see summary in *SDN* v5n8p2]. The study was open (unblinded), used historical controls, and has never been replicated.

There are two concerns regarding piracetam: safety and efficacy. If one focusses only on safety concerns, whether or not the Fiona study has been replicated is of minimal concern. The treatment was well tolerated and produced no clinically significant adverse effects — just like in every other study of piracetam ever conducted in non-DS populations (blinded and non-blinded alike). It is exceedingly rare that studies are ever done for narrow specialty populations for drugs in common use in the general population — let alone the long-term studies that we might all like to see done. Physicians use drugs in practice and report adverse effects through professional and governmental channels. Piracetam is an old drug that has been tested in people and animals for three decades. During this time, no serious problems have ever surfaced. None.

Regarding efficacy, the issue is different. One can certainly question the efficacy of piracetam in treating DS if the Fiona study is the only evidence offered. But is this, in itself, a good reason not to try it? Such decisions involve weighing known benefits, known risks, unknown benefits and unknown risks — a process that is necessarily value dependent. Your physician has his values and you have yours. Personally, I think the benefits clearly outweigh the risks, which is why I take piracetam. But, bottom line, *it's only your family's values that matter* where therapy for your daughter is concerned.

The harm and cost of *not* using TNI and/or piracetam are: 1) brain damage (mental retardation), 2) inhibition of growth, 3) immune suppression (chronic infections), 4) enhancement of degenerative diseases (early senility, premature death), and 5) all of the emotional and social consequences of all of the above. I think your physician is comparing real apples to immaginary oranges. Please consider these issues carefully before agreeing with him. **SWF**

Our pediatrician's main concern is that we don't know what is going to show up five to seven years from now; his example was the wonder-drug L-tryptophan and the problems that it ended up causing. **BH**

I don't know which is worse, your physician's ignorance or his arrogance. L-Tryptophan did *not* cause problems — *contamination did.* The complicity of tryptophan is an FDA-engineered myth, perpetuated by ignorant doctors unwilling to look into the matter for themselves. Every expert that hasn't been "bought and paid for" by Showa Denko (the company that contaminated its tryptophan) or the FDA knows that contaminants were responsible for the eosinophilia myalgia (EMS) epidemic. If your physician had bothered to look up the

New Practitioners

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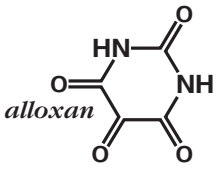
facts, he would have found that Showa Denko 1) introduced a *new strain of genetically engineered bacteria* into their tryptophan fermentation process, 2) *reduced* the amount of activated charcoal (an impurity-adsorbing agent) used in a primary purification process, and 3) *partially bypassed* a reverse-osmosis filtration process (another purification step) — all at the same time! Why would anybody make multiple, simultaneous changes in an industrial process? They did it to make more tryptophan — cheaper! Showa Denko was systematically driving everybody out of the tryptophan-manufacturing business by undercuting their competitors prices. The price for tryptophan had fallen from more than $400 per kilogram (2.2 pounds) to less than $200, and Showa Denko showed no sign of letting up. Their problem at the time was that they could not keep up with the demand they were creating with their low-priced tryptophan. So they needed a miracle — and they thought they had one with their *genetically engineered tryptophan-fermenting bacteria* that might double or quadruple their tryptophan yields.

"Physicians do have serious liability, both civil and regulatory, for prescribing TNI and/or piracetam."

"Contaminated tryptophan was not Showa Denko's first industrial experiment gone wrong."

Of course, there was a catch. The new impurities introduced into Showa Denko's "new-and-improved" tryptophan were never characterized or adequately tested before marketing. Within months of its introduction, customers began to experience a host of complaints that were later identified as eosinophilia myalgia syndrome (EMS). Eosinophils are small white blood cells that are produced when the body is exposed to parasites or toxins. Showa Denko's tryptophan contaminants were systematically stimulating eosinophil production. In a small percentage of people taking it, this production was so great as to literally fill up body tissues with eosinophils, causing great pain in more than a thousand people. More than a hundred died.



Contaminated tryptophan *was not Showa Denko's first industrial experiment gone wrong*. Twenty years earlier, Showa Denko was found to be responsible for mercury-contaminated seafood, created by massive industrial dumping of mercury into one of Japan's bays.

Tryptophan was in widespread use for two decades prior to the contamination incident, and 14 million people were taking it without apparent problems. Logically, the sudden, dramatic increase in EMS could only be caused by a contaminant. This same logic was effectively applied to solving Tylenol poisonings, which turned out to be cyanide contamination. No one *ever* suggested that Tylenol shouldn't be let back into the market. Tryptophan is a *ludicrous* example to justify your physician's point. I'd bet good money that your physician still uses Tylenol in his practice. I'd also bet that he does not consider cyanide poisoning symptoms to be a sign of Tylenol toxicity.

One cruel fact in this tryptophan fiasco was that uncontaminated tryptophan was found to be an effective treatment for the contaminant-induced EMS (US patent #5,185,157). By using the contamination as a political football to ban tryptophan from the US market, the FDA denied EMS victims a viable therapy and condemned them to continued suffering.

But the biggest flaw in your pediatrician's logic is his contention that we don't know what will happen in 5-7 years. In fact, we know we will see mental retardation, substandard growth and chronic infections if TNI and/or piracetam are not used. Your physician may be comfortable using tiny *unknown* risks to justify acceptance of *major* known risks, but you should not be fooled into thinking that his position is medically responsible, scientifically based or ethically sound.

Physicians do have serious liability, both civil and regulatory, for prescribing TNI and/or piracetam. Reluctance to prescribe TNI and piracetam based on 1) fear of being sued in the face of a negative or random outcome, or 2) fear of being disciplined or losing ones license by practicing medicine differently than one's peers, is entirely understandable. Blaming it on imaginary medical concerns is not. **SWF**

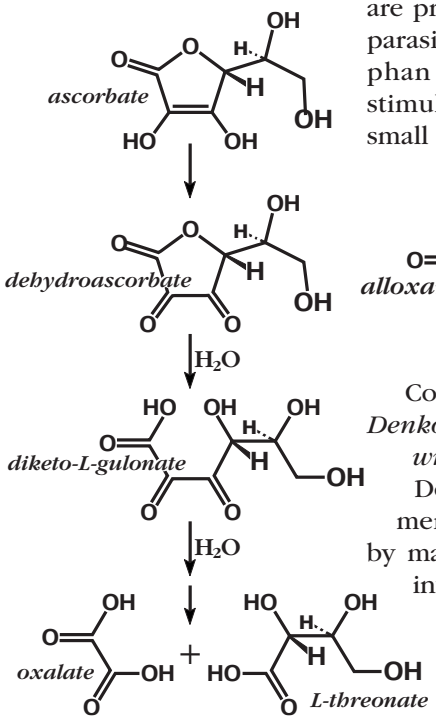
What is the proper pronunciation of piracetam? **BH**

I say per-ASS-ih-tam because I think acetate (ASS-ih-tate) is a root word — and because that's how Dr. Dean says to pronounce it. A fair minority of people say PEER-ah-SEE-tam. **SWF**

Dehydroascorbate Toxicity

In the last issue you talked about vitamin C stability in water. Is dehydroascorbate really that toxic? I've heard that it is found in Ester-C. I've also seen plenty of liquid vitamin C products in my local health food stores. How do they stabilize them? **OTP**

Figure 1:
The Oxidation and Catabolism of Vitamin C



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Down's Syndrome

I am a new father of a Down's baby. My son is now six weeks old. He was born at 34 weeks with some fluid in his chest cavity and two small holes in his heart. The fluid was drained immediately and the holes are already showing signs of closing. He is eating, sleeping and generally thriving nicely. **MM**

Collagen nutrients may possibly speed up closure. These include vitamin C, bioflavonoids, proline and lysine (see Q&A last issue). Both Nutrivene-D and MSB-Plus are formulated to enhance collagen production. See *SDN* v4n1p3 for more information about the overexpression of collagen genes on the 21st chromosome and *SDN* v6n2p7 for information about collagen applications to vascular strength, strokes, heart disease and ease of bruising. **SWF**

Since he was born, my wife and I have visited and read most of the information on the Internet on Down's (including CERI). We have also read a couple of excellent books, received the parent information packet from TRI and have spoken to many parents (some of whom have their children on TNI).

My family and I moved to London three months ago. We would like to start him on Nutrivene-D and possibly, eventually, on piracetam. Since we have been unable to locate a London doctor who is optimistic about TNI and with whom we are comfortable, I was wondering if you know any London doctors who are advocates of TNI? **MM**

No. Sorry. But do you really need an *optimistic* doctor? You can import Nutrivene and piracetam with or without a prescription (at least I think that you can in England).

If the English authorities hassle you, consider hiring Dr. Lawrence Leichtman, M.D. as your *consulting physician* and have him prescribe Nutrivene-D and piracetam. With his prescription, you should be able to minimize any difficulties. Most countries allow medical treatments that are begun in another country to be continued in their country. You just need to provide the necessary documentation. If a US prescription for piracetam is not honored in a British pharmacy, you can use it to import piracetam from a US compounding pharmacy into England. **SWF**

Although my wife and I have done considerable research, my wife is still uncomfortable about the use of piracetam in our infant son. **MM**

Such decisions involve deep values. Some are easily influenced by rational processes, and some are overwhelmingly emotional. You and she can read "The Case for Piracetam in Down's Syndrome" [*SDN* v5n9p1] and get a rational perspective, but I have observed that the emotional content of values are not so easily or quickly swayed. Take whatever time is necessary to make the decision right the first time. Too much pressure to change values too quickly can produce upset and emotional backlash. This can be a real problem in a relationship if one party is emotionally dominant and the other is rationally dominant, especially if there is not enough reciprocity and/or respect for the opposite orientation.

If your wife is rationally oriented, just have her read our materials on piracetam and ask her to call me call me on a Tuesday afternoon. I reserve from noon to 5 PM Pacific Standard Time for subscribers to ask questions about personal matters that are either 1) too private for the newsletter, or 2) too individual-specific for a general answer to suffice. If your wife is emotionally oriented, I suggest you take the time to sensitively explore the emotional side of the decision to her satisfaction with a let's-sleep-on-it attitude (*i.e., a low pressure approach).*

The answers in the *Q&A* column provide general information which should be applicable to a wider variety of situations than the literal question asked. However, there will always be situations where personal circumstances are too involved to adequately explain in writing. That's when its ideal to call with your question. If you call when I'm on the line with another subscriber, we can set up an appointment from 15 minutes later to an hour later, at your convenience, at which time you will have first priority. **SWF**

I am concerned about waiting because of the studies that I have read which discuss the damage to the brain after (here I have seen different opinions) four to twelve months of age. We have spoken to a few parents who wished that they had started their children on piracetam much sooner. Would you mind responding with your stance on piracetam, administering to an infant, safety issues, and any studies on long-term effects? Additionally, although I have searched the Web, I have found very little written negatively about piracetam. I know it must exist somewhere. Do you know of any of these type of sites? **MM**

Sorry, the information you are asking for does not exist. Piracetam has no LD_{50}, it is

"I believe that it is necessary to perform blood tests to obtain reliable results for the sex steroids."

"Although my wife and I have done considerable research, my wife is still uncomfortable about the use of piracetam in our infant son."

"The answers in the Q&A column provide general information which should be applicable to a wider variety of situations than the literal question asked."

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essentially non-toxic and it is universally well tolerated [Vernon and Sorkin, 1991]. Doses from 12-24 grams(!) per day are given to infants and children with myoclonic seizure disorders [Dukes, 1996; Reynolds. 1996]. At these very high doses, piracetam can cause rheological (blood) effects that can potentiate anticoagulant therapy with warfarin (documented), aspirin (undocumented), or fish-oil therapy (also undocumented). However, this blood-thinning effect is not observed at the 30 mg/kg dose that is used for cognitive enhancement purposes [Moriau *et al.*, 1993; Van Vleymen and Van Zandijcke, 1996].

"We have spoken to a few parents who wished that they had started their children on piracetam much sooner."

Starting early is a good idea. Oxidative stress associated with the overexpression of the SOD gene on the 21st chromosome [see *SDN* v4n10] begins at birth with the loss of maternal antioxidant support through the placenta. Since you have already decided on TNI (targetted nutritional intervention), you are not really waiting where issues of brain damage or retardation are concerned. In my opinion, most of the brain damage which occurs in the first two years of life is due to elevated levels of superoxide dismutase and its acceleration of apoptosis (cell suicide) of neurons in the developing brain. I think that this oxidation-related pathology is most effectively countered by the TNI component of the program. Piracetam may help, but *piracetam without TNI* is probably not very effective. I don't have good data to back up this opinion, but there is also a lack of good data showing enhancement of neural development or mental abilities in the 0-2 year age range. We have positive anecdotal reports, but no clinical studies.

"Regret is not fundamentally based on rationality, despite what rationalizations we may heap on it. It is fundamentally emotional. We feel that, somehow, we should have known anyway."

Any parent can regret any decision. It is inherent in being a parent, not in the nature of how you reached a specific decision. The decision to start TNI or piracetam is not fundamentally different from deciding when your child is ready to cross the street unaccompanied, to try riding a bicycle, to stay up past 9 PM, or to date. All such decisions involve a weighing of values, which, in 20-20 hindsight, can be reassessed at a later time. For example, Dixie Lawrence Tafoya regrets not putting her daughter on TNI and piracetam earlier. But that regret is based on knowledge that she didn't have at the time of the decision, knowledge learned after making the decision. Rationally, there is no way that anybody should expect themselves to have considered evidence that they did not have at the time. But regret is not fundamentally based on rationality, despite what rationalizations we may heap on it. It is fundamentally emotional. We *feel* that, somehow, we should have known anyway.

"In my opinion, most of the brain damage which occurs in the first two years of life is due to elevated levels of superoxide dismutase and its acceleration of apoptosis (cell suicide) of neurons in the developing brain."

The process of making a decision actually alters our values. Before the decision, we weigh things differently than after the decision. When deciding between the blue Mercedes or red Porche, the decision may be neck and neck. But after the decision, the blue Mercedes is *definitely* better. My apologies to the red Porsche owners out there, but this story illustrates the *emotional investment* we make in our decisions. It really doesn't matter whether we are talking about blue Mercedes, red Porsches, TNI, staying up late, or age of dating. They all involve a decision-making process that re-prioritizes our values. Worrying too much about regret prior to the fact is itself regrettable. Take some advice: 1) take your child's welfare to heart, 2) forgive yourself in advance for the decision you are about to make, and 3) make your decision. **SWF**

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Vitamin C and Iron Toxicity

Dr. Andrew Weil says not to take vitamin C when you have iron toxicity because vitamin C increases iron absorption from the diet. However, excess iron stimulates free radicals and vitamin C is an antioxidant. Why wouldn't vitamin C help detoxify these free radicals? What do you say?

We agree with Dr. Weil. While vitamin C is an important scavenger of oxidative free radicals, it is also a catalyst in the iron-mediated *Fenton reaction*, which produces the dangerous *hydroxyl radical.* In the Fenton reaction, iron in the +2 state reacts with hydrogen peroxide to form a hydroxyl radical and iron in the +3 state. Vitamin C converts the iron back to the +2 state where it can react with hydrogen peroxide again. Excess iron combined with excess vitamin C is potentially dangerous for this reason.

Dr. Weil's comment about vitamin C

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to compensate for this acidification, we really don't have enough experience to predict what problems might arise and how they can be effectively dealt with. Such experimentation should not be conducted casually. An acidification effect from butyrolactone in a person with an acidic constitution might produce strong effects quite quickly. Acidification in somebody with an alkaline constitution might be initially helpful and therefore discounted or ignored. If you try butyrolactone, please pay close attention and report your experiences to us. We'll update everybody as the information comes in. **SWF**

"What I want to know is how exactly does Prozac work, and could similar results could be obtained through the use of nutrients or St. John's wort?"

Prozac for Down's Syndrome

After listening to recent anecdotal reports that low-dose Prozac (5 mg per day) is producing good results in children with Down's syndrome, I reluctantly put my son on Prozac. While I don't like the idea of using drugs, I have seen great results over the last few days. His behavior is much better, he is verbalizing much more, he is trying harder to communicate, and he is much more affectionate. What I want to know is how exactly does Prozac work, and could similar results could be obtained through the use of nutrients or St. John's wort? **TR**

Prozac increases serotonin activity in the brain. Dixie Tafoya has long argued that there is a significant serotonin deficiency in Down's syndrome, despite the fact that tryptophan deficiency is not a universal aspect of serum amino acid profiles. I think that these recent observations with Prozac support her view.

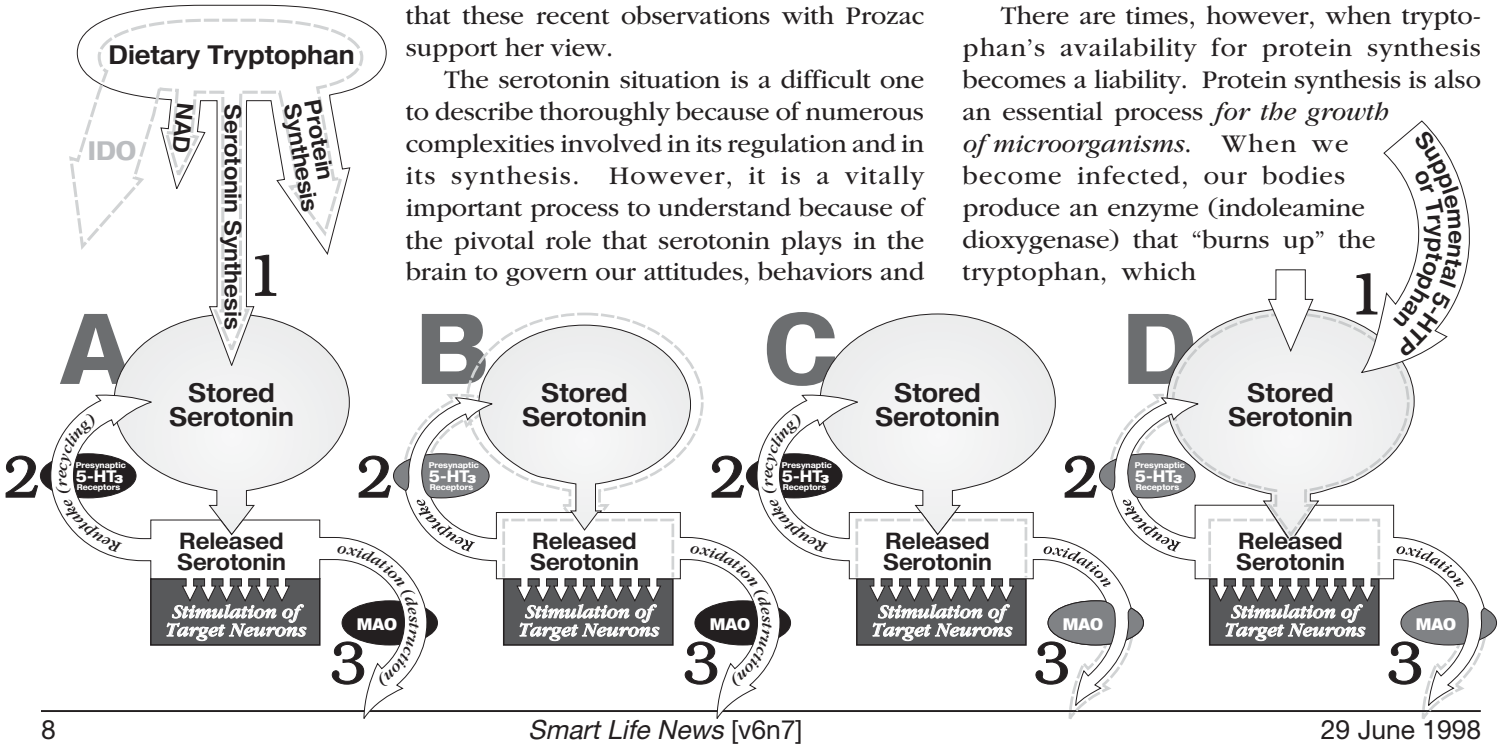
The serotonin situation is a difficult one to describe thoroughly because of numerous complexities involved in its regulation and in its synthesis. However, it is a vitally important process to understand because of the pivotal role that serotonin plays in the brain to govern our attitudes, behaviors and the emotional rewards we get from life.

Serotonin is made from tryptophan, an essential amino acid which serves multiple independent uses in the human body (see Figure A below). Its largest use is for protein synthesis (see the top of Figure A in the margin). Proteins are made from long chains of about 20 different amino acids, of which tryptophan is one. When we say that tryptophan is *essential*, we mean that it cannot be made in our bodies and must be obtained from the foods in our diet. Without tryptophan, we cannot make most of the enzymes and structural proteins necessary to maintain metabolism.

Tryptophan's minor uses (minor by volume, not by importance) are to make serotonin (a vitally important brain neurotransmitter) and *nicotinamide adenine dinucleotide*. NAD (also known as coenzyme 1) is an essential *hydrogen transfer agent* that carries "reducing power" in the body in the form of NADH (the H stands for *hydrogen*). Hydrogen and oxygen are necessary for *energy production* [see v5n2 for a complete explanation of this process]. Suffice it to say here that hydrogen is the electron-rich pole of the biochemical "battery" that powers our biochemistry, and oxygen is the electron-poor pole. This electrochemical battery drives the production of ATP (the energy currency of the human body). Although the amount of tryptophan that goes into making NADH and serotonin is small in absolute amount, the role that these substances play in our health is no less essential than protein synthesis.

There are times, however, when tryptophan's availability for protein synthesis becomes a liability. Protein synthesis is also an essential process *for the growth of microorganisms*. When we become infected, our bodies produce an enzyme (indoleamine dioxygenase) that "burns up" the tryptophan, which

Figure 1:
Serotonon Schematics



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inhibits the growth of invading bacteria and parasites and enhances our immune system's effectiveness. The tryptophan-destroying enzyme IDO is triggered by the general activation of the immune system by chemicals called *cytokines*. These cytokines are secreted by macrophages, lymphocytes and other immune cells. They serve as cell-signaling factors to coordinate the activities of the many cell populations of the immune system. These cytokines can also be activated by allergic responses and elevated corticosteroids as well. The oxidative stress associated with over-expression of SOD (superoxide dismutase) may be responsible for overactivating IDO in Down's syndrome. It is possible that some other factor is responsible as well.

"Dixie Tafoya has long argued that there is a significant serotonin deficiency in Down's syndrome, despite the fact that tryptophan deficiency is not a universal aspect of serum amino acid profiles."

The consequences of limiting tryptophan availability is not restricted to protein synthesis. As far as I know, nobody has yet measured what happens to NAD. However, tryptophan's conversion to serotonin is inhibited, as is serotonin's conversion to melatonin. This is where Prozac and other serotonin reuptake inhibitors (SRIs) come in.

"When we speak of serotonin levels, it is important to distinguish between stored serotonin, which is manufactured by neurons for release to stimulate target cells, and released serotonin, which is actively stimulating the target cells."

When we speak of serotonin levels, it is important to distinguish between *stored serotonin*, which is manufactured by neurons for release to stimulate target cells, and *released serotonin*, which is actively stimulating the target cells in the synaptic gap between the "sending" neuron and the "target" neuron (see Figure A). From a strictly functional point of view, it is only the released serotonin that matters. Stored serotonin is only important if it becomes sufficiently depleted to decrease serotonin release.

So if we narrow our focus to released serotonin, we can see *three pathways* which influence the level of serotonin stimulation of target neurons (see Figure A). Pathway 1 is the biosynthesis of serotonin that serves to build serotonin stores and thereby promote serotonin release. Pathway 2 is the reuptake of released serotonin by presynaptic serotonin receptors on the surface of the "sending" cell. This is a recycling mechanism for serotonin which serves to replenish serotonin stores. This is also the pathway inhibited by Prozac. Pathway 3 is the catabolism (elimination, or destruction) of serotonin. The major enzyme for this is *monoamine oxidase* (MAO), which oxidizes the serotonin so that it no longer has serotonin activity and can be easily removed.

"It is the balance between 1) feeding, 2) recycling, and 3) elimination processes that influence the pool of released serotonin which is stimulating the target neuron."

It is the balance between 1) feeding, 2) recycling, and 3) elimination processes that influence the pool of released serotonin which is stimulating the target neuron. Each of these pathways have different and independent influences on both stored serotonin and released serotonin. Serotonin biosynthesis (pathway 1) increases stored serotonin. This may also increase released serotonin. However, this pathway is limited by the possible complicating effects of IDO (see gray dashed outline in Figure A). The inhibition of reuptake (pathway 2) by SRI drugs like Prozac, Zoloft and Paxil increases released serotonin at the expense of stored serotonin (see Figure B). The inhibition of MAO (pathway 3) by strong MAO-inhibiting drugs or weak inhibiting substances like St. John's wort (which contains *hypericin*) and GH-3 (which contains procaine) increases released serotonin and thereby stored serotonin (see Figure C).

The use of serotonin precursors (pathway 1) with reuptake inhibitors (pathway 2) counteracts the depletion of serotonin stores by SRIs. Dr. Ward Dean and I discussed this strategy in depth in our *Special Report* on "Serotonin Precursors and Reuptake Inhibitors in Depressive Illness" in *SDN* v6n1. This report would be good background material for your doctor.

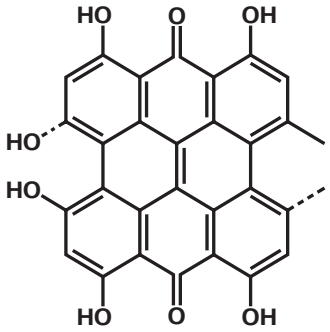
The use of all three approaches simultaneously (Figure D) can cause much greater increases of released serotonin than any alone. This is because these approaches exhibit *positive synergy* with each other. In other words, they add or multiply together. The advantage of such a multi-faceted approach is not in the potential for overloading serotonin, but in being able to reduce the dose of any of the three agents to minimize side effects without sacrificing efficacy.

Just exactly how these agents will synergize together is not yet well studied under either scientific or clinical circumstances. Caution is indicated. There are likely to be strong differences in how different people respond to different combinations due to the influence of biochemical individuality on this synergy. The confounding influence of IDO induction is another variable that can introduce unpredictable responses. There are potential advantages to be obtained through combination therapies, but there are significant unknowns at play that need to be assessed.

One of the unknowns is the mechanism of action of St. John's wort. Although its ability to inhibit MAO has been documented, it appears that it is not hypericin that is doing

the inhibiting, but rather some other flavonoid substance in the plant that is not yet characterized [Bladt and Wagner, 1994]. St. John's wort also appears to inhibit COMT (catechol-o-methyl-transterase), an enzyme that parallels MAO in metabolizing neurotransmitters [Thiede and Walper, 1994]. Some of the active chemicals in St. John's wort may also inhibit serotonin reuptake [Staffeldt *et al.*, 1994], modify serotonin receptors [Muller and Rossol, 1994], and alter cytokine expression [Thiele *et al.*, 1994]. While there's lots we do not know about the exact mechanisms of how St. John's wort works, we do know it's a potent antidepressant with approximately the same activity as the tricyclic antidepressants but with a lower side-effect profile. We also know it has antidepressant activity against SAD (seasonal affective disorder).

Figure 1:
The Structure of Hypericin



"We know St. John's wort is a potent antidepressant with approximately the same activity as tricyclic antidepressants but with a lower side-effect profile. We also know it has antidepressant activity against seasonal affective disorder."

This last point deserves elaboration. The hypericin and pseudohypericin in St. John's wort are photoactive (light-absorbing) chemicals. They absorb light in the green-blue-violet portion of the spectrum, which makes hypericin and pseudohypericin briliantly red in color. When range animals (except goats) overgraze on St. John's wort (also know as "goat weed" by ranchers in the Western United States), this photoactive or photosensitizing property of hypericin leads to red-blood-cell hemolysis (rupture of red blood cells). It has also caused photosensitivity in humans in clinical studies of high-potency *Hypericum* extracts and intravenous hypericin solutions. Some people taking large amounts of low-potency extracts have noted increased sensitivity to sunburn, a manifestation of photosensitivity. However, this effect is quite rare at the low doses that are typically used in treating depression.

The ability of hypericin to absorb light may be an important mechanism of its antidepressant action. One of the standard therapies for SAD is phototherapy, the exposure of the depressed person to high levels of light. However, one study found that low levels of light with hypericin work just as well as high levels of light without hypericin [Martinez *et al.*, 1994].

Figure E:
Oxygen Representations

	Triplet †	Singlet ‡	
a	O—O	⊕O—O⊖	O=O
b	:Ö—Ö:	:Ö—Ö:	:Ö=Ö:
c	:Ö:Ö:	:Ö:Ö:	:Ö::Ö:

† Triplet oxygen is a free radical.
‡ Singlet oxygen is *not* a free radical.

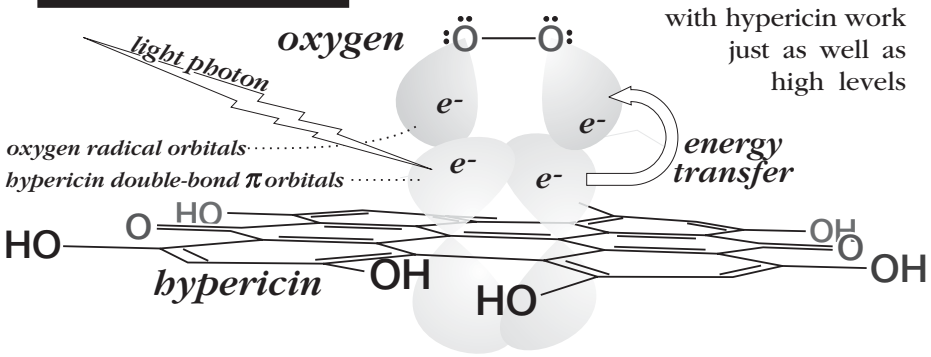
The hypericin molecule absorbs light energy through its extremely large interlinked series of double bonds (see Figure F below). The electrons in these interlinked double bonds fuse into an electron cloud that floats just above and just below the plane of atoms in the hypericin molecule. The electrons in this cloud absorb photons of light energy. The absorbed energy is then transferred to other molecules in the body in a way that is not yet fully understood.

One of the molecules that receives this energy is oxygen. Somehow, regular oxygen (O_2) interacts with the energized hypericin molecule to convert from its normal *triplet* state to a high-energy *singlet* state. Normally, ground-state oxygen (the lowest energy state) exists as a di-radical with two unpaired (free-radical) electrons, one on each oxygen atom (see Figure E). In interacting with hypericin, these electrons become paired up (see Figures E and F). The energy of the photon is transferred to the oxygen molecule, which is kicked off in a paired up (singlet) state. Because singlet oxygen has no unpaired electrons (see Figure E), it is *not* a free radical.

However, singlet oxygen is still an oxidizing agent. In other words, it is still reactive towards electrons. The difference is that singlet oxygen prefers to react with two-electron targets while triplet oxygen (the free radical) tends to react with only one electron at a time. The biological consequences of this shift in reactivity are not well understood or easily predictable. However, it may involve a decrease in general free radical activity (one-electron reactions) with an increase in oxidation of the double bonds of polyunsaturated fatty acids (a two-electron system).

Whether a slight increase in singlet oxygen due to traces of hypericin from St.

Figure F:
Oxygen Interactions with Hypericin



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"Whether a slight increase in singlet oxygen due to traces of hypericin from St. John's wort might pose an oxidative risk or offer some degree of protection in Down's syndrome is unknown."

"Until such time as we develop the equivalent of the Star Trek medical tricorder, we will have to approach cognitive enhancement with some degree of experimentalism."

"Before you begin to treat your mother, you should question the Alzheimer's diagnosis. It is very easy for clinicians to misdiagnose some kinds of senility syndromes as Alzheimer's disease."

John's wort might pose an oxidative risk or offer some degree of protection in Down's syndrome is unknown. We know there is a specific oxidative stress associated with over-expression of superoxide dismutase. What we don't know is whether this oxidative stress would interact positively or negatively with a shift in the ratio of singlet to triplet oxygen. This should be examined. Analysis of fatty acid oxidation and peroxidation patterns might be useful, as might general systemic measurement of antioxidants and oxidative byproducts (*i.e.*, the Pantox and Genox profiles).

Certainly, if you try St. Johns wort, please relate your experiences to us. If you have any questions that I have not addressed here, please feel free to ask. I have concerns that there could be consequences of long-term Prozac use in *developing* infants and children that might not be anticipated from its clinical use in adults. Such concerns may also apply to St. John's wort. However, an alternative to Prozac, or a synergist which might allow the dose of Prozac to be cut in half or more, might be an important discovery.

If you wish to bring your doctor up to speed on St. John's wort, you might suggest Dr. Shari Lieberman's recent short review in *Alternative & Complementary Therapies* [4(3): 163-8, June 1998]. It is accessible, concise, and directed exclusively towards human clinical trials. **SWF**

Bladt S and **Wagner** H. Inhibition of MAO by fractions and constituents of *Hypericum* extract. *J Geriatr Psychiatry Neurol* 7: (Supplement 1); S57-59, 1994.

Martinez B, Kasper S, Ruhrmann S and Moller HJ. *Hypericum* in the treatment of seasonal affective disorders. *J Geriatr Psychiatry Neurol* 7: (Supplement 1); S29-33, 1994.

Muller WEG and **Rossol** R. Effects of *Hypericum* extract on the expression of serotonin receptors. *J Geriatr Psychiatry Neurol* 7: (Supplement 1); S63-4, 1994.

Staffeldt B, Kerb R, Brockmoller J, Ploch M and Roots I. Pharmacokinetics of hypericin and pseudohypericin after oral intake of the *Hypericum perforatum* extract LI 160 in healthy volunteers. *J Geriatr Psychiatry Neurol* 7: (Supplement 1); S47-53, 1994.

Thiede MH and **Walper** A. Inhibition of MAO and COMT by *Hypericum* extracts and hypericin. *J Geriatr Psychiatry Neurol* 7: (Supplement 1); S54-6, 1994.

Thiele B, Brink I and Ploch M. Modulation of cytokine expression by *Hypericum* extract. *J Geriatr Psychiatry Neurol* 7: (Supplement 1); S60-2, 1994.

What are the Best Smart Drugs?

I'm a new subscriber and would like your opinion about which smart drugs are best for starting a smart-drug program? **OTP**

Asking "What's the best smart drug?" is like asking "What's the best garden tool?" You really have to have a context to answer the question. If you want to move dirt, then a shovel is better than a pruner. But if you want to trim a rosebush, then the pruner is better than the shovel. Similar contexts are necessary in picking smart drugs. If you want to enhance cerebrovascular circulation, then ginkgo or vinpocetine are better than phenytoin or DMAE. If you are on a strict budget, maybe ginkgo is better than vinpocetine.

Initially, you may not have much of a context to base such decisions. You aren't likely to know whether you have a cerebral circulatory problem or not until you try ginkgo or vinpocetine and it works to enhance your mental performance or relieve some cognitive complaint. Likewise, it is difficult to know which neurotransmitter system you might want to enhance before you begin the process of altering your neurotransmitter levels. Even if you know you are depressed, you don't automatically know whether to start with the serotonin system (using tryptophan or 5-hydroxytryptophan), the norepinephrine system (using phenylalanine or tyrosine), or the dopamine system (using deprenyl).

At our present state of knowledge, we do not have a magic window into the inner workings of the brain and mind. Until such time as we develop the equivalent of the Star Trek medical tricorder, we will have to approach cognitive enhancement with some degree of experimentation.

If you feel awkward or uncomfortable with experimentation, hire a medical professional to supervise your program. **SWF**

Alzheimer's Treatments

My mother has been getting more forgetful for the last few years and has just been diagnosed with Alzheimer's disease. How effective are smart drugs for treating Alzheimer's? How can I convince her doctor that smart drugs should be considered? And lastly, which smart drugs should we use first? **OTP**

Before you begin to treat your mother, you should question the Alzheimer's diagnosis. It is very easy for clinicians to misdiagnose some kinds of senility syndromes as Alzheimer's disease. It is also easy to misdiagnose some kinds of drug-drug interactions as Alzheimer's disease. These non-Alzheimer's conditions are generally much easier to treat than Alzheimer's disease. Sometimes, with these conditions, a complete reversal of symptoms is possible. This is generally not a reasonable expectation with Alzheimer's disease. Effective therapy for Alzheimer's disease provides a

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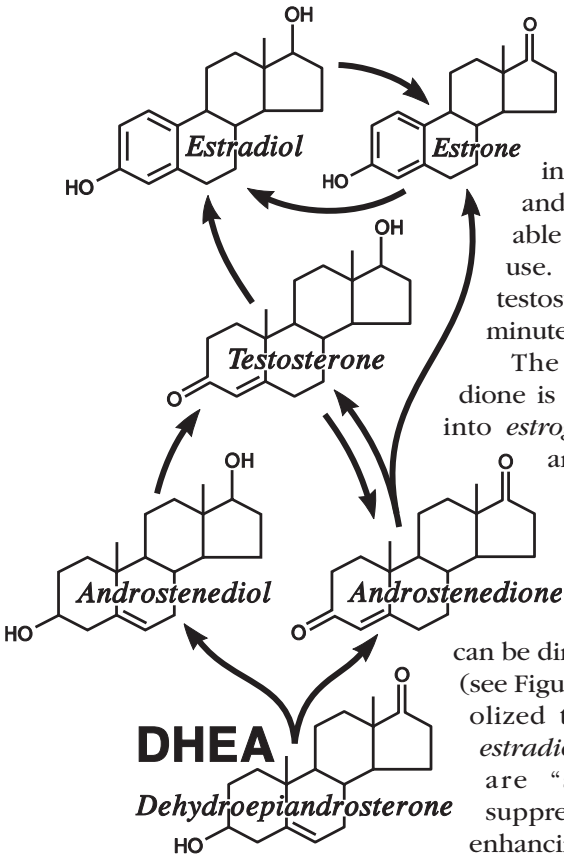
quite deficient) levels.

Transdermal testosterone delivery (via patches, creams and lotions) has recently become a popular alternative to injections. Transdermal testosterone can be applied on and absorbed through the skin to provide a smoother, less volatile testosterone profile which 1) reduces negative feedback to the hypothalamus, and 2) can more closely follow the natural circadian rhythm for testosterone. Testosterone creams are far less painful than injections and often much more convenient for people to use.

Figure 1:
Androstenedione Steroid Pathways



Androstenedione offers a fast-acting, over-the-counter alternative to prescription-only testosterone patches, creams and lotions. It is sold in capsules or pills for oral use, and it has recently become available in a liquid spray for sublingual use. The sublingual spray raises testosterone levels in less than 30 minutes.

The problem with androstenedione is that it is quickly metabolized into *estrogens*. Estrogens have strong anti-testosterone-like metabolic effects that last for a long time (days as opposed to hours). Androstenedione produces estrogens through *two separate pathways*. First, it can be directly metabolized into *estrone* (see Figure 1). Second, it can be metabolized to testosterone and then to *estradiol*. Both estradiol and estrone are "strong" estrogens which suppress the anabolic, metabolism-enhancing, fat-loss and tissue-healing properties of testosterone. I believe that many people will suffer estrogen-related side effects from androstenedione that will have far more negative impact on their health than the positive effects from androstenedione or testosterone.

"The problem with androstenedione is that it is quickly metabolized into estrogens."

The estrogen problem can be clinically managed by measuring before-and-after estrogen levels. This can be done with blood tests that are available through a physician, or with saliva tests that are available over the counter (call Vitamin Research Products or Smart Basics). Such tests can give you some idea of the magnitude of the estrogen risks that may be associated with your use of androstenedione (or its immediate precursor DHEA, which can also be metabolized into estrogens).

Estrogen is not something to be trifled with. In men, estrogen levels increase with age as testosterone and DHEA levels decrease with age. It is possible, and maybe even likely, that some aspects of aging are directly due to the increasing influence of estrogen with advancing age. It is also possible that rising estrogen levels play a major role in prostate enlargement, and prostate and testicular cancers. Androstenedione is more closely linked to the estrogen branches of the steroid tree than DHEA, which also has potential estrogen-related risks.

Androstenediol, a close cousin of androstenedione, is able to be directly metabolized into testosterone but only indirectly into estradiol and estrone (see Figure 1). It is reportedly more efficient at producing testosterone than androstenedione. It is possible that it produces less estrogen as well. As far as I know, the estrogen-enhancing effect of all these compounds has not been systematically evaluated or compared. Even if we knew the comparative risks, testing would still be needed. Clinicians report large differences among their patients in how steroids are metabolized into estrogens. Test and be sure.

Androstenedione is available through Smart Basics, Vitamin Research Products and Olympia Nutrition, all on our *Resources Listing*. Androstenediol is available through Olympia, and Anabol Power Dist. (011-31-26-381-0668, in The Netherlands). Olympia also has a combination formula. **SWF**

New Liquid Deprenyl Sources?

Please advise as to current status of B&B Freight and other sources for Discovery-brand liquid deprenyl citrate, or alternatives that might be available. Thank you. **SK**

B&B Freight has folded. International Antiaging Systems (IAS) is still shipping. A new source, Professional Compounding Pharmacy (1-800-934-6337), just started making DEDI (Discovery) liquid deprenyl available by prescription. Details can be found in the *Sources Update* on page 12 of this issue. **SWF**

Prozac vs Constipation?

Thank you for your response to my last question about the use of Prozac in Down's syndrome. One of the changes that I have noted is that my son is no longer constipated. Dr. [Lawrence] Leichtman has told me that this phenomenon is common. He thinks that Down's children may not be suffering from Hirschsprungs's disease, but from a serotonin deficiency. **TR**

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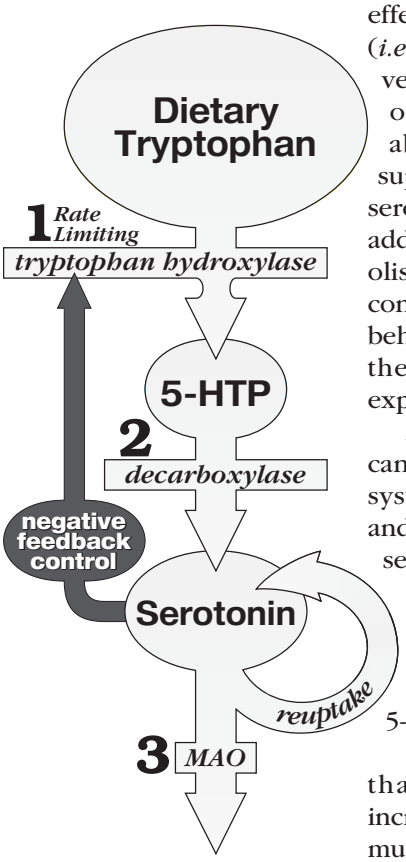
"You might want to investigate the effects of 5-hydroxytryptophan (5-HTP) on peristalsis and constipation."

Constipation can be caused by a lack of peristalsis (rhythmic contractions of intestinal smooth muscles). Peristalsis is under the influence of the cholinergic and serotoninergic nervous systems. Cholinergic neurons use acetylcholine as a neurotransmitter, which is why choline, DMAE and vitamin B_5 increase peristalsis and stimulate bowel movements. Although I have suggested cholinergic stimulation to mothers with constipated children, it has not seemed to work as well in children with Down's syndrome as it does in the general population. It is possible that the constipation problem in Down's syndrome is due to serotoninergic deficit, rather than a cholinergic deficit as I had first assumed. In retrospect, it makes perfect sense.

If true, then you might want to investigate the effects of 5-hydroxytryptophan (5-HTP) on peristalsis and constipation. Unlike tryptophan, whose conversion to serotonin in the gut is limited by feedback control mechanisms (see step 1 in Figures 2 and 3), 5-HTP bypasses the bottleneck (step 2) and can raise serotonin activity beyond the level established by the body's normal feedback control. Indeed, the most common side effect from 5-HTP is gastrointestinal motility (*i.e.*, gut-muscle stimulation) from the conversion of 5-HTP into serotonin in the lining of the intestine, where 5-HTP is first absorbed. It seems likely that 5-HTP supplementation would achieve the same serotoninergic effect in the gut as Prozac. In addition, the 5-HTP that escapes gut metabolism can be absorbed by the brain and converted into serotonin producing central behavioral effects similar to Prozac (refer to the answer in the last issue for more explanation).

Figure 2:
Serotonin Biosynthesis Schematic



Although tryptophan supplementation can increase serotonin in the central nervous system when it is taken without protein and/or with carbohydrate, it does not raise serotonin very effectively in the peripheral nervous system that controls intestinal smooth muscles. The conversion of tryptophan to serotonin is strongly regulated in the gut. The conversion of 5-HTP to serotonin is not.

5-HTP is about ten times more potent than tryptophan, gram for gram, at increasing brain serotonin. I can't say I have much idea about how efficient 5-HTP may be in stimulating peristalsis in serotoninergically deprived Down's syndrome children. Some experimentation may be needed. The Fiona study of piracetam and 5-HTP [see *SDN* v5n9], used 5-HTP doses of 1 mg/kg body weight. But you might want to start with only 5 mg and see if there is any effect for a few days before going to 10, 25 or maybe even 50 mg doses. Currently, 5-HTP is sold most commonly in 25, 50 and 100 mg sizes. These larger sizes are likely to be too large for young children. However, they can be divided up into smaller doses and mixed into beverages or solid foods.

To maximize the brain's absorption of 5-HTP, it is best to take 5-HTP on an empty stomach (*i.e.*, without protein-containing foods). However, for maximizing gastrointestinal stimulation, I think it might be better to take it with food. Plus, giving 5-HTP with meals is probably much more convenient for parents with young children and busy schedules.

LifeLink mentioned to me that they have just produced a mint flavored 25 mg 5-HTP losenge that might be a convenient strategy for giving 5-HTP to children, especially between meals. Interested readers can call LifeLink at 1-888-433-5266. **SWF**

Tobacco vs Carbohydrates

In your last newsletter you compared the addicting properties of carbohydrates with those of tobacco. This is unfair. Carbohydrates don't cause cancer. They don't kill thousands of people every year before their time. Aren't you stretching an analogy to the breaking point? **anon**

I actually chose that example to be deliberately inflammatory. We (most of us, at least) have a double standard about addiction that blinds us to the debilitating effects of carbohydrate addiction or wheat-allergy addiction in comparison to, say, heroin or tobacco addiction. However, from a biological point of view, there is very little difference between tobacco addiction and carbohydrate addiction.

Your suggestion that carbohydrates don't cause cancer is not accurate. Carbohydrates can induce *hyperinsulinemia* (an age- and obesity-associated state of insulin resistance), which is associated with significantly increased risks of cancer. The late Professor Vladimir Dilman, M.D., Ph.D., D.M.Sc. even coined the name "cancerophilia" to describe this state of enhanced susceptibility to cancer. Just because we praise carbohydrates and wheat and vilify tobacco and heroin doesn't change the fact that carbohydrate-induced neuroendocrine dysregulation can strongly increase cancer risks.

It is my opinion that the political pro-

Smart Life Update: Food Allergy and Neurodegenerative Disease

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"For people without cooperative doctors or the financial means to afford blood tests, dietary restriction and food reintroduction can provide an indication of food intolerance."

disease (diarrhea, gut discomfort, maldigestion) and interfere with nutrient absorption in the small intestine. There may also be adverse health consequences from grains that do not act through or require immune sensitization (antibody production). The quest for answers to such questions is still hampered by both social and economic imperatives that make grains a necessary and essential element of our modern diet. The ideological defense of such imperatives is grounded in conventional wisdom that grains are one of the healthiest components of a modern balanced diet.

Testing and Evaluation

Blood tests for gluten-related antibodies are available through physicians. For people without cooperative doctors or the financial means to afford blood tests, dietary restriction and food reintroduction can provide an indication of food intolerance. Complete elimination of grain for a period of 10-14 days followed by reintroduction of very small amounts of grain can produce strong objective and subjective symptoms in grain-intolerant individuals. Intolerance can be indicated by 1) increased body temperature, 2) increases in pulse rate, 3) intestinal complaints (cramps, gas and/or diarrhea), 4) bloating and/or puffiness (*i.e.*, changes in tissue hydration), 5) increased mental acuity initially, possibly followed by mental fuzziness and "zoning out," 6) emotional volatility (anger, irritability, depression), and 7) food cravings for more grain. Due to the possibility of extreme emotional and cognitive changes upon reintroduction of grain in an intolerant individual, the process should be conducted under controlled and supervised conditions. Having a trusted friend or family member present is essential, not only to provide an interactive stimulus from which to judge cognitive and emotional responses, but to provide an independent observer. This person can coordinate temperature

Oxidative Stress in Children during Heart Surgery

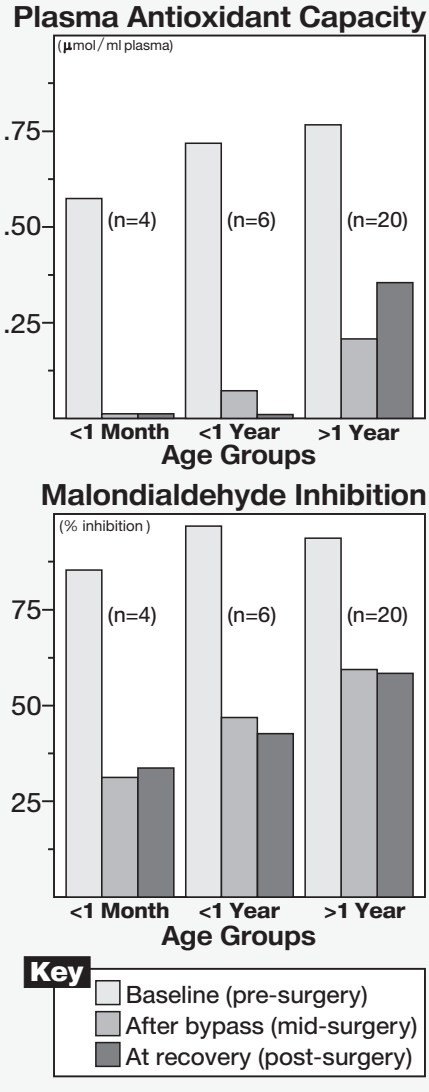
One of the issues that we have raised on a couple of occasions is the advisability of continuing TNI therapy during heart surgery to correct for congenital heart defects associated with Down's syndrome. Our position has been that the standard rationale to discontinue TNI based on a lack of knowledge about how TNI might influence surgery has no documented scientific basis. Furthermore, the metabolic and antioxidant assistance that TNI offers should be of value for children facing the many well known and potentially extreme stresses of surgery.

Direct scientific evidence documenting the extreme oxidative stress of heart surgery has been published. This research confirms that congenital heart surgery in children causes massive depletion of antioxidant reserves, especially in those children less than one year of age. Antioxidant status was measured by two methods: 1) plasma antioxidant capacity (the ability of the children's blood to prevent *in vitro* oxidation of the polyunsaturated fatty acid *linoleic acid*) and 2) malondialdehyde inhibition (the ability of the children's blood to prevent lipid peroxidation in beef brain homogenates). These two measurements were made at three different times (see adjacent illustrations): 1) before surgery (light gray bars), 2) after the heart bypass (mid-surgery, medium gray bars), and 3) after surgery (after transfer to intensive-care facility, dark gray bars).

The results of this study show a drastic depletion of antioxidant reserves caused by the surgery in children of all ages. This depletion was most severe in the younger children, who showed almost complete elimination of all plasma antioxidant capacity. The severity of this antioxidant depletion should give pause to physicians and surgeons recommending discontinuation of TNI prior to heart surgery, and to parents faced with such recommendations.

It is critical to keep in mind that the data of this study were obtained from surgeries in non-DS children, who do not have the additional antioxidant burden of a genetic disruption of their antioxidant defense systems by the overexpression of SOD (superoxide dismutase) from the triplicated 21st chromosome. This would suggest that these results, as severe as they are, would be worse in children with trisomy 21. SWF

LA Pyles, JE Fortney, JJ Kudlak, RA Gustafson and S Einzig. Plasma antioxidant depletion after cardiopulmonary bypass in operations for congenital heart disease. *The Journal of Thoracic and Cardiovascular Surgery* 110: 165-71, July 1995.



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tive protection system. The preventive effect of an antioxidant and the therapeutical effect of an antihypoxant were recorded in the prevention of murine death due to influenza. The mechanisms of the protective effect of the antihypoxant is due both to its immediate antihypoxant function and its correcting influence on lipid peroxidation."

EC Pirtle, JM Sacks and RJ Nachman. Antiviral effectiveness of butylated hydroxytoluene against pseudorabies (Aujesky's disease) virus in cell culture, mice and swine. *American Journal of Veterinary Research* 47(9): 1892-95, September 1986.

AV Pokhil'ko, TA Kramskaia and RIa Poliak. [Stress and viral infection: dynamics of expression of influenza A viral antigens during immobilization stress]. *Voprosy Virusologii*, 40(2): 76-9, Mar-Apr 1995. "The level of expression of influenza virus antigens in the target organ is an important characteristic of the severity of a viral process, as was shown on a model of experimental influenza A. Stress exposure augmenting the severity of the infection stimulates the expression of viral polypeptides in the acute period of the disease. Injection of an antioxidant ionol which may prevent stress-enhanced synthesis of viral proteins. Stress-induced disorder of the mechanisms of formation of immunological memory is paralleled by accumulation of high levels of virus-specific proteins in the lungs after repeated exposure of an animal to a homologous virus. Hence, the level of viral antigens synthesized in the course of reinfection also helps assess the degree of body protection from this agent.

"The endogenous antioxidants (catalase, glutathione peroxidase, SOD, glutathione, etc.) are under metabolic and genetic control, and are therefore not easily manipulated."

Antioxidant Supplements?

Some of the information I recently downloaded off the Internet (CERI's and Dr. Swenson's sites) suggests that antioxidant supplementation is the primary answer to the increased oxidative stress of SOD overexpression in Down's syndrome. Is it really that simple? **P**

Yes and no. Yes, antioxidant supplementation is currently our best therapeutic approach. However, it is not just a matter of increasing all antioxidants equally. A full understanding of how the antioxidant defense system works and how SOD (superoxide dismutase) overexpression disturbs that function is necessary to specify which antioxidants and which cofactors should be supplemented, and which should not.

"A full understanding of how the antioxidant defense system works and how superoxide dismutase overexpression disturbs that function is necessary to specify which antioxidants and which cofactors should be supplemented, and which should not."

The first thing to understand about the antioxidant defense system is that it is composed of two different parts: 1) the *exogenous* antioxidants, which can be obtained from outside the body (through the diet), and 2) the *endogenous* antioxidants, which are made within the body. The exogenous antioxidants (vitamins A, C and E, carotenoids, cysteine, Co-Q_{10}, thiamine, lipoate, *etc.*) and cofactors (iron, zinc, copper, manganese, selenium, B-vitamins, *etc.*) are easily manipulated through diet and supplements. The endogenous antioxidants (catalase, glutathione peroxidase, SOD, glutathione, *etc.*) are under metabolic and genetic control, and are therefore not easily manipulated.

Endogenous antioxidants are *induced* (*i.e.*, *up*regulated or *down*regulated) by changing conditions in the body. They *adapt*. Often, when exogenous antioxidants are increased, endogenous antioxidants decrease. This is due to the fact that SOD, catalase and glutathione peroxidase are produced in response to specific types of oxidative stress. If one decreases that oxidative stress by supplementing antioxidants, the body's response to oxidative stress decreases.

The implications of how these two systems interact is critical to understanding how to optimize antioxidant defenses in both Down's syndrome individuals (where there is a genetically determined imbalance in endogenous antioxidant defenses) and in non-DS individuals (who might want to optimize antioxidant defenses for general health and life-extension purposes).

The second thing to understand about the antioxidant defense system is that *antioxidants work with each other*. This means that *synergy* (enhanced antioxidant function) is often noted with *combinations of antioxidants* that is not noted with single antioxidants. Antioxidants are like the rungs of a ladder; when one rung is weak or missing, it is hard to use the ladder effectively or safely.

Another useful analogy is the old-time bucket brigade for putting out fires. Free-radical stress is like a fire, and the antioxidant defense system carries buckets of water (reducing power) to the sites of the stress to quench the fire. If everybody in the bucket brigade from the water supply to the fire hands off buckets equally quickly, then the chances of putting out fires are maximized. If one person is unable to keep up, then the line is slowed down. This causes buckets to accumulate at certain points along the way, and depletion of buckets at other points. If an extra person can be added "in parallel" to assist the slowest person, then efficiency goes up and the backlog of buckets is returned to the chain. This is what happens when you supplement a deficient antioxidant. If the extra person assists somebody who is keeping up and who does not have a backlog of buckets, there will be minimal improvement, if any. This is what happens when you over-supplement a robust antioxidant.

I like the bucket brigade analogy for another reason: it works by timing and rhythm. Each person has to be ready to accept the next bucket when it is handed. If somebody hands buckets too fast, they can

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upset the rhythm of the next person and overload the chain. The speed and rhythm of the human bucket brigade is analogous to the "balance" between antioxidants in the antioxidant defense system.

In normal antioxidant metabolism (see Figure 1, below), the production of SOD and catalase are optimized to maintain the "ideal" amount of superoxide anion (an "activated" form of oxygen necessary for various metabolic reactions) and hydrogen peroxide (also necessary for metabolism). In Down's syndrome, the extra 21st chromosome produces 50% more SOD (see Figure 2). This decreases superoxide (which is upstream from SOD) and increases hydrogen peroxide (which is downstream from SOD). (In a genetic disorder characterized by *deletion* instead of *duplication* of genetic material, the opposite change occurs: the upstream substances are increased and the downstream substances are diminished.)

"The question as to what to do about the decreased levels of superoxide in trisomy 21 is not one that has yet been answered."

The question as to what to do about the decreased levels of superoxide in trisomy 21 is not one that has yet been answered. Supplementation of superoxide anions (also known as "negative ions") may correct for metabolic impairment of oxygen metabolism due to superoxide deficiency, but it also would increase hydrogen peroxide burdens in the bargain. The current "conventional wisdom" of the *Trisomy 21 Research Scientific Advisory Committee* is that an increase in hydrogen peroxide may pose an unacceptable risk, so we do not try to ameliorate the deficiency of superoxide caused by SOD overexpression.

Figures 1-4:
Flow Diagrams of the Antioxidant Defense System

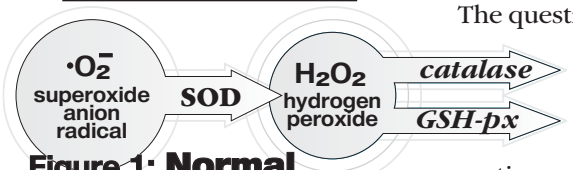

Figure 1: Normal
Genetically balanced antioxidant enzymes

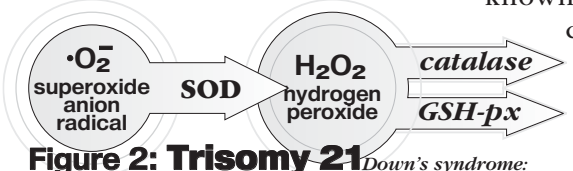

Figure 2: Trisomy 21 *Down's syndrome:*
Overexpressed SOD, induced catalase & glutathione peroxidase

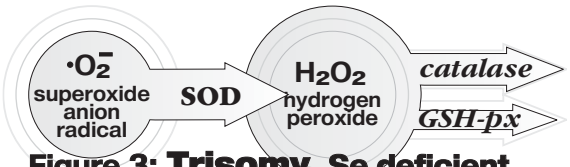

Figure 3: Trisomy, Se deficient
50% more SOD, impaired glutathione peroxidase induction

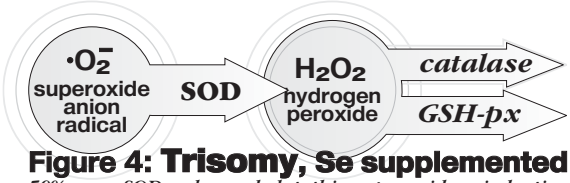

Figure 4: Trisomy, Se supplemented
50% more SOD, enhanced glutathione peroxidase induction

Dealing with increased hydrogen peroxide is more straightforward. We feed the nutrients which maximize the body's ability to induce (produce) catalase and glutathione peroxidase, which keep hydrogen peroxide under control. The nutritional cofactor for catalase is iron. However, excess iron can aggravate hydrogen peroxide toxicity (via the Fenton reaction) (see *SDN* v4n10). So we supplement iron *only when there is a demonstrated state of iron-deficiency anemia.*

The nutritional cofactor for glutathione peroxidase is selenium, four atoms of which are needed to make one glutathione peroxidase enzyme. Selenium supplementation poses no significant toxicity and is therefore a universal element of *targeted nutritional intervention* (TNI) formulas for Down's syndrome.

The constant induction of glutathione peroxidase by elevated hydrogen peroxide (see Figure 2) can deplete selenium levels. In the face of a selenium deficiency (see Figure 3), glutathione peroxidase production may become seriously compromised, further increasing the hydrogen peroxide pool.

The metabolic consequences of selenium deficiency go beyond hydrogen peroxide. Selenium is also necessary for the production of thyroid hormone in the thyroid gland, and for the conversion of T_4 (low-potency thyroid hormone) into T_3 (high-potency thyroid hormone) in the non-thyroid tissues of the body. Indeed, thyroid insufficiency problems have been noted as a clinically significant feature of Down's syndrome.

Selenium supplementation in Down's syndrome removes possible impairment of glutathione peroxidase synthesis, optimizes the body's ability to reduce elevated hydrogen peroxide levels (see Figure 4), and prevents "secondary" (induced) selenium deficiency problems in other systems of the body (*i.e.*, thyroid regulation of protein synthesis, mitochondrial function and basal metabolic rate). For an article discussing *secondary nutrient deficiencies*, see "The Art of Nutritional Therapeutics" (*SDN* v4n9).

The critical importance of selenium and glutathione peroxidase in Down's syndrome may have been revealed recently by a study of endogenous antioxidants in 72 patients [Pastor *et al.*, 1998]. The researchers measured levels of superoxide dismutase (SOD-1), glutathione peroxidase (GSHpx), catalase (CAT), and glutathione reductase (GSHr) enzymes in red blood cells (see Table 1 at left). The activity of SOD-1 was 33%

Table 1: **Antioxidant Enzymes in Down's Syndrome**

	Control Enzyme Activity	DS Enzyme Activity	Increase	Variance Control	Variance DS	Variance Diff.
SOD-1	476 ± 67 U/g Hb	635 ± 70 U/g Hb	133%	±14%	±11%	-3%
CAT	1482 ± 250 U/g Hb	1843 ± 250 U/g Hb	124%	±17%	±14%	-3%
GSHpx	21.5 ± 3.6 U/g Hb	23.2 ± 5.3 U/g Hb	108%	±17%	±23%	+6%
GSHr	6.9 ± 1.3 U/g Hb	9.32 ± 1.4 U/g Hb	135%	±19%	±15%	-4%

Adapted from M C Pastor, C Sierra, W Dolade *et al. Clinical Chemistry* 44(5): 924-9, May, 1998.

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higher than normal controls, which was consistent with its overexpression from the triplicated 21st chromosome. The activity of the "downstream" enzymes CAT and GSHpx were also increased, presumably induced (upregulated) by the increased hydrogen peroxide from the extra SOD. However, the induction of these enzymes was not proportional to the increase of SOD. While CAT activity was increased 24%, a value close to the 33% increase for SOD, GSHpx activity was only increased by 8%. This shortfall of GSHpx may be a focal point for maladaptation to oxidative stress in Down's syndrome. This hypothesis is supported by the slightly higher activity of GSHr, which recycles glutathione and assists the activity of the stressed-out GSHpx.

"This shortfall of glutathione peroxidase may be a focal point for maladaptation to oxidative stress in Down's syndrome."

Further evidence for GSHpx stress can be found in the *variance* in values for the different enzymes. The variance in enzyme levels in the DS group was less than controls, except for GSHpx activity, which was higher. Convergence (lessening) of variance is what we would expect in a stressed system that is adapting adequately, which is what we see with SOD, CAT and GSHr. However, GSHpx values diverge with the oxidative stress of Down's syndrome, suggesting the possibility of maladaptation.

Selenium supplementation also has the potential for decreasing overall cancer risks. In epidemiological studies, selenium levels are strongly correlated with both cancer incidence and cancer mortality. **SWF**

"Selenium supplementation also has the potential for decreasing overall cancer risks."

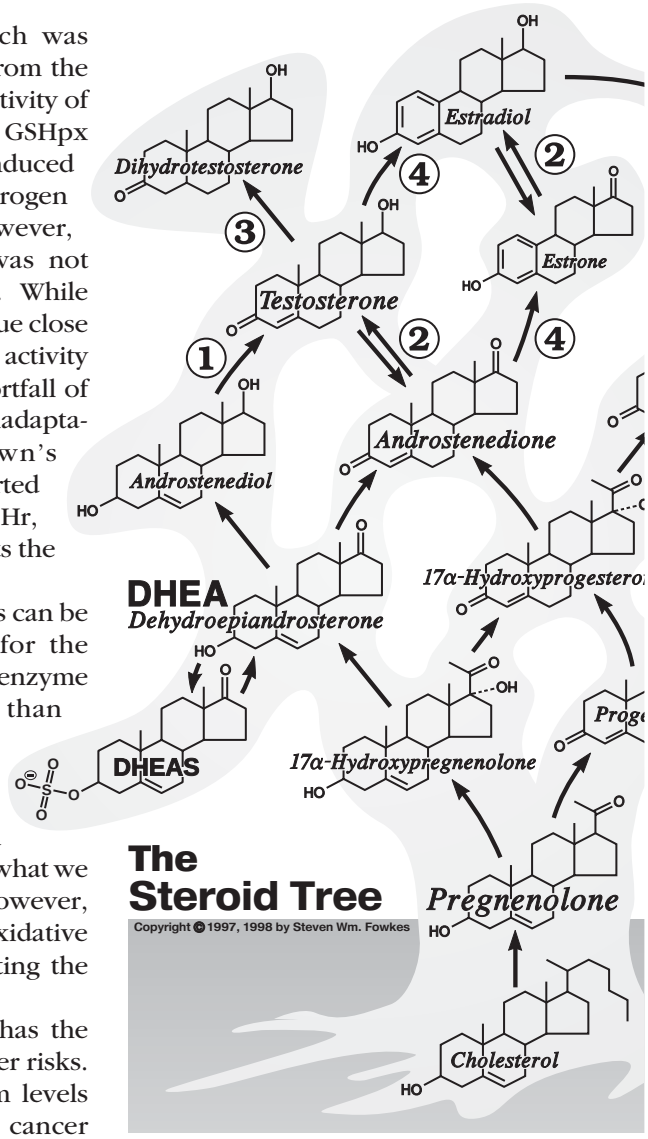
M C Pastor, C Sierra, W Dolade *et al.* Antioxidant enzymes and fatty acid status in erythrocytes of Down's syndrome patients. *Clinical Chemistry* 44(5): 924-9, May, 1998. "The aim of this study was to evaluate the cellular antioxidant system by determining the catalytic activity of the SOD1, glutathione peroxidase, catalase, and glutathione reductase enzymes and the concentrations of alpha-tocopherol in red blood cells (RBCs) in a group of 72 DS patients." "No differences were observed in RBC alpha-tocopherol concentrations between the two groups studied. Long-chain ω6 PUFA (C20:3n6, C20:4n6) concentrations were increased in DS patients, suggesting enhanced delta-6-desaturase activity. The long-chain ω3 PUFA (docosahexenoic acid) does not appear to be affected by increased oxidative stress, probably because of the existence of compensatory antioxidant mechanisms."

Raising Testosterone?

What's the best way to raise testosterone levels in a 58-year-old man? Androstenediol? DHEA? Testosterone itself? **MD**

"What's the best way to raise testosterone levels in a 58-year-old man? Androstenediol? DHEA? Testosterone itself?"

When considering testosterone, we need to step back one level to consider the two opposing influences of 1) biosynthesis (testosterone production) and 2) catabolism (testosterone conversion to other hormones) (see Steroid Tree illustration). Biosynthesis



(steps 1 and 2) *increases* testosterone while catabolism (steps 2, 3 and 4) *decreases* testosterone. It is the *balance* between biosynthesis and catabolism that ultimately determines testosterone levels. Supplementing testosterone, androstenediol, androstenedione, DHEA, pregnenolone and/or progesterone may increase the biosynthetic pathways, but they cannot guarantee increased testosterone levels. One must also consider the catabolic pathways which turn testosterone into *dihydrotestosterone* and *estradiol* (estrogen). *5-α-Reductase* (step 3) converts testosterone into dihydrotestosterone. *Aromatase* (step 4) converts testosterone into estradiol (and androstenedione into estrone).

Although biosynthesis of testosterone decreases with age, I think that most men's testosterone levels are not as strongly limited by the availability of precursors (biosynthesis) as they are by age-associated increases in the activity of 5-α-reductase and aromatase.

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lower temperature, because MCT oil is more volatile and therefore more flammable than long-chain fats).

A strategy for enhancing fat burning that works for me is to take a little bit of MCT oil (1/2 a tsp for instance) before doing some sort of extended exercise. **AMF**

GABA and Muscle Tone in DS?

"I understand that GABA may have a deleterious effect on muscle tone."

Hi Steve. I don't know if you remember me or not, but we met at a few of the TNI seminars. I have have been following the recent discussion regarding use of GABA and muscle tone. I have given it to my 2-year-old daughter (DS) on two different occasions. The first was from lab results done at 6 months of age through Munroe Labs (George Miroff). Miroff suggested I add it to her protocol. I added it for a few months and then remembered Dixie's warning people about changing the protocol, etc. So I stopped. Just about 3 wks ago, started using it again. I understand that GABA may have a deleterious effect on muscle tone.

Yes. Skeletal muscles use the neurotransmitter acetylcholine to stimulate tone, and GABA to relax muscle tone. Acetylcholine can be increased by taking precursors (DMAE, choline, phosphatidylcholine, lecithin) and cofactors (vitamin B5). GABA can be increased by supplementing GABA or GHB.

Maybe I'm being ultra paranoid, but can changes in muscle tone be noticed in as short a time as 2-3 weeks?

Changes in muscle tone from GABA can take place quickly. They may take days to weeks to reach maximum potential, but they are subjectively noticeable in maybe 30 minutes to possibly two hours. Try it yourself so that you can know how it works from a personal perspective. GABA is rather pleasant. It is a good after-work destresser for many people.

"It is possible that a combination of GABA with DMAE or choline would allow the beneficial effects of GABA on speech without excessive loss of muscle tone."

My daughter seems more like "dead weight" to me these last couple of days. I did notice a positive change in her concentration and an increase in her speech (new words were the rule, instead of the exception), but her speech and articulation have fortunately always been quite good. At the age of 2, she uses about 20 different words and is just starting to put two words together occasionally.

It is possible that a combination of GABA with DMAE or choline would allow the beneficial effects of GABA on speech without excessive loss of muscle tone.

Is this possible decline in muscle tone temporary? That is, if she were to be taken off, would the tone return? If I do take her off the GABA, should it be backed down slowly, or can I do it at one time?

I think phasing GABA out over several days to a week should be the least stressful way to proceed. I would expect to see increased muscle tone in just days after lowering the dose.

I, as many parents, value your opinion. I know no one has all the answers, but we are all looking. What are your thoughts about the homeopathic remedy, "serotonium"?

I don't think there is much risk in trying a homeopathic serotonin formulation in serotoninergically deficient children.

I have been following the Prozac trials, but have not tried it with my daughter. We don't have a major constipation issue with her as long as she eats many fruits and veggies. But now that she's getting older and eating only what she wants, fruits and vegetables are getting harder to push all the time. Your thoughts on 5-HTP?

LifeLink has just formulated a sweetened 5-HTP lozenge that might be convenient for dosing children. Their first formulation is really intended for older children and adults with 25 mg 5-HTP, minimal sweetness, and mint flavoring. I think that a sweeter, grape-, cherry-, lemon-lime- or orange-flavored lozenge with maybe 10 mg of 5-HTP would have great potential for young children, but it needs some experience in the trenches to get a better idea about doses, frequency of dosing, threshold effects, combining with food, and possible synergy with Prozac or St. John's wort. I'd very much like to hear any observations you have about these issues.

5-HTP Contamination?

"A recent paper makes the claim that 5-HTP products are contaminated with 'peak X.' Is this true? What is peak X? Is there cause for concern?"

A recent paper makes the claim that 5-HTP products are contaminated with "peak X." Is this true? What is peak X? And is there cause for concern?

It is true. A recent letter to the editor claims that at least *some* of the 5-HTP products currently in the market contain very small amounts of an unknown substance which may be associated with cases of EMS (eosinophilia myalgia syndrome). I say "may" because we do not know that peak X is causally related to EMS. Although a tentative structure for peak X has been proposed, it has yet to be confirmed by an independent laboratory. We really are not yet sure just what peak X is.

Since all substances sold in the market have impurities, "peaks" are the rule rather

Q&A Questions + Answers

"Unfortunately, there's no way to know which port of entry your shipment might have gone through."

"A friend came home loaded with info and a giant-sized warning from Dr. Warner about the use of piracetam."

Deprenyl Delay?

IAS in England said they shipped my order of liquid deprenyl, but it has not yet arrived. I don't know if it is being held by customs or not. I have received no communications from them. I assume the shipment has been routed through Chicago, as this is our closest point of entry. Is there anything I can do? Thanks. **Anon**

There's not much you can do. Assuming that IAS really did ship your order, it could be sitting in a Customs or FDA office somewhere waiting for someone to take action (*i.e.*, send you a letter). Sometimes FDA agents wait 2-3 months before sending a letter notifying the citizen of the detention. Who would know if they *never* sent you a letter? It would take an audit by Customs to cross check detained shipments with FDA letters. I doubt that anybody in the government is willing to do that for two reasons: 1) it is expensive to investigate such matters, and 2) they might find that dereliction of duty is common practice among FDA personnel.

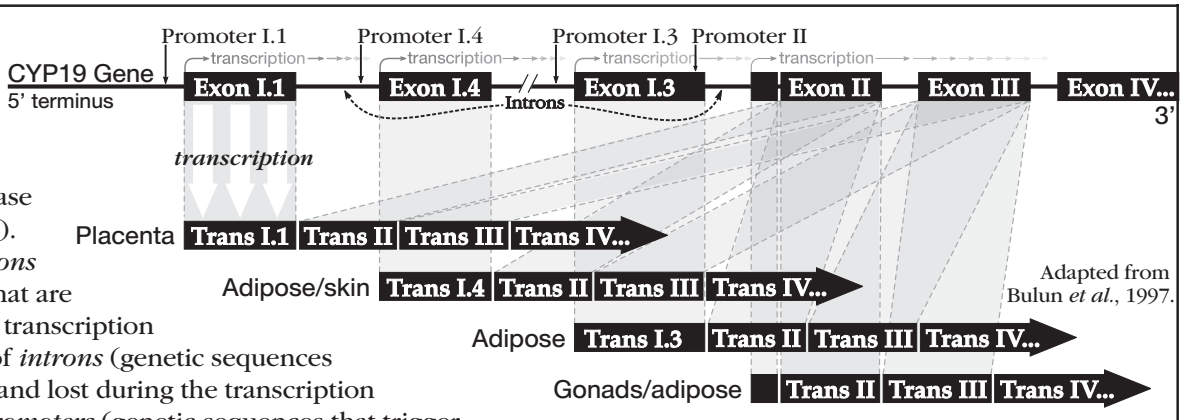
Unfortunately, there's no way to know which port of entry your shipment might have gone through. Chicago may be closest to you, but the first Customs port that your shipment passes through handles the inspection. Mail from Europe is just as likely to have been routed through Baltimore, New York or Atlanta. It could even have gone through Dallas/Fort Worth, Denver or Los Angeles. Inquiring at all possible Customs offices is a large amount of work — and probably a semi-futile proposition. **SWF**

Dr. Warner on Piracetam

The following is an e-mail from a lady on the official NACD list: "A friend just returned yesterday from the Warner Clinic in California with her 4 year DS son. She came home loaded with info and a giant-sized warning from Dr. Warner about the use of piracetam. She knows I have both my kids on it and was concerned about their taking it. Apparently, she said Dr. Warner told her he is seeing clients now who have been on piracetam for some time and they are showing major signs of regression in their speech. She said he attributed this to piracetam thinning or destroying the myelin sheath covering the nerves." Can you address this? **N**

There is no evidence that piracetam thins or destroys myelin or myelin nerve sheaths in anybody, despite 30 years of clinical use. The two most authoritative texts summarizing piracetam's medical uses and side effects are probably *Martindale: The Extra Pharmacopoeia* (published by the Royal Pharmaceutical Society of Great Britain), and *Meyler's Side Effects of Drugs* (published by Elsevier Publishing, one of the largest and most prestigious scientific/medical publishers in the world). Neither of these sources (nor any of the published review articles on piracetam) mention any myelin-

The Genetics of Aromatase



The CYP19 gene provides the genetic sequence for aromatase (also called P450arom). It consists of nine *exons* (genetic sequences that are *preserved* during the transcription process), a number of *introns* (genetic sequences that are "edited out" and lost during the transcription process), and four *promoters* (genetic sequences that trigger gene transcription). *Transcription* is the biological process of translating DNA sequences (genes) into RNA (ribonucleic acid) sequences, and then into amino acid sequences (otherwise known as peptides, proteins and/or enzymes). Transcription is the mechanism underlying protein synthesis. Of the nine exons (II-X), only exons II, III and IV are shown in the above illustration. Transcription of the aromatase protein begins at the 5' terminus (end), just after the promoter, and continues towards the 3' terminus, from exon II through exon X. The intron-derived segments are snipped out during the transcription process so that the exon-derived protein segments end up connected end to end. Finally, the exon I protein segment is removed, leaving the finished protein product, aromatase. Despite multiple promoters and different exon I segments during transcription, the finished aromatase enzymes end up identical, consisting only of protein segments transcribed from exons II through X. The multiplicity of promoters allows a variety of agents to independently influence and/or regulate the production of aromatase. **SWF**

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related effects from piracetam. Yet *all* of these sources conspicuously mention the rheological (blood-thinning) effects of piracetam at the higher doses typically used to treat myoclonic seizure disorders (usually 4-10 times higher than doses than are commonly used to treat Down's syndrome). These rheological effects are not seen at the 30 mg/kg doses used for cognitive-enhancement purposes.

"There have been no studies on long-term speech enhancement in Down's syndrome individuals."

I have searched Medline (the US Library of Medicine), EMbase (Excerpta Medica, the European medical database), and Biosis (Biological Sciences database) and there is no reference for demyelinating effects from piracetam. However, there may be such a report published somewhere in the world, in some language, that discusses such a hypothesis. I rely extensively upon Medline, because it is inexpensive and easy to access. However, Medline only covers about 5% of the world's total published medical literature. EMbase is better, being less provincial and covering maybe 15% of the world's literature. But it is is expensive to access. The point to understand is that there is a lot of published research out there which is not accessible through electronic databases.

"Piracetam produces a pharmacological effect, to which the body partially compensates. This is in no way a sign of degenerating myelin."

As to speech regression, that is possible. There have been no studies on long-term speech enhancement in Down's syndrome individuals. However, I am inclined to discount Dr. Warner's observations for the following reasons: 1) the studies of speech enhancement in non-DS populations do *not* show a regression effect, 2) such an effect has *not* been noted by other practitioners treating DS with piracetam, 3) Dr. Warner's attitude towards piracetam is, in my opinion, highly prejudiced and un-scientific, and 4) parents using piracetam with their DS children are reporting long-term sustained enhancement of verbal abilities.

"These two abstracts on Medline regard the use of a nasal form of bromocriptine, which seems to offer several advantages."

This latter point needs some clarification. Some parents have commented that the initial quite-beneficial effects of piracetam were not sustainable, more specifically, that part of the benefit wore off in a matter of days to weeks, maybe months. However, they generally thought that their child was still doing much better on piracetam than before piracetam. Some parents tried stopping piracetam and noted a drop in verbalization, which was reversed when they resumed it. This type of response — an initially strong reaction which moderates with longer-term use — is common with smart drugs in people of all ages and conditions. I think that part of this response is attributable to the body's homeostasis mechanisms, which attempt to restore "balance" in response to pretty much any metabolic shift. Piracetam produces a pharmacological effect, to which the body partially compensates. This is in no way a sign of degenerating myelin. **SWF**

Calcium Pantothenate?

Are cheap calcium pantothenate tablets good sources for pantothenic acid (vitamin B5)? **DM**

Yes, if they dissolve appropriately. Calcium pantothenate is simply the calcium salt of pantothenic acid. It is, overall, the best commercial source of vitamin B5 available.

You can test your cheap calcium pantothenate tablets by dropping one or more of them into a small glass or glass bottle filled with about half an inch of white vinegar. Any vinegar is OK if it is transparent enough to clearly see the tablets. The vinegar (5% acetic acid) approximates the hydrochloric acid in the stomach. If the tablet(s) dissolve, disperse or disintegrate in 15 minutes or less, they are OK.

If they don't spontaneously disintegrate, there may be a problem. Pick up the glass and tilt the glass back and forth to gently swirl the vinegar around the tablet. If they remain intact, try poking them with a knife or fork and see if they are softened. If not, they are not worth *any* price. Ask for your money back — or throw them away.

This test does not work with timed-release tablets, which are designed not to disintegrate quickly. However, timed-release tablets are usually substantially more expensive to manufacture, so it is unlikely that your "cheap" tablets would be of the timed-release type. **SWF**

Nasal Bromocriptine Better?

Man, I love your articles in the CERI newsletter! It seems that you are answering a question I just found myself asking, or you are anticipating a question I haven't formulated yet. Thanks... and keep up the good work!

I found these two abstracts on Medline. They regard the use of a nasal form of bromocriptine, which seems to offer several advantages, 1) it raises drug levels higher and faster than oral dosing, and 2) it bypasses liver metabolism so that less drug does more. Have you heard anything about this? Since the active ingredient in Parlodel is in a salt form, shouldn't it be soluble in water or saline? Might I be able to make a

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have it (a false negative result). The antigen test is much more likely to detect it than a stool culture.

Not all parasites are sensitive to the above drugs. You have to figure out which one you have to make sure you take the right drug. Those ones do most of them, however.

Chronically high levels of cortisol can sometimes be reduced by taking phosphatidylserine (OTC, expensive) and more often by taking carbamazepine (Rx, inexpensive, potentially toxic at doses near those required). Carbamazepine is a standard antiepilepsy drug and is used for many other things, so most physicians will be familiar with it but will not have heard of this use. It reduces baseline cortisol and makes the response to stress sharper, with higher spikes for acute stress events (and makes these spikes happen properly if you have trouble with that). It doesn't do anything until you get up to a therapeutic level similar to that used to control epilepsy. At this level it may impair coordination like alcohol does. By the way, one good indicator of cortisol excess is a weight problem. **Dr. Andrew Cutler**

I should also add that vitamin A doses above 10,000 IU may pose risks of birth defects (terratogenicity) during the earlierst stages of pregnancy. Women capable of getting pregnant should not take high doses of vitamin A.

The product MGN-3 is another enhancer of natural killer cells.

Herpes and other lipid enveloped viruses (hepatitis virus, influenza virus, cytomegalovirus, Epstein-Barr virus, varicella zoster virus, Newcastle disease virus, pseudorabies virus) seem to respond quite well to BHT (the food preservative) and hypericin (a substance concentrated from St. John's wort). See *SLN* v6n9p4 for a report of BHT and hypericin in a case of hepatitis C, and see *Wipe Out Herpes with BHT* and the *BHT Toxicology Report* for detailed information about BHT therapy.

For subscribers interested in mercury toxicity from dental fillings, Dr. Cutler has produced an extensive book titled *Amalgam Illness: Diagnosis and Treatment* which is available from the author for $35 (US funds drawn on US banks, sent to 10 Thunder Run #28-C, Irvine, CA 92614-7034 USA. Or write to AndyCutler@aol.com). **SWF**

In Utero DS Therapy?

I am about 5 months pregnant. My unborn baby girl has just been diagnosed with Down syndrome. My husband and I have read as much as we've had time to, and are learning so much about the disorder. We are very encouraged about the TNI protocol and would like to start our daughter on it as soon as she's born. But we want to know if there anything I can take while I'm still pregnant that could help her physical and/or mental development? **DS**

"My unborn baby girl has just been diagnosed with Down syndrome. Is there anything I can take while I'm still pregnant that could help her physical and/or mental development?"

There are definitely things you can do during the pregnancy. A minimalist (conservative) approach would be to take prenatal vitamins. There are no scientific data backing it up, but women taking collagen precursors may have DS children with less chance of heart defects and less joint laxity at birth. That's my hypothesis, based on a theoretical understanding of the consequences of over-expression of the two collagen genes on the 21st chromosome, and a few anecdotal reports. Post-natal collagen precursor therapy works wonders in the children.

It is my belief that antioxidant therapy is not needed during pregnancy unless you have an outright deficiency in your antioxidant defense system. Your body does a good job of protecting your baby from oxidative stress, so you can wait until immediately before or after birth for antioxidants. **SWF**

I was surprised that that issue of prenatal therapy was not covered in the TNI informational pages. **DS**

I think that most organizations with "deep pockets" are leery of possible civil and regulatory liability were they to say something that is not approved of or sanctioned by governmental and medical "experts." The general rule is: if you don't know for sure, don't say anything. This rule especially applies to anybody that sells products regulated by FDA. Since we do not, our information is protected by the First Amendment to the US Constitution. We can provide you information, speculations, theory and beliefs, and as long as we correctly identify it as such, we do not violate any laws. We leave it up to you to integrate the information we provide into your personal values.

"Women taking collagen precursors may have children with less chance of heart defects and less joint laxity at birth."

So far, with four cases reported to us, no woman taking collagen precursors has given birth to a DS infant with a heart defect. That's not a very solid finding from a scientific perspective, but only you can make a judgement as to whether such potential benefits are worth the potential risks of taking collagen precursors (which, I think, are minimal). The FDA won't let any product-selling company make that claim, even with disclaimers. A recent Appeals Court decision may change

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"There is no reason why you cannot get yourself tested while you are pregnant. If you have a selenium or zinc deficiency, the earlier you know about it the better for your pregnancy."

that, but I'll believe it when it happens.

There is no reason why you cannot get yourself tested with the Metametrix ION test panel while you are pregnant. If you have a selenium or zinc deficiency, the earlier you know about it the better for your pregnancy. A deficiency of either one can have a serious impact on your baby's antioxidant defense system after birth, and both are relatively easy and inexpensive to correct through dietary supplements.

In my opinion, the use of piracetam is a separate question. If you haven't already done so, please read the "The Case for Piracetam in Down's Syndrome" article [*SDN* v4n9p1 and on our web site]. I think that piracetam is very useful during labor. It is fairly efficiently excreted in breast milk, which makes dosing your baby easy if you are willing to take it yourself. **SWF**

What are collagen precursors and how can I tell if they are in my supplements? **DS**

A precursor is a molecule or substance from which something else is made — like sand is a precursor for a glass bottle. Proteins are made from amino acids. Therefore amino acids are the precursors to proteins.

"If my baby already has a heart defect, could it still help her?"

When you string amino acids together, like beads on a string, you get proteins. The collagen protein is made from a long string of amino acids, every third of which is *glycine*, and almost every third of which is *proline*. A significant percentage of the other third is *lysine*. Since 30% of the protein in the human body is collagen, and 30% of the collagen is glycine and 30% is proline, that's a lot of glycine and proline in absolute terms.

"Could GHB cause a metallic smell in urine?"

So the precursors to look for on your supplement labels are: lysine, proline and glycine. Actually, glycine is so plentiful in the human diet that it rarely needs supplementation. It doens't hurt to take it and it is quite inexpensive in comparison to the other amino acids, but it is unnecessary. Lysine and proline are the important ones.

There are also cofactors required for collagen maturation. These are vitamin C (or mineral ascorbates), bioflavonoids (there are a wide variety that might be used), and the trace minerals copper and iron (which should not be supplemented if they are already present in ample amounts). These cofactors are necessary to convert *pro*collagen to collagen.

"I'm wondering if Microhydrin is something I should consider adding to my supplement intake?"

If they are not present in your supplements, you can take them separately. Vitamin C and bioflavonoid combination products are plentiful in the market. You have three choices for collagen amino acids: 1) liquid predigested collagen protein (made from hydrolyzed animal connective tissues and sold in health food stores), 2) purified lysine and proline (proline is expensive), and 3) Knox unflavored, unsweetened gelatin (also made from connective tissues, but sold in grocery stores).

If my baby already has a heart defect, would/could it still help her?

In my opinion, *yes!* Heart development accelerates in the last trimester. Good luck and best wishes. **SWF**

Metallic Urine from GHB?

Could GHB cause a metallic smell in urine? I know that sounds a bit odd, but in my case it is a genuine question. Please answer.

I believe that pretty much anything can cause anything. If you do an A-B-A-B process on it and every time you take GHB you get the metallic smell in your urine, and every time you stop it goes away, I would conclude that the answer to your question is yes. It is, however, not a typical symptom.

There may be something unique in your metabolism. There is no reason that you cannot investigate this possibility. *Urine organic acids* is a test that might show high levels of succinic acid (a metal chelating agent that would be produced if you were not metabolizing GHB all the way) or other water-soluble metabolic byproducts of abnormal metabolism. *Urine minerals* is a test that will identify the actual metals content of your urine. Ask your doctor to do these tests, and see. **SWF**

Microhydrin?

I'm wondering if Microhydrin is something I should consider adding to my supplement intake. I'm 36 yrs old, in good health, and looking to stay young and in optimum health. Does this stuff live up to the hype I'm hearing? **WL**

Maybe. Microhydrin is a potent reducing agent, and if you are deficient in reducing power (*i.e.*, over-oxidized), you might see some results. I know of only two reasons why you shouldn't try it: 1) you are overly reduced already (a rare phenomenon indeed), and 2) you can't afford the price (it's fairly expensive).

Those people who respond dramatically to Microhydrin may be able to reduce their costs over the long run by purchasing an electrical "microwater" machine. These devices (expensive) use electricity (cheap) to separate water into cation-rich *alkaline*

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drugs your father was taking at the hospital were more responsible for his side effects than the Eldepryl. Since most authorities (medical, legislative and regulatory) believe that all deprenyls are equivalent, only graphic clinical contrary experience is going to convince anybody that Eldepryl is inappropriate and that Discovery's deprenyl is essential to your father's treatment. *You* may believe it, and *I* may believe it, but most people do not. It took me *years* to fully appreciate the differences. If you are going to build a case, with the media or politicians, you will nead clear and unequivocal evidence that Discovery's deprenyl is clinically different from Eldepryl in your father's case.

"If you are going to build a case, with the media or politicians, you will nead clear and unequivocal evidence that Discovery's deprenyl is clinically different from Eldepryl in your father's case."

Under normal circumstances, it might be considered unethical to subject your father to Eldepryl. But since the choice of using Discovery's liquid deprenyl citrate has been forcibly removed from you by the FDA, the two remaining options—using Eldepryl or doing without any deprenyl—are both similarly disadvantageous. Since you and your family are responsible for your father care, I suggest you weigh these options and choose what you consider to be the best of a bad lot.

My third suggestion is to build a support system of people who are as fully informed as possible about what is happening with your father's care. This may involve friends and relatives, but it may also involve home-care specialists, local reporters, elected representatives and maybe even your local police. If you have strong community relationships, it is more difficult for FDA agents to harrass you.

"Is it harmful to start TNI without having his blood tested first?"

Such community ties also may allow you to have greater political influence. A Congressional aide is probably more likely to ask tougher questions of the FDA and Justice Department if they know that you are talking to local reporters and writing letters to local papers. The squeeky wheel gets the greese. Reporters may be more likely to talk with you if your story involves frustration with elected officials. **SWF**

"If you have lots of money, then testing before starting TNI can give you some information that might be of value. But testing after starting TNI is much more likely to give you useful information."

Starting TNI Therapy?

My two-week-old son has Down syndrome. I have done a lot of reading about TNI and I think it would be benefit him in many ways. Yet I am nervous about starting my son on NuTriVene-D, mostly because I do not know much (yet) about vitamins, minerals, amino acids, how they combine, if the levels are safe, and what my son's metabolic make-up is at this point. Is it harmful to start TNI without having his blood tested first? **KA**

Generally no. The doses of substances in Nutrivene are purposefully low so that the chance of overdosing at the recommended dose is nearly zero. If anything, you may have to add more of some ingredients if your son has above-average nutritional needs.

Furthermore, blood tests are not infallible technology. They are actually quite limited. They are a one-dimensional view of a three-dimensional body. They usually have little bearing on potential bad reactions or "harm" *per se*. Hopefully, testing guides you to one or more *needs* of the person, that if addressed, will enhance their health and wellbeing.

For example, if your son has a *severe* zinc deficiency, the Nutrivene may not be sufficient to correct it. But the less-than-adequate zinc level won't make him sick, it will likely make him better—but not as good as a greater amount would. In other words, a mild zinc deficiency is much better than a severe zinc deficiency, but no deficiency is better still.

A good way to think about the blood tests is that they are about "tuning" the program. If you have lots of money, then testing *before* starting TNI can give you some information that might be of value. But testing *after* starting TNI is much more likely to give you useful information. In other words, before-and-after testing is best, but after-only testing is almost as good. Plus, if the after testing finds something significant, then you might want to repeat the after testing a second time to verify that the change in TNI is actually accomplishing what you want it to. Testing is not a trivial cost. Make it count.

Safety and tolerance are not absolutely correlated among people. That's why you pay attention when you give *anything* to your child, even puree of banana or cream of wheat. Some people may react badly to things on which most of us thrive.

Bad reactions to TNI are rare, and they are minimized by gradual dosing (*i.e.*, first 25%, then 50%, then 100%). This is because gastrointestinal flora are an important part of health, and TNI (and anything else you ingest) can disturb the biological balance in the intestine. **SWF**

Do you think it is too soon to start my son on NuTriVene-D? **KA**

My opinion is that it is never too early to start. Ultimately, I think that prenatal TNI therapy will eventually become the standard of care. **SWF**

At what age would piracetam be recommended? **KA**

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"Long-chain polyunsaturated fatty acids are an essential structural element of human brain membranes and absolutely necessary for normal, healthy brain development."

"Do you think that pyruvate may be useful in helping to stop the free radical damage in Down's Syndrome?"

This is a tougher question. Piracetam is considered the treatment of choice for newborn infants with myoclonic seizure disorders, at extremely high doses (up to 12-24 grams!). It is surprisingly well tolerated. So the sub 1-gram doses are not likely to be a significant toxic risk. But there is much more to life than toxicity.

A huge amount of brain development takes place in the first two years of infancy. It is possible that piracetam may have negative, positive, or negative and positive effects on brain growth, differentiation and apoptosis (programmed cell death) that are too subtle to be seen in a clinical therapeutic context. It just hasn't been researched sufficiently.

Brain growth is an extremely complicated process and difficult to view non-invasively. Most people do not know that a huge number of brain cells die during normal brain growth from birth to 2 years of age. In DS, more than the normal number die, presumably from increased oxidative stress. It is my opinion that this increased brain cell mortality causes the mental retardation that is associated with untreated DS. I think that piracetam may assist TNI in preventing that. Maybe it doesn't. We're just not sure. **SWF**

What about Efalex and DHA? Should these be taken with NuTriVene-D? **KA**

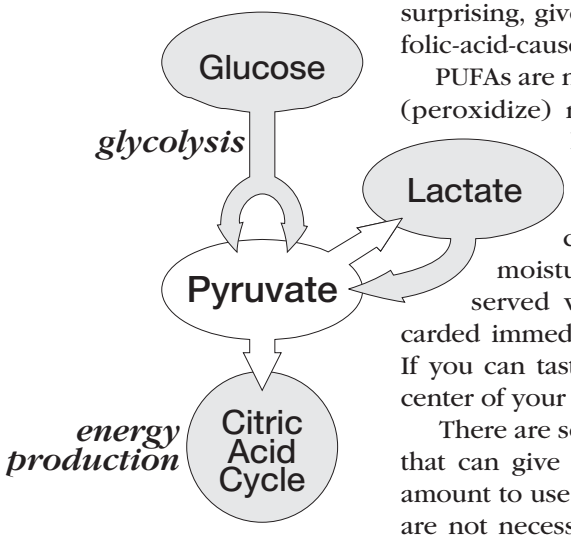
Long-chain polyunsaturated fatty acids (PUFAs) are an essential structural element of human brain membranes and *absolutely necessary* for normal, healthy brain development. We know that PUFA deficiencies cause impairment of brain development and decreased mental capabilities later in life. That's why DHA is added to infant formulas in Europe. The USA, led by the FDA, has yet to get with the program. But this is not too surprising, given their 20-40 year lag on the folic-acid-causes-birth-defects issue.

PUFAs are not without risk. They oxidize (peroxidize) rapidly and become rancid. Rancid fat is immunosuppressive. So DHA and related PUFAs must be fresh, stored carefully (protected from heat, moisture, light and oxygen), preserved whenever possible, and discarded immediately after becoming rancid. If you can taste the rancidity (on the back center of your tongue), throw it out.

There are some blood tests for fatty acids that can give you a clue as to the correct amount to use. However, blood lipid levels are not necessarily linearly correlated with brain lipid levels. **SWF**

Figure A:

Role of Pyruvate in Energy Production



Pyruvate for Down's Syndrome?

While reading up on pyruvate recently, I read that it "can actually help to inhibit free radical production and that it also helps to reduce DNA injury resulting from oxidative stress...and that studies indicated that DNA breaks were reduced 40% by it." **NS**

The glycolysis pathway splits glucose (a six-carbon carbohydrate) into two pyruvates (three-carbon carbohydrates), which feed into the energy cycle (the Krebs citric acid cycle) [see Figure A]. So pyruvate is a major player in energy production. Usually, pyruvate deficiency is not a problem. If anything, pyruvate tends to accumulate. Excess pyruvate is temporarily converted into lactate (lactic acid), which is converted back to pyruvate when the Krebs cycle "catches up" with glycolysis and the pyruvate/lactate excess can finally be burned. **SWF**

Do you think that pyruvate may be useful in helping to stop the free radical damage in DS, or is pyruvate's molecular make up something that would exacerbate the situation? **NS**

The energy produced by pyruvate has potential uses to assist the antioxidant defense system and other potential risks to produce free radicals. This is because energy production 1) causes free radicals, and 2) powers the antioxidant defense system. All fuels, whether carbohydrate, lipid or amino acid have this potential. It is difficult to pre-judge the net effect when you have opposite processes taking place. I would think (assume) that *normalization* of energy production would be beneficial (*i.e.*, increasing sub-normal energy production) and that *over-revving* the energy production system would tend to aggravate the free-radical problem.

There is one more issue that I should mention, given our recent focus on metabolic types and pH balance. There are *two separate input paths* for pyruvate into the Krebs cycle [see Figure B, next page]. One pathway *adds* carbon dioxide (CO_2) to pyruvate to form oxaloacetate [see pathway 1]. Another pathway *removes* CO_2 to form acetyl-CoA (coenzyme A) [see pathway 2]. Pathway 1 is catalyzed by *pyruvate carboxylase*, an enzyme which converts the threecarbon pyruvate into a four-carbon oxaloacetate. Pathway 2 is catalyzed by the *pyruvate dehydrogenase enzyme complex*, which converts the three-carbon pyruvate into a two-carbon acetate (commonly called acetic acid, or vinegar).

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"The balance between oxaloacetate and acetate is also important because it directly affects pH balance in the mitochondrion."

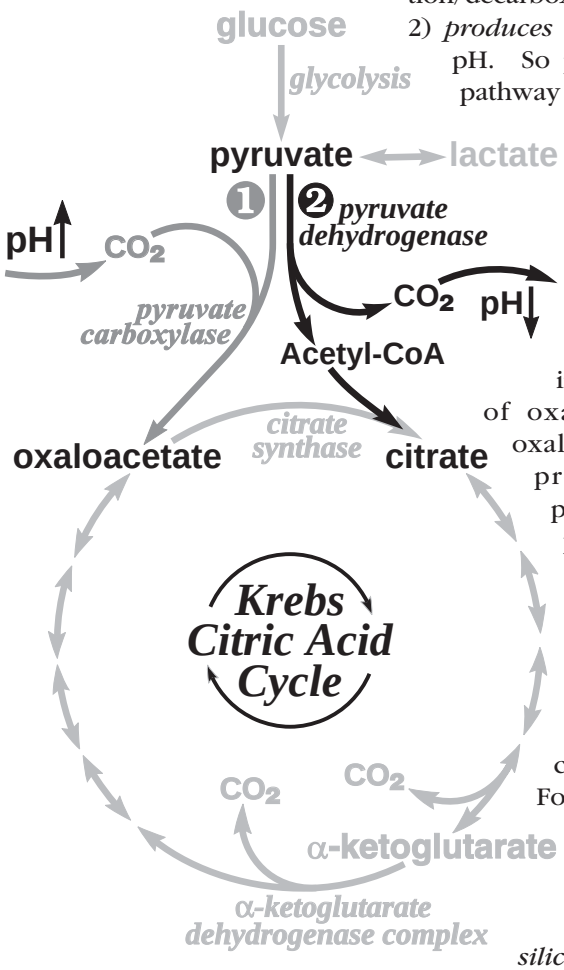
This pyruvate dehydrogenase complex is similar to the alpha-ketoglutarate dehydrogenase complex on the other side of the Krebs cycle [see Figure B below]. They are both composed of three closely associated enzymes that use 1) thiamine diphosphate (vitamin B_1 coenzyme), 2) lipoamide (lipoic acid coenzyme), and 3) FAD (vitamin B_2 coenzyme).

The balance between oxaloacetate and acetate is important because these two molecules condense to form citric acid [see Figure B]. This reaction is catalyzed by the enzyme *citrate synthase*, which joins the four-carbon oxaloacetate with the two-carbon acetate to form a six-carbon citrate. This is a one-way reaction, like the dehydrogenase complex reactions, and unlike the rest of the reactions of the Krebs cycle.

The balance between oxaloacetate and acetate is also important because it directly affects pH balance in the mitochondrion. The carboxylation of pyruvate (pathway 1) absorbs CO_2 from the mitochondrial matrix and thereby raises (alkalinizes) pH [see Figure B]. Another way to say it is that CO_2 is acidic, so *removing* acidity produces alkalinity. On the other hand, the dehydrogenation/decarboxylation of pyruvate (pathway 2) *produces* CO_2, which lowers (acidifies) pH. So pathway 1 drives pH up and pathway 2 drives it down.

Figure B:

pH and Pyruvate Metabolism



The balance between oxaloacetate and acetyl-CoA is regulated locally (in the mitochondrion) by acetyl-CoA-induced activation of pyruvate carboxylase. When acetyl-CoA levels rise, pyruvate carboxylase activity increases to augment the pool of oxaloacetate. However, both oxaloacetate and acetyl-CoA are produced from many other pathways, and not just from pyruvate. These other reactions may skew the balance between oxaloacetate and acetyl-CoA, which then has to be adjusted locally. This can lead to mitochondrial pH stress and metabolic inefficiency.

For these reasons, it may be a good idea to examine the role of metabolic types in Down's syndrome therapy. **SWF**

What can you tell me about silica hydride. It is touted as a powerful free radical neutralizer. Their web site talks about negatively charged electrons and the element "hydrogen." Not being a biochemist, I don't know if using this substance would exacerbate the "hydrogen" peroxide problem or not. Is this marketing hype, or would it be helpful? I wish I'd have taken more chemistry courses so I could evaluate such statements as, "Silica hydride, when combined with an additional, loosely wrapped, negatively charged ion, is the most powerful antioxidant available. It is a free radical neutralizer which has many thousands of times more antioxidant power than any form of vitamin, mineral or food supplement." **NS**

Hydrogen and hydride carry *reducing power*, the opposite of *oxidizing power*. This can be trapped in a silica matrix, or it can be carried by "microwater" (alkaline reduced water). Reducing power is also carried by vitamin C.

Reducing power is necessary to life. So is oxidizing power. Too much oxidation or too much reduction interferes with the body's energy and homeostatic systems. Hydrogen is like the negative pole of a battery while oxygen is like the positive pole of the battery. You need both poles to have power.

The product you are talking about is probably Microhydrin. The reducing power it carries is in direct opposition to both hydrogen peroxide (which is excessive in DS) and superoxide (which is deficient in DS). I wouldn't hazard to guess the net effect because I could see it working both ways, but I would not be surprised if it would be a great benefit in DS. One of the major effects of reducing power is to keep glutathione in its reduced state, and this becomes increasingly important as oxidative stress increases and glutathione levels decline.

There is a testing machine called the BTA (Biological Terrain Assessment) which can measure redox (a contraction of *red*uction and *ox*idation) potential in blood, urine and saliva. You might be able to use that machine to see if the overall oxidative stress in DS can be measured in redox potential, and then if the redox potential can be "normalized" by Microhydrin or microwater. Furthermore, you might be able to use such a test to quantify how much Microhydrin or microwater is sufficient (without over-reducing the redox potential). I think microwater and Microhydrin have their strongest effect in the blood stream, where the ingested water first absorbs across the digestive tract. The saliva is more a measure

Q&A Questions + Answers

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"Technically, these products should be thought of as reducing agents, not antioxidants."

of the *cellular* redox environment. The oxidative stress in Down's syndrome is probably greatest at the cellular level where hydrogen peroxide is produced.

Technically, these products should be thought of as reducing agents, *not antioxidants*. Although reducing agents usually support the antioxidant defense system, most antioxidants are not reducing agents in the biological redox environment.

There is a similar confusion between oxidizing agents and free radicals. Although most free radicals are oxidizing agents in biological systems, the reverse is not true. For example, ground-state (singlet) ozone and singlet oxygen are *not* free radicals, but they *are* strong oxidizing agents.

Reducing agents are not something to be handled carelessly, but they can be very beneficial when applied correctly. **SWF**

New GHB Legislation?

What's happening with the legal battle over GHB?

The federal law is pending. California has passed its new law which is worded similarly to Georgia's. It will criminalize all GHB-related compounds including salts, ethers, esters, isomers and precursors of GHB as of January 1, 2000. This includes GHB, butyrolactone, butyleneglycols, alpha-hydroxy butyrates ("alpha-hydroxy" skin-care products), beta-hydroxy acids (also in cosmetics), GABA, certain polymers (n-butyl polyesters/polyethers, nylon-4, and some harder-than-steel automotive plastics), acetone-free nail polish remover, industrial cleaning solvents, and some medical products (blood plasma extenders). **SWF**

(to be continued in next issue)

Metabolic Balancing: Oxidative and Autonomic Nutrition

(continued from page 1)

"Metabolic balancing is accomplished by counteracting blood pH stress."

to crash as it does with fast oxidizers. Fruit, starchy vegetables (like yams, squash and potatoes) and sweet vegetables (carrots, onions, and beets) are included. Beta-oxidation does not need proactive cultivation. Fat-rich foods like red and dark meats, fatty fish, vegetable oils and nuts are minimized or avoided.

Autonomic Types

Autonomic types come in sympathetic and parasympathetic types. These are defined by the relative dominance of the two complementary arms of the autonomic (involunary) nervous system. Sympathetic dominant types are "activated" by increased activity of the adrenal, thyroid and pituitary glands. They are often described as having "Type A" personality (strong drives, hyper behaviors and goal-orientation). But they may also exhibit poor digestion, headache, high blood pressure and depressed appetite from their sympathetic dominance.

Parasympathetic dominant types are often described by their "Type B" behaviors (more relaxed, laid back, socially oriented, and more likely to procrastinate). The parasympathetic nervous system drives the digestive organs. These includes the liver, intestine, stomach, salivary glands and pancreas (excluding insulin secretion, which is sympathetically driven). Parasympathetic types are more likely to develop hypothyroidism and acid indigestion.

Autonomic and Oxidative Positive Influences

Type I	Type II
Oxidative Metabolic Types	
Slow Oxidizers	Fast Oxidizers
Autonomic Metabolic Types	
Sympathetic	Parasympathetic
Minerals	
magnesium, potassium, iron	calcium, sodium, phosphorus
copper, manganese, chromium, vanadium	zinc, iodine, boron
Vitamins	
beta-carotene	vitamin A (palmitate)
vitamin C (ascorbic acid)	vitamin C (calcium, sodium ascorbates)
vitamins D_3 and K	vitamin E
vitamins B_1 (thiamine) & B_2 (riboflavin)	choline, inositol
vitamin B_3 (niacin)	vitamin B_3 (niacinamide)
vitamin B_6 (pyridoxine)	vitamin B_5 (pantothenate)
folic acid (folate), biotin, PABA	vitamin B_{12}
Amino Acids	
aspartic & glutamic acids	phenylalanine, tyrosine, methionine
glutamine, histidine, proline	leucine, isoleucine, carnitine
Miscellaneous Other	
	bioflavonoids, nucleotides (RNA, DNA)

Metabolic Classifications

The categorizations of nutritional elements into groups with specific metabolic activity (*e.g.*, sympathetic, or catabolic) are not necessarily consistent between metabolic types. However, the groupings for autonomic and oxidative influences are almost identical, which is why we discuss them together. These are listed in the adjacent sidebar (arbitrarily labeled Type I on the left and Type II on the right). This congruence in classifications for oxidative and autonomic types is not shared with other metabolic types (which will be discussed in later articles).

Although the similarity in groupings for

Q&A Questions +Answers

Allergy to Piracetam?

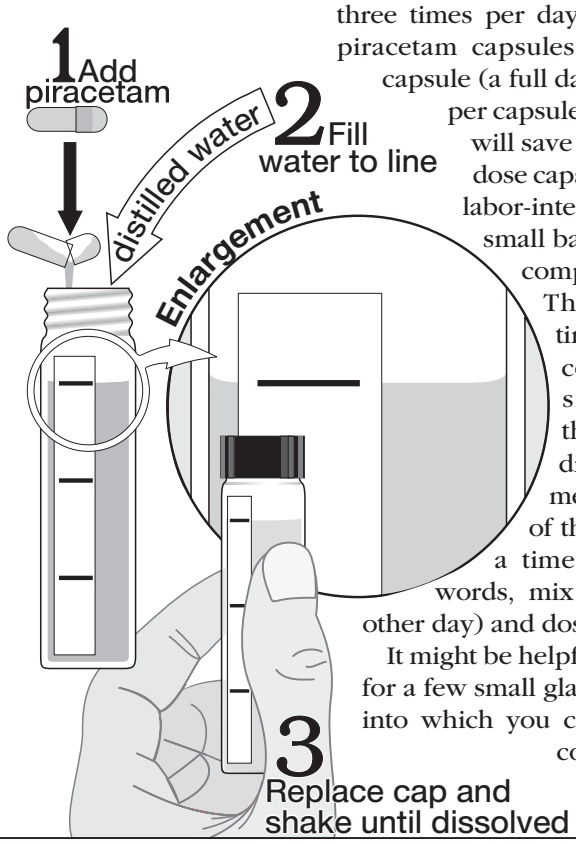
My 2-year-old child with Down's syndrome started piracetam on December 7th and broke out in hives on the 11th. I think its an allergic reaction to the piracetam because there were no other changes involved, no change in Nutrivene-D or diet, and I've seen this allergic reaction before. The piracetam is liquid, prescribed by our doctor, and made by a compounding pharmacy. I thought I should tell you. **K**

Piracetam allergy is extremely rare. It is much more likely that the allergic reaction was caused by the preservatives used in stabilizing liquid piracetam preparations against fungal contamination. Unlike piracetam, *methylparaben* and *propylparaben* are not uncommon triggers of allergic and intollerance reactions. You can check this out by having your physician change the prescription to capsules (or powder) and dissolving it into liquid as you use it (on an ongoing basis). There is no need for preservatives in dry piracetam preparations, or freshly prepared solutions. However, without preservatives, you should dissolve only the amount that can be used in a day — or two with refrigeration.

"Unlike piracetam, methylparaben and propylparaben are not uncommon triggers of allergic and intollerance reactions."

"Piracetam-sicles can allow gradual taste desensitization in children who would otherwise object to a sudden bitter flavor."

This may not be as convenient as pre-prepared liquid piracetam, but there are a few suggestions that I can offer that might be helpful. Assuming that you give piracetam three times per day, you can get the new piracetam capsules with *three* doses per capsule (a full days dosage) or *six* doses per capsule (two days worth). This will save you money over single-dose capsules (encapsulization is labor-intensive, especially in the small batches made by hand by compounding pharmacists). This can also save you time. You can dump the contents of a three- or six-dose capsule into three or six teaspoons of distilled water, and then measure out one teaspoon of the piracetam solution at a time for dosing. In other words, mix once a day (or every other day) and dose three times per day.



It might be helpful to ask the pharmacist for a few small glass vials with screw caps into which you can dump the capsule's contents (throwing away the empty capsule), fill with water, and shake for quick disolution. Get at least two vials so you can wash one while the other is in use. If you put a piece of clear tape on the outside of the vial and mark it with a permanent marker at the three or six teaspoon level, you can save time by filling it with distilled water to the mark instead of having to carefully measure out three or six teaspoons of water each time. You can even put additional marks at each teaspoon level, if that would make dosing easier.

The measure of volume that you use is basically arbitrary. I mentioned teaspoons because they are likely to be in every kitchen, but you could just as easily use milliliters, cubic centimeters, fluid ounces, or drops. The only limitation is that the water volume be sufficient to dissolve the piracetam completely. This is not really a problem because piracetam is *highly* water soluble. One gram of piracetam (1000 mg) will readily dissolve in only two cubic centimeters of water (less than a half teaspoon).

Another technique that can be a big convenience is piracetam-sicles. You can take a plastic ice-cube tray with ten (or twelve) ice-cube compartments and fill it with piracetam solution containing ten (or twelve) doses of piracetam. You can find out exactly how much water to use if you fill the tray with plain water first, and then carefully pour it into a graduated kitchen measuring cup. The only trick to piracetam-sicles is having to fill each compartment in the ice-cube tray to approximately the same level to keep the doses even. A little practice may be needed.

Once the piracetam solution has frozen into ice cubes, a cube can be added to a beverage for dosing. Because the piracetam-sicles melt slowly, the bitter taste of piracetam is lowest with the first sip and gradually gets stonger. This can allow gradual taste desensitization in children who would otherwise object to a sudden bitter flavor. Piracetam can also be dissolved in fruit juices and frozen into piracetam-sicles to make taste more acceptable. Generally, citrus juices are best for masking bitter flavors. When children are old enough, they may appreciate an after-school piracetam-sicle on a stick. Just insert the popsicle sticks into piracetam-juice mixture in the ice-cube trays before it freezes. After it freezes, grab the stick and the piracetam-sickle will pop out in your hand. **SWF**

Metabolic Independence?

In your introduction to metabolic balancing, you say that autonomic and oxidative

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types are truly independent but in the later article you say that the categories are the same. Doesn't this mean that they are tied together and not truly independent? **OTP**

I see what you mean. Metabolic types are truly independent in that *all possible combinations of types* are found in people. There are sympathetic fast oxidizers, parasympathetic fast oxidizers, parasympathetic slow oxidizers and sympathetic slow oxidizers. This was my meaning. But your statement that they must be tied together is also correct in a different context. The oxidative and autonomic systems independently regulate overlapping metabolic systems. In other words, it is a situation of *dual control*. The autonomic system has its control mechanisms for maintaining blood pH homeostasis, and the oxidative system has its control systems. However, they are wired oppositely. Nutrients which produce acidification through the oxidative system produce alkalinization through the autonomic system, and *vice versa*.

"The oxidative and autonomic systems independently regulate overlapping metabolic systems. In other words, it is a situation of dual control."

Imagine a sandwich. The oxidative bread is on the bottom, the blood pH metabolic system "fixings" are in the middle, and the autonomic bread is on the top. Just as the sandwich fixings are contained by both pieces of bread, the blood pH is influenced by the oxidative and autonomic systems. And the bottom-up regulatory systems are not necessarily the same as the top-down systems. The fact that they are wired oppositely probably has survival value in allowing humans to survive better under highly skewed diets. It may also allow these systems to check and balance each other to some extent.

Another analogy could be the control of corporations. The President or CEO runs the corporation on one level and the Board of Directors runs the corporation on another level. They can have different ideas of what is "best" for the corporation. A business proposal going through the president's office might be accepted whereas the Board might reject it. The relative dominance between the Board and CEO can make a big difference in what happens to the corporation. The Board and CEO are independent, but tied together.

I suspect that the reason that oxidative and autonomic types have almost identical nutritional groupings while anabolic/catabolic groupings are totally different has to do with the fact that the oxidative and autonomic systems regulate the same biological "level" which is different from that regulated by anabolic/catabolic systems. I think of the anabolic/catabolic balance as a "deep" or "primitive" aspect of metabolic balance, primarily operating at the subcellular, cellular and maybe tissue levels. I regard the oxidative and autonomic metabolic controls as "higher order" systems that evolved after the anabolic/catabolic systems and which operate at the tissue and organism levels. It makes sense to me that new homeostatic control mechanisms had to evolve as life evolved from single cell organisms to multicellular organisms to complex multicellular organisms. Each new layer of complexity would need to be stabilized against stresses from the external environment.

We'll be reviewing William Wolcott's new book, *The Metabolic Typing Diet*, in the next newsletter. Get it. It's out in hardback. It's excellent. **SWF**

Cell Therapy?

From my investigations, cell therapy seems to have merit as a Down's syndrome therapy. Although I wouldn't trust the live cells in Mexico or France, I do have more trust in the frozen cells made in Germany through Bio-Pharm. The live cells scare me and I do indeed think that viruses can be transmitted. From what I have researched, the cells from BioPharm have not had any viral transmissions in its 60 years of producing cells. What do you think about cell therapy? **NS**

"What do you think about cell therapy?"

I think cell therapy has immense potential—if you can get the right cells. That's the problem in medically overregulated countries like the US, and in countries in which corrupt business practices are condoned.

In the US, the political suppression of "alternative" therapies by medical regulators and "unapproved" therapies by the FDA drives the would-be-legitimate players out of the market and leaves charlatans and crusaders to fill consumer need. Some of the crusaders are providing good product, but on the surface, it is very difficult to tell the crusaders from the charlatans. In Germany and Switzerland, where 1) medical regulation is less oppressive, 2) the costs of the drug-approval process for biological therapies is vastly lower, and 3) anti-fraud law is strongly enforced, cell therapy has thrived.

"In the US, the political suppression of 'alternative' therapies by medical regulators and 'unapproved' therapies by the FDA drives the would-be-legitimate players out of the market and leaves charlatans and crusaders to fill consumer need."

By the way, BioPharm has no way of knowing whether or not viruses have been transmitted in their cells. They can know whether or not there have been any reported cases of viral disease. They can know

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whether or not specific viruses can be detected or cultured. But that is far from definitive evidence. First of all, there are a lot of viruses around, and most of the time we fight them off without dramatic symptoms. Secondly, there is no easy or affordable way to assay for "unknown" viruses that might be present.

In my opinion, *prions* are a much more serious but less likely risk than viruses. Prions cause bovine spongiform encephalopathy (mad-cow disease), scrapie (in sheep), and Kreutzfeld-Jacob disease (in humans).

My last comment has to do with a possible presumption about "frozen cells." The process of freezing cells is a reliable way *to keep cells alive*, which is an important aspect of cell-therapy efficacy. The freezing of sperm, eggs and embryos is routine in animal husbandry and fertility medicine. So frozen cells are not necessarily dead. In addition, even if the cells were frozen in a lethal manner, or freeze dried, viruses wouldn't necessarily be killed. Viruses do not have a metabolism that can be stopped to "kill" them. They have a static structure that must be disrupted, disassembled or broken for them to become non-infectious. Freezing is not a reliable way to kill viruses. Prions are even more stable than viruses. They are known to be able to "survive" boiling water. **SWF**

"Piracetam is a standard therapy in Europe for cognitive and speech rehabilitation following stroke, but it would be highly unusual for a stroke patient to receive piracetam in the US without specifically asking for (or demanding) it."

Anoxia and Coma Therapies?

"Following a heart attack, my wife (49 years young) had eight minutes of anoxia."

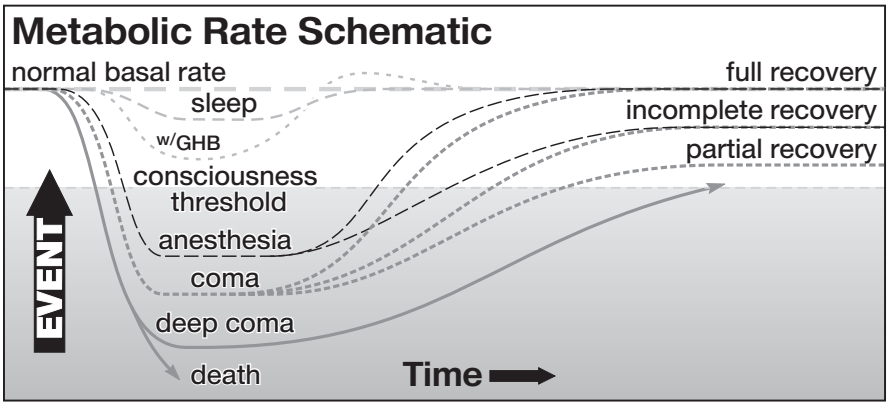
Following a heart attack, my wife (49 years young) had eight minutes of anoxia. She was revived, a blood clot in the left anterior coronary artery was chemically dissolved and she remained in a coma, on life support, for four days. After regaining consciousness, she has started to recover. She is now home with me, receiving physical, occupational and speech therpy. She gets around the house well on good days. Her long-term memory is fragmented and short-term memory is very weak (2 minutes to 4 hours). Depression and low energy are also a problem. Local doctors tell us this is all we can hope for, though we may see minor improvement in the months ahead. We are looking for information about memory rehabilitation. Any help would be greatly appreciated. **LB**

There are many therapies that might be of use that are not necessarily recognized by "local" doctors. For example, B-complex vitamins and trace minerals are so "low tech" that they are virtually ignored in cardiac and stroke rehabilitation. Without professional support, the patient and/or caregiver must assume the primary responsibility of investigating these therapeutic options.

Piracetam is a standard therapy in Europe for cognitive and speech rehabilitation following stroke, but it would be highly unusual for a stroke patient to receive piracetam in the US without specifically asking for (or demanding) it. If you can't get your medical professionals or insurance company to cooperate, you can opt to pay for piracetam out of your own pocket and initiate therapy despite your doctor's objections or discomfort. With a doctor's prescription, you can get piracetam from a US compounding pharmacy in a day or two. Without a physician's prescription, you will have to import it for "personal use," which takes weeks. The FDA's policy on this is covered in back issues and on our web site (www.ceri.com).

You might also want to consider 1) methylation cofactors (vitamin B_{12}, folate, trimethylglycine), 2) oxygen therapy (intravenous hydrogen peroxide, hyperbaric oxygen, superoxide negative ions, aerobic exercise), 3) circulation enhancement (chelation therapy, niacin, vinpocetine, arginine, ginkgo), 4) metabolic balancing (diet and supplements), 5) metabolic enhancement (acetyl-L-carnitine, Hydergine, vinpocetine, coQ_{10}), and 6) collagen support (lysine, proline, ascorbate, bioflavonoids). Ideally, it would be a good idea to have a health-care professional to assist you with prioritizing these options.

Another factor that should be considered is basal metabolism (overall cellular energy production). Coma involves profound suppression of basal metabolism which may not fully resolve spontaneously (see margin illustration). A similar condition can occur following *anesthesia*, a medical procedure which purposefully induces the same kind of metabolic suppression as a coma, but under



energy pathways. **SWF**

No Piracetam for Down's Syndrome?

The Canadian Down Syndrome Society has taken a position against piracetam in the treatment of Down's syndrome. What do you think of their research study? **DS**

"The Canadian Down Syndrome Society has taken a position against piracetam in the treatment of Down's syndrome. What do you think of their research study?"

It was a classic, well designed, blinded, crossover study, but incompetently executed due to the choice of dose. The children were given 80-100 mg/kg of piracetam, which is approximately three times the amount usually recommended for treatment of learning disabilities in children. Not surprisingly, they saw a clear spectrum of stimulatory side effects (four cases of aggressiveness, three of agitation, two of sexual arousal, and one each of irritability and poor sleep). The researchers were unable to see any "significant" changes in cognitive abilities.

"The children were given 80-100 mg/kg of piracetam, which is approximately three times the amount usually recommended for treatment of learning disabilities in children."

This last point needs elaboration. "No significant changes" does not mean that there were no cognitive improvements from piracetam. It means that the technique used to measure cognitive function were not able to generate a statistically significant difference between the piracetam and placebo groups. Based on scientific reports and previous research with piracetam and DS children, the most likely cognitive ability to be expected to be enhanced by piracetam would be *verbal ability*, which was not tested by the researchers. It is also possible that the overt bias of the researchers may have influenced how they looked for results (*i.e.*, not too closely). In addition, cognitive benefits could easily have been missed because of the small size of the study (25 children, only 18 of which completed the study).

"Cognitive benefits could easily have been missed because of the small size of the study."

A similar bias problem cropped up when the sugar industry set out to prove that vitamins did not increase IQ in children [see the interview with Dr. Stephen Schoenthaler in *SDN* v1n7p1]. The researchers designed their study to fail by using assessment tests which were so crude that they would miss an IQ enhancement of less than 10 points, which was three times the IQ enhancement found by Schoenthaler, and Benton and Roberts in more conscientious studies. Sure enough, the industry-funded researchers were able to confirm their preconceived notion that IQ was not statistically enhanced by vitamins. This is the political side of science.

"The most serious problem with the study is that it ignored TNI completely."

The importance of a negative scientific finding is completely dependent on the quality of the investigation. It would be easy to see the bias of scientists claiming that *trumpetting elephants are neither big nor loud* if you could see that they had put brown paper grocery bags over their heads and beans in their ears. Most scientists engaged in obfuscation (the obscuring of the truth) are too clever to qualify their findings by openly disclosing their study's limitations. As you might expect, they purposefully hide the details to make it difficult to evaluate what they did and didn't do.

How many people reading the Canadian Down's Syndrome Society's quarterly publication would know that the generally accepted dose of piracetam recommended for treatment of learning disabilities was only 30 mg/kg and not 100 mg/kg? Only a few, would be my guess.

Let's look at the article written about the study's findings. Dr. Robert Haslam explains piracetam as, "a cyclic derivative of gamma-amino butyric acid, a central nervous system inhibitor." Such a statement is truthful, but at the same time quite misleading. Piracetam is not a GABAergic drug, nor does it inhibit the central nervous system. As a matter of fact, it tends to accomplish the opposite effect. He then states, "piracetam has been reported to improve dementia, particularly in individuals with Alzheimer's disease." The first part is right, the latter is wrong. Piracetam actually works better in non-Alzheimer's dementias than it does in Alzheimer's disease (see *SDN* v3n1p3). Then he states that piracetam "has also been used to treat myoclonic epilepsy, autism, aphasia, dyslexia, and learning disorders." Although this is a fair summary, he immediately qualifies it with, "Unfortunately, there have been few scientifically well-designed studies to test the efficacy of piracetam in the above conditions." Not only is that not true, that's the kettle calling the pot black. Piracetam is one of the most thoroughly studied drugs on the planet. It is recognized as the treatment of choice for myoclonic seizure disorders by the world's medical communities (excepting the US and Canadian medical authorities, of course). The evidence is so strong, it it considered medical negligence to fail to treat myoclonus with piracetam (again, except in the US and Canada).

Dr. Haslam's criticism of the quality of other piracetam research studies in the face of his own fundamentally flawed study is a good example of the political hypocrisy principle in action: attack your opposition for

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your own failings and their honest criticisms appear to be "sour grapes" retaliation.

The most serious problem with the study is that it ignored TNI completely. In Down's syndrome therapy, TNI is essential, piracetam is elective. The many metabolic imbalances created by trisomy 21 are not addressed by piracetam. So the efficacy of piracetam in an untreated DS population would not be indicative of its efficacy in a TNI-supplemented population.

Bottom line: its good politics, not good science. **SWF**

"The order I placed is a Schedule-IV drug, and I am wondering what kind of punishment I may face."

Ordering Scheduled Drugs?

I now see that the order I placed is a Schedule-IV drug, and I am wondering what kind of punishment I may face. Also, what are the chances my package will not be intercepted? **anon**

It is my understanding that possession of small amounts of a schedule IV drugs without a prescription is a misdemeanor crime, as long as there is absolutely no question of intent to sell. A lawyer can confirm that for you. Whether or not there may be an additional charge of violating import laws, I do not know. Talk to a lawyer.

"The chance of a package being intercepted is approximately one in ten. In certain areas, interception may be as low as one in a hundred."

Although it might be unreasonable for the government to assume that you would have advance knowledge of every drug's scheduling status, the law does require you to know this. "Ignorance of the law is no excuse" is the standard line, although there are exemptions (precedents) that have been made by the courts from time to time — especially when *lawmakers* break the law. We ordinary citizens are held to a higher standard than politicians.

The worst scenario will probably be somebody at DEA wanting a promotion who may try to make an example of you. I don't really see what a Schedule-IV example is worth, but they might try a bit of intimidation anyway and see how you react. Playing dumb may be a good strategy.

"Our problem has been finding a good source of NADH."

In general, the chance of a package being intercepted is approximately one in ten. That is a crude approximation. In certain areas, interception may be as low as one in a hundred. It also depends on the size and weight of the package. Small, lightweight flats are the least likely to get inspected. Heavy, bulky boxes are much more likely to get inspected.

If you haven't yet taken possession of the schedule-IV substance in question, you are not yet "in possession" of anything, regardless of whether or not you ordered it. If you haven't received it, simply refuse to accept it when it arrives. One procedure used for Schedule I and II substances is for a narcotics officer dressed in a US Postal Service uniform to attempt delivery in person. They knock on your door, hand you the package, and then arrest you — then, or a few minutes later. If you have a post office box, they might put it in the box and wait for you to pick it up, or they might put a yellow slip in the box for pick-up at the counter. If you refuse to accept it, the DEA has a much harder time proving possession. They may still try to charge you with "intent" or "conspiracy" to violate the Controlled Substances Act.

In the future, to avoid this problem, *don't order any controlled substances!* **SWF**

NADH Source?

In the Parkinson's Report Q&A you suggested trying a sublingual form of NADH. My dad has taken NADH for a number of years and has had a profound effect from it. He has been able to stay off of other Parkinson's medications so far. However, our problem has been finding a good source of NADH. The only one currently available that we are aware of is manufactured by Enada, which does not work for my Dad at all. If you have information on a sublingual form, we would be very interested in who the manufacturer is, and how we could order some. **JB**

The enteric-coated Enada NADH can be taken sublingually by thoroughly chewing up the tablets and refraining from swallowing for a while. It also helps to move the NADH-rich saliva around the cheeks and gums with the tongue.

We have had a few other complaints by subscribers that the "new" Enada is not as good as the "old" Enada, but this is entirely anecdotal. You can order grams of powdered NADH from BIOS Biochemicals (1-800-404-8185) and then use it sublingually. It's a lot less expensive on a mg-to-mg basis, but it's much more difficult to measure out the extremely tiny doses of powder. I'd be interested to know if you develop other ways of taking it. **SWF**

"We have had a few other complaints by subscribers that the 'new' Enada is not as good as the 'old' Enada."

Alcohol Remedy?

I was fascinated by your article "Alcohol, Reducing Power and Oxidative Stress." I had to read it several times to follow it (no fault of yours). It is amazing what complicated systems we have, how intricate the reactions are. Thank you for this great piece

Q&A Questions + Answers

"Any word on the court case and when Discovery's liquid deprenyl might or might not become available?"

"Reducing agents sound to me like antioxidants. Are they? If not, how are they different?"

"Antioxidants protect against oxidizing free radicals like an umbrella protects against the hot rays of the sun. Reducing agents protect against oxidizing stress like a cold drink protects against overheating."

Liquid Deprenyl Citrate?

Any word on the court case and when Discovery's liquid deprenyl might or might not become available? **many**

James Kimball, President of Discovery Experimental & Development (DEDI), has been convicted of multiple counts, from misbranding (a misdemeanor) to defrauding the FDA (a felony). From what I witnessed, and heard from lawyers and participants, I can only regard the court case as a travesty of justice. Witnesses described to me 1) submission of falsified evidence (forged documents) by the prosecutor, 2) perjury by government witnesses, 3) arbitrary dismissal of relevant laws by the court, 4) court refusal to allow defense witness testimony, and 5) misinstruction of the jury by the judge. Sentencing is scheduled for August.

As a result of this case, DEDI has ceased business. Assets have been sold to another company, Strictly Supplements, which states that they are now producing an over-the-counter, dietary-supplement version of DEDI's liquid deprenyl product. They are calling it Citr-A-Sol. Anne and I have switched to it, and it seems identical to the old DEDI liquid deprenyl citrate. We are tracking ongoing developments and will have more detailed things to say in a future issue. At this time, we can provide their address and phone number:

Strictly Supplements
2920 N. Greenvalley Parkway, Suite 321
Henderson, Nevada, 89014 USA
Phone: 702-547-9009

Citr-A-Sol comes in a one-ounce bottle (600 drops), which is *twice the size* of the old DEDI bottles (300 drops). This may be an excellent package size for Parkinson's patients using 10 mg per day (a two-month supply), but it poses a technical problem for people (like me) taking deprenyl in extremely low doses (one drop every other day), where the 600-drop bottle would last 40 months (3.3 years). This is well past the expiration date of the product. A solution: pour half of the contents of the Citr-A-Sol bottle into an old, empty, smaller, scrupulously cleaned DEDI bottle (with the plastic seal under the cap if you've still got it) and freeze it for later use. **SWF**

Redox Term	Temperature-Analogous Term
redox potential	temperature
oxidation	warming, heating
reduction	cooling, refrigeration
oxidizing agent (oxidant)	sunlight, fire, hot water, steam
reducing agent (reductant)	cold water, an ice cube, snow, dry ice
oxidized	hot, heated, warmed, cooked
reduced	cool, cold, cooled, iced, refrigerated
oxidizing power	a furnace, heater or other heat source
reducing power	an air conditioner or cooling influence

Antioxidants vs Reductants?

In several newsletters, you have written about reducing agents and reducing power being useful for fighting oxidative stress. These sound to me like antioxidants. Are they? If not, how are they different? **OTP**

Reducing agents are a subcategory of antioxidants. Generally, reducing agents act as antioxidants, but antioxidants do not necessarily act as reducing agents. For examples: Vitamin A and vitamin E are good antioxidants, but their role as reducing agents in biological systems is minor. Then there is vitamin C, which has important antioxidant *and* reducing functions. And finally, there are NADH, NADPH and $FADH_2$, which rarely act as antioxidants, but play a central role as reducing agents. **SWF**

I'd like a basic conceptual explanation so that I can intuitively understand what you are talking about. **OTP**

Temperature is a good analogy. Oxidation and reduction are like hot and cold. Oxidizing free radicals are extremely hot, like the sun's rays on a hot Summer day. Reducing agents are cold. Antioxidants protect against oxidizing free radicals like an umbrella protects against the hot rays of the sun. Reducing agents protect against oxidizing stress like a block of ice or a cold drink protect against overheating.

An umbrella works by intercepting the sun's rays and converting them to warmth (the umbrella surface and the air in the vicinity of the umbrella surface are hotter than the ambient air). In an analogous manner, antioxidants intercept oxidizing free radicals to create oxidized antioxidants, which are far less oxidizing than the original free radical. So the umbrella converts heat to warmth, like antioxidants convert strong oxidants to mild oxidants. Just as the umbrella casts a shadow of safety from the suns rays, so do antioxidants create a zone of protection from oxidative stress.

What an umbrella does *not* do is cool you off. If it is 101°F [38°C] in the shade, you are still uncomfortably hot under the umbrella. But a block of ice, a cold drink or a air conditioner will cool you off. That is what reducing agents do.

In this analogy, temperature represents

Q&A Questions + Answers

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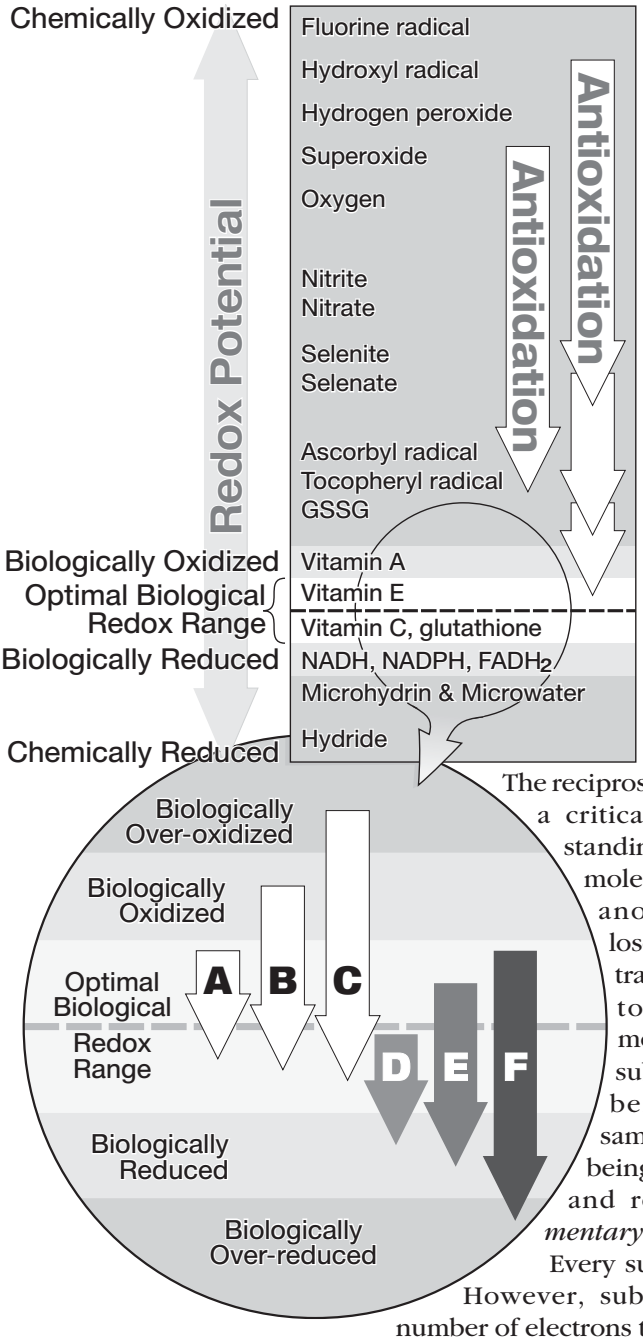
"Redox potentials for biological systems are not in the middle of the redox range."

Figure 1:
Redox Schematic



redox potential. (The term "redox" is a contraction of *red*uction and *ox*idation.) Hot and cold are extremes of temperature like oxidation and reduction are extremes of redox potential.

The concept of reduction is difficult for most people. Not only does reduction have absolutely nothing to do with the common meaning — to lessen or decrease in amount — but there is no common experience of reduction in the real world to which we can easily relate. Iron does not un-rust, wood does not un-burn, and apples do not un-brown.

Yet if you look closely, these examples of oxidation are also hidden examples of reduction! In each, the air (atmospheric oxygen) is being reduced. Because we do not see the air, or see the air change from one form to another, we tend to ignore it, but *oxygen* is being reduced to *oxide* (or *hydroxide*) when iron rusts, wood burns and apples brown. Though transparent, the oxygen in air is an essential participant in rusting, browning and combustion.

On a physical level, oxidation involves the loss of electrons and reduction involves the gaining of electrons. The reciprosity of these processes is a critical concept for understanding reduction. For one molecule to gain electrons, another molecule must lose them. When electrons travel from one substance to another, from one molecule to another, one substance or molecule is being oxidized at the same time that the other is being reduced. Oxidation and reduction are *complementary* processes.

Every substance has electrons. However, substances differ in the number of electrons they contain, and in the strength or weakness with which they hold on to those electrons. Some substances (oxidizing agents) are electron poor and have strong affinity for gaining electrons (oxidizing power). Other substances (reducing agents and biological molecules) are electron rich, some of which have an easy time giving up electrons (reducing power). Examples of these substances are qualitatively ranked in Figure 1. The oxidizing agents are towards the top and reducing agents towards the bottom.

The first thing to notice about Figure 1 is that the redox potentials for biological systems are not in the middle of the redox range for chemicals. They are, in fact, rather far off center, being entirely located in the reduced end of the redox range (towards the bottom of Figure 1). This is a graphic way to describe the fundamental polarity between living biological systems (electron-rich, reduced environments) and their non-living external environments (electron-poor, oxygen-rich, oxidizing environments). To say it poetically, life is an oasis of electrons in an electron-poor desert.

Getting back to the original question: the function of antioxidants is *to mitigate the destructive effects of powerful oxidizing agents* (those close to the top of Figure 1). Antioxidants do this by interacting with oxidizing (electron-grabbing) substances and lowering (de-energizing, reducing, or antioxidizing) them to levels close to the biological redox range (see downward-pointing white arrows). Antioxidation (reduction) of oxidants can happen in a single step (leftmost white arrow) or in multiple steps (rightmost, overlapping white arrows).

The function of reducing agents is different than antioxidants. Reducing agents have redox potentials *below the dashed line* (the one in the middle of the "optimal biological redox range" in Figure 1). In this way, reducing agents can lower the general redox potential of the living system, to prevent it from getting too warm and to keep it within the optimal biological redox range. Said simply, antioxidants specialize in "hot spots," while reducing agents specialize in the regulation of ambient temperature. **SWF**

So how does one take advantage of reducing agents to optimize health or extend lifespan? **OTP**

The magnified inset in Figure 1 shows the potential benefits (and potential harm) of reducing influences. Reducing influences A, B and C all normalize redox potential based on different starting redox potentials. However, reducing influences D, E and F over-reduce the biological system, which can have

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adverse influences on redox reactions necessary for biosynthesis and respiration (energy production). Since people exist with a wide variety of starting redox potentials, some care must be taken to ensure that reducing therapy is not taken too far. The same strong reducing influence can be beneficial (in situation C) or deleterious (in situation F). Even subtle reducing influences may be harmful in those rare individuals who are over-reduced to begin with (situation D). However, the vast majority of individuals, particularly those middle-aged and older, tend to be overly oxidized. This means that moderate use of reducing agents is very much more likely to be beneficial than harmful, at least at the beginning of therapy. Children and infants — and possibly fetuses — tend to be more reduced than adults.

"The redox potential of a blood sample starts to drift immediately after it is drawn."

"Since people exist with a wide variety of starting redox potentials, some care must be taken to ensure that reducing therapy is not taken too far."

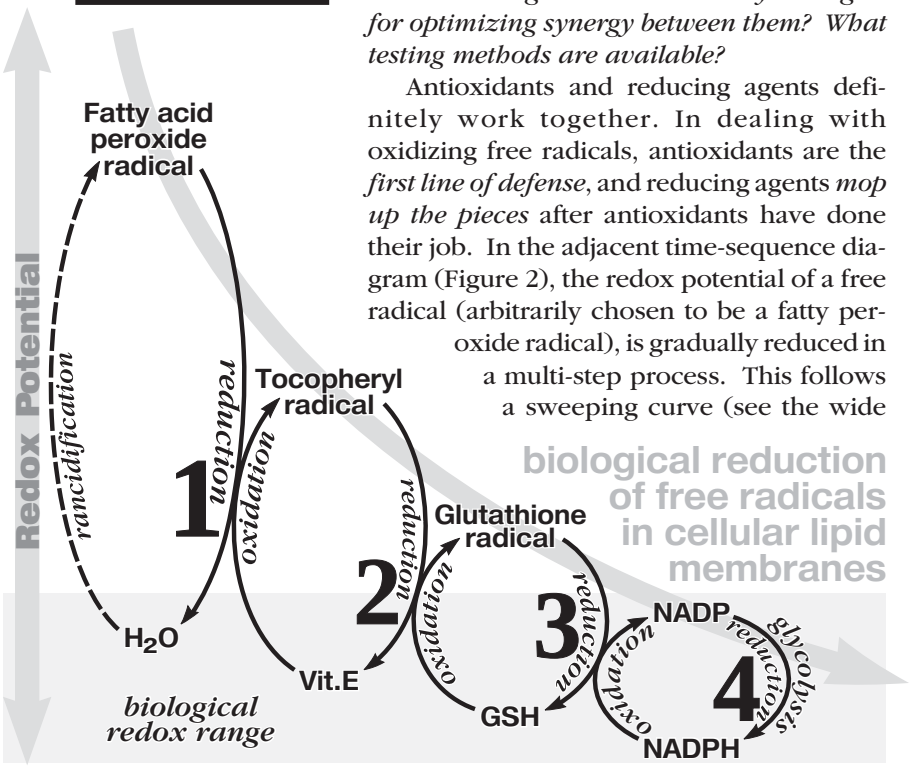
Reducing therapies based on substances whose redox potentials are within the optimal biological range (vitamins A, E and C, glutathione, NADH, etc.) are self-limiting in their potential to reduce the cellular redox environment. They cannot lower redox potential below their own redox potential.

Stronger reducing agents like microwater (alkaline-reduced water), Microhydrin, and alkali hydrides have redox potentials below the optimal biological redox range. Used indiscrimiately and to excess, these stronger reducing agents have the power to over-reduce biological systems.

How do reducing agents and antioxidants work together? Are there any strategies for optimizing synergy between them? What testing methods are available?

Antioxidants and reducing agents definitely work together. In dealing with oxidizing free radicals, antioxidants are the *first line of defense*, and reducing agents *mop up the pieces* after antioxidants have done their job. In the adjacent time-sequence diagram (Figure 2), the redox potential of a free radical (arbitrarily chosen to be a fatty peroxide radical), is gradually reduced in a multi-step process. This follows a sweeping curve (see the wide gray arrow), which starts out steep (when antioxidants are involved) and ends up approaching horizontal (when reducing agents take over).

Figure 2:
Antioxidation and Reduction



In step 1, the antioxidant (*e.g.*, vitamin E or tocopherol) interacts with the oxidizing free radical (a byproduct of rancid fat) to dramatically lower the radical's redox potential towards the biological redox range (the light gray area at the bottom of Figure 2). This takes place in cell membranes. Step 2 takes place at the membrane surface, where the oxidized antioxidant (the tocopheryl radical) interacts with a cellular antioxidant/reducing agent (in this case glutathione) to become recycled (reduced) back to tocopherol. In step 3, the oxidized glutathione then interacts with a reducing angent (NADPH), to become reduced glutathione again. In step 4, the oxidized reducing agent (NADP) is reduced back to NADPH by the pentose phosphate pathway (or by NADH). Through these steps, the oxidizing potential of the free radical is reduced (*both* meanings intended) to the biological redox range (see the curved gray arrow).

There is lots of attention being paid to the preventive and therapeutic value of antioxidants. Perhaps we should be spending equal time addressing the value of reducing agents?

One way to do this is to measure reducing potential directly. I am aware of one commercial device, the Biological Terrain Assessment (BTA) system, which is capable of measuring redox potential of urine, saliva and blood in a clinical environment. The BTA is not yet in widespread use, so it may be difficult to locate a practitioner who employs it. A BTA test usually costs between $100 and $200 to perform.

Unlike most standard blood tests, redox potential cannot be easily measured at a remote laboratory. The redox potential of a blood sample starts to drift immediately after it is drawn. Oxygen from the air and dissolved oxygen in the blood shift the redox potential of blood samples within minutes to hours. Samples must be measured immediately after collection. **SWF**

Testosterone Patch Problem?

For six weeks I have been using Androderm patches (1 patch per day). The results from testosterone are excellent, but the testosterone patches cause unpleasant skin irritations. Therefore, I would like to use a testosterone cream. Neither my doctor nor my pharmacist know the makeup of testosterone cream. Do you have this information? **DCA**

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years, most people feel that they have better things to do than fight with the FDA.

If there's something in your life that you can exploit, you do not necessarily need a lawyer. Intimidation can be based on *publicity* (your cousin's inlaw is an assistant producer on Oprah, or the editor of the local community newspaper) or *politics* (your husband's Best Man is on Senator Boxer's campaign re-election committee, or you were a volunteer for George Bush's [your state] campaign committee). But it is my opinion that such tactics are best reserved for the *second* letter. If your first letter is mild and polite yet direct to each and every point in the FDA's personal use import policy, then you become an "average citizen victimized by a FDA bureaucrat" instead of a "radical troublemaker out to circumvent the law." Publicity and politics are 93% perception and 7% content [And I'm an optimist ;-)].

"If there's something in your life that you can exploit, you do not necessarily need a lawyer. Intimidation can be based on publicity or politics."

I also agree with Ward in that I think that every citizen can benefit from knowing the technical details of governmental authority. With this knowledge, you can be better able to make the right statements and ask the right questions to get a government agent to 1) engage in unauthorized action, 2) extend that into an overtly illegal act, and then 3) incriminate themselves in a way that cannot be denied, without them necessarily realizing what you are doing. **SWF**

"Every citizen can benefit from knowing the technical details of governmental authority."

Vinpocetine in Down's Syndrome?

I know I said I don't usually pester much, but I've got one question here that is bugging me ;-), so may I impose on you just one more time? I was reading VRP's newsletter re vinpocetine and apparently it is an excerpt from the first smart-drug book. It states that vinpocetine facilitates cerebral metabolism, by improving the blood microcirculation, stepping up brain cell ATP production, and increasing utilization of glucose and oxygen. It also has been used for memory problems, heart problems, aphasia, apraxia, motor disorders, inner ear problems and eye problems. This list seems oddly similar to problems that our DS children experience. Might vinpocetine be helpful? Or does piracetam address these things in the same way? Or can vinpocetine be used along side piracetam? **N**

"The benefits of vinpocetine seem oddly similar to problems that our DS children experience. Might it be helpful?"

The metabolic-enhancing and anti-ischemic effects of vinpocetine might be of significant value in treating Down's syndrome. However, I have been reluctant to suggest vinpocetine because I think that the vascular system is already over-relaxed in DS. The vascular smooth muscle relaxing factor that controls blood flow is nitric oxide (NO) [see the sidebar in *SLN* v6n10p4 for the internal mechanism]. It is believed that vinpocetine works, at least partially, by enhancing the action of NO. The precursor for NO is the amino acid arginine, which tends to be high in DS. Furthermore, NO levels are reduced by reaction with superoxide (O_2^-), which is *low* in DS.

"The metabolic and anti-ischemic effects of vinpocetine might be of significant value in treating DS. However, I have been reluctant to suggest vinpocetine because the vascular system is already over-relaxed in DS."

Let me go through this another way. The superoxide dismutase (SOD) gene is on the triplicated 21st chromosome and gets over-expressed in Down's syndrome (trisomy 21). *Over*expression of SOD means *under*representation of superoxide, which is SOD's substrate. By analogy, the more dogs you have, the faster you go through dog food (which is the substrate for dogs). Low superoxide means increased NO (they are antagonistic to each other). So I am left with the question: do we want to risk increasing something that is already elevated?

It is possible that vinpocetine has non-NO mechanisms of action that might prove more valuable than any overdriving of vascular relaxation. It is also possible that there is some kind of adaptation, resistance or habituation to increased NO that would respond positively to vinpocetine, ginkgo or arginine. There is no fundamental incompatibility between piracetam and vinpocetine. If you try it, please share your observations.

These concerns about vinpocetine apply only to Down's syndrome. Non-DS individuals do not have the elevated arginine and low superoxide that might constitute a contraindication for vinpocetine. **SWF**

Basal Metabolism?

I am recent subscriber to your newsletter. I ordered all the back issues and I am slowly working my way through them. My first impression is WOW! You guys are way ahead of the curve.

The November 2000 feature on basal metabolism convinced me to start taking my temperature. I had all the symptoms of an underactive thyroid and sure enough, my temperature is consistently 1.5 to 2 degrees below normal. It is usually around 97 degrees or slightly lower upon waking, and often below 98 degrees throughout the day. Three months ago, my former doctor had told me my thyroid was "basically normal," but now I have an appointment with a doctor that is a subscriber to your newsletter. I feel that thanks to you, I am getting more