Autism and Vitamin D
by John J. Cannell, MD

Any theory of autism's etiology must take into account its strong genetic basis, but also explain how genetics interacts with the environment to produce autism's unusual epidemiology. Activated vitamin D, calcitriol, is a potent neurosteroid hormone with critical roles in mammalian brain development. Calcitriol's physiology is unique among the steroid hormones, because normal steroid feedback kinetics does not regulate neural levels of calcitriol; human behavior does so. The apparent dramatic increase in the prevalence of autism and other neurodevelopmental disorders over the last 20 years corresponds with the medical profession's increasing advice to avoid the sun during that same time, advice that may have dramatically lowered brain calcitriol levels. Estrogen and testosterone have very different effects on calcitriol's metabolism, differences that may explain the striking male/female sex ratios in autism. Cognitive abilities are positively associated with vitamin D levels, even after correction for sun exposure. Autistic individuals have immunological abnormalities that are similar to those produced by vitamin D deficiency. Calctriol downregulates production of inflammatory cytokines in the brain, which have consistently been associated with cognitive impairment. Severe maternal vitamin D deficiency leads to rat pups with increased brain size and enlarged ventricles, abnormalities similar to those found in autistic children. Vitamin D deficiency impairs glutathione metabolism, which may explain the link between oxidative stress, mercury accumulation, and autism. Multivitamins containing vitamin D reduce symptoms of autism and increase cognitive abilities in children. Consumption of vitamin D-containing fish during pregnancy reduces autistic symptoms in children. Most studies show autistic births are higher in the winter, especially in March, when vitamin D levels are their lowest.

Neurodevelopmental abnormalities appear to be higher among those with low vitamin D levels, such as African Americans, and maternal vitamin D deficiency is exceptionally common, especially among African Americans, regardless of prenatal vitamin use. While future epidemiological, genetic, and interventional studies should test this theory, physicians should diagnose and treat vitamin D deficiency during pregnancy and childhood now.

Introduction
Arguably, the five most striking epidemiological aspects of autism are its high monozygotic (40%-90%) vs. dizygotic (0% -10%) twin concordance rates, widely varying phenotypic expression even among monozygotic twins, striking male/female ratio (~3:1), apparent increased prevalence in African Americans, and apparent rapid increase in incidence rates over the last 20 years. Whatever its genetic roots, and they are strong, autism hardly follows classic Mendelian inheritance. A useful theory of causation must explain all these discrepant epidemiological observations - and should do so parsimoniously.

When a disease with strong genetic roots displays such peculiar epidemiology, it is reasonable to seek an explanation among environmental genetic contributors. While the predisposing autistic lesion is genetic, the above epidemiological observations indicate the environment is dramatically affecting phenotypic expression. That is, the environment is altering the brain, epigenetically, or through gene-environment interactions.

Environmental genetic contributors directly influence the genome, but the environment directly influences them as well, the neurosteroid hormones being one example. Furthermore, if current claims of increasing prevalence rates of autism and other neurodevelopmental disorders over the last 20 years (Figure 1) are due to some actual increases in incidence - and this seems increasingly likely - then it is reasonable to search for neurosteroids that have changed over the same time autism has increased. Furthermore, if a neurosteroid exists that profoundly affects brain development, whose metabolism is different in males and females, whose levels are lower in African Americans than Whites, whose levels are directly affected by diet or human behavior, and whose brain levels have dramatically decreased in the last 20 years, surely that neurosteroid is a prime causation candidate.

In a recent article discussing autism and genetics, Herbert et al. warned that "environmentally responsive genes, not specifically associated with the nervous system, but potentially associated with systemic changes in autism, have not hitherto received sufficient attention in autism genetics investigations" (p. 671). Although not among their final candidate genes, they could not have better described the genes that code for various components of the hormone system whose end-product is the neurosteroid, calcitriol, or activated vitamin D.

Of the neurosteroids involved in brain development, calcitriol is unique - the least understood but arguably one of the most profound. McGrath et al. alerted us to this fact in 2001, pointing out that vitamin D is "the neglected neurosteroid." In the same paper, the authors pointed out that calcitriol is a potent up-regulator of nerve growth factor and that the vitamin D receptor (VDR)
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is found in a wide variety of brain tissue quite early in embryogenesis. These two facts alone led them to conclude that "hyopovitaminosis D should be examined in more detail as a candidate risk factor for neurodevelopmental...disorders" (p. 571).

In 2006, Kalueff et al. went further, suggesting vitamin D offers "neuroprotection, antiepileptic effects, immunomodulation, possible interplay with several brain neurotransmitter system and hormones, as well as regulation of behaviors." (p. 363). In 2007, Kalueff and Tuohimaa reviewed the nootropic properties of vitamin D in even more detail and concluded the data "stress the importance of vitamin D prenatal, neonatal, and postnatal supplementation for normal brain functioning" (p. 16).

If true, then candidate genes for autism should include all those that code for the various proteins involved in the metabolism, catabolism, transport, or binding of calcitriol. For example, expression and nuclear activation of the vitamin D receptors (VDR) are necessary for the effects of vitamin D. Several DNA sequence variations – polymorphisms – occur frequently in the population and may have biological effects. Their abundance in the human genome as well as the high frequency with which VDR polymorphisms occur in humans make them candidates to explain variation in risk, but the influence such polymorphisms have on function is largely unknown.10

A pilot study of VDR receptor variants using a robotically enhanced multiplexed scanning method did not detect mutational abnormalities in 24 autistic individuals, but they did not assess for VDR polymorphisms.11 VDR polymorphisms are not associated with schizophrenia, but a highly significant association exists between one VDR polymorphism and larger head size.12 Mean head circumference is larger and rates of macrocephaly higher in autism.13

Vitamin D pseudodeficiency, an inborn error of metabolism involving the defective conversion of 25(OH)D to calcitriol, which should lower brain calcitriol, has never been studied in autistic individuals, but they did not assess for VDR polymorphisms.11 VDR polymorphisms are not associated with schizophrenia, but a highly significant association exists between one VDR polymorphism and larger head size.12 Mean head circumference is larger and rates of macrocephaly higher in autism.13

Vitamin D and Autism below. However, children with the Williams syndrome,14 who often have elevated calcitriol levels for several months in very early life,15 usually present in later life with remarkable sociability, overfriendliness, empathy, and willingness to initiate social interaction,16 strikingly the opposite phenotype of autism.

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Perhaps because the term, vitamin D, contains the word "vitamin," many people wrongly assume it is a vitamin. Instead, vitamin D is the only known substrate for a steroid hormone system that – until recent sun avoidance campaigns – always began in the skin, not in the mouth. Ninety percent of human vitamin D stores come from skin production, not oral intake.17,18 Large populations of people putting small amounts in their mouths, instead of generating large amounts in their skins, is novel to both human experience and human brain development.

Obviously, for such a change to be compensatory, oral intake must be adequate to make up for diminished skin production. But the skin’s production of vitamin D is rapid and robust, easily exceeding recognized dietary sources by an order of magnitude.19 For example, when fair-skinned adults sunbathe in the summer (one, full-body, minimal erythemal dose of ultraviolet light), for 20 minutes, they deliver about 20,000 units of vitamin D to their systemic circulation within 24 hours.20 A pregnant woman would have to drink two hundred glasses of milk or take 50 prenatal multivitamins to do the same.

Equally novel to human experience is recent advice that humans should avoid the sun, advice widely and successfully promulgated by medical and governmental bodies since the late 1980s. The increase in autism appears to have begun at the same time.21 Indeed, most of the popular graphs showing rising prevalence rates of autism over the last 20 years (Figure 2) would be strikingly similar to graphs showing the rising rates of programs promoting sun avoidance.

No longitudinal studies of vitamin D levels exist; that is, we don’t know how successful sun avoidance campaigns have been in lowering vitamin D levels. However, if one assumes that at least some Americans follow their government’s and their physician’s advice, then a subgroup must have had declining vitamin D levels over time – unless they took enough supplemental vitamin D to make up for lack of sun exposure, but few people take the thousands of daily units needed to do that.

Certainly, there is evidence that prominent medical organizations targeted sun-avoidance campaigns to infants and children.22 For example, in 1989, around the time autism rates began to dramatically rise, the American Medical Association’s (AMA) Council on Scientific Affairs warned
About the dangers of sun exposure and advised mothers to, "keep infants out of the sun as much as possible" (p. 383). In 1999, the American Academy of Pediatrics went further, advising mothers to always protect infants out of direct sunlight, use sun-protective clothes and sunscreen, and make sure children's activities in general minimize sunlight exposure. Furthermore, quite inexplicably, they reported there was "no evidence" such procedures would affect vitamin D levels (p. 330). By 2002, the Centers for Disease Control (CDC) reported the efforts were quite successful: "protection from sun exposure is reported for a high proportion of children" (p. 360).

Apparently, no effort was made to counteract the vitamin D deficiency such sun protection would predictably induce. For example, when the AMA's Council on Scientific Affairs — cited above — warned about the dangers of sunlight, they did not even mention that sunlight triggers the formation of vitamin D. Furthermore, the Food and Nutrition Board's (FNB) vitamin D recommendations for young women, pregnant women, infants, and children did not change during the decades of sun avoidance advice (200 units per day for all children, pregnant women, and young adults — regardless of weight. That is, they did and do recommend the same daily 200 units for two kg infants as they do for 100 kg pregnant women). Unfortunately, in 2003, the American Academy of Pediatrics cut their longstanding 400 units per day recommendation in half, apparently simply to comply with FNB recommendations, and did so despite their advice four years earlier that infants and children should avoid sunlight.

Among the body's steroid hormone systems, the vitamin D system is unique. Unlike other steroids, the body cannot make calcitriol de novo from cholesterol to meet its needs; all of the body's calcitriol must come from vitamin D, either made in the skin or ingested orally. Furthermore, besides its endocrine role in maintaining the calcium economy, calcitriol has multiple independent autocrine hormonal functions, if enough vitamin D substrate is available.

Most importantly, unlike any other steroid hormone, the enzyme that first hydroxylates vitamin D in the liver and the enzyme that makes calcitriol in the tissues both operate below their respective Michaelis-Menten constants throughout the full range of their normal substrate concentrations. That means tissue levels of calcitriol during brain development directly depend on maternal 25(OH)D blood levels, which, in turn, directly depend on the amount of vitamin D the mother makes in her skin or puts in her mouth. That is, the rate-limiting step for the production of this neurosteroid is unique; concentrations of brain calcitriol literally depend on human behavior, be it the step into the sun, the step to the supplements, the step into the shade, or the step to the sunscreen.

**Calcitriol and the Developing Brain**

Like all steroid hormones (hormone: from the Greek, to urge on), calcitriol binds to a member of nuclear hormone receptor superfamily where the complex then acts as a molecular switch to signal its target genes; about 0.5% of the human genome (200 genes) are primary targets of calcitriol, and the list is steadily growing. (Kaluff et al., 2006) If, and only if, adequate substrate is available, most organs in the human body produce their own calcitriol, have a VDR, regulate their own needs in an autocrine manner, and thus do not depend on hemogenous endocrine supply of calcitriol from the kidney. The brain is such an organ, and the developing brain is heavily invested in calcitriol from very early gestation. Both the VDR and the enzyme necessary to make calcitriol are present in a wide variety of human brain tissues.

Serum calcitriol levels increase by 50-100% by the second trimester and by 100% during the third trimester, probably of placental origin. The enzyme necessary to make calcitriol in human placenta and decidua increases by several orders of magnitude starting in very early gestation. Expression of the VDR in the developing mammalian brain rises steadily beginning several weeks after conception where calcitriol induces the expression of nerve growth factor and stimulates neuronal cell growth. For a review of vitamin D's multiple effects on brain development and function, see Brachet et al. In a series of recent animal experiments, an Australian group found severe maternal vitamin D deficiency in rats produce offspring with aberrant apoptosis and cell proliferation at both the cellular and molecular level, reduced expression of a number of genes involved in neuronal structure, hyperlocomotion, and subtle alterations in both learning and memory. When vitamin D deficiency is restricted to late gestation only, such deficiencies are sufficient to disrupt adult brain functioning. Recently, a
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( Herbert et al.). Hope for a nootropic treatment effect lies in calcitriol's powerful anti-inflammatory properties; its administration down-regulates production of inflammatory cytokines in the brain, which have consistently been associated with cognitive impairment.49 Furthermore, calcitriol is remarkably neuroprotective by stimulating neurotopin release, reducing toxic calcium levels in the brain, and inhibiting the production of nitrous oxide; by its immunomodulating properties—especially in reducing inflammatory cytokines46; and by increasing brain glutathione.47

This last function of vitamin D, increasing brain levels of glutathione, may explain the purported link between heavy metals, oxidative stress, and autism. The primary route for the neurotoxicity of most heavy metals is through depletion of glutathione and subsequent generation of reactive oxygen and nitrogen species.48 Furthermore, besides its function as a master antioxidant, glutathione acts as a chelating agent to remove mercury, cadmium, and nickel.49 Kern and Jones review several studies indicating autistic individuals have difficulty excreting heavy metals, especially mercury. If calcitriol-deficient brains are unable to utilize glutathione properly, and thus unable to remove heavy metals, they may be oxidatively damaged by heavy metal loads normal children easily excrete. It bears repeating that the amount of calcitriol in the brain directly depends on how much vitamin D is made in the skin or put in the mouth.

Vitamin D and Autism

Although no studies associating vitamin D levels with cognitive abilities exist for children, several studies have found significant associations in adults.50,51 Recently, Vanlint and Nugent reported a very high incidence of vitamin D deficiency among 337 individuals with intellectual disabilities in residential care.52 The obvious explanation for these findings is that cognitively impaired individuals do not go outdoors as often as higher-functioning individuals and thus have lower vitamin D levels. However, two groups found the association after controlling for outdoor activities, making it likely that low vitamin D levels per se impair cognition.

Although no birth cohort studies exist that examined vitamin D supplementation during pregnancy or childhood and later development of autism, 2,000 units a day during the first year of life was associated with a fourfold reduction in the later development of schizophrenia in males (Risk ratio = 0.23), but not in females.53 This is even more interesting when one remembers that males are four times more likely to develop autism than females.

In fact, estrogen and testosterone appear to have quite different effects on vitamin D metabolism, which may explain the striking gender differences in autism. The majority of studies have found that estrogen has multiple facilitating effects on vitamin D metabolism while the same is not true of testosterone.54 For example, Epstein and Schneider report, “the majority of studies have found a positive effect of estrogen on calcitriol levels.” However, after reviewing similar studies on testosterone, they go on to say that, “it is unlikely that testosterone is a major controlling factor in vitamin D metabolism” (p. 1261). If estrogen potentiates the effect of calcitriol, but testosterone does not, the differences in concentrations of sex steroids during brain development may mean that estrogen protects developing female brains from calcitriol deficiencies, while testosterone exposes male ones.

Further evidence that vitamin D may favorably affect mentation comes from a series of randomized controlled interventional studies evaluating the effect of vitamin D containing multivitamins on childhood cognition. (For a review, see Schoenthaler et al.)55 All 14 studies the authors reference, including their own, reported small (one to two percent) to modest (five to six percent) improvements, most of them significant, usually in nonverbal IQ; the first study was reported in the Lancet in 1988 (Figure 3).56 More interestingly, most studies showed no effect on the majority of children but very significant effects (15% gains) in about 20% of the children, perhaps the vitamin D-deficient subgroup.

If vitamin D has any treatment effect, autistic children may improve with change in latitude, sun exposure, or diets containing large amounts of vitamin D rich fatty fish. Consistent with the theory, not all children diagnosed with autism retain that diagnosis in adulthood, and some improve, either spontaneously or after the myriad of various treatment programs available (Herbert et al.). Naturally, the abundant anecdotal reports of improvement generate skepticism that the initial diagnosis was correct, an obvious possibility. However, a randomized, placebo-controlled, three-month study of 20 autistic children found multivitamins with even low doses of vitamin D (150 units or 3.75 mcg) significantly improved sleep and gastrointestinal problems compared to placebo.60 Furthermore, a recent small controlled trial reported substantial benefits for omega-3 fatty acids in autism.61 Such long-chain fatty acids dissociate calcitriol from the vitamin D binding protein, do so well within the physiological concentrations of these fats, and should increase the amount free brain calcitriol.

The vitamin D theory of autism predicts that vitamin D-rich fish consumption during pregnancy would favorably affect fetal development and improve the offspring’s mentation although several factors confound such studies. Some ocean-going fatty fish, such as salmon,
herring, and sardines, are rich sources of vitamin D, but most freshwater fish are not. Furthermore, some fish contain mercury, which may impair mentation. Fatty fish, fish liver oils, and fish body oils also contain omega-3 fats, which favorably affect mentation. As mentioned above, fish oils dissociate vitamin D from its binding protein, raising free calcitriol levels. Finally, fish liver oils, but not fish or fish body oils, contains substantial, variable, but potentially toxic, amounts of vitamin A, which antagonizes the action of vitamin D.\(^6\)\(^7\)

Consistent with the vitamin D theory of autism, the group of women who received advice to consume sea fish during pregnancy produced infants with higher birth weights and had fewer preterm births than control women.\(^6\) Higher fish consumption during pregnancy was associated with better infant cognition with the greatest effect for infants whose mothers consumed the most fish.\(^6\) Very recently, low maternal seafood consumption was associated with infants with an increased risk of lower verbal IQs and suboptimal outcomes for prosocial behaviors and fine motor, communication, and social development,\(^6\)\(^5\) outcomes eerily similar to autism.

In reviewing studies of fish and fish oil on pregnancy outcomes, Rogers et al. found fish consumption has a positive effect on fetal growth, but fish oil consumption has little or no effect on fetal growth.\(^6\)\(^6\) The authors concluded, "It may be that some constituent of fish other than omega-3 fatty acids is responsible for the association of fish intake with birth weight" (p. 490). Consistent with that constituent being vitamin D are studies finding low maternal vitamin D intakes are associated with low birth weights and intrauterine growth retardation.\(^6\)\(^9\)\(^7\)\(^0\)

I know of no latitudinal studies of autism that would support or refute the theory that maternal vitamin D deficiency contributes to neurodevelopmental disorders. That is, if vitamin D played a role in autism, the disorder should be less common at more equatorial latitudes, at least before modern sun avoidance. Recent CDC prevalence data from 14 states show no obvious latitudinal variations although the state with the highest prevalence, New Jersey, was the second most northern; Alabama, with the lowest prevalence, was the most southern of the 14 states surveyed.\(^7\)\(^1\) Studies on season-of-birth and autism are contradictory, as would be expected if calcitriol deficiencies can impair brain development during either gestation or in early childhood. However, several studies show excessive autism births in the winter, especially March (Figure 4), when vitamin D levels are at their lowest.\(^7\)\(^2\)

If vitamin D was useful in the treatment of autism, then symptoms should improve in the summer, when vitamin D levels are the highest. Again, to the best of my knowledge, no such studies of seasonality exist. However, a case study reported dramatic improvements in both sleep and behavioral problems in the summer (Figure 5).\(^7\)\(^3\) Furthermore, Hung and Thelander reported significant improvements in autistic behaviors during a summer camp program that included swimming, hiking, boating, and other activities that would increase brain levels of calcitriol.\(^7\)\(^4\)

If maternal or postnatal vitamin D deficiency caused autism, then parents who rigorously complied with sun avoidance advice would be more likely to have children with autism. Parents from higher socioeconomic strata are more likely to apply sunscreen to their children,\(^7\)\(^8\) as are parents with a higher education.\(^7\)\(^9\) Although numerous studies, especially early ones, linked higher social class with autism, ascertainment bias confounds such associations.

If postnatal vitamin D deficiency caused autism, then rachitic children would be at greater risk for the disease. To the best of my knowledge, no studies have looked at the neuropsychological profiles of children with vitamin D-deficient rickets, although such children are more likely to be hypotonic, display decreased activity, and have developmental motor delay.\(^7\)\(^7\) Hypotonia is common in children with autism,\(^7\)\(^8\) as is decreased activity,\(^7\)\(^9\) and developmental motor delays are the rule.\(^8\)\(^0\)

Vitamin D deficiency in childhood is associated with an increased risk of respiratory infections.\(^8\)\(^1\) The vitamin D theory of autism predicts autistic children would be more prone to respiratory infections in early life, but a recent study found no such association.\(^8\)\(^2\) However, a Japanese study found a strong positive correlation (r = 0.92) between the prevalence of infantile autism in one-year birth cohorts and the number of children hospitalized for pneumonia and bronchiolitis during their birth year.\(^8\)\(^3\)

Finally, if postnatal – and not just prenatal – vitamin D deficiency causes autism, then the disease should be rare before weaning in formula-fed babies (as infant formula contains significant amounts of vitamin D when calculated on a per pound basis), and rare in breastfed babies who are supplemented with vitamin D. However, the disease should rapidly progress after weaning, unless the child takes vitamin D supplements or drinks significant amounts of vitamin D fortified milk. Although, to the best of my knowledge, many such dietary studies do not exist, a recent prospective longitudinal study of 87 infants, some at high risk for autism and others not, found no statistically significant neurocognitive differences between the two groups at six months.\(^8\)\(^4\) That is, the children who later developed autism appeared normal at six months. However, around the age of weaning, the babies who developed autism first showed impaired neurocognitive development with rapid additional impairments occurring between 14 and 24 months, the age many children begin consuming sodas and juice drinks instead of vitamin D-enriched formula or milk.\(^8\)\(^5\)

**Vitamin D and Skin Color**

Vitamin D deficiency discriminates based on race, or more precisely, skin color, as melanin in the skin is an effective and ever-present sunscreen. The vitamin D theory predicts that neurodevelopmental disorders would be more common in children born to darker-skinned mothers. Such studies are difficult as they raise sensitive social issues, although three of four recent US studies found a higher incidence of autism in black children, sometimes appreciably higher.\(^8\)\(^6\)\(^8\)\(^9\)\(^0\) Furthermore, at least three studies outside the US indicate autism rates are higher in children with immigrant parents and such immigrants are often dark-skinned. (See Newschaffer et al. for a review of autism’s epidemiology.\(^9\)\(^0\)\(^9\)\(^1\))

Several studies indicate black mothers are more likely to give birth to infants who weigh less and die shortly after birth,\(^9\)\(^1\)\(^2\)\(^3\)\(^9\) and low birth weight is a clear risk factor for autism.\(^9\)\(^4\) Black babies also have lower Apgar scores.\(^9\)\(^5\) In fact, low Apgar scores are associated with poor prenatal vitamin D intake\(^9\)\(^6\) and with autism as well.\(^9\)\(^7\) The CDC and others report black children have significantly higher rates of mild mental retardation than white children, and the difference cannot be explained by socioeconomic factors.\(^9\)\(^8\)\(^9\)\(^9\) (For a review of such studies, see Yeargin-Allsopp et al.)
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Bodnar et al. recently reported that the incidence of preecclampsia significantly decreases in white women during the summer months, but not in black women, suggesting vitamin D has an effect in such disorders, as long as skin color is light enough to rapidly generate vitamin D from incidental sun exposure.\(^{100}\) Furthermore, multivitamins containing vitamin D reduces the risk of preterm and low birth weight infants.\(^{101,102}\)\(^{103}\) Twelve hundred units (30 mcg) per day of vitamin D in the third trimester significantly increased birth weights while 600,000 units (15 mg) given in both the seventh and eighth month of pregnancy increased birth weights even more.\(^{104}\)

Recent studies of vitamin D deficiency during pregnancy show striking racial inequities in maternal vitamin D levels. Bodnar et al. recently found that only 37% of white women and only four percent of black women in the northern United States were vitamin D-sufficient in early gestation (four to 21 weeks).\(^{105}\) That is, 96% of pregnant black women and 63% of pregnant white women did not have adequate 25(OH)D blood levels. Their infants fared little better and showed the same racial inequality. Furthermore, 45% of the pregnant black women, but only two percent of the pregnant white women, were severely deficient (Figure 6). Prenatal vitamins containing vitamin D (400 units or 10 mcg) offered little protective effect for mother or infant; 90% of the women in the study reported taking them.

Unless infants are supplemented after birth via direct supplementation or via vitamin D-enriched formula, infant vitamin D levels are remarkably low with African American infants at highest risk; 78% of unsupplemented breast-fed Iowa infants had levels less than 11 ng/ml during winter.\(^{106}\) For those who wonder how vitamin D could be important for brain development, given its very low levels in breast milk, Hollis and Wagner discovered that breast milk is always a rich source of vitamin D - enough to maintain healthy levels in infants - as long as the mothers took 4,000 units (100 mcg) per day.\(^{107}\)

In 2002, Nesby-O’Dell et al. found almost 50% of young black women of childbearing age had vitamin D levels lower than 15 ng/ml and 12% had levels less than 10 ng/ml, compared to one-half of one percent of white women.\(^{108}\) While it is unknown if such levels approach those seen in the animal studies reviewed above, it may be that white children have a huge developmental advantage over black children, an advantage that begins immediately after conception - one that has nothing to do with innate ability and everything to do with environment.

**Discussion**

The theory that vitamin D deficiency contributes to neurodevelopmental disorders, in utero, in infancy, or in childhood, is of medical and social consequence, has a tenable mechanism of action, subsumes several other theories, implies simple prevention, and is easily disprovable - all components of a useful theory. A genetic lesion in some component of the vitamin D system would explain its high monozygotic twin concordance rate, while decreased neural levels of calcitriol during later life would explain its varying phenotypic expression, increased prevalence in African Americans, and rapid increase in incidence. Discrepant effects of sex steroids on calcitriol metabolism may explain its male preponderance. Several types of studies could easily address the theory.

For example, is there an association between sun exposure during pregnancy or childhood and autism? Are parents of autistic children more likely to practice sun avoidance for their children than controls? Is dietary vitamin D intake associated with autism? Do rachitic children show symptoms of autism? Do autistic symptoms improve in the summer? Are 25(OH)D levels of mothers who had autistic children - available from stored sera - different from controls? Are there latitudinal variations in autism? (Latitudinal studies would require similar and strict diagnostic criteria be used at different sites, an effort currently under way by the CDC)

Do autistic symptoms improve when vitamin D deficiency is treated? Does ultraviolet irradiation, either natural or artificial, improve autistic symptoms? Is the severity of autistic symptoms associated with 25(OH)D levels? What 25(OH)D levels, if any, are associated with maximal mental functioning? Do adequate doses of vitamin D reduce markers of oxidative stress? Do they correct immunological markers? Do they restore normal glutathione metabolism? Do they promote heavy metal excretion? Obviously, many studies await.

The question is, what to do while we wait for such studies? If we do nothing, we are in effect continuing an unplanned, naturalistic experiment on those pregnant women, their unborn children, and autistic individuals who are currently vitamin D-deficient due to sun avoidance. That is, the abrupt change in sun exposure over the last several decades has almost certainly had the unforeseen consequence of lowering brain levels of calcitriol in many of us. The choice is either doing nothing while we wait for more studies, or diagnosing and treating vitamin D deficiency while we wait for more studies.

A risk/benefit analysis tells us that the risk of doing nothing is potentially great, while the risk of treating vitamin D deficiency is minimal and simply good medicine.

Therefore, while we wait for additional studies, pregnant women and autistic children should be assessed for vitamin D deficiency and promptly treated if
found. As the hypothesis that vitamin D may ameliorate autistic symptoms is only theoretical, doses that may ameliorate symptoms are unknown. However, the window of opportunity to affect brain development is limited, so time may be of the essence to detect and treat vitamin D deficiency in pregnancy and early childhood.

The critical question of "What is an ideal 25-hydroxy-vitamin D level?" must be answered, "In regard to what?" Levels needed to prevent rickets and osteomalacia (10 ng/ml) are lower than those that dramatically suppress parathyroid hormone levels (20-30 ng/ml). In turn, those levels are lower than levels needed to optimize intestinal calcium absorption (34 ng/ml). In turn, Lappe et al. recently found levels of around 40 ng/ml effectively reduced the incidence of internal cancers. Finally, neuromuscular performance in 4100 older patients steadily improved as 25(OH)D levels increased, and maximum performance was associated with levels around 50 ng/ml. Levels for optimal brain development and function are unknown.

Given what we do know, adequate 25(OH)D levels are now thought to be somewhere above 40 and probably closer to 50 ng/ml. Ideal 25(OH)D levels are unknown but they are probably close to levels the human genome evolved on. Natural levels, that is, levels found in humans who live or work in the sun, are around 50 - 70 ng/ml - levels obtained by only a small fraction of modern humans.

Conclusions

The current "epidemic of autism" may be iatrogenic, brought on by medical organizations that advised sun avoidance without making provisions to compensate for the predictable consequent "epidemic of vitamin D deficiency." The theory should be tested by a variety of properly conducted epidemiological, genetic, and interventional trials. However, physicians caring for pregnant women and autistic individuals should take immediate steps to restore adequate vitamin D levels in deficient patients. In the complete absence of sun exposure, humans require substantial doses of vitamin D to compensate for lack of sun exposure. The goal of treatment of vitamin D deficiency is to restore 25(OH) D levels to normal summertime levels, 40-70 ng/ml. Those who care for afflicted individuals should target blood levels towards the higher reference range in the hope that vitamin D's anti-inflammatory, immunomodulatory, and nootropic properties will modify autism's clinical course.

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Declarations of Interest

Dr. Cannell heads the non-profi educational group, "The Vitamin D Council."

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Notes


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John Cannell, MD, is a physician with 30 years experience in general medicine, psychiatry and emergency medicine. He is president of the Vitamin D Council, a non profit corporation working to end vitamin D deficiency. He is also a board certified by the American Board of Psychiatry and Neurology. Dr. Cannell frequently speaks about the physiology, pharmacology, toxicology, and clinical uses of cholecalciferol or vitamin D.
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