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## REPORT

### The Link Between Autism and Low Levels of Vitamin D

By Julius Goepp, MD

An epidemic of autism appears to be underway in the United States. According to several respected leaders in child and adult nutrition from across the United States, the current meteoric rise in autism and autism spectrum disorders (ASD) may well be a direct consequence of significant vitamin D deficiencies in pregnant women and their infants.<sup>1-6</sup> And evidence points to vitamin D deficiency as the cause of other debilitating brain conditions as well.<sup>5,7-10</sup> This insidious deficiency is readily remedied—yet tragically often missed.

For years, Life Extension has been exploring the potentially devastating consequences of vitamin D deficiency, ranging from cardiovascular disease to cancer. Now in this report, Life Extension magazine examines the link between low levels of plasma vitamin D and autism. At the forefront of this research is Dr. John J. Cannell, executive director of the Vitamin D Council and a forensic psychiatrist at Atascadero State Hospital in California. The stunning findings suggest that rampant vitamin D deficiency is causally related to brain dysfunction, and may be readily preventable by adequate supplementation.<sup>2-4,11</sup>



#### AUTISM—WHAT'S KNOWN, WHAT'S GUESSED, AND WHAT'S STILL TO BE LEARNED

Autism, or the Autistic Spectrum Disorders (ASD), involves poor social and verbal functioning accompanied by repetitive or “stereotyped” behaviors.<sup>12</sup> Symptoms begin sometime in early childhood. Just what the deficits are, when they first become evident, and what causes them are still unknown, though both genetic and environmental factors seem to play major roles.<sup>12-14</sup> Similarly, it seems apparent that there are many different developmental conditions that meet at least some of the definitions of autism or ASD.<sup>12</sup>

In fact, scientists agree that we actually know very little about this puzzling, multi-faceted, and tragic condition, which ranges in severity from very subtle alterations in social behavior to full-blown developmental delays that may result in placement in long-term care facilities.<sup>15-17</sup>

What is undeniable is that there has been a marked increase in the number of children being diagnosed with autism over the past two decades, not just in the US but in most industrialized nations.<sup>18-21</sup> Some experts argue that this rise is due to increased detection by parents and physicians, as well as changing criteria and diagnostic categories.<sup>22-25</sup> By now, however, most agree that the increase is real, and probably represents an interaction of basic genetic tendencies with something new and different in our current turn-of-the-century world.<sup>3,19-21</sup> One report showed the incidence of autism rose 30-fold in just seven years.<sup>25</sup> This 2006 British study estimated that one in every 86 children met criteria for autism or ASD<sup>20</sup>—a shocking figure that alone justifies use of the term “epidemic.”<sup>3</sup>



What is causing this apparent dramatic rise in autism cases? The answer or answers have been elusive, generating heated controversy among (and between) physician groups, other scientists, and many parent groups. Considerable attention has been given to mercury and other environmental toxins that cause oxidative stress,<sup>26,27</sup> and scientists are conducting further studies to determine if mercury in the environment and mercury preservatives in vaccines are casually linked to autism. Genetic factors are also important, as demonstrated by high rates of occurrence in other family members, particularly in twin studies.<sup>28,29</sup> Today's consensus identifies both genetic and environmental factors as being relevant to the causes of autism.<sup>14,30</sup>

#### THE “VITAMIN D DEFICIENCY THEORY” OF AUTISM

What possible factors involving both genetics and environment could account for the dramatic change in autism rates in just 20 years? Our genes surely aren't changing that fast, and while our environment is clearly being altered, no serious scientist suggests that anything radical enough to cause an epidemic of brain dysfunction has taken place in the past two decades.

That's correct, argues Dr. John Cannell, but in fact our behavior with regard to our environment has indeed undergone significant changes—changes that, because of their effects on the vitamin D neurosteroid system, can and do account for many of the observed facts about the autism epidemic.

Dr. Cannell, a widely-published expert on vitamin D's many-faceted effects,<sup>4,31-33</sup> believes that these facts line up in a compelling fashion to implicate vitamin D deficiency and support the “vitamin D deficiency theory” of autism.<sup>3</sup> Let's follow Dr. Cannell's line of thinking as he lines up the extraordinary evidence that we may be able to stop the autism epidemic in its tracks with simple vitamin D supplementation.



Cannell starts with the incredible increase in our understanding of vitamin D's fundamental contributions to human health. Though most people (sadly including many physicians) still associate it only with bone mineralization, we now understand that the active form of vitamin D, called calcitriol, plays an equally important role as a neurosteroid hormone, directly responsible for many elements in brain development and behavior<sup>34</sup> (other examples of neurosteroids include the sex hormones estrogen and testosterone, which have effects on the full spectrum of human behaviors). Vitamin D obtained from supplements or sunshine must undergo two biochemical processes before it becomes active. First, it is metabolized by the liver to 25-hydroxyvitamin D, the main circulating form of vitamin D and the only vitamin D metabolite that should be measured to assess vitamin D status.

Circulating 25-hydroxyvitamin D then undergoes a final biochemical step to form calcitriol, a potent neurosteroid that controls brain cell growth, and acts on receptor molecules found in brain cells from the first days of embryo formation.<sup>35</sup> Because of these potent effects, researchers in 2001 labeled vitamin D the “neglected neurosteroid” and concluded that vitamin D deficiency “should be examined in more detail as a candidate risk factor” for neurodevelopmental disorders such as autism.<sup>36</sup> More recently, researchers have suggested that vitamin D, acting as a neurosteroid, offers “neuroprotection, antiepileptic effects, immunomodulation, [impact on] several brain neurotransmitter systems and hormones, as well as regulation of behaviors,”<sup>37</sup> stressing the importance of prenatal, neonatal, and postnatal vitamin D supplementation for normal brain functioning.<sup>38</sup>

But what has happened in the past 20 years that could affect the neurosteroid function of vitamin D and relate it to the explosion of autism cases? Plenty, argues Cannell: put very simply, we have become excessively “sun-phobic” in our efforts to reduce the very real risk of skin cancers.<sup>3,39</sup> Couple this with our decreasing natural exposure to sunlight as we've moved from agricultural to manufacturing to service-based activities, and you have the “perfect storm” for vitamin D deficiency.<sup>1,11</sup> Vitamin D levels in industrialized countries are known to be much lower than those of fully sun-exposed individuals.<sup>40</sup> Thus, our behavior has had the paradoxical and unintended consequence of limiting our blood levels of the only known precursor of a vital neurohormone that, in turn, can influence the very organ of behavior itself, the brain.<sup>3</sup>



What is the evidence to support the vitamin D deficiency theory of autism? A recent review by Dr. Cannell provides a substantial and cogent evidence base,<sup>3</sup> starting with the characteristics of the vitamin D neurosteroid system itself. Calcitriol acts as a “molecular switch” in brain tissue, turning on powerful genes that influence brain development. There are about 1,000 genes already known to be targets of calcitriol activity, and that number is growing fast.<sup>37,41</sup>

But unlike any other vitamin system, the bulk of human vitamin D stores come not from oral intake but from skin production under the influence of sunlight.<sup>42,43</sup> As Dr. Cannell notes in his review, “Large populations of pregnant women putting small amounts [of vitamin D] in their mouths—in the form of prenatal vitamins—instead of generating large amounts in their skins, is novel to human brain development;”<sup>44</sup> since we no longer get ample sun exposure, we need to pay closer attention to how much vitamin D we do get through our mouths.

The case for significant oral supplementation is made even clearer when one considers that skin production of vitamin D is vastly more efficient than oral intake.<sup>2</sup> In fact, just 10-40 minutes of summer sunbathing by a fair-skinned adult, notes Cannell, produces about 20,000 units of vitamin D which is presented to the systemic circulation over the next 24 hours<sup>45</sup>—to get the same amount orally a pregnant woman would have to drink 200 glasses of milk (at 100 IU per glass) or take 50 standard prenatal multivitamins (400 IU per tablet) to realize the same gains!<sup>3</sup>

But, as Cannell goes on to point out, we've been assiduously avoiding sun exposure for the past 20 years, dutifully following AMA guidelines.<sup>39</sup> It is precisely during that same 20-year period that we've seen the rapid rise in autism rates,<sup>14</sup> though as Dr. Cannell acknowledges, “Thousands of other environmental changes occurred during this same time and such associations, on their own, mean little.”<sup>3</sup>

But there are plenty of additional persuasive arguments supporting the theory. The calcitriol neurohormone system is different from all the body's other steroid hormone systems. While other steroids are produced directly from the body's natural store of

cholesterol “precursor” compounds, the amount of calcitriol produced is completely dependent on having enough precursor 25-hydroxyvitamin D present in the first place. And brain levels of activated vitamin D, as Cannell observes, “directly depend on the amount of vitamin D the mother makes in her skin or puts in her mouth.”<sup>3</sup>

Cannell’s dramatic conclusion is that “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, determine brain calcitriol levels.”<sup>3</sup> In the case of the human fetus, as we’re about to see, brain calcitriol levels are directly linked to very early cognitive development, with tremendous implications for the developing baby’s brain.

## WHAT YOU NEED TO KNOW: AUTISM AND VITAMIN D

- An epidemic of autism is sweeping the US and other industrialized nations.
- Causes and cures for autism have long eluded researchers, with often conflicting data making progress difficult.
- At the same time a less well-publicized but undeniable epidemic of vitamin D deficiency has been underway as a result of diminished sun exposure.
- The inspired leadership of several forward-thinking experts has finally tied the two epidemics together and may allow for the first real progress in preventing and treating autism since the epidemic began.
- Since most Americans don’t get nearly enough sunlight to meet their daily vitamin D needs, and since too much sun exposure can be dangerous, experts now recommend oral supplementation of vitamin D far in excess of standard government recommendations.
- Pregnant and nursing mothers as well as young infants need special attention to vitamin D status, since vitamin D works as a neurohormone to stimulate proper brain development and potentially reduce risk for autism.

## CALCITRIOL—NUTRIENT AND NEUROHORMONE OF BRAIN DEVELOPMENT

A wealth of animal data has emerged demonstrating just how essential calcitriol is in early fetal brain development. Offspring of vitamin D-deficient rats, for example, have abnormal cell growth, structure, and functions in their brains,<sup>46-48</sup> excessive and undirected movements,<sup>49-52</sup> and subtle alterations in learning and memory.<sup>8</sup> Even when the deficiencies occur only late in gestation, they are capable of causing disruptions in adult brain functioning,<sup>48</sup> demonstrating the exquisite dependence of brain development on this vital neurohormone.

A group of French researchers has in fact found 36 crucial brain proteins that are disrupted when vitamin D is deficient during fetal development,<sup>7,53</sup> and others have shown increased brain size and enlargement of the fluid-filled ventricles of the brain<sup>9</sup>—both abnormalities that are common in autism.<sup>54,55</sup>

## TOXINS AND OXIDANTS—ANOTHER IMPORTANT ROLE FOR CALCITRIOL IN AUTISM?

What about the apparent importance of toxins and inflammation in autism? Does the vitamin D deficiency theory of autism offer an explanation? Resoundingly yes—for example, it is already known that autistic people have abnormalities in immune functions similar to those that are affected by vitamin D—including increased inflammatory cytokine levels.<sup>12,56,57</sup> And we know that much of the ongoing inflammation in autistic brains is the result of oxidative stress<sup>12</sup>—just where vitamin D’s powerful anti-inflammatory properties are most useful **(and most critical if missing)**.

Calcitriol has nootropic properties—that is, it protects brain tissue by reducing inflammatory cytokine levels which, when elevated, are strongly associated with cognitive impairment.<sup>3,58</sup> Calcitriol also protects brain tissue by stimulating production of neuro-trophins, chemicals that combat toxicity from a number of sources including toxic levels of intracellular brain calcium.<sup>59</sup> Calcitriol also increases brain levels of glutathione,<sup>60,61</sup> a powerful natural antioxidant that is the body’s most important tool for detoxifying and excreting heavy metals and that is rapidly consumed during oxidant stress from toxins and other sources.

Cannell argues convincingly that it is especially this calcitriol-induced increase in glutathione levels that can explain the link between autism and heavy metal toxicity.<sup>3,62</sup> Heavy metals deplete intracellular glutathione,<sup>63</sup> however, animals supplemented with calcitriol show a reduction in iron- and zinc-induced brain injury.<sup>64,65</sup>



A study by Dr. Jill James sheds further light on the connection between heavy metals, glutathione, and autism. Children with a variant of autism called regressive autism demonstrated a severe imbalance in the ratio of active to inactive glutathione, compared with healthy children. Regressive autism occurs when previously healthy children lose acquired language or behavioral

skills and go on to develop autism. Children with regressive autism displayed chronically elevated levels of oxidative stress, which would make them more vulnerable to damaging neurotoxic agents such as heavy metals.<sup>66</sup>

### **VITAMIN D INTERACTIONS—AN ANSWER TO THE GENDER ISSUE IN AUTISM?**

The fact that vitamin D metabolism differs markedly under the effects of the sex hormones may go a long way towards explaining yet another puzzling fact about autism, namely its strong predilection for boys over girls.<sup>3</sup> For example, researchers in Sweden and in Utah have now shown that estrogen has effects on developing brain tissue that serve to make it more responsive to the neurohormonal growth-stimulating effects of calcitriol—results which suggest that estrogen can enhance any beneficial effects of vitamin D on the brain.<sup>67,68</sup> It has been found that estrogen increases the activity of an important vitamin-D-related calcium binding protein in neurons<sup>69,70</sup> that plays several important roles during central nervous system development.

Though complex, these studies do support the notion that the developing brain of a female fetus, with its predominance of estrogen relative to testosterone, could make more efficient use of available vitamin D than would the brain of a male fetus. In a situation where there was plenty of vitamin D present, such differences would go unnoticed—but introduce the all-too-prevalent maternal vitamin D deficiency state, and the stage is set for possible impairment in boys more commonly than in girls, which is of course precisely the situation we see with autism's gender discrimination.<sup>3</sup>



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### VITAMIN D INTAKE AND COGNITIVE PERFORMANCE

If even some of the damage done by vitamin D deficiency during fetal development is reversible, we'd expect to find that vitamin D supplementation would help reduce autistic symptoms at least to some extent. There aren't yet many good studies on this subject, but what we know is encouraging. A multivitamin supplementation study of 20 autistic children in 2004 showed improvements in sleep and gastrointestinal problems that are common in autism (that study only provided 150 units of vitamin D per day, which as we'll see is probably well below the minimum requirement).<sup>71</sup> Similar multivitamin studies have shown improvements in cognitive function even in apparently normal schoolchildren, according to one review of 14 separate studies.<sup>72</sup>



What's remarkable (and heartbreaking) is that while these studies show very little effect on most of the children evaluated, about 20% of the children had substantial gains in performance.<sup>72</sup> This 20% might represent a vitamin D-deficient subgroup of children—a tremendous number if these figures hold nationwide.<sup>3</sup>

We would also expect that consumption of vitamin D-rich foods by pregnant women would improve cognitive performance in their infants, and indeed Cannell provides evidence that high maternal consumption of fish, rich in vitamin D, is associated with better cognitive outcomes in infants.<sup>73,74</sup> Another recent study demonstrated that infants born to mothers with very low seafood intake had higher risks for having low verbal IQs, less well-socialized behaviors, and poorer fine motor and communication skills.<sup>75</sup> As Cannell persuasively argues, these deficiencies are “eerily similar to [those found in] autism.”<sup>3</sup>

### A WORD ABOUT DOSING

To reach the 25-hydroxyvitamin D blood levels that Life Extension recommends for optimal health of 50-60 ng/mL, most typical Americans will need to use dietary supplements, given the real risks of prolonged exposure to sunlight or UV tanning lights. But neither officially-recommended daily intakes of vitamin D (400 IU/day) nor consumption of vitamin D-fortified foods can effectively prevent vitamin D deficiency.<sup>4,85,86</sup> As leading researcher Dr. John Cannell points out, “Adequate oral supplementation will require doses that might make a practitioner initially uncomfortable, as physiological doses of vitamin D, in the absence of sun exposure, probably range between 400 IU/day for premature infants to 10,000 IU/day for the morbidly obese.”<sup>4</sup> Cannell goes on to cite another expert, Dr. Robert P. Heaney of Nebraska's Creighton University, who estimates that 3,000 IU/day is required to assure that 97% of Americans obtain levels greater than 35 ng/mL.<sup>87</sup> The Canadian Pediatric Society recommends that pregnant women should take 2,000 IU vitamin D daily to reduce the risk of autism and other adverse health conditions in their children.<sup>88</sup> In a recent comprehensive review, Dr. Cannell recommends that “parents supplement breast-fed infants with at least 800 IU of vitamin D daily, while formula-fed infants need 400 IU per day. Toddlers and young children who do not get regular sun exposure should take 1,000-2,000 IU daily year round, depending on body weight, keeping in mind that current Food and Nutrition Board recommendations state doses up to 2,000 IU per day are safe for children over the age of one.”<sup>4</sup> Dr. Cannell and other experts believe that autistic children may require even higher blood levels of vitamin D than other individuals, and should take enough vitamin D to maintain serum 25-hydroxyvitamin D levels of approximately 70 ng/mL.

### EXPOSURE TO UV LIGHT—ANOTHER CLUE?

We know that certain brain diseases such as multiple sclerosis are much more common in high latitudes where sunlight is scarce, and many scientists suspect that those conditions are directly related to chronic or seasonal vitamin D deficiencies.<sup>1,2,76</sup> A strong positive association between latitude and the prevalence of autism has been reported for groups of children before 1985, which is what we'd expect if autism were related to vitamin D deficiency.<sup>3,4</sup> Additional support comes from recent data from the Centers for Disease Control and Prevention (CDC), which found the highest prevalence of autism in New Jersey (the second most northern state in the survey), and the lowest in Alabama.<sup>18</sup>

One might expect that babies born in late winter would have higher rates of autism if vitamin D deficiency were involved, since their mothers would have spent most of their pregnancies in fairly low-sunlight settings. While one report suggests that late winter birth dates are associated with higher rates of autism,<sup>77</sup> the literature isn't consistent on this topic. Cannell argues that in fact this would be expected if the critical time for the deficiency to cause damage was not only during gestation, but also in early childhood, and indeed animal studies suggest just that.<sup>46,50</sup> Lower rates of autism have been found in rural compared with urban areas, further supporting the idea that low sunlight exposure may be a contributor.<sup>78</sup> And a fascinating study recently demonstrated that autism rates are substantially higher in geographic areas where precipitation is highest<sup>79</sup> (the implication is that people in such areas spend less time outdoors, thereby reducing their vitamin D-producing sun exposure).



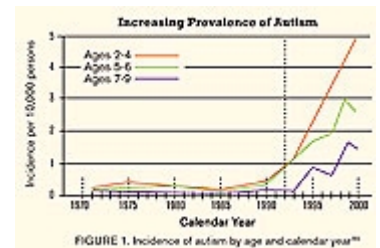
Finally, air pollution is now known to reduce UV light exposure sufficiently to lower vitamin D levels to the point at which experts are recommending supplementation,<sup>80</sup> and one recent study demonstrated an association between air pollution and autism<sup>27</sup> (of course this particular association could as easily be due to toxins in the air—demonstrating how much we still have to learn about this mysterious condition).

## UV-BLOCKING SKIN PIGMENT—FURTHER SUPPORT FOR THE VITAMIN D DEFICIENCY THEORY

If fetal vitamin D deficiency is at the root of autism, we should expect to find higher rates of autism among children born to dark-skinned mothers, because melanin, the major skin pigment, is an extremely efficient blocker of UV light.<sup>42</sup> As Dr. Cannell points out in his review, studies of this nature are difficult to perform and interpret, though there is limited evidence of higher incidence of autism in American black children.<sup>81</sup> Two European studies published in 1995 also showed higher rates of autism among children of dark-skinned immigrants (up to 200-fold higher in one study).<sup>82,83</sup> Since some studies suggest that darker-skinned individuals are more likely to be deficient in vitamin D than those with lighter skin tones,<sup>84</sup> this provides another compelling reason for those with darker skin tones to diligently monitor their vitamin D status.

## SUMMARY

There seems to be little doubt that a significant proportion of the epidemic of autism is real, and not just a fluke of over-reporting and over-diagnosis by anxious parents and physicians. As many Life Extension reports have documented, there's equal certainty that we also face an epidemic of vitamin D deficiency as we steadily move away from old ways that exposed us to more vitamin-D producing sunlight. The theory that the two epidemics are inextricably linked is supported on myriad independent grounds, and as Dr. Cannell himself points out, is readily susceptible to rigorous testing.<sup>3</sup> While we are awaiting those results, however, it seems prudent to maximize vitamin D status in pregnant women, infants, and young children and infants, aiming for levels found in humans living in a sun-rich environment, between 50-60 ng/mL (blood testing for 25-hydroxyvitamin is recommended as the only way to make the diagnosis and to assure treatment is adequate and safe).<sup>4</sup> One recent study noted, "Supplemental doses of vitamin D and sensible sun exposure could prevent deficiency in most of the general population."<sup>2</sup> Under the leadership of brilliant scientists like Dr. John Cannell, we may be privileged to witness at least the beginning of the end of the scourge of autism among our children.



Click Here for Figure 1

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

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