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Atypical Antipsychotics:
Monitoring for Metabolic
Syndrome

PRIMARY CARE

Promoting Vitamin D
Sufficiency

WOMEN'S HEALTH

HT Recommendations
Using Evidence-based
Decision Making



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Vitamin D Sufficiency: An Approach to Disease Prevention

Barbara S. Jockers, MS, RN, NP-C

Recent evidence suggests that vitamin D, an inexpensive, easily obtainable substance, has far-reaching effects in terms of preventing disease. This article reviews recent research concerning vitamin D sufficiency and insufficiency and the effects of both on various disease processes. In light of these research findings, the author proposes adopting new adequate intake recommendations and appropriate supplementation guidelines for vitamin D, as well as adjusting laboratory definitions of vitamin D sufficiency, insufficiency, and toxicity. If a simple supplement such as vitamin D can do so much to prevent illness, then nurse practitioners (NPs) need to promote vitamin D sufficiency and make sure that patients are receiving adequate amounts in the diet or through supplements



Vitamin D has been classified as both a vitamin and a hormone. A vitamin is defined as any of a group of organic substances other than proteins, carbohydrates, fats, or organic salts that are essential for normal metabolism, growth and development.¹ In general, none of the vitamins needed by the body can be formed in the body; instead, they must be obtained through animal or plant sources.¹ A hormone is defined as a substance originating in an organ, gland, or body part that is conveyed through the blood to another body part, chemically stimulating that part to increase or decrease functional activity or to increase or decrease secretions of another hormone.¹ Thus, vitamin D is not a true vitamin because it is synthesized in the skin in the presence of sunlight. A few dietary sources of vitamin D exist as well,

and include fish oils, fatty fish, egg yolk, fortified milk, and other fortified foods.

Vitamin D Metabolism

Since the 1920s, vitamin D, a fat-soluble vitamin, has been known for its essential action on calcium and phosphorus absorption and bone formation. Vitamin D also has anti-rachitic effects (ie, it prevents/cures rickets). If serum vitamin D levels are too low, then calcium and phosphorus are not properly absorbed, resulting in imperfect skeletal formations, rickets, and caries, as well as bone diseases such as osteomalacia.¹ In light of new evidence, researchers consider the action of vitamin D on calcium absorption and bone formation the endocrine arm of the vitamin D system.² Within the past 25 years, researchers have discovered vitamin D receptor (VDR) sites throughout the body, suggesting a wide variety of autocrine (intracellular) effects of the vitamin as well.^{2,5} Elements of the vitamin D endocrine system include the following:⁶

- Photoconversion of 7-dehydrocholesterol to vitamin D₃ in the skin or dietary intake of vitamin D₃ (cholecalciferol);

- Metabolism of vitamin D₃ by the liver to 25-hydroxyvitamin D (25-OH-D)—the major form of vitamin D circulating in the blood compartment;

- Conversion by the kidneys of 25-OH-D (functioning as a hormone) to the two principal dihydroxylated metabolites, 1,25-OH-2D₃ (the most biologically active form of vitamin D) and 24R,25-OH-2D₃;

- Systemic transport of the dihydroxylated metabolites to distal target organs;

- Binding of the dihydroxylated metabolites, particularly 1,25-OH-2D₃, to a nuclear receptor at the target organs followed by the subsequent generation of appropriate biologic responses; and

- Manufacture of 1,25-OH-2D₃ by VDR sites on cells of the brain, pancreas, breast, prostate, lung, skin, lymph nodes, colon, and adrenal medulla.

The autocrine arm of the vitamin D system was virtually unknown during development of the 1997 Dietary Reference Intakes (DRIs).⁷ These DRIs were developed by the Institute of Medicine's Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutri-

tion Board (FNB) and are the nationally accepted guidelines for vitamin D intake (Table 1).⁷

Clinical Questions

In light of this new evidence, are the 1997 DRIs still relevant today? Or is new evidence about vitamin D worthy enough to necessitate setting new guidelines for vitamin D sufficiency? If the answer to the second question is yes, then how do NPs apply these guidelines in clinical practice? NPs must also consider the issue of toxicity; vitamin D is fat-soluble and thus has the potential for toxicity. How much vitamin D is too much? To answer these questions, the author used a multi-database search strategy to determine the amount and quality of

TABLE 1 1997 DIETARY REFERENCE INTAKES FOR VITAMIN D⁷

DRI values in this table for vitamin D, also known as calciferol (1 µg = 40 IU), are based on an absence of adequate exposure to sunlight. The function of vitamin D is to maintain serum calcium and phosphorus concentrations. Selected food sources of vitamin D include fish liver oil, flesh of fatty fish, liver and fat from seals and polar bears, eggs from hens fed vitamin D, fortified milk, and fortified cereals. Excessive consumption leads to elevated plasma 25-OH-D concentrations, causing hypercalcemia. Patients using corticosteroids may require additional vitamin D.

LIFE STAGE	ADEQUATE INTAKE (µg/day)	UPPER LIMIT (µg/day)
Infants (0-12 months)	5	25
Children (1-8 years)	5	50
Males (9-50 years)	5	50
Males (50-70 years)	10	50
Males (>70 years)	15	50
Females (9-50 years)	5	50
Females (50-70 years)	10	50
Females (>70 years)	15	50
Pregnant or lactating females	5	50

new evidence supporting the multiple and far-reaching effects of vitamin D, possible toxicity, new grounds for sufficiency/insufficiency levels, and variables affecting vitamin D synthesis.

Weaknesses of the 1997 Vitamin D Recommendations

The 1997 recommendations regarding adequate intake (AI) of vitamin D were based on the amount needed to prevent rickets in young children—200 IU daily, a dosage not designed to ensure vitamin D adequacy.⁸⁻¹⁰ Donald Fraser, a member of the Committee on Nutrition of the American Academy of Pediatrics, whose reports formed the basis of the 1997 recommendations for the AI of vitamin D, explained that the AI for young adults—also set at 200 IU daily—was based on the results of one questionnaire-style report of the average vitamin D intake of 52 young women without disease symptoms living in Omaha, Nebraska.⁹

However, an AI and a required daily allowance (RDA) of a certain vitamin or mineral are not the same. For a particular amount or dosage to qualify as an RDA, evidence must show that 97% of adults taking that amount would achieve a measurable health benefit.^{9,10} Because no evidence supporting a qualified RDA of vitamin D was available, the FNB described its recommendations regarding vitamin D intake as an “adequate intake” level, which does not guarantee anything at all.⁹

In addition to showing the AI level for vitamin D, Table 1 shows the upper limit (UL) for vitamin D, which was set for the first time. Robert Heaney, a member of the committee that devised the 1997 vitamin D recommendations,

acknowledged that evidence supporting the published UL of 2000 IU of vitamin D intake was scanty, and that the daily circulating blood level of vitamin D needed by the body was probably twice that provided by a daily intake of 2000 IU.⁴ In a randomized controlled trial of doses and effects of vitamin D, Heaney et al reported that the recommendations of the FNB for an AI of vitamin D “fell into a curious zone between irrelevance and inadequacy.”^{10(p 209)} In this study, serum calcium levels did not rise above the UL for calcium (10.5 mg/dL)¹¹ after participants received vitamin D supplementation at a daily dose of 5500 to 11,000 IU for 20 weeks.¹⁰

But would daily vitamin D doses in this range be safe? Because vitamin D is fat soluble and thus not easily excreted from the body, it could accumulate, possibly to a toxic level. Have cases of vitamin D toxicity been reported? What are the symptoms? Does the form of vitamin D that is ingested make a difference in terms of toxicity risk?

Vitamin D: Toxic Versus Physiologic Doses

Vitamin D has two forms, D₂ and D₃ (in this article, the term vitamin D refers to vitamin D₃ unless otherwise specified). Scientists once assumed that vitamin D₂, the form found in plants, was equal in nutritional value to vitamin D₃, the form photosynthesized in mammals. Vitamin D₂, which can be manufactured in a laboratory, is added to certain foods and many multivitamins, and has been the usual form of vitamin D written in prescriptions.⁹ However, vitamin D₂ has been found to be inefficiently metabolized in humans; only 20% to 40% of it is metabolized into

biologically active 1,25-OH-2D₃.^{9,12} Reports of toxicity and overdose have been related to vitamin D₂ intake, not vitamin D₃ intake.^{9,12}

Normal production of vitamin D₃ in bathing suit-wearing Caucasians during 10 minutes of sun exposure in a southern noonday sun in the United States averages 20,000 IU.^{4,8,13,14} Yet, in referring to vitamin D, *Mosby's Guide to Physical Examination* states that “even a small excess is toxic.”¹⁵ The evidence does not support this statement. Saul cited accounts from the 1930s in which one-time doses of up to 600,000 IU of vitamin D were administered to most infants in countries outside the United States without any signs of toxicity.¹² Oral doses of this magnitude were also given to pregnant women during their seventh or eighth month of gestation, again without incident.¹² Vasquez et al reported that induction of vitamin D toxicity in adults would require several months of daily supplementation with 100,000 IU.² Saul also cited a 2003 double-blind study performed in Great Britain in which older adults received 100,000 IU of vitamin D orally every 4 months for 5 years, without toxic effects.¹² Saul added that “potentially toxic” was very different from “toxic” and that “toxic” was very different from “lethal,” because vitamin D toxicity has warning signs, including anorexia, nausea/vomiting, polyuria, polydipsia, weakness, nervousness, and pruritus.¹² Other studies have supported these findings.¹⁴

Saul concluded his study on vitamin D toxicity by describing a dairy serving the Boston area in the 1990s that sold milk for 2 years with more than 230,000 IU of vitamin D added per quart instead of the usual 400 IU per quart.¹² Fewer

than two dozen toxicity reports and one alleged fatality were reported for the entire Boston area. This episode demonstrates the relative latitude for safety of this vitamin/hormone.¹² In their commentary, Vieth and Fraser stated that “toxicity has never been observed in the physiologic amounts that can be derived from sunshine....The lowest observed effect level, 4000 IU of vitamin D₃ per day, officially a toxic dose, is in reality a physiologic dose that has no effect on calcium levels in serum or urine.”⁹

How is the physiologic dose or toxic dose of vitamin D determined? The most objective method is to measure circulating serum 25-OH-D levels with the DiaSorin assay.⁸ Intact parathyroid hormone (PTH) levels can also be measured. If vitamin D concentrations are marginal or low, circulating PTH levels will be elevated. PTH signals the body to shunt calcium from bones into the bloodstream to maintain safe calcium levels. Because vitamin D is essential for calcium absorption, if vitamin D concentrations are high, levels of serum calcium will also be elevated.^{14,16} The 25-OH-D DiaSorin assay is more expensive than the measurement of serum PTH or calcium. Therefore, if serum PTH or calcium level is measured first and found to be elevated, direct measurement of circulating 25-OH-D via the DiaSorin assay can be performed. According to a review by Vieth, hypercalcemia related to vitamin D intake was always accompanied by serum concentrations of vitamin D exceeding 220 nmol/L.¹⁴ In addition to the use of calcium levels to determine vitamin D intoxication and PTH levels to gauge vitamin D deficiency, bone mineral density (BMD) and bone turnover markers

can be used as biomarkers to verify vitamin D deficiency.¹⁷

Vasquez et al found that, with respect to vitamin D, hypersensitivity is more common than toxicity.² In persons with vitamin D hypersensitivity, 25-OH-D levels are low or normal and serum calcium levels are elevated. Signs of hypersensitivity are the same as those for toxicity, and include anorexia, weakness, nervousness, pruritus, nausea, polyuria and polydipsia.¹² This hypersensitivity phenomenon occurs when cellular production of 1,25-OH-2D₃ becomes aberrant. Vitamin D hypersensitivity has been found in patients with adrenal insufficiency, hypothyroidism, primary hyperthyroidism, Crohn’s disease, certain cancers, or tuberculosis, or as an adverse reaction to certain drugs, particularly thiazide diuretics.² The observation that certain conditions and medications may affect cellular synthesis of vitamin D prompts the question of what other variables may affect its synthesis.

Variables Affecting Vitamin D Synthesis

Vitamin D deficiency is widespread worldwide, especially in persons residing at latitudes further removed from the equator but also in residents of tropical or subtropical areas who wear a lot of (especially dark) clothing.^{16,18-20} In 2004, Holick reported that several epidemiologic studies have shown associations between latitude-related vitamin D deficiency and many diseases.¹³ Even controlling for other variables, researchers have discerned relationships between residing at latitudes north of 35° and a higher incidence of breast, colon, and prostate cancers; heart disease; hypertension; osteomala-

cia; type 2 diabetes; mental illnesses such as depression, bipolar disorder, and obsessive-compulsive disorder; and many autoimmune disorders. At latitudes north of 35°, people cannot synthesize vitamin D cutaneously for 6 months of the year.^{8,13,21}

In a 2005 report, Grant and Holick explained the difference between the two types of UV rays, UVA and UVB.⁸ UVB waves are those from which vitamin D is synthesized. They are shorter than UVA rays and are more easily affected by atmospheric scatter and ozone. UVB rays are best absorbed when they are most directly penetrating the atmosphere—at and around solar noon. Solar lamps with a UVB spectral output mimicking summertime noonday sun can be used to synthesize cutaneous vitamin D. However, exposure must be for only 4 to 10 minutes for light skin and 60 to 80 minutes for dark skin. Longer exposure can increase the risk of skin cancer.

One group of researchers, in an attempt to prove that use of sunscreen with a sun protection factor (SPF) of 15 did not lower vitamin D concentrations below the 1997 minimum that would be achieved with an intake equivalent to 200 IU per day, pointed out that an SPF of 15 is assumed to reduce skin absorption of UV light (needed to synthesize vitamin D) by 93%.²² Although not its intention, this study supported the evidence that the effect of sunscreen is a significant contributor to vitamin D deficiency.

Vitamin D levels are inversely affected by the amount of pigmentation in the skin, as well as by obesity, particulate air pollution, use of sunscreen, age (50+ years), and use of certain medications.^{8,12,19-21} According to Vieth, to attain the

same concentration of vitamin D, highly pigmented skin, as compared with lighter skin, requires 3 to 6 times as much sunlight exposure.¹⁴ As a result, darker-skinned persons have a higher incidence of vitamin D deficiency and childhood rickets than do lighter-skinned persons.^{13,19,22}

Age is a factor in vitamin D synthesis.^{14,16} In 1997, the FNB recognized this fact by setting AI levels at 400 IU daily for adults older than 50 years and 600 IU daily for adults older than 70 years.⁷ However, Vieth reported that PTH levels in the elderly declined into the normal range only when D₃ concentrations exceeded 100 nmol/L (4000 IU/day, which is twice the tolerable UI recommended by the FNB).¹⁴ Medications (taken more frequently by older adults than by younger ones) that are known to decrease D₃ metabolism include phenytoin, heparin, cimetidine, isoniazid, rifampin, phenobarbital, corticosteroids, and primidone.¹²

Immunity/Autoimmunity

Along with the discovery of VDR sites came a gradual understanding of how vitamin D affects cell function. In 2000, Cantorna reviewed evidence that vitamin D was essential in regulating immune function.²³ All antigen-specific immune responses have been found to depend on thymus-derived lymphocytes known as T helper (Th) cells, of which two main types exist: Th1 and Th2. Immunity/autoimmunity was found to depend on the balance between Th1 and Th2. Th1 cells are the driving force behind all types of autoimmune disease; when not balanced with Th2 cells, they can become misdirected against self proteins.^{3,23} Cantorna et al found

evidence in animal studies that 1,25-OH-2D₃, when injected into autoimmune-diseased animals, regulated imbalanced T cell development.³ By contrast, in the absence of 1,25-OH-2D₃, the autoimmune disease progressed rapidly. The evidence supported the hypothesis that maintaining a balance between Th1 and Th2 cells could mean the difference between a beneficial outcome (ie, the clearing of infection) and a detrimental one (ie, autoimmune disease).³

Wraith et al, in a 2003 study on vaccination and autoimmune disease, reported that the incidence of autoimmune disorders has been increasing worldwide.²⁴ Serum vitamin D levels have been found to have a significant inverse correlation with many autoimmune disorders, including multiple sclerosis (MS), rheumatoid arthritis, Crohn's disease, inflammatory bowel disease (IBD), ulcerative colitis, type 1 diabetes mellitus, lupus, psoriasis, and scleroderma.^{2,8,12,21,25} Type 1 diabetes and MS have been the most studied autoimmune disorders in relation to vitamin D deficiency. Hypponen et al, in a large birth cohort study, found that infants who received vitamin D supplements regularly, regardless of dose, had a lower rate of type 1 diabetes than did those who did not.²⁶ In addition, infants who received 2000 IU of vitamin D/day in the first year of life had an 80% reduced risk of being diagnosed with type 1 diabetes by age 30.²⁶ These findings were supported by those of the EURODIAB study group's large cross-sectional investigation of vitamin D supplementation in early childhood, which found a 33% decrease in type 1 diabetes risk in children who received vitamin D supplements in infancy.^{27,28}

Variations in the allele of the VDR gene have been found in patients with type 1 diabetes, MS, and prostate cancer, suggesting a genetic link involving the metabolism of 25-OH-D into 1,25-OH-2D₃.^{5,29-32} This evidence is strengthened by the preponderance of cases of type 1 diabetes and MS that develop in persons born in late spring or early summer, as opposed to other times of the year. The last two trimesters of pregnancy in these births would have occurred during the seasonal low for D₃ levels in the expectant mothers. The pancreas and brain go through rapid development during the last trimester of pregnancy, and animal studies suggest that the genetically defective VDRs in pancreatic beta cells and myeloid cells develop at this time.^{13,30,32} Two recent, good-sized studies have found significant associations between maternal vitamin D insufficiency and early childhood wheezing/asthma,^{33,34} and another study conducted in England showed maternal vitamin D insufficiency associated with reduced bone mineral accrual and increased fracture incidence in children.³⁵

Other Diseases Associated with Vitamin D Deficiency/Insufficiency

Vitamin D insufficiency has far-reaching effects, likely due, according to Holick, to the presence of VDRs in most body tissues.¹³ The activated vitamin D metabolite, 1,25-OH-2D₃, is also produced outside the kidney at the cell site, and is one of the most potent regulators of cellular growth (normal cells and cancer cells). Activated vitamin D can be made in physiologic amounts only in the presence of adequate 25-OH-D.¹³ Diseases or disorders associated with insufficient or deficient levels of 25-OH-D

include 17 different types of cancer, low birth weight (maternal vitamin D insufficiency), premature labor, rickets, type 2 diabetes, hypertension, osteomalacia, increased body sway and subsequent falls in the elderly, osteopenia and osteoporosis, tuberculosis, depression, bipolar disorder, obsessive-compulsive disorder, and anxiety disorders.^{9,36-48} Vasquez et al associated the following diseases with vitamin D insufficiency: cardiovascular disease, epilepsy, migraine, and polycystic ovary syndrome (PCOS).² In his 2005 review of the requirement for vitamin D in health and disease, Heaney added gingivitis and seasonal affective disorder to the list.⁴ In certain cancers, PCOS, Crohn's disease, and IBD, inadequate calcium intake, as well as vitamin D deficiency, was a crucial risk factor.^{4,8,13}

New Guidelines for Vitamin D Intake

If the level of 25-OH-D is adequate—at least 80 ng per mL—then cellular VDR sites can produce the active metabolite, 1,25-OH-2D₃, in sufficient amounts for healthy cellular functioning.^{2,4,8,10,48} Based on evidence to date, Grant and Holick listed serum 25-OH-D deficiency/sufficiency levels in their 2005 review (Table 2).⁸ In addition, Heaney et al estimated the oral input of vitamin D that would be needed to achieve the sufficiency level of at least 80 nmol per L as a steady state (through winter seasonal drop).¹⁰ They began with a starting value of 50 nmol per L, and found that vitamin D 4600 IU daily would be needed to maintain sufficiency levels. The researchers also found that among subjects who received vitamin D 5500 or 11,000 IU daily for 20

weeks, none experienced an elevation of serum calcium level above the UL of normal.

Implications for Practice

As of April 2007, mounting evidence has supported significant associations between vitamin D insufficiency and many chronic diseases. A January 2007 systematic review by Hathcock et al found no adverse effects of vitamin D supplementation in daily doses of less than 10,000 IU, and that this dose level—10,000 IU—may be the tolerable UL intake.⁴⁹ Various studies have demonstrated little if any physiologic effect of vitamin D in the body with supplemented daily doses below 800 IU^{2,4,26,49,50} and that the greatest physiologic effects have occurred in daily doses of 2000 IU or higher.^{2,26,49,50} In the summer, these amounts can easily be achieved by unblocked sun exposure for short periods. However, in northern climates, in individuals whose ability to synthesize vitamin D is compromised by age, obesity, darker pigmentation, or the use of certain medications, more vitamin D is necessary during winter and early spring.

Evidence points to 2000 IU daily as the lower of the physiologic dosing levels for maximum effect.^{2,4,8,9,37,49} Table 3 provides suggestions for vitamin D supplementation based on age, weight, and pigmentation.

Blood serum measurements of calcium and intact PTH, as well as the DiaSorin Assay of 25-OH-D, should become an integral part of the yearly physical examination, and are ideally performed in mid-autumn (to assess the peak blood level of 25-OH-D before winter lows) or in early spring (to assess seasonal lows). BMD and other biomarkers can also be assessed in patients whose age or condition places them at high risk, or if blood test results are questionable. The average cost of the serum calcium and intact PTH level is less than \$100 a test and that for the DiaSorin Assay for 25-OH-D ranges from \$165 to \$265.⁵¹ Results of the DiaSorin Assay should be interpreted based on the recommended levels in Table 2, rather than on textbook or laboratory values relying on 1997 guidelines.^{8,10}

Hypersensitivity to vitamin D has been noted in patients with

TABLE 2 HEALTH IMPLICATIONS OF VARIOUS LEVELS OF SERUM 25-OH-D⁸

25-OH-D LEVEL		HEALTH IMPLICATIONS
(ng/mL)	(nmol/L)	
<20	<50	Deficiency
20-30	50-80	Insufficiency
32-100	80-250	Sufficiency
54-90	135-225	Normal in sunny countries
>100	>250	Excess
>150	>325	Intoxication

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TABLE 3 SUGGESTED VITAMIN D SUPPLEMENTATION

LIFE STAGE	WINTER/EARLY SPRING (IU/day)	SUMMER/FALL (IU/day)*
Caucasian infants and children <100 lb	2000	1000
Darker-pigmented children <100 lb	3000	2000
Adult Caucasians aged 18-49 [†] , >100 lb, BMI <27.0 kg/m ²	4000	2000
Darker-skinned adults aged 18-49, >100 lb, BMI <27.0 kg/m ²	5000	4000
Pregnant/lactating women		
–Light skinned	4000	3000
–Dark skinned	5000	4000

*May delete supplementation on a given day if at least 20% of the body has been exposed long enough to sunlight to color slightly.

[†]Higher doses may be needed in persons older than 49 years, persons with a BMI >27 kg/m², persons taking certain medications, and persons with certain existing medical conditions.

BMI = body mass index.

hyperparathyroidism, hypothyroidism, some cancers, tuberculosis, and fat malabsorption syndromes. In addition, NPs should carefully monitor the effects of vitamin D in elderly women with hypotension and in anyone with osteopenia or osteoporosis.

Based on available research, new guidelines for vitamin D intake are warranted in NP clinical practice for the following reasons:

- Even by 1997 standards, vitamin D deficiency is epidemic worldwide.

- The global incidence of autoimmune disorders and cancer is increasing.

- Toxicity risk with vitamin D is minimal and can be monitored and controlled.

- The cost of testing and supplementation is miniscule, especially compared with the economic burden of the diseases that vitamin D sufficiency may prevent.

- Further human studies using vitamin D as a treatment, as well as a preventive therapy, are needed, and can be conducted meaningfully

using appropriate physiologic dosing.

- As a treatment, vitamin D has effectively:

- reduced falls and hip fractures in the elderly;
- increased the length of the “honeymoon period” in patients with newly diagnosed diabetes; and
- reduced the development of arthritis.

Conclusion

If vitamin D as a preventive therapy can be as effective as research suggests, then it is urgent to begin incorporating it into evidence-based practice. In its section on diabetes, the *Healthy People 2010* government guidelines state that “the rapidity and utility of scientific discourses will influence the control of the [disease] burden, but any information that is not translated and used in daily practice is ultimately wasted.”⁵² ■

Barbara S. Jockers is a family nurse practitioner. The author states that she does not have a financial interest in or other relationship with any commercial product named in this article.

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