

# Vitamin D Deficiency in Pre- and Postmenopausal Women

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The past several years has seen the emergence of a new interest in a very old vitamin, vitamin D. Although its role in skeletal health has long been recognized, only recently have we realized that this vitamin plays a ubiquitous role in the function of essentially all major organ systems. Furthermore, there is evidence that the clinical manifestations of a vitamin-D-deficiency state may also vary across the lifespan, as does the vulnerability to the deficiency state. This is particularly apparent for women. In premenopausal women, the primary manifestations of vitamin D deficiency are osteoporosis and an increased risk of breast and colon cancer. In postmenopausal women a further increase occurs in the expression of these malignancies and in bone loss. In addition, muscle weakness, postural instability, falls, osteoporotic fractures, cognitive impairment, depression and, ultimately, the frailty syndrome become expressions of the deficiency state.

This article will examine the emerging evidence for vitamin D's role in these diverse conditions, and will address the emerging data concerning the requirements for vitamin D across the menopausal transition and in the aging postmenopausal woman.

## Vitamin D Metabolism and Regulation

To appreciate why vitamin D plays an important role in women's health, it is necessary to understand the effects of age and menopause on the metabolism and mechanism of action of the vitamin. The "prohormone" vitamin D exists in two forms; the plant source (ergocalciferol [vitamin D<sub>2</sub>]) and the animal source (cholecalciferol [vitamin D<sub>3</sub>]). Vitamins D<sub>2</sub> and D<sub>3</sub>

are ingested from the diet; however, the major source of vitamin D is vitamin D<sub>3</sub> synthesized in the skin upon exposure to ultraviolet-B (UVB) light. Vitamin D is then hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D). This metabolite is further hydroxylated to 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), the biologically active form of the vitamin, by the enzyme 1 $\alpha$ -hydroxylase, found in the kidney. The activity of

this enzyme and the production of 1,25(OH)<sub>2</sub>D are regulated in a positive feedback loop by parathyroid hormone (PTH) to maintain constant serum calcium levels. The 1 $\alpha$ -hydroxylase has also been identified in multiple target tissues, suggesting an autocrine or paracrine function in these tissues. Like other steroid hormones, the 1,25(OH)<sub>2</sub>D binds to a nuclear receptor protein, the vitamin D receptor (VDR), to exert most of the biologic actions of the hormone. The VDR protein is widely distributed throughout the body, consistent with the actions of this hormone on multiple tissues (Table 1).

Multiple factors affect the availability of the vitamin as well as the body's response to it. Because the major source of vitamin D is, for most populations, skin synthesis of vitamin D<sub>3</sub>, factors that limit sunlight exposure and intensity determine the prevalence of vitamin D deficiency. With increasing distances from the equator, the intensity of sunlight diminishes; in much of the US the skin is able to generate significant quantities of vitamin D only during the summer months between the hours of 10:00 am and 4:00 pm. This vitamin D is stored by the circulating vitamin-D-binding protein to be released during the winter months. For many women these stores are inadequate to maintain skeletal and mental

health, as evidenced by the loss of bone mineral density and the appearance of seasonal affective disorder during the winter.

Sunlight exposure is limited by clothing and sunscreens. Lifestyle also plays an increasingly important role in sunlight exposure, as more women join the work force. In a study of young health professionals, 32% were found to be vitamin D deficient.<sup>1</sup> Darker skin pigmentation reduces skin synthesis of vitamin D<sub>3</sub>;<sup>2</sup> as a result, African-Americans and dark-skinned Asians are at increased risk for vitamin D deficiency, particularly in the more northern latitudes.

Aging affects multiple steps in the metabolism of vitamin D, beginning with the reduced efficiency in the vitamin's synthesis by aging skin upon exposure to UVB radiation.<sup>3</sup> Consequently, the older adult requires approximately 3 times the duration of exposure as the younger adult to generate the same amount of vitamin D. Institutionalized and frail elderly are, therefore, particularly vulnerable to the deficiency state, with a prevalence approaching 90% due to their limited

exposure to sunlight. Drugs, such as phenytoin (Dilantin) and other anti-convulsants that induce hepatic and

increased activity of the 1 $\alpha$ -hydroxylase and reduced renal production of 1,25(OH)<sub>2</sub>D.<sup>4</sup> Finally, the end organ



renal cytochrome hydroxylases, may deplete vitamin D stores through increased metabolism of the vitamin to inactive metabolites. Thus, polypharmacy in the elderly becomes a risk factor for the deficiency state.

Another factor is the age-related loss of renal mass resulting in de-

creased activity of the 1,25(OH)<sub>2</sub>D is also impaired in the elderly. The resulting vitamin D resistance can be attributed to a decrease in VDR activity<sup>5,6</sup> and number<sup>7</sup> due to the effects of age, the decline in estrogen levels<sup>8</sup> and a decline in renal function.<sup>9</sup> Menopause represents an important transition in vitamin D requirements because of the dependence of the VDR on estrogen.<sup>8</sup> The increased requirement for calcium across the menopausal transition is a reflection of the loss of VDRs and an increased requirement for vitamin D. Multiple polymorphisms of the VDR protein have been recognized,<sup>10</sup> which may also increase the requirement for vitamin D.

### Mechanisms of Action

In the laboratory, 1,25(OH)<sub>2</sub>D has anti-proliferative effects on various malignant cell types, including breast, prostate, colon and leukemic cells. The hormone and its analogs have been used to treat psoriasis. Multiple epidemiologic studies have demonstrated reduced incidence and mortality rates

**Table 1.** Mechanisms of Vitamin D Action

Tissue	Tissue Response to Deficiency State
Blood vessels	Vasodilatory dysfunction
Bone	Decreased mineralization of matrix
Breast	Increased density and carcinoma incidence
Epidermis	Decreased growth rate; decreased nail thickness
Immunoregulatory cells	Increased production of IL-1, IL-6, TNF; inflammation, de-differentiation of monocytes; impaired response to infection; increase in leukemias
Intestine	Decreased transport of calcium and phosphate; increased colon carcinoma
Kidney	Decreased tubular resorption of phosphate; increased renin production
Muscle	Increased protein breakdown; decreased force of contraction
Neurons	Decreased production of neurotransmitters and neurotrophic factors
Pancreas	Decreased islet cell function; carbohydrate intolerance
Parathyroids	Increased growth and production of parathyroid hormone
Prostate	Increased expression of prostate carcinoma

IL=interleukin; TNF=tumor necrosis factor.

for several forms of common cancers (for example, colon, breast and prostate) in geographic areas associated with high levels of UVB light exposure or in populations supplemented with vitamin D.<sup>4</sup> The immune system is another example of the effects of 1,25(OH)<sub>2</sub>D on cell function and differentiation. In both in vitro and clinical trials,<sup>11,12</sup> 1,25(OH)<sub>2</sub>D inhibited the production of interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha in a dose-dependent manner, and also suppressed C-reactive protein.<sup>13</sup> Rheumatoid arthritis and inflammatory bowel disease, which are classic examples of dysregulation of the immune system, have been associated with low levels of 25(OH)D.<sup>14</sup> This past decade has seen an increasing awareness of the role of inflammation in the pathogenesis of vascular disease, and epidemiologic data support the association of vitamin D deficiency with cardiovascular disease (CVD).<sup>15</sup> VDR polymorphisms are associated with an increased incidence of CVD.<sup>16</sup> The effects of vitamin D on the cardiovascular system are likely multifactorial. In addition to the direct effects on inflammatory cytokines and the vascular endothelium, vitamin D deficiency is associated with impaired pancreatic B-cell function, insulin resistance and diabetes.<sup>17</sup> Hypertension is also linked to vitamin D deficiency, and vitamin D repletion has been shown to decrease blood pressure, an effect which may, in part, be mediated by vitamin D's effects on the renin-angiotensin system.<sup>18</sup> Obesity, an important risk factor for CVD and the metabolic syndrome, is also associated with vitamin D deficiency.<sup>19</sup>

Another mechanism whereby vitamin D deficiency may lead to CVD is the secondary hyperparathyroidism associated with the deficiency state. Elevated levels of PTH have multiple and independent effects on the car-

diovascular system.<sup>20</sup> Hyperparathyroidism is also associated with endothelial vasodilatory dysfunction that is reversed by parathyroidectomy.<sup>21</sup> These effects on the cardiovascular system may also be due to increased production of IL-6 by PTH.<sup>22</sup> Secondary hyperparathyroidism is an independent predictor of mortality<sup>23</sup> and, in patients on chronic hemodialysis, vitamin D administration to treat hyperparathyroidism provides a significant survival benefit.<sup>24</sup>

### Effects on Breast and Colon Cancer

Breast and colon cancers are the leading causes of mortality in pre- and early postmenopausal women. Multiple observational studies have implicated vitamin D deficiency as a major risk factor in the expression of these malignancies.<sup>25</sup> In a nested case-control study of participants in the Women's Health Initiative (WHI), women in the lowest quartile of baseline serum 25(OH)D had 2.5 times the risk of colorectal cancer as did women in the highest quartile (>23 ng/ml).<sup>26</sup> The trend for risk reduction with increasing 25(OH)D levels was significant, with no evidence of a threshold effect. Thus, levels >32 ng/ml may have been associated with an even greater reduction in risk. Observational studies also show an inverse association with increased breast density, a risk factor for breast cancer;<sup>27</sup> only recently have intervention trials established the causality of this association. The WHI clinical trial failed to demonstrate a reduction in risk with a dose of 400 international units (IU) of vitamin D<sub>3</sub>. Observational studies that have examined the association between dietary intake of vitamin D, typically 200-400 IU/day, have also been largely negative. However, in a randomized placebo-controlled trial involving more than 1,000

postmenopausal women, Lappe and colleagues<sup>28</sup> demonstrated a 77% reduction in cancer incidence over the last 3 years of the 4-year trial. These investigators used 1,100 IU of vitamin D<sub>3</sub> combined with a diet containing 1,400 – 1,500 mg calcium. Mean serum 25(OH)D levels achieved were 38.4 ng/ml. Reduction in cancer incidence did not reach statistical significance with calcium supplementation alone (compared to placebo). Vitamin D status during treatment may also favorably influence cancer survival.<sup>29</sup> This is an area that needs much more research.

### Effects on Postmenopausal Syndromes and Frailty

We shall consider the evidence that the postmenopausal syndromes of osteoporosis, muscle weakness, falls, osteoporotic fractures, depressed mood, cognitive impairment and dementia may be a consequence of the vitamin D deficiency state. Although we recognize that multiple factors likely contribute to each of these syndromes, vitamin D deficiency, because of its prevalence in postmenopausal women and the elderly, may be a major determinant of these syndromes. Appreciating the role of vitamin D deficiency in these syndromes may provide a simple, cost-effective modality for treatment and prevention of these conditions, which are also associated with frailty.

*Osteoporosis and osteoporotic fractures.* The most well-documented syndrome associated with vitamin D deficiency is osteoporosis and osteoporotic fractures. Vitamin D has long been recognized as a critical factor in the maintenance of normal bone metabolism and turnover. Both the resorption and formation phases of the bone remodeling cycle are stimulated by 1,25(OH)<sub>2</sub>D. Bone mineralization is facilitated by effects of 1,25(OH)<sub>2</sub>D

in stimulating the active intestinal transport of calcium and phosphorus. Severe deficiency causes a failure to mineralize bone matrix, resulting in osteomalacia, whereas mild deficiency or insufficiency results in the loss of bone mass and osteoporosis. The latter is associated with secondary hyperparathyroidism that increases bone remodeling, bone loss and structural damage (such as cortical thinning and porosity), which characterize the osteoporotic state and the increased risk of osteoporotic fractures. Supplementation with vitamin D slows the rate of bone loss and increases bone mineral density. Clinical trials in older adults have demonstrated that vitamin D supplementation decreases the risk of osteoporotic fractures, with doses ranging from 700–800 IU/day.<sup>30–32</sup> Two other clinical trials in older adults failed to demonstrate a reduction in fractures using 400 IU/day of vitamin D.<sup>33,34</sup>

**Muscle weakness.** Since the earliest descriptions of vitamin D deficiency rickets, proximal muscle weakness has been a prominent feature of this disorder. In experimental animal models vitamin D repletion restores the force of contraction<sup>35</sup> and reverses the accelerated protein breakdown that characterizes the deficiency state.<sup>36</sup> Clinical trials demonstrate improved muscle strength with vitamin D supplementation.<sup>37,38</sup> Vitamin D repletion with adequate calcium supplementation results in the suppression of secondary hyperparathyroidism. The latter has an independent effect on muscle function and structure.<sup>39</sup> In a population of men and women over age 65, elevated levels of PTH as well as low levels of 25(OH)D were associated with muscle wasting, defined as decreased grip strength and decreased muscle mass.<sup>40</sup> Furthermore, surgical correction of primary hyperparathyroidism restores impaired muscle

strength evident prior to surgery.<sup>41</sup> In summary, although vitamin D has direct effects on muscle function, there is evidence that suppression of secondary hyperparathyroidism may be critical to the restoration of muscle

min D may be acting on postural control via other mechanisms. The dominant determinant of postural stability in older adults appears to be the speed by which the central nervous system processes sensory input and generates

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function. Thus, vitamin D repletion must be accompanied by adequate calcium intake.

**Falls.** There is now compelling evidence that vitamin D therapy, when combined with adequate calcium intake, can dramatically reduce the incidence of falls in frail elderly. In a nursing home population, falls were reduced by 49% with the administration of 800 IU/day of vitamin D plus 1,200 mg of calcium/day.<sup>42</sup> The reduction in falls was apparent after only 3 months of treatment. When vitamin D was given alone, only those with dietary calcium intakes greater than 500 mg/day experienced a reduction in falls.<sup>43</sup> As with osteoporotic fractures, a clinical trial using 400 IU/day of vitamin D was not successful in reducing falls.<sup>33</sup> The apparent dependence of the effect on calcium suggests that the effect of the vitamin D may be mediated through reduction of secondary hyperparathyroidism. Indeed, in a prospective study of nursing home residents,<sup>44</sup> serum levels of PTH were a predictor of falls independent of serum levels of 25(OH)D. Thus, the mechanisms whereby vitamin D reduces falls include direct effects of vitamin D and/or PTH on muscle function.

Despite showing improved balance and a reduced incidence of falls following vitamin D treatment, not all studies have been able to demonstrate improved muscle strength. Thus, vita-

an appropriate and timely musculoskeletal response. Measures of central processing speed are independent predictors of falls and injurious falls.<sup>45</sup> Dhesi and colleagues<sup>46</sup> note an association between vitamin D status and psychometric measures of central processing speed in a population of elderly subjects with a history of a recent fall. Another manifestation of impaired central processing speed is an increase in body sway. In an 8-week clinical trial involving 148 elderly women, 800 IU of vitamin D and 1,200 mg of calcium/day resulted in a decrease in body sway without changes in muscle strength.<sup>47</sup> Following menopause there is an increase in body sway that can be reversed or prevented by hormone therapy.<sup>48</sup> Although estrogen has direct effects on the brain, its effects on body sway and postural stability may also be mediated, in part, through activation of the VDR. Thus, vitamin D may be preventing falls by improving postural control, as well as other aspects of central nervous system function.

**Osteoporotic fractures.** Osteoporotic fractures, especially non-vertebral fractures, are associated with falls. Persons with low bone mass are more likely to fall, and to have impaired balance and muscle strength,<sup>49,50</sup> and dementia of the Alzheimer's type.<sup>51</sup> Thus, low bone mass and osteoporotic fractures appear to be markers of an underlying disorder characterized by

muscle weakness, postural instability and neurodegenerative changes within the central nervous system. Vitamin D deficiency provides a unifying physiologic basis for these common syndromes associated with low bone mass. This concept has important implications in our approach to the management and prevention of osteoporotic fractures. Although bone anti-resorptive agents, such as bisphosphonates, decrease vertebral fractures, their efficacy in the prevention of non-vertebral fractures is relatively limited. Over 80% of osteoporotic fractures (low-trauma fractures) occur in women without osteoporosis.<sup>52</sup> In this population, bisphosphonates would be expected to be ineffective.<sup>53</sup> Improving bone strength in the elderly (over age 80) is also relatively ineffective in preventing hip fracture,<sup>54</sup> whereas vitamin D treatment reduces hip fracture by 50% in this elderly population.<sup>55</sup>

*Central nervous system (cognitive impairment and dementia).* It has been known for some time that the VDR, and more recently that  $1\alpha$ -hydroxylase, are localized to select regions of the human brain, suggesting that the vitamin may modulate brain function. Indeed, there is now ample evidence that vitamin D is a neuroactive hormone with both neurotropic and neuroprotective effects, recently reviewed by Kiraly and colleagues.<sup>56</sup> Finally, vitamin D may modulate neuronal function by stimulating the synthesis of certain neurotransmitters—acetylcholine, for example.<sup>57</sup>

What is the evidence that these effects of vitamin D on brain physiology have identifiable clinical correlates? First, certain neurologic and psychiatric disorders have been associated with the deficiency state. For example, there is an increased prevalence of multiple sclerosis and Parkinson's disease in northern latitudes relative to more equatorial latitudes.<sup>58,59</sup> More

recently, low vitamin D intake has also been linked to multiple sclerosis.<sup>60</sup> In the mid- to late 1990s, Kipen and colleagues<sup>61</sup> and Sato et al<sup>62</sup> also described the association of vitamin D deficiency and osteoporosis with both Parkinson's disease and Alzheimer's disease. In 2006, vitamin D deficiency was associated with cognitive impairment.<sup>63</sup> The mechanism whereby vitamin D may ameliorate progression of these neurodegenerative disorders may, again, relate to the potent immunoregulatory effects of the vitamin, as inflammatory cytokines have been implicated in the pathogenesis of these disorders.<sup>64</sup>

Another important effect of vitamin D on brain function may be its effects on cerebral vasculature. As noted above, vitamin D deficiency may have multiple adverse effects on cerebral circulation, including the induction of inflammatory cytokines. The ischemic brain injury associated with these changes is believed to be the proximate cause of postural instability, impaired gait, falls, cognitive impairment, dementia and depression seen in older adults.<sup>65</sup> As with the effects of vitamin D deficiency on other systems, PTH may have an independent effect on brain function and cerebral circulation.<sup>66</sup>

*Depression.* The effects of vitamin D on mood have not been studied in great detail. Seasonal affective disorder has been linked to low levels of vitamin D in winter, and treatment with vitamin D has been shown to improve mood in these individuals.<sup>67</sup> In another study of healthy subjects, vitamin D supplementation led to significant enhancement of mood during winter months.<sup>68</sup>

*Frailty.* There is a growing consensus that frailty is a biologic syndrome involving multisystem impairment and reduced physiologic reserve. Empirical indicators of the frailty syndrome are muscle wasting, muscle

weakness, easy fatigue, slow gait and decreased physical activity. Others would include impaired cognitive and psychological function.<sup>69</sup> Given the effects of vitamin D deficiency on the above syndromes associated with postmenopausal women, it is not surprising that vitamin D deficiency has recently been found to be associated with a greater than 2-fold increased risk of frailty.<sup>70</sup> It is believed that inflammatory cytokines contribute to the multisystem dysfunction and the associated comorbidities. Although multiple factors may contribute to the increased expression of these cytokines, vitamin D deficiency may be a relatively common candidate in the elderly. Vitamin D deficiency/resistance therefore provides a plausible cause for the frailty syndrome because of its effects on muscle and brain function as well as its modulation of inflammatory cytokines. Investigations are urgently needed to establish whether adequate vitamin D supplementation can prevent and reverse this syndrome.

### Assessment

Assessment of a vitamin D deficiency is based on measurement of serum levels of 25(OH)D because of its long half-life. The active metabolite,  $1,25(\text{OH})_2\text{D}$ , should not be used for this purpose because levels decline only in severe deficiencies and may not reflect levels in target tissues where it is generated. Because of the increasing incidence of vitamin D resistance with age, higher circulating levels of 25(OH)D are required to drive the tissue response. As a result, the normal range for 25(OH)D is dependent on age. Resistance would also be reflected by increased levels of PTH because of the negative feedback loop involving the parathyroids; thus, measurement of PTH becomes a more reliable assessment of vitamin D status than 25(OH)D alone in older adults.<sup>71</sup>

In healthy young adults, the upper limit of normal for PTH is approximately 42-46 pg/ml.<sup>72</sup> Vitamin D status can then be defined as in Table 2, recognizing that the cut-points are somewhat arbitrary. The normal range for postmenopausal women has recently been revised upward to 30-100 ng/ml, based on the levels needed to prevent osteoporosis.<sup>73</sup>

### Recommendations for Screening and Treatment

The high prevalence and implications of the deficiency state with respect to common postmenopausal syndromes underscore the need for all women to be routinely screened for vitamin D status by measuring serum levels of both 25(OH)D and PTH. Because vitamin D may reduce breast and colon cancer by almost 80%, screening should be a part of the annual mammogram visit. Treatment should be aimed at achieving a 25(OH)D level at which no further suppression of PTH occurs or a PTH of less than 42 pg/ml. This usually is achieved in older adults at 25(OH)D concentrations of 30-40 ng/ml.

The requirement for vitamin D in healthy adults is estimated to be 3,000-5,000 IU per day,<sup>74</sup> most of which is derived from sunlight exposure. Thus, women in the work force (with limited sunlight exposure) will also need supplementation. In a rural population of postmenopausal women, average age 67 years, it was estimated that 2,000 IU/day of supplemental vitamin D<sub>3</sub> would be required to achieve 25(OH)D levels of 32 ng/ml in 97.5% of these women (criteria for recommended daily allowance).<sup>75</sup> In the home-bound and institutionalized, dietary supplements that approach 3,000-5,000 IU/day would be required. Recent analyses suggest that the safe, tolerable upper intake level for vitamin D should be revised upward

from the current 2,000 IU to 10,000 IU.<sup>76</sup> The elderly, the obese and patients with renal insufficiency will require doses higher than 5,000 IU/day—and even 10,000 IU/day—due to vitamin D resistance. In these pa-

women are more susceptible to the deficiency state. However, because of lifestyle changes resulting in limited sunlight exposure, premenopausal women are also vulnerable. In premenopausal women, the consequences

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tients, to normalize the PTH, vitamin D<sub>2</sub> (ergocalciferol) 50,000-IU capsules (Drisdol®), are commonly used. To sustain blood levels of 25(OH)D, this preparation of vitamin D<sub>2</sub> must be given no less frequently than every 1 to 2 weeks because the half-life is only 7-10 days. Less frequent dosing may initially decrease the levels of 25(OH)D.<sup>77</sup> Vitamin D<sub>3</sub> (cholecalciferol) is available only over-the-counter in capsules of 10,000 IU or less. Because of its longer half-life, potency of cholecalciferol is approximately 3 to 10 times that of ergocalciferol.<sup>78</sup>

### Summary and Conclusions

Vitamin D deficiency is increasingly recognized as a major health issue, particularly for women. Because of the dependency of the vitamin D receptor on estrogen, postmenopausal

are increased risk of breast and colon cancers, and bone loss. In postmenopausal women, deficiency is exacerbated by the loss of estrogen and age-related changes in the VDR and vitamin D synthesis. The result is a further increased risk of malignancy, bone loss, hypertension, diabetes, depression, falls and osteoporotic fractures. The evidence is also mounting that the deficiency state may affect other systems, including the vascular system and the brain, manifested by cognitive impairment and dementia, and frailty. Fortunately, vitamin D repletion can prevent the former syndromes common in postmenopausal women. Additional research is needed to demonstrate the efficacy of treatment in the latter. The opportunities for the safe and cost-effective treatment of these syndromes are

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**Table 2.** Assessment of Vitamin D Status in Older Adults

Vitamin D Status	25-hydroxyvitamin D (ng/ml)	PTH (pg/ml)
Deficiency	<15	>42
Insufficiency	15 – 30	>42
Normal	>15	<42
Resistance*	>30	>42

PTH=parathyroid hormone

\*Primary hyperparathyroidism excluded by absence of hypercalcemia

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enormous, and are limited only by the lack of effective screening. ■

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## From the Editor

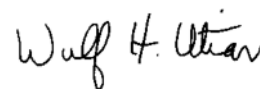
(continued from page 7)

dementia risk. Limited data do not support the use of HT as treatment for AD.

Clearly, the existing data, despite demonstrating the limitations of current knowledge, open ideas and offer possibilities for further research into the relationships between hormones and cognition. That research is, at present, covering basics of cell culture, the use of artificial neural networks, study of animal biology and behavior, other hormone systems like insulin pathways and gonadotropins, protein metabolism, and attempts to eventually translate this basic scientific endeavor into clinical research studies. While epidemiologic observations help direct some lines of research, such observations cannot, themselves, directly link cause and effect. This raises the necessity for testing multiple steroidal drugs in varying doses, combinations and routes of delivery. Beyond that will be the testing of earlier-generation estrogen agonist-antagonist molecules and, as an area of rapid drug development in a relatively early stage, the potential of testing new and ever better designed molecules. As basic mechanisms of brain cell

metabolism and neural pathways are revealed, the possibility exists for specific ligand receptor products to be developed with planned and precisely targeted activity.

All in all, even though this is an exciting frontier in the new science of brain and memory research, currently HT use does not appear to be the answer to memory loss, and much work lies ahead. Real support is necessary to stimulate and encourage basic science and clinical researchers going forward. We are just scratching the surface of the science and the potential for defeating what is one of the most devastating problems facing humanity; namely, loss of memory and its impact on the individual and the family.



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The North American Menopause Society

## Reference\*

The North American Menopause Society. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause* 2008;15:584-603.

\*References to material described are listed in the NAMS statement cited above.