The Physiological and Treatment of Vitamin D Deficiency

To the Editor: The results of the study by Plotnikoff and Quigley,1 as well as the content of the accompanying editorial by Holick,2 are alarming. Because the replacement of vitamin D is simple and reduces the risk of osteoporosis and other complications associated with vitamin D deficiency, understanding changing demands for vitamin D supplementation is important.

In addition to the factors mentioned by Plotnikoff, Quigley, and Holick, the dietary intake of vitamin D may be affected by the variable amount of vitamin D in fortified products3 and by decreased intestinal absorption of vitamin D with age. Synthesis of vitamin D from exposure to the sun declines due to the increased zenith angle of the sun.4 For example, in Boston, Mass (42° north), little vitamin D is produced from November through February even after 5 hours of sun exposure.5 Hypovitaminosis D has also been linked to increased risk of tuberculosis6 and impaired macrophage activation.7

Because the fear of skin cancer may limit the amount of exposure to the sun, vitamin D supplementation seems to be the best solution, with seasonal dose adjustment to achieve the desired range of serum 25-hydroxyvitamin D. Standard clinical risk factors seem to be poor predictors of vitamin D deficiency. Thus, physicians should be alert for vitamin D deficiency in patients of all ages.

Manmeet Padda, MD
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4. Holick MF. Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health. Curr Opin Endocrinol Diabetes. 2002;9:87-98.

In reply: Dr Padda’s point is well taken: physicians should be alert for vitamin D deficiency in all age groups. The vitamin D nuclear receptor is found not only on intestinal, bone, liver, and kidney tissues but also on lymphocytes, monocytes, and macrophages as well as hematopoietic, skin, muscle, heart, pancreas, adrenal, brain, reproductive, lung, pituitary, thyroid, and cartilage tissues.1 Deficiency is likely associated with multiple clinically relevant issues.

Dr Padda asserts that vitamin D supplementation is the best solution. However, defining the dose is problematic. Prenatal supplementation in 58 pregnant women in Wales who had profound to severe hypovitaminosis D only raised their mean serum 25-hydroxyvitamin D level to a moderately severe deficiency value of 11 ng/mL by delivery.2

The best guidelines for dosing will be gained from serial quantification of serum 25-hydroxyvitamin D levels. Our study supports routine assessment of vitamin D status for all patients with persistent, nonspecific musculoskeletal pain regardless of immigrant status, age, or gender.3

Gregory A. Plotnikoff, MD, MTS
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In reply: It is clear from his letter that Dr Padda is aware of the epidemic of vitamin D deficiency in the United States. What he perhaps does not fully appreciate is that exposure to sunlight is probably the best source of vitamin D and often provides 90% to 95% of the vitamin D requirement for people of all ages. For example, wearing a bathing suit and being exposed to sunlight that would cause a mild pinkness (ie, 1 minimal erythral dose [MED]) is equivalent to taking between 10,000 and 20,000 IU of vitamin D.1 Thus, limited sensible exposure to sunlight, ie, no more than 25% of the time required to produce a MED, 2 to 3 times a week is usually adequate. Mother Nature has dealt with the problem of humans being unable to produce sufficient vitamin D during the winter by storing excess vitamin D in the body fat so that it can be released during the winter. Fear of skin cancer is real. However, chronic excessive exposure to sunlight and sunburning incidents are most responsible for the high incidence of skin cancer.2 There is little evidence that minimal sensible exposure to sunlight will considerably increase the risk of skin cancer. Although it is easy to say that vitamin D can be obtained from supplements and foods fortified with vitamin D, this is not an easy task. Eight ounces of milk or vitamin D–fortified orange juice contains only 100 IU of vitamin D. A person would have to eat salmon, mackerel, or sardines almost daily to satisfy their body’s vitamin D requirement. Most experts agree that 1000 IU of vitamin D daily is required to meet vitamin D needs in the absence of any sun exposure.3,4

Although it is true that aging decreases the body’s ability to produce vitamin D in the skin, investigators have shown that, because the skin has such a great capacity to produce vitamin D, elderly persons’ exposure to 15 minutes of sunlight 3 times a week in the summer or exposure in a tanning bed 3 times a week can raise their blood levels of 25-hydroxyvitamin D.5,6 Furthermore, Chuck et al7 reported that in nursing home residents, exposure to indirect ultraviolet radiation was the most effective means of maintaining circulating concentrations of 25-hydroxyvitamin D, even better than a vitamin D supplement.

References

The draconian message that people should never be exposed to sunlight without sun protection is totally unwarranted and should be replaced with the message that sensible sun exposure is good for overall health and well-being. Hypovitaminosis D has been linked not only to increased risk of tuberculosis, as noted by Dr Padda, but also to increased risk of type 1 diabetes, hypertension, congestive heart failure, and cancers of the colon, breast, prostate, ovaries, and other organs.1,8 Thus, I hope that the study reported by Plotnikoff and Quigley9 has enlightened physicians about how common and underdiagnosed hypovitaminosis D is and about its consequences on bone and muscle health.

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1. Holick MF. Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health. Curr Opin Endocrinol Diabetes. 2002;9:87-98.

Vitamin D Deficiency and Chronic Pain: Cause and Effect or Epiphenomenon?

To the Editor: Because of the article on hypovitaminosis D in the December 2003 issue of Mayo Clinic Proceedings, I now have patients with chronic pain requesting measurement of their vitamin D levels in addition to the usual list of unjustified tests. Plotnikoff and Quigley1 propose that the management of an exceedingly common condition—musculoskeletal pain of indeterminate origin—should include a routine assessment of vitamin D status. This conclusion is not supported by any data presented in the article, and the accompanying editorial by Holick2 challenges none of the authors’ hypotheses. The patient group analyzed in the study—patients with “persistent, nonspecific musculoskeletal pain”—is by definition an amalgam of disparate physical and emotional problems. The presence of biochemical vitamin D deficiency in this group indicates only that such a deficiency can be recognized commonly in Minnesota. In the absence of a concurrent comparison group, the study says nothing about whether vitamin D deficiency is more common in such patients than in the population at large or whether it has any role in causation. The comparison groups provided from historical controls are predominantly white, and it is not surprising that their 25-hydroxyvitamin D levels are higher than those of the selected ethnic groups in this study. Furthermore, this hypothesis immediately leads to several conclusions that are inconsistent with observed patterns of illness. If vitamin D deficiency is an important contributor to chronic musculoskeletal pain, why is the incidence of the disorder not profoundly different in different races once socioeconomic status is accounted for? Similarly, why is there no dramatic decrease in the incidence of chronic musculoskeletal pain on moving from northern to southern latitudes? Working as a rheumatologist in Tennessee, I am unfortunately certain that this entity is not a rare diagnosis in the South.

Before proposing a new clinical care standard for a common health problem, a confirmatory case-control study followed by an evaluation of the effects of vitamin D repletion would be advisable. To quote the authors, “The findings may simply reflect the background prevalence of hypovitaminosis D.”

Kevin J. Myers, MD
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In reply: Dr Myers’ letter questions the value of quantified serum vitamin D levels in patients with musculoskeletal pain of indeterminate origin. He asserts that such pain is, by definition, an amalgam of disparate physical and emotional problems. This is unfortunate. By definition, physical problems are determinable and “emotional problems” are diagnoses of exclusion.

In Table 2 in our article, we summarized findings in 5 of our patients with pain of indeterminate origin. Although these patients had consumed considerable health care resources with minimal benefit, no one had considered and ruled out a known cause of their musculoskeletal pain symptoms, osteomalacia. At best, these 5 patients had vitamin D levels of only 2 ng/mL (the lowest level of detection is 3 ng/mL). Surprisingly, 3 were women of childbearing age.

Dr Myers assumes that residents of Nashville, Tenn (36° north), are not at risk of vitamin D deficiency. However, significant deficiency in young people has been documented at similar latitudes in both the boreal hemisphere (including Beirut, Lebanon [34° north], and Niigata, Japan [38° north]) and the austral hemisphere (including Melbourne [37° south] and Sydney [34° south], Australia,14 and Buenos Aires, Argentina [34° south]). This is true despite the austral hemisphere’s approximately 2° difference in effective latitude (W. B. Grant, PhD, personal communication, February 2004). Even at 33° south (Cape Town, South Africa, 33° south)
Town, South Africa), winter sun has comparatively less than one third the capacity of summer sunlight to promote production of vitamin D. Furthermore, this limited capacity is restricted to precisely the hours that people are urged to avoid the sun.

Although vitamin D deficiency in young people across the United States is significant,1 we cannot afford to screen everyone. However, can we afford $10 to $15 billion each year in direct costs for treatment of osteoporosis and its complications?2 Our study justifies screening patients with persistent, nonspecific musculoskeletal pain because it documented that many patients considered at low risk for vitamin D deficiency were, in fact, severely or even profoundly deficient. Testing does not place the patient at risk—failure to diagnose deficiency may.

Gregory A. Plotnikoff, MD, MTS
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In reply: Dr Myers makes several good points about the incidence of nonspecific musculoskeletal pain as it relates to race, socioeconomic class, and latitude. Unfortunately, what he does not take into account is that vitamin D deficiency is common and widespread in both children and adults of all races throughout the United States.12 In many patients (especially those with lower socioeconomic status) who complain of muscle aches and bone pain, these symptoms are simply dismissed by their doctors, or more urgent concomitant medical problems overshadow these nonspecific complaints, which are discounted or considered associated with the patient’s poor health. Malabanan et al1 reported that an African American woman with excruciating bone pain and muscle aches responded dramatically to vitamin D therapy; the bone pain and muscle discomfort resolved completely, and she had a 25% increase in bone density in just 2 years. Gloth et al2 and Gluerup et al2 reported that bone pain and myopathy are common features of vitamin D deficiency, and Bischoff et al2 reported that muscle weakness is commonly associated with vitamin D deficiency. Thus, substantial data in the literature support the role of vitamin D deficiency in the nonspecific musculoskeletal pain syndrome. Myers may be unaware that the lower limit of the 25-hydroxyvitamin D assay that is used to determine vitamin D status is inadequate. A 25-hydroxyvitamin D level of less than 20 ng/mL should be considered as vitamin D deficiency, not the less than 10 ng/mL level that most commercial laboratories report.2,6 Furthermore, a 25-hydroxyvitamin D level of between 30 and 50 ng/mL is preferred.2,6 I suspect that most of Myers’ patients are vitamin D deficient, which is why he has not appreciated the relationship between vitamin D deficiency and the nonspecific musculoskeletal pain syndrome. I agree that a controlled trial should be conducted to define the role of vitamin D deficiency in nonspecific musculoskeletal pain that is not associated with a rheumatologic disorder. Finally, in my experience, patients who receive 50,000 IU of vitamin D once or twice a month feel better, and when they stop the medication, they often develop muscle weakness and nonspecific aches and discomfort. I encourage Dr Myers to prescribe this regimen for his patients.

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Vitamin D Deficiency as a Contributor to Multiple Forms of Chronic Pain

To the Editor: It was a delight to see another description of the association between vitamin D deficiency and pain in the medical literature. My colleagues and I published an early, if not the first, description of non-osteomalacia-related pain in the Archives of Internal Medicine in 1991 and recently reviewed this
entity in the pain literature. Despite the wide circulation of the Archives, our study was apparently not recognized, even by many experts, as one could surmise by the absence of a reference to this important observation either in the article by Plotnikoff and Quigley or in the accompanying editorial by Holick. Although the authors’ reference to our JAMA article was greatly appreciated, your readers might find our original article on the vitamin D deficiency pain syndrome helpful.

Of note, we prefer the term vitamin D deficiency rather than hypovitaminosis. It has long been recognized that a physiological or biochemical aberration caused by a low vitamin status (or hypovitaminosis) constitutes a vitamin deficiency. Certainly, pain due to physiological mechanisms and other manifestations, eg, secondary hyperparathyroidism, justifies the term vitamin deficiency.

F. Michael Gloth III, MD
William B. Greenough III, MD
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In reply: In a 1991 article, Dr Gloth et al1 raised the question, “Can vitamin D deficiency produce an unusual pain syndrome?” They documented hyperesthesia worsened by light, superficial pressure, or even small increments of movement in 5 patients. This disorder appeared to resolve with vitamin D therapy and recur when vitamin D levels declined.

Our article2 addressed the prevalence of vitamin D deficiency in patients with musculoskeletal pain rather than skin hyperesthesia. Because our study was presented in original article, not literature review, format, we were unable to reference many valuable articles, including a case study documenting impressive resolution of severe generalized bone pain with administration of vitamin D by our article’s editorialist and his colleagues.

Since publication of our article in the Proceedings, numerous substantive articles have appeared in the medical literature that further document the association of severe health consequences with vitamin D deficiency. Readers are encouraged to search under vitamin D deficiency at http://www.ncbi.nlm.nih.gov/PubMed/.

The scientific data now overwhelmingly support Gloth and Greenough’s recommendation that vitamin D deficiency be the term of choice.

Gregory A. Plotnikoff, MD, MTS
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In reply: Gloth and Greenough note that they described non-osteomalacia-related pain in 1991. Indeed, the pain and devastating consequences of vitamin D deficiency have been documented in the scientific literature for more than 100 years.1,3 There is little distinction between the terms vitamin D deficiency and hypovitaminosis D, just as there is little difference between vitamin D intoxication and hypervitaminosis D. I agree that vitamin D deficiency may be better understood by physicians and that this is the preferable term when describing a patient who has a 25-hydroxyvitamin D level of less than 20 ng/ml.2 What is more important is that the term vitamin D deficiency, which is often used in the literature, is very misleading. It is like being pregnant—either you are, or you are not. The same is true for vitamin D deficiency. The associated secondary hyperparathyroidism is relative. As noted by Malabanan et al3 and Chapuy et al,5 secondary hyperparathyroidism may be present even if the serum parathyroid hormone level is within the reference range of the reported assay. The body (ie, parathyroid glands) knows whether a patient is or is not “D-icient.”

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Sun Exposure, Vitamin D Metabolism, and Skin Cancer

To the Editor: The editorial by Holick1 published in the December issue of Mayo Clinic Proceedings misleads readers. Holick writes, “Some dermatologists advise that people of all ages and ethnicities…should always use sun protection when outdoors. This message is not only unfortunate, it is misguided and has serious consequences, ie, the risk of vitamin D deficiency and increased risk of many chronic diseases. There is little evidence that adequate sun exposure will substantially increase the risk of skin cancer; rather, long-term excessive exposure and repeated sunburns are associated with non-melanoma skin cancers.”
Overwhelming evidence links the development of most skin cancers to exposure of skin to ultraviolet radiation contained in sunlight. Holick hints that judicious daily exposures might be safe. However, I believe that every photon hitting the skin could produce a photomutation leading to skin cancer.

Even if Holick’s allegations were true, patients generally cannot gauge the correct amount of “noninjurious” exposure. Indeed, Holick admits that “the amount of time for adequate exposure depends on time of day, season, latitude, skin pigmentation, and the area of skin surface that has no sun protection.” Trying to stay well by exposing skin to just the right amount of sun-provided ultraviolet radiation would likely overexpose at least some skin, sometimes to a point that even Holick would agree causes injury. One cannot see or feel ultraviolet radiation, and the brightness of sunlight offers little clue to the ultraviolet dose received.

Finally, patients with xeroderma pigmentosum scrupulously avoid all sun exposure because their bodies cannot repair sun-damaged DNA, and skin cancers develop if they do not avoid sunlight. In 8 sunlight-protected patients with xeroderma pigmentosum (none of whom had consumed vitamin D supplementation beyond normal dietary intake), mean levels of 25-hydroxyvitamin D, calcium, ionized calcium, and parathyroid hormone were normal. Thus, implying that sun exposure is good is really bad. The risk-benefit ratio clearly favors dietary vitamin D supplementation over sun exposure. According to Holick, “Long-term prevention of vitamin D deficiency can be accomplished by giving 50,000 IU of vitamin D once or twice a month.” Personally, I would take the pill and leave the ultraviolet radiation for the flowers.

Mark V. Dahl, MD
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In reply: There is no question that chronic excessive exposure to sunlight and the number of sunburning incidents in teenagers and young adults increases the risk of nonmelanoma skin cancers. What is alarming is that sunphobic propaganda from the American Academy of Dermatology and affiliated nonprofit, sunscreen industry–sponsored organizations such as the Skin Alliane has resulted in a resurgence of vitamin D deficiency in both children and adults throughout the United States. Recently, Gordon et al reported that 48% of adolescent children in Boston were vitamin D deficient. Sullivan et al reported that, at the end of the summer, 17% of girls aged 9 to 11 years who attended summer camp in Maine were vitamin D deficient. Dr Dahl notes that patients with xeroderma pigmentosum, an extremely rare and complex disease, are not vitamin D deficient and suggests that simple vitamin D supplementation is more than adequate to satisfy vitamin D requirements. He may be unaware that, in more realistic circumstances, some farmers who had a history of nonmelanoma skin cancers and were advised to always apply sunscreen and wear sun protection clothing when outdoors were found to be vitamin D deficient at the end of the summer. Most experts in the field agree that children and adults who do not have adequate sun exposure require 1000 IU of vitamin D daily. It is extremely difficult, if not impossible, to get this amount from dietary sources alone. For example, an 8-oz glass of milk or orange juice fortified with vitamin D contains only 100 IU of vitamin D, a multivitamin contains 400 IU, and a serving of salmon contains about 350 IU. Thus, most Americans receive no more than 20% to 40% of the body’s requirement for vitamin D. This is why sensible sun exposure should be promoted as the most effective way to satisfy the body’s requirement for vitamin D.

Finally, patients with xeroderma pigmentosum are warned that exposure to sunlight is not only unwarranted but also puts both children and adults at risk for many chronic diseases later in life, including type 2 diabetes, multiple sclerosis, cardiovascular disease, and the most common deadly cancers. Humans evolved in sunlight and depended on sunlight for their vitamin D requirement. It is the most reliable source of vitamin D and should not be dismissed. Plants and flowers take advantage of the visible portion of the solar spectrum for photosynthesis, whereas most vertebrates and humans use the ultraviolet B portion of sunlight to satisfy their vitamin D requirement. I hope that Dr Dahl follows his own advice and takes a 50,000-IU vitamin D pill once or twice a month because he needs it if he is a sunphobe.

Michael F. Holick, PhD, MD
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Editor’s note: Dr Holick and Mr Mark Jenkins are authors of The UV Advantage (New York, NY: iBooks; 2003). Boston University Medical Center has received funds from the Indoor Tanning Association in the form of unrestricted gifts to support research in Dr Holick’s laboratory on the biological effects of ultraviolet irradiation on human health and disease. Dr Holick is not a paid consultant for the tanning industry.

Ocular Ethambutol Toxicity

To the Editor: The article by Melamud et al in the November 2003 issue of the Mayo Clinic Proceedings illustrates the importance of ocular toxicity secondary to ethambutol. The case presented shows the potential for long-term, irreversible loss of vision. However, several other points should be made.

The authors listed a standard dosage of ethambutol as 25 mg/kg per day for 60 days for patients who have previously received antituberculosis therapy. The recommendation from the American Thoracic Society and Centers for Disease Control and Prevention is a dosage of 15 to 20 mg/kg per day for adults regardless of previous treatment. This dosage must be adjusted for patients with renal insufficiency. The patient described by Melamud et al had end-stage renal disease and received a dosage of 15 mg/kg per day, whereas the recommended adjustment for patients with end-stage renal disease is 15 mg/kg given 3 times a week after dialysis.

Melamud et al concluded that toxicity may occur despite regular monitoring with close medical and ophthalmologic follow-up. However, their patient apparently did not undergo any color vision testing during therapy with ethambutol. Polak et al reported that major blue-green vision errors occur as an early sign of ethambutol toxicity in patients with normal visual acuity and no visual symptoms.

Finally, Sivakumaran et al reviewed 4 cases of ocular toxicity due to ethambutol. Language difficulties were present in 3 of the 4 patients. In patients with communication impairments, more frequent clinical monitoring may be necessary.

Thomas E. Herchline, MD
Wright State University School of Medicine
Dayton, Ohio


In reply: We appreciate Dr Herchline’s interest in our article and present several points in response.

Dr Herchline notes that the recommended standard dosage of ethambutol is 15 to 20 mg/kg per day for adults, without regard for previous treatment. This recommendation is from the American Thoracic Society. We cited Mosby’s Drug Consult 2002 in our article, which recommends 25 mg/kg per day for 60 days followed by 15 mg/kg per day for patients who have received tuberculosis therapy previously. Harrison’s Principles of Internal Medicine also notes that “the usual daily adult dosage of ethambutol is 25 mg/kg (which may be given in one dose) for the first 2 months, with a subsequent reduction to 15 mg/kg.” Thus, there appear to be several different recommendations in the literature. The point is, however, that the literature contains several cases in which ethambutol toxicity occurred at recommended dosages of the medication.

Our patient had a dedicated home health care nurse and was followed up carefully in the infectious disease clinic. Dr Herchline describes using color vision testing to monitor patients taking ethambutol. He cites an article by Polak et al in which the authors reported using the desaturated Lanthony test to identify blue-yellow color vision changes that were not detected by Farnsworth-Munsell D-15 testing. In their final recommendation, the authors urged examinations every 3 months to monitor for ethambutol toxicity. The Lanthony desaturated color vision tests are highly specialized tests of color discrimination that are not available at most medical centers. For accuracy of diagnosis of color deficiency, specific lighting conditions are required. This is best accomplished in a color vision laboratory, which is clearly impractical for many patients treated with ethambutol. Our patient’s visual symptoms progressed within 2 weeks, which would preclude a timely diagnosis with testing every 3 months as Polak et al recommended. Harrison’s Principles of Internal Medicine advises monitoring red-green (not blue-yellow) color vision monthly with Ishihara plates. In the report by Polak et al, even the more commonly available D-15 test did not detect the subtle blue-yellow defects.

Dr Herchline also cites a study by Sivakumaran et al in which 4 cases of ocular ethambutol toxicity are ascribed to language difficulties. The authors of that study recommended more frequent clinical monitoring. In general, we agree that there may be several barriers to health care. Language, transportation, and financial difficulties are some of the problems that may be encountered. However, our patient was a native English speaker with access to public transportation, and his situation was not different from other patients treated for tuberculosis at the infectious disease clinic. We advocate aggressive education regarding the toxicity of ethambutol in such patients. If language issues are a concern, a translator should be present during any education and testing.
sessions. We are unaware whether language- and culture-associated factors can influence the accuracy of vision loss testing, as may be the case with other forms of cognitive testing. However, this limitation of patient care should also be considered.

Michael S. Lee, MD
Alex Melamud, MD
Cole Eye Institute
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The Hunter-Gatherer Diet

To the Editor: I read with interest the review article by O’Keefe and Cordain1 on cardiovascular disease resulting from a diet and lifestyle “at odds with our Paleolithic genome.” They make several important points, not the least of which was a failure of previous studies to link cardiovascular disease to the intake of meat, cholesterol, or total fat.2

In their article, the authors stated that, although ancient humans consumed meat, this meat was lower in saturated fat than meat from “modern domesticated animals.” It is with this that I take exception. First, when the authors state that humans evolved “from 2.6 million to 10,000 years ago,” they are including many hominids that are clearly not human in the modern sense of the term. This suggests that there could be an evolution in dietary requirements just as there has been evolution in appearance, language, and brain size. It is more accurate to state that all modern humans are related to a group of humans that left Africa as late as 50,000 years ago.3 These ancestors would be recognized by us as humans and could be distinguished from nonhuman hominids such as Neanderthals.

Modern humans spread throughout the planet between 50,000 and 10,000 years ago, and their proficiency as hunters is attested by the mass extinction of many hunted species.4 Zoological evaluation of modern humans (those of us alive today) has concluded beyond doubt that we are predators.5 We have not evolved into anything else. The exact nutritional content of meat eaten by ancient man is unknown to me, but it seems possible that ice age mammals could have had more fat than modern game. The archeological evidence of bone marrow harvesting by ancient man also suggests they preferred osso buco to venison. Modern hunter-gatherers in Greenland consume fatty mammal flesh that is high in ω-3 fatty acids because these mammals consume fish that contain these fatty acids.6 It remains possible that others could consume different mammals and still derive benefit.

We are at a unique point in history when obesity has become the primary nutritional issue in some societies, including our own. Saturated fat from red meat is uniquely suited to induce satiety by both its ability to induce insulin secretion and its ability to induce cosecretion of cholecystokinin, which augments insulin’s anorexic effects.7 When O’Keefe and Cordain shy away from prescribing saturated fat, they may be depriving modern humans of their most effective tool against overindulgence.

James H. Hays, MD
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In reply: We appreciate Dr Hays’ interest in our recent review article,1 but several points he made require further clarification. His assertion that ancestral human (Homo sapiens) diets were dominated by animal foods is correct and is supported by both ethnographic2 and quantitative3 studies of hunter-gatherer diets as well as by isotopic analyses of Upper Paleolithic human fossils.4 However, it is erroneous to conclude that these animal food–based diets would have been high in saturated fatty acids (SFAs). Furthermore, little or no objective data support the assertions that dietary SFA is nonatherogenic under eucaloric conditions or that SFA represents an effective satiating macronutrient.

From stone tool cut marks detected on the fossilized bones of animals that coexisted with humans during the Paleolithic era (approximately 2.6 million to 10,000 years ago), one can infer the species of animals that were consumed.5 Many of the African animals eaten during the Paleolithic period still exist today. These include theildebeest, hippopotamus, and zebra. Similar fossil evidence exists for mammals such as musk oxen and caribou that were hunted by hominids during glacial (ice age) periods in the Paleolithic era. Total body fat analyses of both caribou6 and musk oxen7 show that fat mass varies seasonally in a cyclic, waxing-and-waning manner. Hence, maximal or peak body fat percentages are maintained only for a few months during the course of a year, even for mammals residing at tropical and...
southern latitudes. In most mammals, storage of excess food energy as fat occurs primarily as triacylglycerols in subcutaneous and abdominal fat depots. The dominant (>50% fat energy) fatty acids in the fat storage depots (adipocytes) of wild mammals are SFAs, whereas the dominant fatty acids in muscle and all other organ tissues are polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs). Since subcutaneous and abdominal body fat stores are depleted during most of the year in wild animals, PUFAs and MUFAs constitute the majority of the total carcass fat. Because of the seasonal cyclic depletion of SFAs and enrichment of PUFAs and MUFAs, a year-round dietary intake of high levels of SFA would not have been possible for preagricultural hominids preying on wild mammals.

With the advent of agriculture and the domestication of wild animals, it became possible to attenuate or prevent the seasonal decline in SFAs by provisioning animals with stored fodder. Additionally, domesticated animals can be slaughtered at peak body fat percentages, whereas hunter-gatherers preying on wild animals were at the mercy of the seasons. In the United States, 99% of the beef we consume is produced in feed lots in which a characteristically obese (30% body fat) animal is always slaughtered at its peak fat mass regardless of the season.

By employing known seasonal changes in the whole-body fat mass of caribou, the known fatty acid composition and mass of all edible tissues and organs, and third-order polynomial equations regressing carcass fat mass to carcass fat energy, it is possible to estimate total edible carcass SFA on a month-by-month basis. For a group of 3 caribou (mature bull, mature female, young bull), the yearly mean total edible carcass SFA content represents 11.1% of the total available calories, a value similar to that recommended by the American Heart Association for reducing the risk of cardiovascular disease (10% of total energy).

We do not recommend consuming a high-SFA diet because SFA down-regulates the low-density lipoprotein receptor, thereby elevating total plasma cholesterol and low-density lipoprotein cholesterol concentrations even in normal-weight individuals. Numerous epidemiological studies have shown that elevated plasma cholesterol concentrations increase the risk for coronary heart disease, a necessary caveat to this statement is that dietary SFAs elicit this effect only under chronic hypercaloric or eucaloric conditions. Recent clinical trials of high-SFA diets such as the Atkins diet have proved them to be effective in improving the blood lipid profile on a short-term basis (<1 year); however, these beneficial lipid changes occurred only under hypocaloric conditions.

A final point is warranted. Ancestral hunter-gatherer diets would always have contained less carbohydrate and more protein in comparison to contemporary Western diets. This macronutrient composition (elevated protein at the expense of carbohydrate) was recently shown to be effective in both promoting weight loss because of the greater satiety and thermic effect of protein compared to either carbohydrate or fat. Consequently, it is elevated protein that promotes satiety, not elevated SFA.

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Successful Treatment of Chronic Meningitis Caused by Scedosporium apiospermum With Oral Voriconazole

To the Editor: Scedosporium apiospermum (teleomorph Pseudallescheria boydii) is a ubiquitous saprophytic fungus found worldwide. Although it most commonly causes cutaneous infection, reports of invasive and fatal disease in immunocompromised patients, those with impaired anatomical barriers, and near-drowning victims are increasing.1 Central nervous system (CNS) scedosporiosis remains relatively rare, is notoriously difficult to treat, and is fatal in 76% of cases.2,3 A recent review of the 39 published cases of CNS scedosporiosis revealed that brain abscesses and meningitis account for the majority of such infections.2 We describe a woman with no clearly predisposing condition who developed chronic S apiospermum meningitis and was treated with an entirely oral course of voriconazole.

Report of a Case.—A 59-year-old woman with type 2 diabetes mellitus, hypertension, hyperlipidemia, and a distant history of idiopathic thrombocytopenic purpura presented to our institution with headache, fatigue, and subjective neurologic complaints (right hand weakness and clumsiness). Her idiopathic thrombocytopenic purpura had resolved after splenectomy, and her diabetes was well controlled. She took no immunosuppressive medications and had no history of sinus surgery, near drowning, or trauma. Neurologic examination findings were normal. Lumbar puncture yielded cerebrospinal fluid (CSF) with mild lymphocytic pleocytosis. Magnetic resonance imaging of the head revealed only evidence of maxillary sinus disease. The headache and fatigue persisted, but fever never developed. The patient underwent lumbar puncture 6 times over a 5-month period (Table 1). Cerebrospinal fluid serology, cytology, stains, and cultures were unremarkable until S apiospermum was recovered from a CSF specimen obtained on her sixth lumbar puncture. Repeated magnetic resonance imaging of the head yielded normal findings.

We initiated treatment with itraconazole oral solution, 200 mg 3 times daily. Lack of improvement at 1 month prompted a change to voriconazole (obtained for compassionate use from Pfizer, Inc, Groton, Conn; we monitored its safety with appropriate laboratory investigations). Given its estimated 96% oral bioavailability and the patient’s clinical stability, therapy was initiated at 400 mg orally twice daily.

The patient’s headache resolved within several weeks, and repeated lumbar puncture 4 months later revealed sterile CSF with normal indices. Voriconazole levels in the plasma and CSF were 6.14 µg/mL and 2.43 µg/mL, respectively. The minimum inhibitory concentration of voriconazole for S apiospermum ranges from 0.06 to 1.0 µg/mL.4 The dose was decreased to 200 mg orally twice daily, and therapy was continued for an additional 8 months. More than 2 years after cessation of therapy, the patient remains symptom free.

Discussion.—Central nervous system scedosporiosis is usually fatal, and treatment options have historically been limited due to the lack of efficacious agents that adequately penetrate the CSF. S apiospermum is typically resistant to amphotericin B and fluconazole. Itraconazole is variably active in vitro against S apiospermum and is favored by many experts for treating invasive scedosporiosis, but CSF concentrations are less than 1% of serum concentrations.2 Voriconazole concentrations in the CSF are 50% of serum concentrations, and reports of successful outcomes in patients with CNS scedosporiosis treated with this agent are increasing.2,4,5 Currently, voriconazole seems to be the antifungal agent of choice for CNS scedosporiosis.

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<th>Table 1. Cerebrospinal Fluid Findings in 6 Specimens Obtained by Lumbar Puncture Over 5 Months*</th>
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</thead>
<tbody>
<tr>
<td>Reference range</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
</tr>
<tr>
<td>WBC (cells/mL)</td>
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<tr>
<td>Lymphocytes (%)</td>
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</tbody>
</table>

*WBC = white blood cells.


References

Two Causes of Hypercalcemia: Learning by the Holmesian Method

To the Editor: Because medical reasoning has a detective-like quality,1 the Sherlock Holmes method based on detailed history and careful examination2 can help physicians solve problems and avoid errors. We agree with Holmes’ statement: “Deceit is an impossibility in the case of one trained to observation and analysis.”2 This positive attitude in caring for patients requires attention and eliminates boredom, an important source of medical errors.3 The Holmesian method teaches us to not “close” a case before all the data fit properly because clinicians have a tendency “to look for evidence that supports an early working hypothesis and to ignore data that contradict it.” The following case report demonstrates the Holmesian approach to patient care.

Report of a Case.—A 77-year-old woman was admitted to the hospital because of diffuse skeletal pain and pathologic bone fractures. The patient had hypertension that was well controlled with diet and valsartan. She had never taken thiazide diuretics or lithium. One month before admission, she experienced nonspecific diffuse chest pain that did not respond to nonsteroidal anti-inflammatory drugs; her general health deteriorated.

On admission, the patient had muscle weakness and somnolence. Laboratory studies disclosed the following values: hemoglobin, 10.5 g/dL; mean corpuscular volume, 102 fL; erythrocyte sedimentation rate, 85 mm/h; creatinine, 0.9 mg/dL; hemoglobin, 10.5 g/dL; mean corpuscular volume, 102 fL; blood urea nitrogen, 20 mg/dL; calcium, 12.9 mg/dL; phosphorus, 3 mg/dL; and alkaline phosphatase, 323 U/L with normal transaminase levels. Serum ferritin, vitamin B₁₂, folic acid, and lactate dehydrogenase levels were normal. Serum electrophoresis showed hypogammaglobulinemia (IgG, 344 mg/dL; IgA, 23 mg/dL; and IgM, 13 mg/dL). A bone scan revealed chondrocalcinosis of the knees and wrists and old fractures of the ribs and pelvis. Immunoradiometric assay showed an elevated intact parathyroid hormone value of 154.87 pg/mL (reference range, 10-65 pg/mL). Parathyroid hormone–related peptide, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D₃, and thyrotropin levels were normal. Serum electrophoresis showed hypoalbuminemia (4.5 g/dL). Immunofixation studies yielded negative results. A bone marrow aspirate contained 30% dismorphic plasmacytic infiltrate, and immunohistochemical study of a bone marrow biopsy specimen was positive for κ light chains in infiltrating plasma cells. Stage IA nonsecretory multiple myeloma (MM) was diagnosed. The patient refused surgery and chemotherapy. Although the hypercalcemia was well controlled with oral bisphosphonates, the MM progressed, and the patient died a year later.

The coexistence of PHP with monoclonal gammopathy and MM has been described; however, a causal relationship has not been established.5 Usually, MM is diagnosed first, and PHP is suspected only when hypercalcemia persists despite treatment.6 Nonsecretory MM accounts for less than 3% of all cases of MM.7 Without typical bone lesions, nonsecretory MM poses a clinical challenge, and an important diagnostic delay can occur. To our knowledge, this is the first reported case of concomitant PHP and nonsecretory MM.

During our diagnostic work-up, we remembered Holmes’ advice: “Do you really think that your solution must be correct?...Does your explanation cover every point?” Diagnostic hypotheses must be confirmed by clinical findings to “avoid missing the little points or fine details which are in the basis of the deduction.” In our case, PHP explained most, but not all, of the patient’s abnormalities. Overt PHP masked underlying MM, the most serious condition in our patient, which eventually caused her death.

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A 1921 Letter From Vermont With a Tribute to the Charles H. Mayo Family

To the Editor: In 1921, Mrs P. of South Strafford, Vt, wrote a long, touching letter to a friend, Elizabeth Katherine Daub, who lived in Wabasso, Minn. The letter, dated January 23, 1921, told how this Vermont family brought an ailing husband and father to the Mayo Clinic on December 26, 1919, for what was evidently a second visit. Their son was given a job on Dr Charles H. Mayo’s farm, and the family lived at the farm for several months. Mrs Charles H. Mayo visited the patient in the hospital before he was discharged, and the consulting physician went to the train station to say farewell to him when the family left town on April 27, 1920. Clearly, the compassionate care given to the entire family went well beyond any medical advice that would have been expected.

The Vermont letter was found among the effects of Elizabeth Daub Brey, who died in 1989. She and Mrs P. were evidently friends of long standing, and it is believed that they had graduated together from the Rochester State Hospital School of Nursing in 1914. Excerpts from the letter (Figure 1) are of interest because they help to explain why people have come from far distances for many years to obtain help from the Mayo Clinic. The letter, which specifically highlights the caring attitude and generosity of an unidentified Mayo Clinic physician and the Charles H. Mayo family, is important because it exemplifies the unique medical culture of the Mayo Clinic community as it existed in the past and continues today.

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Elizabeth Daub Brey was Dr T. Haddy’s mother and Dr R. Haddy’s grandmother. Her letter was preserved by another daughter, Ann C. Brey.

Figure 1. Excerpts from a letter from Mrs P. to Elizabeth Daub Brey. “My youngest son went with us that time and got work on Dr. Charley Mayo’s farm. We stayed in town until Feb. 14th [1920] when we went out to the farm. Stayed there until Apr. 27th when the Dr. told us they could do no more and we best come home before he got too weak…. His Dr. out there was all that he could be. He told Delwin that his father was the best patient he ever had. Said he never saw a patient with such a cancer in such a place that had the courage and grit he had. The Dr. went to the train to bid him good bye. We considered that a good deal for such a busy man as he was. The day before we came home Mrs. Dr. Charley [Mayo] came in to see us. She was so nice you would think she was one of us.”

CORRECTION

Incorrect information: In the article by Younge et al entitled “Initiation of Glucocorticoid Therapy: Before or After Temporal Biopsy?” published in the April 2004 issue of the Mayo Clinic Proceedings (Mayo Clin Proc. 2004; 79:483-491), incorrect numbers were printed in the tenth and eleventh lines of the “Final Diagnoses” section on page 488 and an incorrect expansion was printed in the footnote to Table 5 on page 488. The sentence should read, “These results provide a value for diagnostic accuracy or efficiency of temporal artery biopsy of 97% (373 + 703/1113).” The footnote to Table 5 should read, “ESR = erythrocyte sedimentation rate.”