

## The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know

A. Catharine Ross, JoAnn E. Manson, Steven A. Abrams, John F. Aloia, Patsy M. Brannon, Steven K. Clinton, Ramon A. Durazo-Arvizu, J. Christopher Gallagher, Richard L. Gallo, Glenville Jones, Christopher S. Kovacs, Susan T. Mayne, Clifford J. Rosen, and Sue A. Shapses

Department of Nutritional Sciences (A.C.R.), Pennsylvania State University, University Park, Pennsylvania 16802; Department of Medicine (J.E.M.), Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02215; Department of Pediatrics (S.A.A.), Baylor College of Medicine, Houston, Texas 77030; Department of Medicine (J.F.A.), State University of New York at Stony Brook, Stony Brook, New York 11794; Winthrop University Hospital (J.F.A.), Mineola, New York 11501; Division of Nutritional Sciences (P.M.B.), Cornell University, Ithaca, New York 14853; Division of Hematology and Oncology (S.K.C.), The Ohio State University, Columbus, Ohio 43210; Department of Epidemiology and Preventive Medicine (R.A.D.-A.), Loyola University Stritch School of Medicine, Maywood, Illinois 60153; Bone Metabolism Unit (J.C.G.), Creighton University Medical Center, Omaha, Nebraska 68131; Department of Medicine (R.L.G.), University of California, San Diego, La Jolla, California 92093; Department of Biochemistry (G.J.), Queen's University, Kingston, Ontario, Canada K7L 3N6; Departments of Medicine and Endocrinology (C.S.K.), Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1C 5S7; Department of Epidemiology and Public Health (S.T.M.), Yale School of Public Health, New Haven, Connecticut 06520; Center for Clinical and Translational Medicine (C.J.R.), Maine Medical Center Research Institute, Scarborough, Maine 04074; and Department of Nutritional Sciences (S.A.S.), Rutgers University, New Brunswick, New Jersey 08901

This article summarizes the new 2011 report on dietary requirements for calcium and vitamin D from the Institute of Medicine (IOM). An IOM Committee charged with determining the population needs for these nutrients in North America conducted a comprehensive review of the evidence for both skeletal and extraskeletal outcomes. The Committee concluded that available scientific evidence supports a key role of calcium and vitamin D in skeletal health, consistent with a cause-and-effect relationship and providing a sound basis for determination of intake requirements. For extraskeletal outcomes, including cancer, cardiovascular disease, diabetes, and autoimmune disorders, the evidence was inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements. Randomized clinical trial evidence for extraskeletal outcomes was limited and generally uninformative. Based on bone health, Recommended Dietary Allowances (RDAs; covering requirements of  $\geq 97.5\%$  of the population) for calcium range from 700 to 1300 mg/d for life-stage groups at least 1 yr of age. For vitamin D, RDAs of 600 IU/d for ages 1–70 yr and 800 IU/d for ages 71 yr and older, corresponding to a serum 25-hydroxyvitamin D level of at least 20 ng/ml (50 nmol/liter), meet the requirements of at least 97.5% of the population. RDAs for vitamin D were derived based on conditions of minimal sun exposure due to wide variability in vitamin D synthesis from ultraviolet light and the risks of skin cancer. Higher values were not consistently associated with greater benefit, and for some outcomes U-shaped associations were observed, with risks at both low and high levels. The Committee concluded that the prevalence of vitamin D inadequacy in North America has been overestimated. Urgent research and clinical priorities were identified, including reassessment of laboratory ranges for 25-hydroxyvitamin D, to avoid problems of both undertreatment and overtreatment. (*J Clin Endocrinol Metab* 96: 0000–0000, 2011)

A new public health report on dietary intake requirements for calcium and vitamin D from the Institute of Medicine (IOM) (1), released on November 30, 2010, updates the IOM report of 1997 (2). The three central questions addressed by the report, in light of the growing body of research on these nutrients over the past 10–15 yr, are: 1) which health outcomes are influenced by vitamin D and/or calcium intake?; 2) how much calcium and vitamin D are needed to achieve desirable health outcomes?; and 3) how much is too much? This article, authored by the IOM Committee, describes the Committee's process for meeting this charge, reviews the evidence base for both skeletal and extraskeletal outcomes examined by the Committee, summarizes the new Dietary Reference Intakes (DRIs) for these nutrients (Table 1), highlights challenges and uncertainties in the process, and summarizes future research priorities. Although this article provides a readily accessible overview of the Committee's work, we encourage readers to review the full report (1) at [www.iom.edu/vitamind](http://www.iom.edu/vitamind) for a fuller understanding of the process and the pertinent evidence base.

## The IOM Committee and Its Charge

The IOM, at the request of agencies of the U.S. and Canadian governments, assembled a committee to update the DRIs for calcium and vitamin D based upon a rigorous and

comprehensive review of the scientific data. The IOM Committee included 14 scientists with a broad range of expertise, assisted by experienced IOM staff members. The DRI process involves identification of health outcomes, or “indicators,” that are consistently and causally linked to the nutrient of interest, determination of the Estimated Average Requirement (EAR; corresponding to the median intake needs of the population), and calculation of the level of intake that would “cover” (meet) the requirements of at least 97.5% of the population [defined as the Recommended Dietary Allowance (RDA), corresponding to 2 SD above the median needs]. The DRI process also specifies the tolerable upper intake level (UL; the highest daily intake of the nutrient that is likely to pose no risk). When the evidence base is insufficient for development of the EAR/RDA, an adequate intake (AI) level may be estimated instead. Importantly, the DRIs are developed for “normal healthy persons” in the North American population (not intended for individuals with specific disease states) and are provided separately for several age and gender life-stage groups (Table 1). Other charges for the Committee were to assess the dietary intakes of calcium and vitamin D in the U.S. and Canadian populations, as well as to identify research needs. The IOM Committee further specified that, due to the unique feature of cutaneous synthesis of vitamin D and the variation in synthesis due to seasonality of solar exposure, skin pigmentation,

**TABLE 1.** Calcium and vitamin D dietary reference intakes by life stage

Life-stage group (age and gender)	Calcium		Vitamin D		
	RDA (mg/d) (intake that covers needs of ≥97.5% of population)	UL (mg/d) <sup>a</sup>	RDA (IU/d) (intake that covers needs of ≥97.5% of population)	Serum 25OHD level (ng/ml) (corresponding to the RDA) <sup>b</sup>	UL (IU/d) <sup>a</sup>
1–3 yr (M+F)	700	2500	600	20	2500
4–8 yr (M+F)	1000	2500	600	20	3000
9–13 yr (M+F)	1300	3000	600	20	4000
14–18 yr (M+F)	1300	3000	600	20	4000
19–30 yr (M+F)	1000	2500	600	20	4000
31–50 yr (M+F)	1000	2500	600	20	4000
51–70 yr (M)	1000	2000	600	20	4000
51–70 yr (F)	1200	2000	600	20	4000
71+ yr (M+F)	1200	2000	800	20	4000
Pregnant or lactating (F)					
14–18 yr	1300	3000	600	20	4000
19–50 yr	1000	2500	600	20	4000
Infants					
0–6 months (M+F)	200 <sup>c</sup>	1000	400 <sup>c</sup>	20	1000
6–12 months (M+F)	260 <sup>c</sup>	1500	400 <sup>c</sup>	20	1500

M, Male; F, female. EARs for calcium were 500 mg/d for ages 1–3 (M+F); 800 mg/d for ages 4–8 and 19–50 (M+F), and ages 51–70 (M); 1000 mg/d for ages 51–70 (F) and 71+ (M+F); and 1100 mg/d for ages 9–18 (M+F). EAR for vitamin D was 400 IU/d for all life-stage groups.

<sup>a</sup> UL indicates level above which there is risk of adverse events. The UL is not intended as a target intake (no consistent evidence of greater benefit at intake levels above the RDA).

<sup>b</sup> Measures of serum 25OHD levels corresponding to the RDA and covering the requirements of at least 97.5% of the population.

<sup>c</sup> Reflects AI reference value rather than RDA. RDAs have not been established for infants.

individual genetic factors, sunscreen use, latitude, outdoor activity, and other factors, as well as concerns about sun exposure and skin cancer, the DRIs for vitamin D would be based on an assumption of minimal or no sun exposure.

## The Process: Health Outcomes Considered and Key Challenges

The IOM Committee's work extended from March 2009 to November 2010, including eight in-person meetings in Washington, D.C., an open public workshop, two open sessions to receive input from other scientists, and the maintenance of a public web site for stakeholder input. The Committee conducted an extensive and comprehensive review of the existing evidence on calcium and vitamin D in relation to diverse health outcomes. Two key systematic reviews used by the Committee included reports conducted by the Agency for Healthcare Research and Quality (AHRQ) in 2007 (3) and 2009 (4), providing evidence-based reviews of the research on calcium and vitamin D in relation to both skeletal and extraskeletal chronic disease outcomes. The Committee conducted its own literature review in addition to consideration of the AHRQ reports.

The Committee, using a risk assessment framework, considered a wide range of chronic disease and other indicators to assess nutrient adequacy for calcium and vitamin D. Indicators that were considered and reviewed in detail in the report included: bone and skeletal health (including bone mineral content and density, fracture risk, and rickets/osteomalacia), calcium absorption and balance, measures such as serum 25-hydroxyvitamin D (25OHD) and PTH, cancer and site-specific neoplasms, cardiovascular disease, hypertension, diabetes, metabolic syndrome, falls and physical performance, autoimmune disorders, infectious diseases, neuropsychological functioning (including autism, cognition, and depression), and disorders of pregnancy.

After careful consideration of the evidence, the Committee concluded that bone health was the only outcome that satisfied criteria for use as an "indicator" whereby causality was established and the available evidence on dose-response was sufficient to support its use for DRI development. In addition, serum 25OHD levels were considered to be the most useful marker of vitamin D exposure, incorporating endogenous synthesis from solar exposure, dietary intake from foods, fortified products, and/or supplements, and other factors. For cancer, cardiovascular disease, diabetes, falls, physical performance, autoimmune disorders, and other extraskeletal chronic disease outcomes, the evidence was deemed to be inconsistent, inconclusive as to causality, and insufficient to

serve as a basis for DRI development. Importantly, randomized trial evidence was sparse, and few clinical trials of calcium and/or vitamin D had been done with these extraskeletal outcomes as the primary prespecified outcomes. The AHRQ systematic review of 2009 (4) had also concluded that the evidence for an association between these nutrients and extraskeletal outcomes was inconsistent and inconclusive.

Key challenges included the strong interrelationship between calcium and vitamin D and the difficulty separating their effects in many studies, the small number of relevant randomized clinical trials allowing for assessment of dose-response relationships, the complexity that vitamin D is obtained not only from diet but also synthesized endogenously, and the potential for confounding in observational studies. Although measures of 25OHD were considered to be a useful marker of exposure, the Committee was cognizant of its limitations as a biomarker of effect. Correlation does not prove causation in observational studies, underscoring the need for caution in interpretation of study findings. Specific factors relevant to vitamin D are sources of potential confounding, such as obesity (due to sequestration in adipose tissue), physical activity (correlated with time outdoors and solar exposure), race/skin pigmentation, and nutritional status including supplementation practices. Reverse causation bias is also a threat to study validity if poor health curtails outdoor activities and sunlight exposure or adversely affects diet. These potential biases must be carefully considered in the interpretation of observational studies. In this regard, it should be noted that many micronutrient interventions that seemed promising in observational studies (*e.g.*  $\beta$ -carotene, vitamins C and E, folic acid, and selenium) did not withstand rigorous testing in clinical trials, and many even suggested hazards with high levels of supplementation (5, 6).

## Bone Health: Dietary Reference Intakes and Updates since 1997

The DRIs shown in Table 1 are based on dietary requirements using bone health as an indicator. DRIs for each nutrient were predicated on intakes meeting requirements for the other nutrient. For both calcium and vitamin D, available evidence allowed for estimation of EARs and RDAs for all life-stage groups except infants (for whom AIs are provided). At the time of the 1997 report on calcium and vitamin D, evidence was insufficient for estimation of EARs and RDAs; thus, AIs were estimated for all life-stage groups. For calcium, the 2011 DRIs are based largely on the calcium content of human breast milk for infants, calcium balance studies for ages 1–50 yr, and ob-

servational and clinical trial evidence after age 50. For vitamin D, the 2011 DRIs are based primarily on the integration of bone health outcomes with evidence concerning 25OHD levels, which suggest that levels of 16 ng/ml (40 nmol/liter) meet the needs of approximately half the population (median population requirement, or EAR), and levels of at least 20 ng/ml (50 nmol/liter) meet the needs of at least 97.5% of the population (akin to the RDA). Intakes of vitamin D required to achieve these 25OHD concentrations are shown in Table 1, based on a simulation of available data across ages under conditions of minimal sun exposure. The AI in infancy is estimated to be 400 IU/d. After age 1, the RDA is estimated to be 600 IU/d for all life-stage groups except men and women aged 71 and older (for whom the RDA is 800 IU/d). The Committee did not find compelling evidence that 25OHD levels or dietary intakes above these levels were associated with greater benefit for bone health or other outcomes. The assumption of minimal or no sun exposure for estimation of these intake levels provided further safety for individuals with lower endogenous synthesis of vitamin D. The specific studies contributing to these estimates are reviewed in detail in the full report (1).

The 2011 DRIs are based on much more information and higher-quality studies than were available when the reference values for these nutrients were first set in 1997, allowing for the estimation of EARs and RDAs rather than AIs. Because the old and new DRIs reflect different calculations, the figures are not directly comparable. In 1997, the AIs for vitamin D were 200 IU/d through age 50, 400 IU/d for ages 51–70, and 600 IU/d for ages 71 and older. The 2011 DRIs for vitamin D specify RDAs, with levels of 400 IU/d for infants, 600 IU/d for children and adults through age 70, and 800 IU/d for ages 71 and older. However, the 2011 DRIs for vitamin D are nonetheless lower than those proposed by some in the current literature based on higher 25OHD levels that the Committee did not find justified by the evidence.

### **Cancer, Cardiovascular Disease, Diabetes, Infections, Autoimmune Disorders, and Other Extraskelatal Outcomes**

The IOM Committee concluded that the evidence that vitamin D or calcium reduced risk of nonskeletal chronic disease outcomes was inconsistent, inconclusive, and did not meet criteria for establishing cause-and-effect relationships. Randomized trial evidence was sparse, and few trials assessed these outcomes as primary prespecified endpoints. Moreover, emerging evidence suggested a curvilinear or U-shaped curve for several outcomes related to vitamin D, including cardiovascular disease, vascular cal-

cification, falls, frailty, pancreatic cancer, and all-cause mortality (7–11), with the lowest risk at moderate levels and increased risk at both low and high levels of 25OHD. These studies are reviewed in detail in the report (1). Although future research may elucidate clear benefits and possibly even different requirement levels for vitamin D in relation to these nonskeletal outcomes, existing data cannot support such conclusions.

### **Tolerable Upper Intake Levels**

The indicators considered in the determination of ULs included hypercalcemia, hypercalciuria, vascular and soft tissue calcification, nephrolithiasis, and, for vitamin D, emerging evidence of a U-shaped relationship for all-cause mortality, cardiovascular disease, selected cancers, falls, and fractures. The 1997 ULs for calcium were 2500 mg/d for all ages above 1 yr, whereas the ULs for calcium now range from 1000–3000 mg/d, depending on life-stage group (Table 1). For vitamin D, the ULs are now 4000 IU/d for ages 9 and older but are lower for infants and young children (Table 1). The 1997 ULs for vitamin D were 2000 IU/d for most age groups. The starting point for the current UL for vitamin D was 10,000 IU/d, because lower intakes have not been linked to hypercalcemia or acute toxicity. However, given that toxicity is not the appropriate basis for a UL that is intended to reflect long-term chronic intake and to be used for public health purposes, this value was corrected for uncertainty based on chronic disease outcomes and all-cause mortality, as well as emerging concerns about risks at serum 25OHD levels above 50 ng/ml (125 nmol/liter). Thus, the Committee followed an approach to maximize public health protection. The UL is not intended as a target intake; rather, the risk for harm begins to increase once intakes surpass this level.

### **Serum 25OHD Levels and Screening**

Guidelines regarding the use of serum markers of vitamin D status for medical management of individual patients and for screening were beyond the scope of the Committee's charge, and evidence-based consensus guidelines are not available. However, these issues should be addressed by appropriate federal agencies and professional organizations in light of the findings in this report. As noted above, the Committee recognized that serum 25OHD is a useful integrated marker of vitamin D exposure, incorporating endogenous synthesis from solar exposure, dietary intake from foods, fortified products, and/or supplements, and other factors. However, the Committee also recognized that observational studies of correlations between



25OHD and clinical outcomes are subject to confounding and do not prove causation. Concerns about inaccurate or imprecise serum 25OHD measurements are being overcome by methodological advances, frequent quality assessments, and accurate calibration tools. In contrast, serum 1,25-dihydroxyvitamin D represents a more complex endocrine parameter, regulated by calcium and PTH status and affected by kidney function. After a careful review of available literature, the Committee concluded that serum 25OHD levels of 16 ng/ml (40 nmol/liter) cover the requirements of approximately half the population, and levels of 20 ng/ml (50 nmol/liter) cover the requirements of at least 97.5% of the population. These levels will be useful to clinicians as they consider management of patients under their care. For upper levels of serum 25OHD, sparse data are available, particularly regarding long-term effects of chronically high concentrations, and a margin of safety for public health recommendations is prudent. Thus, serum 25OHD levels above 50 ng/ml (125 nmol/liter) should raise concerns among clinicians about potential adverse effects.

### Dietary Intake Assessments

Major food sources of calcium include dairy products, selected low-oxalate vegetables, legumes, nuts, and fortified foods; for vitamin D, primary sources are fortified dairy products, fortified foods, and fatty fish. Based on national government surveys in the United States and Canada, it appears that most groups have adequate intake of calcium (as defined by intakes above the EAR), with the exception of girls aged 9–18 who have high requirements. The data underscore the need to increase calcium intake among girls in mid-to-late childhood and adolescence; in contrast, among postmenopausal women, high calcium intake from supplements may be concerning. Regarding vitamin D, average intake from foods tends to be less than 400 IU/d, but mean 25OHD levels have been above 20 ng/ml (50 nmol/liter) in representative samples. Thus, based on these data and a level of 20 ng/ml (50 nmol/liter) identified as meeting the needs of at least 97.5% of the population across all life-stage groups, it appears that the majority of the North American population currently is meeting its needs for vitamin D. Nonetheless, subgroups of individuals, particularly those with poor nutrition, those living at northerly latitudes or in institutions, or those with dark skin pigmentation may be at increased risk of not meeting their needs, especially if their 25OHD levels are below 16 ng/ml (40 nmol/liter), the level identified as the average requirement as discussed above.

### Uncertainties and Future Research Needs

The Committee identified a large number of uncertainties surrounding the DRI values, as well as extensive research needs. A particular priority is rigorous, large-scale, randomized clinical trials to test the effects of vitamin D on skeletal and nonskeletal outcomes, as well as to identify threshold effects and possible adverse effects where present. Elucidating the biology of the diverse effects of vitamin D, as well as effects of sun exposure, adiposity, body composition, race/ethnicity, and genetic factors on these associations, is also of great importance.

### Conclusions

The available scientific evidence supports a key role for calcium and vitamin D in skeletal health, providing a sound basis for DRIs. The evidence, however, is not yet compelling that either nutrient confers benefits for, or is causally related to, extraskeletal health outcomes. Moreover, existing evidence suggests that nearly all individuals meet their needs at intake levels (RDAs) provided in this report and, for vitamin D, at 25OHD levels of at least 20 ng/ml (50 nmol/liter) even under conditions of minimal sun exposure. Furthermore, higher levels have not been shown consistently to confer greater benefits, challenging the concept that “more is better.” The Committee finds that the prevalence of vitamin D inadequacy in the North American population has been overestimated by some groups due to the use of inappropriate cut-points that greatly exceed the levels identified in this report. Serum concentrations of 25OHD above 30 ng/ml (75 nmol/liter) are not consistently associated with increased benefit, and risks have been identified for some outcomes at 25OHD levels above 50 ng/ml (125 nmol/liter). Additional research, including large-scale, randomized clinical trials, is needed. In the meantime, however, we believe that there is an urgent clinical and public health need for consensus cut-points for serum 25OHD inadequacy to avoid problems of both undertreatment and overtreatment.

### Acknowledgments

The committee wishes to express its appreciation for outstanding support from IOM staff: Christine L. Taylor, Study Director; Ann L. Yaktine, Senior Program Officer; Heather B. Del Valle, Associate Program Officer; and Heather Breiner, Program Associate.

Dr. A. Catharine Ross is the Chair of the Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dr. JoAnn E. Manson contributed greatly to the

development of this article, which serves as a summation for clinicians of the Committee's report.

Address all correspondence and requests for reprints to: Dr. Catharine Ross, Pennsylvania State University, 110 Chandlee Laboratory, University Park, Pennsylvania 16802. E-mail: [acr6@psu.edu](mailto:acr6@psu.edu).

Disclosure Summary: None of the authors have conflicts of interest or other disclosures relevant to this publication.

## References

1. Institute of Medicine 2011 Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press
2. Institute of Medicine 1997 Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: The National Academies Press
3. Cranney A, Horsley T, O'Donnell S, Weiler H, Puil L, Ooi D, Atkinson S, Ward L, Moher D, Hanley D, Fang M, Yazdi F, Garritty C, Sampson M, Barrowman N, Tsertsvadze A, Mamaladze V 2007 Effectiveness and safety of vitamin D in relation to bone health. Evidence Report/Technology Assessment no. 158 (prepared by the University of Ottawa Evidence-based Practice Center. AHRQ Publication no. 07-E013. Rockville, MD: Agency for Healthcare Research and Quality
4. Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, Lichtenstein A, Patel K, Raman G, Tatsioni A, Terasawa T, Trikalinos TA 2009 Vitamin D and calcium: a systematic review of health outcomes. Evidence Report no. 183 (prepared by the Tufts Evidence-based Practice Center). AHRQ Publication no. 09-E015. Rockville, MD: Agency for Healthcare Research and Quality
5. Byers T 2010 Anticancer vitamins du jour— the ABCED's so far. *Am J Epidemiol* 172:1–3
6. Clarke R, Halsey J, Lewington S, Lonn E, Armitage J, Manson JE, Bønaa KH, Spence JD, Nygård O, Jamison R, Gaziano JM, Guarino P, Bennett D, Mir F, Peto R, Collins R 2010 Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: meta-analysis of 8 randomized trials involving 37,485 individuals. *Arch Intern Med* 170:1622–1631
7. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS 2008 Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 117:503–511
8. Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, Qi D, Patel AV, Helzlsouer KJ, Weinstein SJ, McCullough ML, Purdue MP, Shu XO, Snyder K, Virtamo J, Wilkins LR, Yu K, Zeleniuch-Jacquotte A, Zheng W, Albanes D, Cai Q, Harvey C, Hayes R, Clipp S, Horst RL, Irish L, Koenig K, Le Marchand L, Kolonel LN 2010 Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 172:81–93
9. Melamed ML, Michos ED, Post W, Astor B 2008 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 168:1629–1637
10. Toner CD, Davis CD, Milner JA 2010 The vitamin D and cancer conundrum: aiming at a moving target. *J Am Diet Assoc* 110:1492–1500
11. Visser M, Deeg DJ, Puts MT, Seidell JC, Lips P 2006 Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. *Am J Clin Nutr* 84:616–622; quiz 671–672