#### CHAPTER

# **10**

# **Nutrients Involved in Antioxidant Function and Vision**

# **Chapter Summary**

Antioxidants are compounds that protect cells and substances in the body from the damage caused by free radicals formed during metabolism, immune responses, and exposure to environmental toxins. Antioxidants include vitamins, minerals, and other compounds that stabilize free radicals independently or function within complex antioxidant enzyme systems. Vitamin E is a fat-soluble vitamin and protects LDLs, vitamin A, the lungs, and cell membranes from oxidative damage. Suboptimal intake of vitamin E may result in increased risk of cardiovascular disease. Vitamin C is a water-soluble vitamin that primarily acts as an antioxidant in the extracellular fluid. Vitamin C also prevents scurvy and assists in the synthesis of collagen, hormones, neurotransmitters, and DNA.

Toxicity with vitamin C or E is rare. Beta-carotene is a carotenoid and a precursor of vitamin A. It protects cell membranes and LDL from oxidative damage, enhances immune function, and protects vision. Vitamin A is critical for maintaining our vision. It is also necessary for cell differentiation, reproduction, and growth. Toxicity symptoms may occur at levels of only three to four times the RDA. Deficiency symptoms lead to theory on vitamin A's role as an antioxidant, but research is ongoing. Selenium is a trace mineral that functions as part of the glutathione peroxidase enzyme system. It assists with immune function and the production of thyroid hormone. Because it is found in a wide variety of foods, selenium deficiency is rare in the United States, but toxicity symptoms do occur with excessive supplementation. Copper, iron, zinc, and manganese play a peripheral role in antioxidant function by acting as cofactors in antioxidant enzyme systems.

Cancer is a group of diseases in which cell growth is out of control. Eating foods high in antioxidants is associated with lower rates of cancer. Antioxidants may help reduce the risk for heart disease by preventing oxidative damage to LDL, reducing inflammation, and reducing the formation of blood clots. There are components in fruits and vegetables other than antioxidant nutrients that have shown a protective role against these diseases.

Nutrition Myth or Fact addresses the question: Dietary Supplements: Necessity or Waste?

# **Learning Objectives**

After studying this chapter, the student should be able to:

- 1. Explain how free radicals form, why they are a health concern, and how antioxidants oppose them (pp. 380–383).
- **2.** Identify the most potent form of vitamin E in foods, and describe how it functions as an antioxidant (pp. 383-384).
- **3.** Discuss at least three critical functions of vitamin C and identify good food sources (pp. 387-390).
- **4.** Discuss the roles of five trace minerals in opposing oxidation (pp. 391–394).
- **5.** Classify beta-carotene and describe its key functions in the body (pp. 394–395).
- **6.** Explain how vitamin A works to ensure healthy vision (pp. 398–400).
- **7.** Identify the functional and health problems associated with vitamin A toxicity and deficiency (pp. 402-404).
- **8.** Describe the three stages of cancer development (pp. 404–406).
- **9.** Identify a variety of factors, including consumption of antioxidant nutrients and phytochemicals, that influence cancer risk (pp. 406–407).
- **10.** Discuss the role of free radical damage in cardiovascular disease and the potential benefit of consuming a diet rich in antioxidant nutrients (pp. 408–409).

# **Key Terms**

| antioxidant           | hyperkeratosis  | retinoic acid    |
|-----------------------|-----------------|------------------|
| bleaching process     | iodopsin        | retinol          |
| cancer                | Keshan disease  | rhodopsin        |
| carotenoids           | night blindness | rod cells        |
| cell differentiation  | opsin           | selenocysteine   |
| collagen              | oxidation       | selenomethionine |
| cone cells            | prooxidant      | tocopherols      |
| erythrocyte hemolysis | provitamin      | tocotrienols     |
| free radical          | retina          | tumor            |
| glutathione           | retinal         | xerophthalmia    |

# **Chapter Outline**

#### I. What Are Antioxidants and How Does the Body Use Them?

- **A.** Antioxidants are compounds that protect cells from the damage caused by oxidation.
- **B.** Oxidation is a chemical reaction in which atoms lose electrons.
  - 1. During metabolism, atoms exchange electrons in a process called oxidation–reduction, the loss and gain of electrons (exchange reactions).
  - **2.** Oxidation sometimes results in the formation of free radicals.

- a. When stable atoms lose an electron during oxidation and the electron remains unpaired, the result is an unstable free radical.
- **3.** Energy metabolism involves oxidation and gives rise to free radicals.
- **4.** Other factors can also cause free-radical formation.
  - **a.** While fighting infection, the immune system produces free radicals.
  - **b.** Free radicals are the result of exposure to many environmental contaminants.
- **C.** Free radicals can destabilize other molecules and damage cells.
  - 1. Free radicals can damage the cell membrane, damaging the cell and all systems the cell affects.
  - 2. Free radicals can also damage LDLs, cell proteins, and DNA, disrupting transport of substances in and out of cells, altering protein function, and disrupting cell function.
  - **3.** Free-radical production is linked to many chronic and degenerative diseases.
- **D.** Antioxidants work by stabilizing free radicals or opposing oxidation.
  - 1. Antioxidant vitamins independently donate electrons or hydrogen molecules to free radicals, reducing oxidative damage.
  - 2. Antioxidant minerals function as cofactors within complex antioxidant enzyme systems that render free radicals harmless.
    - a. Superoxide dismutase converts free radicals to less damaging substances, such as hydrogen peroxide.
    - **b.** Catalase removes hydrogen peroxide by converting it to water and oxygen.
    - c. Glutathione peroxidase removes hydrogen peroxide and stops the production of free radicals in lipids.

**Key Terms:** antioxidant, oxidation, free radical

Nutrition Animation: Free Radical Formation (located in IR-DVD folder).

#### **Figures and Table:**

**Figure 10.1:** Exchange reactions consist of two parts.

Figure 10.2: Normally, an oxygen atom contains eight electrons.

**Figure 10.3:** The formation of free radicals in the lipid portion of our cell membranes

**Table 10.1:** Nutrients Involved in Antioxidant Function and Vision

#### II. What Makes Vitamin E a Key Antioxidant?

- **A.** Vitamin E is a fat-soluble vitamin.
  - 1. Vitamin E is transported by VLDLs and LDLs and is stored in adipose tissue.
  - 2. Of the two forms of vitamin E, tocotrienol does not appear to play an active role in our bodies.
  - **3.** Tocopherol compounds are the biologically active forms of vitamin E.
    - **a.** The RDA for vitamin E is expressed as mg alpha-tocopherol per day.
    - **b.** Food and supplement labels express vitamin E in alpha-tocopherol equivalents or IU.
  - **4.** Vitamin E donates an electron to free radicals.
    - **a.** The primary function of vitamin E is as an antioxidant.
    - **b.** Its action specifically protects polyunsaturated fatty acids and LDLs from oxidation, lowering the risk of heart disease.

- **c.** Vitamin E protects red blood cells and lung cells from oxidative damage.
- **d.** Vitamin E is critical for normal development of nerves and muscles.
- e. Vitamin E enhances immune function.
- **f.** Vitamin E can improve absorption of vitamin A if dietary intake is low.
- **5.** How much vitamin E should we consume?
  - **a.** The RDA for vitamin E is 15 mg alpha-tocopherol per day for adults.
  - **b.** The need increases with increased PUFA consumption.
- **6.** Vitamin E is widespread in the foods we eat.
  - a. Sources include vegetable oils, nuts, seeds, and some vegetables.
  - **b.** Vitamin E is destroyed by exposure to oxygen, metals, ultraviolet light, and heat.
- 7. What happens if we consume too much vitamin E?
  - **a.** Newer research has caused debate over the potential increase in heart failure with vitamin E supplementation.
  - **b.** Certain medications, particularly anticoagulants, can interact negatively with vitamin E.
  - c. Long-term use of standard vitamin E supplements may lead to hemorrhagic stroke.
- **8.** What happens if we don't consume enough vitamin E?
  - **a.** In adults, vitamin E deficiency is usually caused by diseases that cause malabsorption of fat.
  - **b.** Vitamin E deficiency is rare but can lead to erythrocyte hemolysis, loss of muscle coordination and reflexes, and impaired immune function.

Key Terms: tocotrienols, tocopherols, erythrocyte hemolysis

#### Figures:

Figure 10.4: Chemical structure of tocopherol.

**Figure 10.5:** Common food sources of vitamin E.

#### II. Why Is Vitamin C Critical to Health and Functioning?

- **A.** Vitamin C is a water-soluble vitamin.
  - 1. Humans cannot synthesize their own vitamin C and must consume it in their diet.
  - **2.** Vitamin C helps synthesize tissues and functional compounds.
    - **a.** Vitamin C prevents scurvy, primarily by assisting in collagen synthesis.
    - **b.** Vitamin C assists in the synthesis of DNA, serotonin, and bile and helps regulate such hormones as thyroxine, epinephrine, norepinephrine, and steroid hormones.
  - 3. Vitamin C acts as an antioxidant and boosts absorption of iron.
    - **a.** Vitamin C acts as an antioxidant by donating electrons to free radicals and protects LDLs, the lungs, white blood cells, and the stomach.
    - **b.** Vitamin C regenerates oxidized vitamin E and is in turn regenerated by glutathione.
    - **c.** Vitamin C enhances iron absorption.
  - **4.** How much vitamin C should we consume?
    - **a.** The RDA for vitamin C is 90 mg per day for men and 75 mg per day for women with the UL of 2000 mg.
    - **b.** Smokers have increased vitamin C needs, as do those healing from trauma, burns, and surgery.

- **5.** Fruits and vegetables are the best sources of vitamin C.
  - a. Heat and oxygen destroy vitamin C.
  - **b.** By eating the recommended servings of fruits and vegetables, we can easily obtain the RDA with food.
- **6.** What happens if we consume too much vitamin C?
  - **a.** We excrete excess vitamin C easily because it is water soluble.
  - **b.** Side effects of megadoses (UL > 2,000 mg) may include nausea, diarrhea, nosebleeds, and abdominal cramps.
  - c. In people with certain disease conditions, excessive vitamin C supplementation can lead to iron toxicity or kidney stones.
  - **d.** Although critics of vitamin C supplementation contend that high doses lead to the vitamin acting as a prooxidant, the scientific evidence has not confirmed it.
- 7. What happens if we don't consume enough vitamin C?
  - **a.** Vitamin C deficiencies are rare in developed countries.
  - **b.** Scurvy is the most common vitamin C deficiency disease.
  - **c.** Anemia can result from vitamin C deficiency.
  - **d.** Alcohol and drug abuse can lead to vitamin C deficiency.

**Key Terms:** collagen, glutathione (GSH), prooxidant

#### **Figures:**

**Figure 10.6:** Chemical structures of ascorbic acid and dehydroascorbic acid.

**Figure 10.7:** Regeneration of vitamin E by vitamin C.

**Figure 10.8:** Common food sources of vitamin C.

#### III. What Minerals Act in Antioxidant Enzyme Systems?

- **A.** Selenium is a critical component of the glutathione peroxidase enzyme system.
  - 1. Selenium is contained in the amino acids selenomethionine and selenocysteine in the body and plays a critical role in human health.
    - a. Selenium breaks down peroxides so that they cannot form free radicals.
    - **b.** Selenium is needed for thyroxine production and appears to play a role in immune function.
  - **2.** How much selenium should we consume?
    - **a.** The RDA for selenium is 55 μg per day for adults, with a UL of 400 μg.
    - **b.** Selenium is present in both plant and animal foods but in variable amounts.
  - 3. Toxicity, caused only by supplementation, can be as mild as brittle hair and nails and as severe as liver cirrhosis.
  - **4.** Selenium deficiency is associated with Keshan disease, a form of heart disease, and Kashin-Beck disease, a disease of the cartilage.
    - a. Other deficiency symptoms include impaired immune function, infertility, and muscle wasting.
- **B.** Copper, iron, zinc, and manganese assist in antioxidant function.
  - 1. Copper, zinc, and manganese are cofactors for the superoxide dismutase antioxidant enzyme system.
  - 2. Iron is part of the structure of catalase.

3. These trace minerals play a major role in the optimal functioning of many of the body's enzymes.

**Key Terms:** Keshan disease, selenomethionine, selenocysteine

#### Figures:

**Figure 10.9:** Selenium is part of glutathione peroxidase.

Figure 10.10: Common food sources of selenium.

#### IV. What is Beta-Carotene, and What Are Its Roles in the Body?

- **A.** Beta-carotene is a phytochemical classified as a carotenoid.
- **B.** Beta-carotene is a provitamin.
  - 1. Beta-carotene is a provitamin, an inactive form of a vitamin that the body cannot use until it is converted to its active form.
    - **a.** Our bodies convert it to an active form of vitamin A, retinol.
    - **b.** Because beta-carotene absorption is incomplete and not all of it is converted to vitamin A, 12 g of beta-carotene equals 1 g of vitamin A.
  - 2. Beta-Carotene Has Antioxidant Properties
    - **a.** Beta-carotene and other carotenoids are fat soluble and function as antioxidants.
    - **b.** Carotenoids enhance immune function.
    - c. Carotenoids protect skin from damage caused by UV light.
    - d. Carotenoids protect our eyes from damage, delaying age-related vision impairment.
    - **e.** Carotenoids are associated with decreased risk of certain types of cancer.
  - **3.** How much beta-carotene should we consume?
    - a. There is no formal DRI for beta-carotene; however, an intake of 6 to 8 mg from food per day has been suggested.
  - **4.** Red, orange, yellow, and deep green fruits and vegetables provide adequate carotenoids when eaten daily.
    - **a.** Absorption of beta-carotene is better from cooked vegetables.
  - **5.** What happens if we consume too much beta-carotene?
    - **a.** Beta-carotene is not toxic but can turn skin yellow or orange.
    - **b.** Taking beta-carotene supplements is not recommended.
  - **6.** There are no known deficiency symptoms of inadequate beta-carotene as long as sufficient amounts of vitamin A are consumed.

**Key Terms:** carotenoid, provitamin,

#### Figures:

Figure 10.12: Chemical structure of beta-carotene.

Figure 10.13: Common food sources of beta-carotene.

#### V. How Does Vitamin A Support Health and Functioning?

- A. The three active forms of vitamin A are retinol (the most useful form), retinal, and retinoic acid.
  - 1. Vitamin A is absorbed in the small intestine, attached to fatty acids, carried through the lymph system in chylomicrons, and stored in the liver.
  - 2. Retinol is bound to protein for transport from the liver to cells.

- **B.** Vitamin A is essential to sight.
  - 1. Vitamin A enables us to react to changes in the brightness of light.
    - **a.** Retinal is found in and is integral to the retina.
    - **b.** In the retina, retinal combines with opsin to form rhodopsin, which is found in the rod cells.
    - **c.** When light hits the retina, the rod cells go through a bleaching process.
    - **d.** Changes in retinal and opsin during the process generate a nerve impulse to the brain, resulting in the perception of a black-and-white image.
    - **e.** With each cycle, some retinal is lost and must be replaced by retinol in the blood-stream.
  - 2. Vitamin A enables us to distinguish between different wavelengths of light.
    - **a.** The cone cells use retinal to interpret wavelengths into different colors.
    - **b.** Iodopsin is the pigment involved in color vision.
- **C.** Vitamin A contributes to cell differentiation and many other body functions.
  - 1. Vitamin A contributes to cell differentiation, including stem cells, epithelial cells, and T-cells.
  - **2.** Vitamin A is involved in reproduction and contributes to healthy bone growth.
  - **3.** Derivatives of vitamin A are used to treat acne.
- **D.** How much vitamin A should we consume?
  - 1. The RDA for vitamin A is 900  $\mu$ g per day for men and 700  $\mu$ g per day for women with a UL of 3,000  $\mu$ g.
  - **2.** Most of our dietary vitamin A is the preformed vitamin A found in animal foods such as liver, eggs, and dairy products.
  - **3.** Other sources of vitamin A intake comes from foods high in beta-carotene and other carotenoids.
  - **4.** What happens if we consume too much vitamin A?
    - **a.** Vitamin A is highly toxic at just three to four times the RDA, which usually occurs due to supplementation.
    - **b.** Consumption of excess vitamin A in any form during pregnancy can result in birth defects.
    - c. Toxicity symptoms include fatigue, loss of appetite, blurred vision, hair loss, skin disorders, bone and joint pain, GI abnormalities, and damage to the liver and nervous system.
  - **5.** What happens if we don't consume enough vitamin A?
    - a. Night blindness can result from vitamin A deficiency.
    - **b.** Other deficiency symptoms include xerophthalmia, hyperkeratosis, impaired immunity, reproductive system disorders, and growth failure.
    - c. Vitamin A deficiency is common in underdeveloped countries and can also be found in Americans who have inadequate intakes or suffer from diseases where fat is malabsorbed.

**Key Terms:** retinol, retinol, retinoic acid, retina, opsin, rhodopsin, rod cells, bleaching process, night blindness, cone cells, iodopsin, cell differentiation, xerophthalmia, hyperkeratosis

**Nutrition Animations:** Vitamin A and Epithelial Tissue; Vitamin A and the Visual Cycle (located in IR-DVD folder).

#### **Table and Figures:**

- **Figure 10.14:** The three active forms of vitamin A in our bodies.
- Figure 10.15: Vitamin A's Role in Vision
- Figure 10.16: A deficiency of vitamin A can result in night blindness.
- Figure 10.17: Common food sources of vitamin A.

#### VI. What Disorders Are Related to Free Radical Damage?

- **A.** Cancer is a group of diseases that are characterized by cells with out-of-control growth, which often produce tumors.
  - **1.** Cancer develops in three stages:
    - a. Initiation: mutations of cell DNA;
    - **b.** Promotion: stimulation of cell division;
    - c. Progression: out-of-control growth of cancerous cells.
  - 2. A variety of factors influence cancer risk.
    - **a.** Radom mutations during replication of DNA in noncancerous stem cells ("bad luck")
    - **b.** Heredity (genetic predisposition) increases risk but does not guarantee development of cancer.
    - **c.** Tobacco use increases cancer risk.
    - **d.** Weight, diet, and physical activity are related to approximately one-third of cancer deaths.
      - i. Alcohol, animal fats, and compounds found in cured and charbroiled meats increase cancer risk.
      - ii. Antioxidants, fiber, and phytochemicals are protective against cancer.
      - **iii.** Physical activity protects against colon cancer and is likely protective against several other cancers.
    - **e.** Infectious agents like HPV and *Helicobacter pylori* account for 15% to 29% of cancers worldwide.
    - **f.** Exposure to UV radiation, both from sun and tanning beds, increases risk of skin cancer.
    - **g.** Physical activity of moderate to high intensity reduces overall risk for cancer and protects against breast and colon cancer.
  - **3.** Antioxidants play a role in preventing cancer.
    - **a.** Antioxidants enhance immune function, inhibit cancer cell growth, prevent oxidative damage to the cells, and inhibit the capacity of cancer cells to avoid aging and apoptosis.
    - **b.** Studies show an association between eating foods high in antioxidants and decreased risk of cancer.
    - **c.** Studies of supplementation with antioxidants have shown mixed results, some negative.
- **B.** Free radical damage plays a role in cardiovascular disease.

- **1.** Vitamin E and lycopene scavenge free radicals, reduce low-grade inflammation, and reduce blood coagulation and clotting.
- **2.** Studies of reducing cardiovascular disease risk by consuming whole grains, fruits, and vegetables have been positive.
- **3.** Other components in fruits and vegetables besides antioxidant nutrients may protect against CVD.

**Key Terms:** cancer, tumor

#### **Figures:**

**Figure 10.18:** Cancer cells develop as a result of a genetic mutation in the DNA of a normal cell.

**Figure 10.19:** Cigarette smoking significantly increases our risk for lung and other types of cancer.

**Figure 10.20:** High-risk human papillomaviruses (high-risk HPVs) are a group of viruses that can cause cancer.

Figure 10.21: A lesion associated with a malignant melanoma.

#### **Activities**

- 1. According to the Dietary Supplement Health and Education Act (DSHEA), manufacturers of dietary supplements are allowed to use claims about structure-function of the substance, relationship of the substance to disease, and nutrition support claims (description of the link between nutrients and deficiency diseases). To help students learn the functions of the antioxidant nutrients identified in this chapter and understand how easy it is to make a supplement sound like a miracle drug, ask students to develop an advertisement for a new antioxidant supplement. Tell them what kinds of information they are allowed to use in the advertisement. Explain that they should try to make the supplement sound so appealing that their fellow students would want to purchase it. Share the advertisements in class, allowing fellow students to evaluate them for "truth in advertising."
- 2. To help students learn the antioxidant nutrients discussed in this chapter, their functions, and their food sources, start by asking a student to name one nutrient. Then ask the next student to add a piece of information about that nutrient. Continue until you get four or five items of information about that nutrient. The next student names another nutrient. Repeat in this manner until all nutrients covered in this chapter have been reviewed.
- 3. Ask students to bring vitamin/mineral supplements to class, with an emphasis on antioxidant supplements. Add vinegar to small, clear cups, and add one supplement to each cup. Let the supplements sit in the cups for 15 to 30 minutes. Swirl each cup every 5 minutes. Record observations. Discuss the implications of supplements that haven't dissolved at the end of the testing period. You might want to note the meaning of USP on the label.
- **4.** Have students bring in the label from one multivitamin/mineral (if they take one, they should bring that label), or bring some for your students to use. Using the following questions, have students evaluate the supplement while discussing information on the label and proper supplement selection:
  - **a.** What is the name of the supplement? The company can use the title of the product for marketing purposes and is not required to indicate contents in the name.

- **b.** What is the recommended daily adult dosage? Directions for use are required on the label, but there are no standard supplement dosages established by the government.
- c. Does the supplement provide a variety of vitamins and minerals? Vitamins and minerals will be listed first on the Supplement Facts Panel and will include a DV. There will be a black line at the end of the vitamins and minerals, and all other substances will be listed below that line. Discuss the benefits of taking a multi as opposed to singular nutrient supplements. Why would some vitamins or minerals be excluded from the supplement? Do the contents differ for gender and age?
- **d.** Are most of the vitamins and minerals between 75% and 125% of the DV? Are any lower? Discuss the possible reasons. Are any higher than 200% of the DV? Use the UL chart to determine whether any nutrients are dangerously high. Discuss the possible problems with moderately high doses, such as competition for absorption.
- **e.** Are there any substances listed in the Supplement Facts that are not vitamins or minerals (below the black line with no DV)? Why are they in the supplement? You can discuss antioxidants, vitamin-like compounds, soy, herbs, and so on. Do these substances improve the marketability of the product? Students may ask about "Other ingredients" listed below the Supplement Facts. Anything used to bind, flavor, or enhance the shelf life must be listed here.
- **f.** Are there claims made on the label about the product? See activity number 1 for the types of claims that can be made. What words are used to increase the desire to buy the product? You may want to discuss natural versus synthetic here. Does the label contain USP, a reputable brand name, or a guarantee of potency or dissolvability? Explain the quality measures of USP. A brand produced by a drug company will use the same quality standards and need not contain USP. Does a guarantee mean the same in terms of quality?
- **g.** What is the expiration date? Discuss the need for expiration dates on supplements and proper storage of supplements.

# **Diet Analysis Activity**

- **5.** Using the nutritional assessment previously completed, students should note the following:
  - **a.** What is your daily intake of:
    - vitamin E?
    - vitamin C?
    - vitamin A?
  - **b.** How does your intake of these nutrients compare with recommendations?
  - c. What changes can you make in your diet to more closely meet recommendations?
  - **d.** Considering your family history, which antioxidants would be most beneficial to your personal disease prevention? How would you increase them in your diet?

### **Nutrition Debate Activity**

- **6.** Many foods are being promoted for their antioxidant properties, implying that they will reduce risk of chronic disease or provide some other health-giving benefit. Divide the class into small groups (4-6) and assign each group one or more foods that are promoted for their antioxidants. Have students debate the following about their foods:
  - a. Currently, the FDA approves foods that contain risk-reducing substances as "functional foods." Is there enough research to include this food on the list?
  - **b.** Have the antioxidants in this food been studied adequately to determine their benefits?
  - c. Does the amount of specific antioxidants in this product warrant the advertisement?
  - **d.** Do the health benefits warrant the price?

Give students time to collect information to support their side (outside class time). Debates can be held in small group settings or as a whole class, depending on size. Establish the rules and time frames of the debate when topics are assigned so that students know how much material to prepare and what will be expected.

#### **Web Resources**

**World Health Organization (WHO)** 

www.who.int/en

**American Heart Association** 

www.americanheart.org/HEARTORG

**American Cancer Society (ACS)** 

www.cancer.org

**National Cancer Institute** 

www.cancer.gov

**U.S. Food and Drug Administration** 

www.fda.gov

Food and Nutritional Information Center, **U.S.** Department of Agriculture **National Agricultural Library** 

www.fnic.nal.usda.gov

Office of Dietary Supplements

www.ods.od.nih.gov