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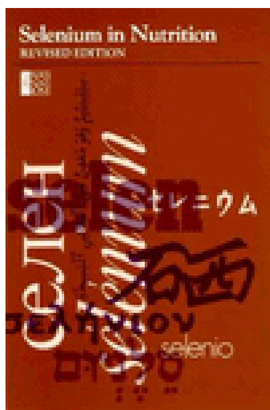

Selenium in Nutrition, Revised Edition

Subcommittee on Selenium, Committee on Animal Nutrition,National Research Council

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Selenium in Nutrition

REVISED EDITION

Subcommittee on Selenium
Committee on Animal Nutrition
Board on Agriculture
National Research Council

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Preface

Early interest in selenium by nutritionists concerned its high concentration in certain range plants and the consequent toxicosis in animals that grazed those plants. More recently, the essential nature of selenium has become the center of attention, and this element is now known to be required by laboratory animals, food animals (including fish), and humans. Its role as an integral feature of glutathione peroxidase has been established, and other possible functions are under active investigation.

This report reviews current knowledge concerning selenium in nutrition, including chemistry, distribution, metabolism, biochemical functions, deficiency signs, and effects of excess intake. For further background, the reader may wish to refer to the earlier reports of the National Research Council: *Selenium in Nutrition* (1971), *Medical and Biological Effects of Environmental Pollutants: Selenium* (1976), and *Mineral Tolerance of Domestic Animals* (1980).

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1

Introduction

In 1818, Berzelius in Gripsholm, Sweden, identified selenium as a new chemical element. From humble beginnings as a residue in a sulfuric acid vat, selenium has found exciting uses in commerce. Many of these depend on the remarkable susceptibility of selenium electrons to excitation by light, resulting in generation of an electric current. This has led to use of selenium in photoelectric cells, light meters, rectifiers, and xerographic copying machines. It is also used to decolorize the greenish tint of glass due to iron impurities or, in excess, to create the ruby-red color seen in warning signals and automobile tail lights. These and other uses are met by production of approximately 266 metric tons of selenium annually in the United States and worldwide production of 1,559 metric tons (Anonymous, 1979a, 1979b).

The biological significance of selenium was not recognized until it was identified as the toxic principle causing lameness and death in livestock grazing certain range plants in the Dakotas and Wyoming (Franke, 1934). Dr. Madison (1860) had earlier observed a number of toxicity signs, including hair loss, in cavalry horses at Fort Randall in the old Nebraska Territory. Lameness resulted from inflammation of the feet, followed by suppuration at the point where the hoof joins the skin and ultimate loss of the hoof. The consequent tenderness inhibited the search for food and water, and since no stored forage was available, death was at least partly attributable to starvation. Similar signs were described by Marco Polo (Komroff, 1926) in his travels in western China near the borders of Turkestan and Tibet about the year 1295. Loss of hair and nails in humans pre

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sumably suffering from chronic selenosis was first described in Colombia by Father Pedro Simon in 1560.

The discovery in 1957 (Schwarz and Foltz, 1957) that selenium was an essential nutrient led to an entirely new era of research that continues today. Instead of a primary concern with the toxicity of selenium, nutritionists turned their attention to the metabolic function of this element and the consequences of its deficiency. Hepatic necrosis in rats, probably associated with inadequate selenium and vitamin E, was seen by Klaus Schwarz in 1939 as he used purified diets to study vitamins in Richard Kuhn's laboratory at the Kaiser Wilhelm Institute (now the Max Planck Institute) in Heidelberg (Schwarz, 1976). Interestingly, Alvin Moxon, as a graduate student at South Dakota State University in the early 1930s, documented a growth response in chicks fed low levels of selenium in a series of studies designed to explore the toxicity of selenium at graded levels (Oldfield, 1981). When workers in William Hoekstra's laboratory at the University of Wisconsin (Rotruck et al., 1973) and Dr. Flohé and his associates (1973) at Tübingen established the unequivocal relationship between selenium and glutathione peroxidase, a fundamental connection between this element and metabolic processes was made. Despite the significance of this finding, it is probable that this is not the only metabolic role that selenium fulfills. A number of research groups are actively investigating evidence that other functions exist. These studies and others suggesting a relationship between selenium deficiency and human disease are documented in the following pages. The reader is invited to peruse them critically, but the authors would caution that the final chapter for selenium in nutrition has not yet been written.

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2

Chemistry

PROPERTIES OF ELEMENTAL SELENIUM

Selenium (Se) was identified in 1818 by Berzelius as an elemental residue during the oxidation of sulfur dioxide from copper pyrites in the production of sulfuric acid. It is similar in properties to tellurium (discovered some 35 years earlier) and was named for the moon (*selene* in Greek) while tellurium had been named for the earth (*tellus* in Latin). Little was known about the biological action of selenium until its toxicity (Franke and Painter, 1936) and nutritional essentiality (Schwarz and Foltz, 1957) were recognized. Nevertheless, the discovery of selenium was followed by study of its chemistry, which led to many industrial uses for this element that is almost as rare as gold. Excellent reviews of the chemistry of selenium are available (Rosenfeld and Beath, 1964; Chizhikov and Shchastilivyi, 1968; Nazarenko and Ermakov, 1972; Klayman and Gunther, 1973; Zingaro and Cooper, 1974).

Selenium is classified in group VIA in the periodic table of elements. It has both metallic and nonmetallic properties and is considered a metalloid. It is located between the metals tellurium and polonium and the nonmetals oxygen and sulfur by group, and between the metal arsenic and the nonmetal bromine by period. The atomic properties and electronic configuration of selenium are summarized in Table 1. Six naturally-occurring stable isotopes of selenium have been identified, and at least seven unstable isotopes may be produced by neutron activation. Of the latter, ^{75}Se, ^{77m}Se, and ^{81} Se may be used for the quantitative measurement of selenium

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by neutron activation analysis, and ^{75}Se has proved to be particularly suitable for biological experimentation because of its relatively long half-life (120 days).

TABLE 1 Atomic Properties and Electronic Configuration of Selenium

Atomic weight	78.96
Atomic number	34
Electronic configuration	$(Ar)3d^{10}4s^2 4p^4$
Covalent radius, Å	1.16
Atomic radius, Å	1.40
Ionic radius, Å	1.98
Atomic volume, w/d	amorphous: 18.55
	monoclinic: 17.72
	hexagonal: 16.31-16.50
Common oxidative states	−2, 0, +4, +6
Bond energy (M-M), kcal/mole	44
Bond energy (M-H), kcal/mole	67
Ionization potential, eV	9.75
Electron affinity, eV	−4.21
Electronegativity	2.55
Polarizability (M^{-2}), $cm^3 \times 10^{-25}$	105
pKa: $MO(OH)_2$, aqueous	2.6
$MO_2(OH)_2$, aqueous	−3
(H_2M), aqueous	3.8
(HM^-), aqueous	11.0

Like the other group VIA elements (sulfur and tellurium), selenium shows allotropy, existing in an amorphous state or in any of three crystalline forms. Amorphous selenium is a freeflowing liquid at temperatures above 230°C; its viscosity increases as the temperature is reduced to about 80°C, followed by decreases in viscosity with further reductions in temperature. This phenomenon, like that demonstrated by amorphous sulfur, results from the formation at low temperatures of ring-shaped aggregates with lower viscosity; whereas selenium forms polymeric chains with greater viscosity at higher temperatures. Elemental selenium is, thus, vitreous at 31°C–230°C and is a hard and brittle glass below 31°C. A red particulate form, colloidal amorphous selenium, can be prepared by the reduction of aqueous solutions of selenious acid; however, this form becomes crystalline at temperatures above 60°C.

Three crystalline forms of selenium occur: alpha-monoclinic, beta-monoclinic, and hexagonal. The monoclinic forms are composed of Se_8 rings and may be referred to as red (alpha-monoclinic) or dark red (beta-

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monoclinic) selenium. Alpha-monoclinic selenium is composed of flat hexagonal and polygonal crystals, whereas the crystals of beta-monoclinic selenium are needlelike or prismatic. Hexagonal selenium is called gray, black, metallic, gamma, or trigonal selenium. It is composed of spiral Sen chains. It is this form that is the most stable; amorphous selenium is transformed to the hexagonal form at 70°–210°C, and both monoclinic forms convert to the hexagonal form at temperatures above 110°C. The physical properties of elemental selenium vary according to its allotropic form. These have been reviewed by Chizhikov and Shchastlivyi (1968) and Crystal (1972).

Elemental selenium can be oxidized to +4 or +6 oxidation states. In the +4 state, selenium exists as the dioxide (SeO_2), selenious acid (H_2SeO_3), or selenite (SeO_3^{-2}) salts. Elemental selenium burns in air to form SeO_2. This compound can also be formed by the oxidation of elemental selenium by concentrated nitric acid. The production of SeO_2 is important in the combustion of fossil fuels that may be rich in selenium. However, SeO_2 is easily reduced, and SeO_2 formed by combustion is largely reduced back to the elemental state by sulfur dioxide produced concomittantly during that combustion. When amorphous selenium is oxidized in the presence of water, H_2SeO_3 is formed. The latter is a weakly dibasic acid that frequently acts as an oxidizing agent. Dissolved selenites are present as biselenite ions in aqueous solutions at pH 3.5 to pH 9. Selenite is readily reduced to elemental selenium at low pH by mild reducing agents such as ascorbic acid or sulfur dioxide.

In the +6 state, selenium exists as selenic acid (H_2SeO_4) or selenate (SeO_4^{-2}) salts. Selenic acid is a strong acid formed by the oxidation of selenium or selenious acid by strong oxidizing agents such as $NaBrO_3$ in $NaHCO_3$ or by Br_2, Cl_2 or H_2O_2 in water. Most selenate salts are appreciably more soluble than the corresponding selenite compounds. Their solubilities and stabilities are greatest in alkaline environments, and the conversion of selenates to the less stable selenites and to elemental selenium is very slow. Selenium reacts with halogens to form halides in which Se (+4) or Se (+6) are found (i.e., SeF_6, SeF_4, $SeCl_4$, $SeBr_4$). Selenium halides form acido complexes with the halogen derivatives of acids and with some of their salts.

In its most reduced state (−2) selenium exists as selenide. Hydrogen selenide (H_2Se) is a fairly strong acid and is a colorless, highly toxic gas produced by hydrolysis of metal selenides or by heating (400°C) elemental selenium in air. Hydrogen selenide rapidly decomposes in air to form elemental selenium and water. Whereas H_2Se is fairly soluble in water, the selenides of metals have either low solubility (e.g., CuSe, CdSe) or are very insoluble (e.g., HgSe).

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CHEMISTRY OF SELENIUM-CONTAINING COMPOUNDS

The chemistry of organic selenium compounds has been reviewed in detail by Klayman and Gunther (1973). Numerous organoselenium compounds can be prepared from elemental selenium (usually amorphous selenium is used) by addition reactions: from H_2Se or alkali selenides by addition or nucleophilic displacement reactions, from potassium selenocyanate by nucleophilic displacement or electrophilic substitution reactions, from phosphorus pentaselenide by reactions with primary alcohols, and from selenium oxides by substitution reactions at carbon atoms or by electrophilic substitution reactions. Several reagents containing highly nucleophilic selenium anions are available. These reagents are prepared from elemental selenium and are all capable of nucleophilic attack on carbon with displacement of aliphatic halides or sulfonic esters, or of ring opening of epoxides or lactones. These reagents include potassium selenosulfate (K_2SeSO_3), solutions of selenium in aqueous sodium formaldehyde sulfoxylate ($NaSO_2CH_2OH$) in the presence of sodium hydroxide, alkali selenides, and bis (methoxymagnesium) diselenide $(CH_3OMgSe)_2$. In addition, selenium halides and oxyhalides may be used to prepare organoselenium compounds by addition reactions to C═C double bonds, or by electrophilic substitutions of hydrogen in aliphatic or aromatic species. A few organoselenium compounds with applicability for the formation of new C—Se bonds are selenourea, $SeC(NH_2)_2$, which is readily alkylated to give isoselenouronium salts in organic solvent; benzylselenol which, along with its anion, reacts as other selenium nucleophiles to produce the rather stable benzyl alkyl monoselenides; and carbon diselenide (CSe_2), which reacts with primary amines to give symmetrical selenoureas and with secondary amines to give N,N-dialkyldiselenocarbamic acids.

Hydrogen selenide (H_2Se) and the organoselenium compounds of interest in nutrition and health are the methylated forms of selenium, i.e., dimethyl selenide, $(CH_3)_2Se$; trimethylselenonium ion, $(CH_3)_3Se^+$; the selenoamino acids, i.e., selenocysteine, selenocystine, selenomethionine, selenohomocystine; and the homocyclic and heterocyclic selenium compounds. The biological properties of these compounds in metabolism have been discussed (Levander, 1976b). Although the chemistry of selenium is similar to that of sulfur, certain differences result in these elements being metabolized differently. First is the difference in the ease of oxidation of Se (+4) and that of S (+4), the former tending to undergo reduction and the latter tending to undergo oxidation. Thus, biological systems tend to reduce selenium compounds and to oxidize sulfur compounds. Second is the difference in the relative strengths of acids H_2Se and H_2S, which is also seen in the acidic strengths of the hydrides of selenium and sulfur. The pK

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of the selenohydryl group of selenocysteine is 5.24, whereas that of the sulfhydryl group of cysteine is 8.25. Therefore, at physiological pH the selenohydryl group of selenocysteine or other selenols exists largely in the dissociated form, whereas the sulfhydryl group of cysteine or other thiols exists largely in the protonated form.

METHODS OF ANALYSIS

Selenium may be detected qualitatively by reduction to the elemental form (see Table 2). The best reducing agents for selenites are thiourea and hydroxylamine hydrochloride. Selenite can be determined in the presence of selenate by virtue of the different redox potentials for selenite and selenate ($Se \xleftrightarrow{+0.74V} H_2SeO_3 \xleftrightarrow{+1.15V} H_2SeO_4$) in a strongly acid bromide solution,

TABLE 2 Analysis of Selenium

Reagent	Se Detected	Result of Reaction	Detection Limit (μg/ml)	Interfering Substances
Thiourea	Se^{+4}	pink color or red ppt.	5	Te, NO_2^-, Cu, Hg, Bi, Au, Pt, Pd
Hydroxylamine HCl	Se^{+4}	pink color or red ppt.	5	many elements except Te
Iodide	Se^{+4}	red-brown ppt.	40	As^{+3}, Ge^{+4}, Mo^{+6}
Thiocyanic acid	Se^{+4}	red-brown ppt.	2	As, Sb, Sn, Fe^{+2}, MoO_4^{-2}
Pyrrole	Se^{+4}	pyrrole blue color	0.5	oxidizing elements, Se^{+6}, Te^{+4}, Te^{+6}
Asymmetric diphenyl-hydrazine	Se^{+4}	red color	2	oxidizing agents
Methylene blue and NaS_2	Se^0	decolorization	3	oxidizing agents
Ammonium molybdate	Se^{+4}	molybdenum-selenium blue color	3	PO_4^{-3}, SO_4^{-2}
3,3 ′- diamino-benzidine	Se^{+4}	yellow color or red fluorescence	0.01	oxidizing agents, Fe^{+3}, Cu^{+2}
2,3- diamino-naphthalene	Se^{+4}	yellow color or green fluorescence	0.002	oxidizing agents

SOURCE: Nazarenko and Ermakov (1972)

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wherein the oxidation of Se^{+4} to Se^{+6} is detected by the redox indicator, p-ethoxychrysoidine.

The most sensitive methods of detecting selenium involve the formation of piazselenols with orthodiamines (2,3-diaminonaphthalene; 3,3 ′-diaminobenzidine; 1,8-naphthalenediamine; 4-dimethyl-1,2-phenylenediamine; 4-methylthio-1,2-phenylenediamine). In the presence of these reagents in weakly acid solutions, selenites form piazselenols, which take on a straw-yellow color or, at higher levels of selenium, form brown-red precipitates. After extraction into organic solvent (e.g., cyclohexane, dioxane, toluene, benzene), piazselenols fluoresce upon irradiation with ultraviolet light.

Several methods have been employed for the quantitative determination of selenium. Among these are gravimetric procedures based upon the quantitative precipitation of selenium from selenites and selenates after reduction (Nazarenko and Ermakov, 1972). The purest precipitates are formed when sulfurous acid is used as the reducing agent and when selenium is precipitated from concentrated hydrochloric acid. Other reducing agents (e.g., Fe^{+2}, Sn^{+2}, Cr^{+2} and V^{+2} salts, sodium hypophosphite, thiourea, glucose, lactose, ascorbic acid, thiosemicarbazide, sodium diethylthiocarbamate and mercaptobenzimidazole) have been employed in various gravimetric methods for determining selenium. The problem common to all such procedures is that of production of precipitates free of contaminating elements. Selenium can also be determined by electrolytic deposition with copper; however, the presence of tellurium interferes with this method.

Milligram quantities of selenium can be determined by titration methods, most of which are based on redox reactions. In such procedures, selenites and selenates are quantitatively reduced to selenium by sodium thiosulfate; iodide; or ferrous, chromous, and trivalent titanium salts. Selenium is then titrated by solutions of oxidants. Alternatively, selenites can be oxidized to selenate by excess $KMnO_4$ or $K_2Cr_2O_7$, with back titration of the excess by Fe^{+2}.

Small amounts of selenium can be determined by formation and colorimetric measurements of hydrosols. Hydrazine, $SnCl_2$, and ascorbic acid are suitable reducing agents for the formation of selenium sols. Gum arabic, gelatin, or hydroxylamine hydrochloride can be used to stabilize the sol. The extinction density of selenium sols is measured at 260 nm.

Among widely employed methods for the quantitative determination of low levels of selenium are: (a) photometric and fluorometric procedures based on the formation of piazselenols with aromatic o-diamines; (b) procedures based on the formation of complexes with sulfur-containing organic reagents (e.g., dithizone, bismuthiol II); (c) procedures based on the oxidation of organic compounds by Se^{+4} to diazonium salts, which react

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with aromatic amines to give intensely colored azo compounds; and (d) procedures based on the formation of complexes of Se^{-2} with phenyl-substituted thiocarbazide or phenyl-substituted semicarbazide (e.g., 1,4-diphenylthiosemicarbazide). Of these procedures, the most widely used are reactions with *o*-diamines. The most selective and also most sensitive of these reagents is 2,3-diaminonaphthalene (DAN). Thus, the DAN procedure is most suitable for the determination of selenium in biological materials (Olson et al., 1975). It involves the reaction of DAN with selenious acid to form the selenodiazole 5-membered ring. Due to the intense fluorescence of piazselenol (maximum at 520 nm; excited at 390 nm or 366 nm), it is possible to determine 2 ng Se/ml by this procedure. Other procedures are less frequently employed. While photometric methods with sulfur-containing organic reagents have been used, they are relatively less selective; the diazonium salt procedures require preliminary elimination of interfering elements and of oxidizing and reducing agents; procedures involving the formation of complexes with selenium of lower valence show relatively poor sensitivity.

Selenium can be determined by atomic absorption spectroscopy or by neutron activation analysis. These methods were reviewed by Watkinson (1967) and Olson (1976). While these methods generally have been considered less sensitive than that of the DAN procedure, some investigators have reported a sensitivity of 5 ng or less using neutron activation (McKown and Morris, 1978), flameless atomic absorption spectroscopy with a graphite furnace (Henn, 1975), hydride generation with condensation (Hahn et al., 1981) or gas chromatography (McCarthy et al., 1981).

Biological samples for analysis of submicrogram amounts of selenium have been prepared in various ways. Allaway and Cary (1964) described a procedure in which the sample is combusted in an oxygen atmosphere in a Shöniger flask. Subsequently, the selenium is separated by coprecipitation with arsenic, then dissolved in nitric acid and measured using the DAN method. Samples can also be “wet” digested using nitric and perchloric acids (Watkinson, 1966) or sulfuric and perchloric acids (Ewan et al., 1968a). A useful method for the determination of selenium in plant and animal tissues was reported by Olson (1969a). This method employs a digestion using nitric and perchloric acids followed by reaction with DAN. Upon extraction with decahydronaphthalene or cyclohexane, the piazselenol is measured fluorometrically. This procedure has become the official first action method of the Association of Official Analytical Chemists and has been improved and simplified (Olson et al., 1975). Further modifications have been made (Whetter and Ullrey, 1978) to reduce labor and equipment requirements and to increase the number of samples that can be analyzed per day.

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3

Distribution

GEOLOGICAL DISTRIBUTION

Selenium is widely distributed in minute amounts in virtually all materials of the earth's crust, having an average abundance of about 0.09 ppm (Lakin, 1972). Its occurrence has been determined in a wide variety of rocks, minerals, lunar and volcanic materials, fossil fuels, soils, plant materials, and waters.

Selenium is rarely found in the native state. It has been found as a major constituent of 40 minerals and a minor component of 37 others, chiefly sulfides (Cooper et al., 1970). The minerals are finely dispersed without forming a selenium ore. Selenium is located in mineral deposits and some soil formations where a high concentration of sulfur is found (Painter, 1941).

The greatest abundance of selenium is in igneous rocks, where it occurs as selenite minerals; in sulfides, isomorphous with sulfur; in hydrothermal deposits, commonly associated epithermally with antimony, silver, gold, and mercury; and in massive sulfide and porphyry copper deposits, where it occurs in small concentrations but large quantities (Elkin and Margrave, 1968). Selenium is richest in chalcopyrite, bornite, and pyrite minerals (Cooper et al., 1970). High concentrations of selenium are found in sedimentary rocks such as shales, sandstones, limestones, and phosphorite rocks.

Considerable variation has been found in the selenium content of sulfide minerals (Lakin and Davidson, 1967), with values ranging from 0 to 2,100

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ppm. In a study of Canadian ores in which the selenium content was determined in pyrite, pyrrhotite, pentlandite, and chalcopyrite minerals, the highest concentrations of the element (500 to 1,000 ppm) were found in Precambrian nonnickeliferous copper sulfide ores (Hawley and Nichol, 1959). The Canadian ores are considerably richer in selenium than those of Australia but less rich than some of the sedimentary deposits of the western United States (Anderson et al., 1961). Selenium is obtained commercially by treatment of anode slimes produced during the electrolytic refining of copper. The principal sources of selenium are the sulfidic copper ores in Canada, the United States, and the Soviet Union (Cooper et al., 1970).

Sedimentary rocks cover more than three-quarters of the land surface of the earth and are therefore the principal parent materials of agricultural soils (Lakin and Davidson, 1967). It has been estimated that 58 percent of all sedimentary rocks are shales, which in turn commonly contain the highest concentrations of selenium (Anderson et al., 1961). The average concentration of selenium in shales has ranged from 0.24 ppm for Paleozoic shales of Japan to 277 ppm for black shales of Permian age from Wyoming (Lakin and Davidson, 1967). Approximately 2 ppm selenium has been estimated to be present in Cretaceous Pierre Shale, the parent material for much of the seleniferous soil in the United States (Lakin and Davidson, 1967). However, selenium concentrations found in members of the Pierre formation that have actually weathered to seleniferous soil are much higher (Moxon et al., 1939). Shales are also the principal sources of selenium-toxic soils in Ireland, Australia, and several other countries of the world (Johnson, 1975).

It has been difficult to reach a realistic estimate of the selenium content of sandstones. Lakin and Davidson (1967) obtained values ranging from 0 to 112 ppm. Ganje (1966) has reported selenium concentrations between 2 and 130 ppm. Apparently selenium is often concentrated in organic debris in sandstones (Johnson, 1975).

The selenium content of limestones is generally low, although some have contained relatively high levels (Lakin and Davidson, 1967). The element has been found in seleniferous pyrite and in organic debris.

The relatively high concentration of selenium in some phosphate rocks may be significant in agriculture because of the wide use of phosphate fertilizers made from these deposits. It has been suggested that normal superphosphate can be expected to contain about 60 percent and concentrated superphosphate about 40 percent as much selenium as the phosphate rock from which it is made (Robbins and Carter, 1970). Samples from the western U.S. phosphate field, extending over parts of Wyoming, Utah, Nevada, Idaho, and Montana, contained from 1.4 to 178 ppm selenium (Robbins and Carter, 1970). Earlier analyses of phosphate rocks from Florida, South

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Carolina, and Tennessee were lower, ranging between 0.8 and 9 ppm selenium (Rader and Hill, 1935).

Seleniferous sulfur is of agricultural interest as a source of selenium in phosphatic fertilizers and sulfur-containing inorganic salts included in livestock diets. The selenium content of Japanese and Hawaiian volcanic sulfur ranged from 67 to 206 ppm and 1,026 to 2,000 ppm, respectively (Lakin and Davidson, 1967). However, not all volcanic sulfur was found highly seleniferous. Twenty-eight samples from various localities around the world contained between 2 and 15 ppm of the element (Lakin and Davidson, 1967).

Selenium has been found to occur in fossil fuels. In samples obtained in the United States, coal contained 1 to 5 ppm selenium and crude oil (Texas) 0.06 to 0.35 ppm (Cooper et al., 1970). In a coal sample taken from a seleniferous region in the People's Republic of China, approximately 90,000 ppm selenium were found (Levander, 1982). Fly ash obtained from electrostatic precipitators in stacks at coal-powered electricity generating plants in the United States has been shown to contain 1.2 to 16.5 ppm selenium (Gutenmann et al., 1976). Volunteer white sweet clover growing on a landfill containing fly ash showed up to 200 ppm (dry basis). Sheep (Furr et al., 1978) and swine (Mandisodza et al., 1979) fed such sweet clover exhibited large increases in tissue selenium. Swine fed fly ash directly also exhibited such an effect.

COMMERCIAL SOURCES

Known deposits of selenium are insufficient to permit their mining for the element alone. Virtually all new production of selenium is via its extraction from copper refinery slimes along with the recovery of precious metals (National Research Council, 1976b). Decopperization is the first procedure, after which selenium may be recovered either by volatilization during roasting or furnacing or by leaching of roasted calcine or furnace slag. In 1973, total free world production of selenium was 1.1 million kg, with Japan, the United States, and Canada the leading producers in that order.

The principal commercial selenium compounds are selenides of aluminum, arsenic, bismuth, cadmium, calcium, copper, and indium; ammonium selenite and sodium selenite; selenates of copper, potassium, and sodium; selenium dioxide; selenium disulfide; selenium hexafluoride; and selenium monosulfide. These compounds are used mainly in the manufacture of glass; in xerography; in conductors, rectifiers, electron emitters, and insulators; as reagents; in remedies for eczemas and fungus infections in pets; in antidandruff agents for humans; and in veterinary therapeutic agents. In agriculture, early uses for selenium compounds were for control of

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mites and insects; these compounds are no longer used for this purpose. Sodium selenite and sodium selenate are presently used in agriculture as injectables and feed additives to control selenium-related deficiency disorders.

SELENIUM IN SOILS

The selenium content of most soils lies between 0.1 and 2 ppm (Swaine, 1955). The maximum quantity of selenium found in several thousand soil samples in the United States did not exceed 100 ppm, and the majority of the seleniferous soils analyzed contained on the average less than 2 ppm (Rosenfeld and Beath, 1964). Soils developed from Cretaceous shale of South Dakota, Montana, Wyoming, Nebraska, Kansas, Utah, Colorado, and New Mexico tend to be high in selenium, ranging from 2 to 10 ppm (Jackson, 1964).

A portion of the selenium in soils is available to the vegetation they support. Soils that supply sufficient selenium to produce toxic plants are commonly referred to as toxic seleniferous soils. Nontoxic seleniferous soils, although their selenium content may be high, yield insufficient available selenium for plants to become toxic. The total selenium content of many toxic seleniferous soils is appreciably lower than that of some nontoxic soils.

Because of the high levels of selenium in sedimentary rocks and the importance of such rocks as soil-forming materials, the processes contributing to high selenium concentrations are of interest. The selenium content of sedimentary rocks varies considerably throughout a geological profile (Moxon and Olson, 1970). This indicates that during their formation the selenium was provided from a primary source at a different rate than that at which sediments were deposited. In the United States, virtually all seleniferous soils have weathered from sedimentary rocks of the Cretaceous period. Only a few such formations contain sufficient selenium that they become parts of soils that produce toxic vegetation. Lakin (1961) has suggested that selenium is concentrated in sedimentary rocks by the following processes: (1) precipitation by rain of selenium from volcanic emanations; (2) deposition of erosional products from volcanic sulfur, seleniferous tuffs, and sulfide deposits; and (3) precipitation of selenium from streams or groundwater carrying unusual quantities of selenium from older seleniferous sediments. Strock (1935) has suggested that selenium was removed from the erosion cycle and held in sedimentary deposits by its adsorption on freshly precipitated ferric hydroxide. Subsequent elevation and erosion would release selenium from sedimentary deposits and start it on a new cycle. The frequent association of high concentrations of selenium with limonite concentrations composed of ferric oxide and hydroxide (Rosen

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feld and Beath, 1964) and with pyrite and marcasite (Rosenfeld and Beath, 1964; Elkin and Margrave, 1968) in sediments lends support to Strock's explanation.

TOXIC SELENIFEROUS SOILS

Toxic seleniferous soils are usually alkaline in reaction and contain free calcium carbonate (Lakin, 1961; Rosenfeld and Beath, 1964). They occur in regions of low rainfall, usually less than 8 cm total annual precipitation. The presence of water-soluble selenium is an important characteristic of toxic soils (Lakin, 1961). Beath et al. (1946) concluded that selenate is the dominant water-soluble form of selenium in toxic soils.

There are extensive areas of seleniferous soils in South Dakota, Wyoming, Montana, North Dakota, Nebraska, Kansas, Colorado, Utah, Arizona, and New Mexico that produce vegetation toxic to livestock (Rosenfeld and Beath, 1964). The occurrence of toxic vegetation and indicator plants is most widespread in Wyoming and South Dakota (Rosenfeld and Beath, 1964). The average selenium content of 500 samples of soil from seleniferous areas in the western United States was 4.5 ppm, with a maximum of 80 ppm (Trelease, 1945).

Seleniferous soils supporting toxic vegetation in Canada are associated with Cretaceous rocks in large areas of Alberta, Saskatchewan, and Manitoba (Rosenfeld and Beath, 1964). The range in total selenium content of 80 soil samples, taken where indicator plants were present, was 0.1 to 6 ppm, with 30 percent of the samples containing 1 ppm or more.

Contamination of soils by seleniferous mine wastes caused a toxicity problem in a river valley in Mexico (Rosenfeld and Beath, 1964). The mine wastes contained an average of 4.6 ppm selenium, while the contaminated surface soils contained between 0.3 and 20 ppm.

Several seleniferous areas are found under humid conditions in Colombia (Rosenfeld and Beath, 1964). Surface soils collected in Boyaca State contained from 1 to 14 ppm, and soil in the region located between the Negro and Negrito rivers averaged from 2 to 7 ppm selenium.

Selenium occurs in toxic amounts under humid conditions in certain parts of Limerick, Tipperary, and Meath counties of Ireland (Rosenfeld and Beath, 1964). The seleniferous soils lie in a poorly drained valley, and leaching of topographically higher rocks and soils has led to selenium enrichment of these soils.

In 1957, alkali disease was reported in cattle herds in the Huleh Valley of Israel (Rosenfeld and Beath, 1964) where soils had over 6 ppm selenium. In a seleniferous area in the Naot-Mordechai region the soils contained from traces to 6.0 ppm.

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In South Africa, the areas located on the Karoo sedimentary rock produce chronic selenosis in livestock (Rosenfeld and Beath, 1964).

NONTOXIC SELENIFEROUS SOILS

Selenate has been identified as the main water-soluble form of selenium in soil that is translocated into vegetation containing toxic quantities of the element (Lakin, 1972). Many soils of the world contain high levels of selenium but low levels of water-soluble selenium and consequently do not produce vegetation that has a toxic selenium level for animals. Hawaiian soils containing 6 to 15 ppm and Puerto Rican soils containing 1 to 10 ppm selenium do not produce seleniferous vegetation, whereas soils of Israel and South Dakota with lower total selenium contents produce toxic plants (Lakin, 1972). The nontoxic seleniferous soils of Hawaii and Puerto Rico have an acid pH range (4.5 to 6.5) which, in the presence of ferric hydroxide, renders the selenium unavailable to plants. The soils are characterized by a zone of accumulated iron and aluminum compounds and are developed under humid conditions (Lakin, 1961).

LOW-SELENIUM SOILS

Recent volcanic deposits, which are low in selenium, and materials transported from them are the principal soil-forming materials in the very low selenium region of the Pacific Northwest. Soils in the very low selenium region of the South Atlantic seaboard are formed from coastal deposits washed from a highly weathered land mass. The soil parent materials of the low-selenium areas in Montana are mostly derived from granites and very old metamorphic rocks. Low total selenium concentrations in the tertiary volcanic rocks of Arizona and New Mexico are suspected to be the cause of the low selenium levels in crops in this part of the United States. The soil-forming materials of the northeastern United States are derived primarily from sedimentary rocks that predate the major Cretaceous period of selenization of the North American continent. Most of the soils from low-selenium areas of the United States contain less than 0.5 ppm selenium (Cary et al., 1967). Low-selenium soils of eastern Canada contain less than 0.2 ppm selenium (Levesque, 1974). The low-selenium soils of Canada occur in the interior of British Columbia, in west-central Alberta, in northern Ontario, in the eastern townships and lower St. Lawrence regions of Quebec, and in the Atlantic provinces (Levesque, 1974). Most New Zealand soils contain between 0.1 and 2 ppm selenium (Watkinson, 1962). Low-selenium soils appear to be responsible for selenium deficiency disorders in livestock raised in certain regions of Australia, New Zealand,

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Scotland, Finland, Sweden, Austria, Germany, France, Western Russia, Turkey, Greece, Canada, and the United States (Underwood, 1962, 1966; Oksanen, 1967; Allaway, 1968).

FORMS OF SELENIUM IN SOILS AND FACTORS AFFECTING AVAILABILITY TO PLANTS

Separation and identification of the chemical forms of selenium in soils is difficult because of the small amounts of the element present (Trelease and Beath, 1949; Allaway et al., 1967) and the complexities of soil systems (Rosenfeld and Beath, 1964). The forms of selenium generally considered to be present in soil are selenides, elemental selenium, selenites, selenates, and organic selenium compounds. The chemical forms of selenium in soils and sediments are apparently closely related to oxidation reduction potential, pH, and solubility (Lakin, 1961; Allaway et al., 1967; Cary et al., 1967; Allaway, 1968; Geering et al., 1968). The principal chemical reactions of selenium in soils and weathering sediments, as summarized by Allaway (1968), are shown in Figure 1.

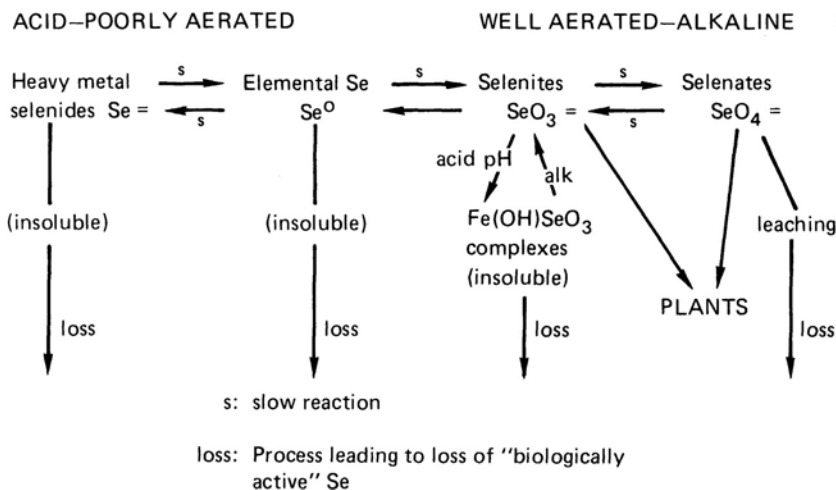

FIGURE 1 Generalized chemistry of selenium in soils. From Allaway, 1973.

There is evidence that insoluble selenides associated with sulfides may occur in some soils (Williams and Byers, 1936; Trelease and Beath, 1949;

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Allaway et al., 1967). The low solubility of metal selenides, especially copper selenide, may lead to their persistence in agricultural soils (Allaway et al., 1967). Although redox potentials indicate that selenides would be oxidized to selenite in most soils, the rate of oxidation is probably sufficiently slow to effectively stabilize this form of selenium under some soil conditions (Cary et al., 1967). Elemental selenium is apparently present in small amounts in some soils. (Beath et al., 1937; Byers et al., 1938; Trelease and Beath, 1949; Olson, 1967). It may be either an important intermediate in the oxidation of the element to a soluble form (Olson, 1967) or a transitory constituent of neutral and acid soils during the reduction of selenites under acid conditions (Allaway et al., 1967). There are indications that significant amounts of elemental selenium may be oxidized by microorganisms in neutral and alkaline soils (Geering et al., 1968). The fate of elemental selenium in acid soils is uncertain. Watkinson (1962) and Allaway et al. (1967) have suggested that when elemental selenium is added to acid and neutral soils, it may be oxidized to selenites, which in turn react with hydrous oxides to form complexes of low solubility and availability to plants. A large fraction of the selenium in acid soils may occur as stable complexes of selenites with hydrous iron oxides (Williams and Byers, 1936; Trelease and Beath, 1949; Swaine, 1955; Lakin, 1961; Allaway et al. 1967). Geering et al. (1968) showed that the thermodynamically stable selenium compound in acid-to-neutral soils may be a ferric selenite-ferric hydroxide adsorption complex. As the pH rises above 8, decomposition of the ferric hydroxide-selenite complexes begins, and the equilibrium solubility of selenite increases rapidly. The rate of transformation of selenite to selenate proceeds rather slowly. Selenates have been reported to be present in water extracts of soil by several workers (Williams and Byers, 1936; Byers et al., 1938; Olson et al., 1942; Beath et al., 1946; Trelease and Beath, 1949). According to Lakin (1961), selenates are stable in an alkaline, oxidizing environment such as that found in many well-aerated, semiarid seleniferous soils. Selenates do not appear to be present in appreciable quantities in acid and neutral soils. Marked increases in selenium uptake by plants have resulted from application of soluble selenates to soils (Hurd-Karrer, 1935; Grant, 1965; Bisbjerg and Gissel-Nielsen, 1969; Gissel-Nielsen and Bisbjerg, 1970). Very little is known about the nature of organic forms of selenium in soils. Beath et al. (1935) suggested that soluble organic selenium compounds are liberated through the decay of seleniferous plants. Williams and Byers (1936) found that soil organic matter contained water-soluble and easily recoverable organic selenium compounds. The availability of selenium in seleniferous soils was found by Olson and Moxon (1939) to be correlated with or dependent upon the selenium in the organic or humus

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fraction. According to Cary et al. (1967), organic forms of selenium are probably more soluble under alkaline than under acidic soil conditions.

The principal factors affecting the availability of soil selenium to plants have been summarized as follows (NRC, 1971): In alkaline, well-aerated soils, selenium tends to form selenates. The selenates in these soils are very available to plants, and they may lead to toxic concentrations in plants. In acid soils, a ferric iron-selenite complex is formed that is only slightly available to plants. This is the reason acid soils rarely produce plants that contain toxic concentrations of selenium. Elemental selenium appears to be stable in soils and, except for microbial action, is not readily oxidized to forms that are easily taken up by plants (Watkinson and Davies, 1967; Cary and Allaway, 1969). There is evidence that there are some organic selenium compounds in soils that are water-soluble and available to plants (Moxon et al., 1939). The uptake of soil selenium by plants is dependent on plant species; this will be discussed later.

The overall relationships among the concentrations of selenium in rocks, soils, and plants have been summarized as follows (NRC, 1971):

- Where rocks with a high content of selenium decompose to form well-drained soils in subhumid areas (less than 8 cm of annual rainfall), the selenides and other insoluble forms of selenium will be converted to selenates and organic selenium compounds. These compounds will be available to plants, and vegetation containing potentially toxic levels of selenium will probably be produced on these soils.
- Where rocks with a high content of selenium weather to form soils in humid areas, slightly soluble complexes of ferric oxide or hydroxide and selenite ions will be formed. These soils will also be slightly to strongly acid, and the plants produced on them will not contain toxic concentrations of selenium, but they may contain sufficient selenium to protect livestock consuming them from selenium deficiency.
- Where rocks with a high content of selenium weather to form poorly drained soils or where selenium from higher lying areas is deposited in poorly drained areas by alluvial action, and the soils are alkaline, plants containing toxic levels of selenium are likely to be produced. This will be especially probable if the aeration of these soils is improved by artificial drainage. The more acid the soils in an area, the less the likelihood of vegetation containing toxic levels of selenium.
- Where rocks with a low content of selenium decompose to form soils under either humid or dry conditions, the plants produced are likely to contain insufficient selenium to protect animals from selenium deficiency. The more humid the area and the more acid the soil, the greater the likelihood of extremely low selenium concentrations in the plants.

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SOIL MANAGEMENT PRACTICES AND SELENIUM IN PLANTS

The value of management practices in control of selenium toxicity in various areas of the United States has been reviewed by Anderson et al. (1961), Rosenfeld and Beath (1964), and Olson (1969b). Subsequent to the mapping of seleniferous areas, the U.S. government withdrew large areas from wheat production and converted the areas to controlled grazing (Anderson et al., 1961).

Muth (1955) and Schubert et al. (1961) have observed aggravated selenium deficiency following application of gypsum to soils. However, Johnson (1975) found that application of gypsum to seleniferous soils was ineffective in reducing selenium absorption by plants. Likely the sulfate content of the soils was already high, or the sulfate did not penetrate to the deep-rooted native plants. On the other hand, the concentration of selenium in some seleniferous soils has been markedly reduced both by leaching during the soil development process (Moxon et al., 1939) and by irrigation water (Lakin, 1961). Kubota et al. (1967) found that forage growing on the bottomlands along the Missouri and Mississippi rivers contained more selenium than did forage growing on the upland soils, indicating that the rivers are transporting selenium from their upper watersheds. It appears, however, that selenium is being removed from the surface layers of the seleniferous areas of the United States and not from the lower profiles where deep-rooted plants can still accumulate toxic amounts of selenium (Johnson, 1975).

In areas where soils are low in selenium, certain agricultural practices may have some effect in increasing the level available. Applying manure to low-selenium soils from animals fed imported selenium-adequate feeds increases the soil selenium content slightly. Superphosphate fertilizers contain selenium, but the extent of their contribution to soil selenium is not known. Cary et al. (1967) have shown that liming some soils deficient in selenium results in only a very small increase in selenium uptake by plants.

SELENIUM IN PLANTS

EFFECT OF SPECIES

Factors influencing the selenium content of plants have been reviewed by Johnson et al. (1967). One of the most important of these is the kind of plant. Rosenfeld and Beath (1964) have divided plants into three groups on the basis of their ability to accumulate selenium when grown on high-selenium soils. The first two groups of plants are referred to as selenium accumulator or indicator plants. These grow well on soil containing high levels of selenium and thereby assist in the location of seleniferous soils. Plants in

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group 1 are called primary indicators and include many species of *Astragalus, Machaeranthera, Haplopappus,* and *Stanleya.* They normally accumulate selenium at very high levels, often several thousand parts per million. Plants in group 2 are referred to as secondary selenium absorbers. They belong to a number of genera, including *Aster, Atriplex, Castelleja, Grindelia, Gutierrezia, Machaeranthera,* and *Mentzelia.* They rarely concentrate more than a few hundred parts per million of selenium. Plants in group 3 include the grains, grasses, and many weeds, that do not normally accumulate selenium in excess of 50 ppm when grown on seleniferous soil.

Some plants growing on seleniferous soils accumulate surprisingly low levels of selenium. White clover (*Trifolium repens*), buffalo grass (*Hilaria belangeri*), and gramma grass (*Bouteloua spp.*) are poor accumulators of the element (Beeson and Matrone, 1972). On the other hand, high sulfur-containing plants such as the *Crucifera* (mustard, cabbage, broccoli, cauliflower) are relatively strong concentrators of selenium.

The accumulator plants in groups 1 and 2 have been found to grow in 140 counties in 16 states of the United States (NRC, 1971). However, these plants probably add very little to the selenium content of feeds because they normally grow in dry nonagricultural areas.

Hamilton and Beath (1963, 1964) have reported on the accumulation of selenium by field crops and vegetables grown in high-selenium soils, and Williams et al. (1941) have published data on the selenium contents of wheat and feed grains produced in the high-selenium areas of the United States. All of the vegetable and crop species grown in soils containing high levels of available selenium concentrated the element to potentially toxic levels (> 5 ppm). However, Williams et al. (1941) found that less than 10 percent of the wheat and feed grain samples grown in the seleniferous areas of the United States had selenium levels in excess of 5 ppm.

Differences in the accumulation of selenium by plants growing in soils low in selenium have been reported by Davies and Watkinson (1966) and Ehlig et al. (1968). After the addition of selenite to a soil, brown top (*Agrostis tenuis*) took up two to seven times as much selenium as white clover (*Trifolium repens*). Allaway (NRC, 1971) has found that for soils having moderately low selenium levels, alfalfa accumulates more selenium than red clover, timothy, or brome grass. No reliable differences were noted among species grown on very low levels of available selenium. Crops growing on neutral or acid soils absorb very little selenium, and any attempt to increase crop selenium uptake by shifting to some other species is not likely to be successful (Ehlig et al., 1968).

SELENIUM AS A PLANT MICRONUTRIENT

Early work by Trelease and Trelease (1938, 1939) indicated that the accumulator species *Astragalus racemosus*and *A. beathii* required selenium

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for growth. Broyer et al. (1972a,b) were not able to repeat the findings and concluded that in the Trelease work phosphate toxicity had occurred in the plants, with the condition being alleviated somewhat by the addition of selenium. Broyer et al. (1966) found no beneficial effect of adding selenite to cultures of alfalfa (*Medicago sativa* L.) and subterranean clover (*Trifolium subterraneum*) up to 2 ppm, at which a depressing effect was observed. Bisbjerg and Gissel-Nielsen (1969) observed a growth depression in some plants when 0.5 to 2.5 ppm selenate selenium was added to the soil.

TOXICITY TO PLANTS

In some of the nonaccumulator species, soluble selenium compounds have been shown to interfere with seed germination (Levine, 1925) and growth (Levine, 1925; Hurd-Karrer, 1934, 1937; Martin, 1936). In some cereal crops, selenate toxicity produced a characteristic snow-white chlorosis (Hurd-Karrer, 1933). The rate of crossing over in barley was found to be reduced by selenium (Walker and Ting, 1967), apparently by causing a relaxation of the meiotic chromatin. The accumulator plants on the other hand are able to absorb high levels of selenium without any adverse effect.

Apparently there are no published accounts of naturally occurring selenium causing damage to crops (Cooper et al., 1970). It has been found by Rosenfeld and Beath (1964) that crop plants are not injured until they accumulate more than 300 ppm selenium, a concentration never found in even the most seleniferous areas of the United States.

CHEMICAL FORMS

In early studies on the alkali disease syndrome it was found that high levels of selenium were associated with the protein in grains (Franke and Painter, 1936; Horn et al., 1936). This was confirmed in more recent studies in which most of the selenium in nonaccumulating species was found in the form of protein-bound selenomethionine (Butler and Peterson, 1967). Early investigations also showed that the selenium in indicator plants was mostly water-soluble and was not associated with the protein (Beath et al., 1934). Horn and Jones (1940) were the first to isolate an organic selenium compound from plant material. They isolated a mixture from water extracts of *Astragalus pectinatus* that they considered to be the isomorphic compounds cystathionine and Se-cystathionine. Later, Trelease et al. (1960) reported the isolation of Se-methylselenocysteine from *Astragalus bisulcatus.* Since then many other selenium compounds have been isolated from plants, including Se-methylselenomethionine, the glutamyl peptide of selenocystathionine, selenohomocystine, selenocystine and its oxides, selenomethionine selenoxide, selenoglutathione, selenite, selenate, selenocysteic acid, selenocysteine seleninic acid, dimethyl selenide, and dimethyl diselenide (Moxon and Olson, 1970;

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NRC, 1976b). It has been pointed out by Walter et al. (1969) that diselenide-sulfhydryl and diselenide-selenol interchange reactions might occur during isolation of selenium metabolites and might lead to the identification of artifacts.

Shrift (1973) has pointed out that there appear to be some biochemical distinctions between selenium-accumulator and selenium-nonaccumulator *Astragalus* species. Se-methylselenocysteine has been consistently found in much higher amounts in the accumulator than in the nonaccumulator species (Martin et al., 1971). Both species methylate selenomethionine to give Se-methyl-selenomethionine, but only the accumulators convert it to selenohomocystine and Se-methylselenocysteine (Virupaksha et al., 1966). Another distinction is the large amount of selenocystathionine in the accumulator species of *Astragalus*; only trace amounts occur in the nonaccumulators (Martin et al., 1971).

METABOLISM IN PLANTS

Shrift (1973) has summarized present knowledge of the metabolism of selenium by plants. Although the selenium metabolites identified in plants are analogs of sulfur compounds, the metabolism of selenium in plants cannot be identified from known mechanisms involving sulfur metabolism. For example, selenocystathionine has been found in plants without cystathionine (Martin et al., 1971), and glutathione has been found in the absence of selenoglutathione (Shrift and Virupaksha, 1965). Nissen and Benson (1964) found that the roots of several crop plants formed choline sulfate but not the selenate derivative. They failed to detect 3′-phosphoadenosine-5′-phosphoselenate in plants provided selenate and concluded that this was due to the conversion of SeO_4^{-2} to adenosine 5-phosphoselenate by sulfate adenyltransferase and subsequent reduction to SeO_3^{-2}.

A similar metabolic reaction, however, was observed by Lewis et al. (1971) for sulfur and selenium in *Brassica oleracea.* They obtained an enzyme preparation that cleaved Se-methylmethionine into dimethyl sulfide and homoserine, and S-methylselenomethionine into homoserine and dimethyl selenide. The latter compound was found earlier in *Astragalus bisulcatus* by Froom (1963).

Our understanding of the metabolic pathways for selenium in plants remains very limited.

SELENIUM IN ANIMAL FEEDSTUFFS

The selenium content of feedstuffs varies with plant species and geographical area of production. Concentration of selenium in plants is governed

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primarily by the presence and availability of the element in the soil. In some areas of the United States, forages contain sufficiently high selenium concentrations to cause selenium toxicity in livestock; in other regions the levels of selenium in crops and forages are too low to meet animal requirements. At the same time, there are extensive areas where virtually all the crops and forages contain sufficient selenium to meet livestock requirements.

In the seleniferous areas, accumulator plants frequently contain selenium at levels that are toxic to farm animals. However, the impact of these plants on the livestock industry in the seleniferous areas is small because of the widespread adoption of practical techniques for controlling the problem (Olson, 1969b). There are relatively small differences among species of forage and feed plants in the accumulation of selenium when they are grown in the seleniferous areas. Hamilton and Beath (1963, 1964) have described the accumulation of selenium by field crops growing in soil containing a high level of available selenium. Lakin and Byers (1941) and Williams et al. (1941) have published an extensive compilation of the selenium content of wheat and feed grains produced in the high-selenium areas of the western United States. Lakin and Byers (1941) found 82.5 percent of their wheat samples contained 1 ppm selenium or less, and 7.5 percent contained in excess of 4 ppm. Similar concentrations were found in bran, shorts, and middlings. In Canada, Thorvaldson and Johnson (1940), analyzing 230 composites made up from 2,230 samples of wheat from widespread areas of Saskatchewan and Alberta, found an average value of 0.44 ppm selenium, with a maximum of 1.5 ppm. Robinson (1936) found concentrations between 0.1 and 1.9 ppm selenium in samples of market wheat obtained in various parts of the world.

Davies and Watkinson (1966) and Ehlig et al. (1968) studied the differences among plant species in accumulating selenium from soils having low concentrations of the element. In New Zealand, browntop (*Agrostis tenuis*) contained more selenium than white clover (*Trifolium repens*) when grown on low-selenium soil. In the United States, alfalfa accumulated more selenium than red clover, timothy, or bromegrass from soils containing moderately low selenium concentrations, but differences among forage species have not been consistent when the soils contained very low levels of available selenium.

In Canada, Miltimore et al. (1975) found that British Columbia wheat grain had a considerably higher mean selenium concentration than barley and oats. Significantly higher levels of selenium also occurred in wheat than in grasses and legumes. The percentages of samples below 0.1 ppm selenium were wheat, 12 percent; barley and oats, 32 percent; legumes, 22 percent; grasses, 21 percent; and corn silage, 76 percent.

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REGIONAL DISTRIBUTION IN CROPS

The regional distribution of forages and grain, containing low, variable, or adequate levels of selenium in various areas of the United States and Canada is shown in Figure 2. Under most circumstances the selenium requirements of ruminants and nonruminants will be met by a dietary level of 0.1 to 0.2 ppm (NRC, 1973 [swine], 1975 [sheep], 1976a [beef cattle], 1977 [poultry], 1978 [dairy cattle]). If feed containing less than 0.10 ppm selenium is fed to livestock, selenium/vitamin E-responsive disorders may develop in varying degrees, with a much higher incidence occurring when the selenium concentration drops below 0.05 ppm. Figure 2 indicates where selenium deficiency might occur if farm animals are fed locally grown crops. Feed supplements that have been grown elsewhere and are fed lo

FIGURE 2 Regional distribution of forages and grain containing low, variable, or adequate levels of selenium in the United States and Canada.

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cally may contribute sufficient selenium to the diet to prevent the development of selenium deficiency disorders.

Figure 2 shows that there are broad areas of Canada and the United States where plants contain low levels of selenium. In the United States the most selenium-deficient areas are the Northwest, Northeast, the Atlantic coastal area, Florida, and regions surrounding the Great Lakes. In Canada, in almost all areas east and north of the Great Lakes, in the northern areas of the prairie provinces, and in parts of the Rocky Mountains, selenium deficiency disorders have been most prevalent. Crops grown in the central and west-central regions of Canada and the United States, and in the southern states, usually contain adequate (> 0.10 ppm) levels of selenium for livestock. Presently, it is legally possible to provide farm animals in the United States and Canada with specific dietary selenium supplements to prevent the deficiency disorders.

The preparation of countrywide and even international maps illustrating the relative concentrations of selenium in forages and grains, as in Figure 2, has become possible by integrating the results of numerous surveys conducted on specific areas of the United States and Canada, taken in conjunction with data obtained on a national basis. Some of these include:

United States

Low-selenium areas: Kubota et al. (1967) and Scott and Thompson (1971), many different regions; Carter et al. (1968), Northwest; Patrias and Olson (1969) and Ullrey (1974), Midwest

Selenium-adequate areas: Kubota et al. (1967) and Scott and Thompson (1971), many different regions; Ullrey (1974), Midwest

Seleniferous areas: Byers and Lakin (1939) and Lakin and Byers (1941), Central Plains; Williams et al. (1941), Western States; Beeson (1961) and Rosenfeld and Beath (1964), Wyoming.

Canada

Low-selenium areas: Lessard et al. (1968), Beauchamp et al. (1969), and Young et al. (1977), Ontario; Arthur (1971), most regions; Walker (1971), Martin et al. (1973), and Macdonald et al. (1976), Alberta; Winter et al. (1973), Gupta and Winter (1975), and Winter and Gupta (1979), Atlantic Provinces; Miltimore et al. (1975), British Columbia

Selenium-adequate areas: Arthur (1971), most regions; Walker (1971), Martin et al. (1973), and Macdonald et al. (1976), Alberta; Miltimore et al. (1975), British Columbia; Owen et al. (1977a), Saskatchewan

Seleniferous areas: Byers and Lakin (1939), Thorvaldson and Johnson (1940).

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VARIABILITY IN CONCENTRATION

The concentration of selenium in feed ingredients varies widely depending on the area in which the feedstuff is produced. This can best be seen from analyses described by Williams et al. (1941), Thompson and Scott (1968), Patrias and Olson (1969), Scott and Thompson (1971), NRC (1971), and Wauchope (1978) for the United States; and Arthur (1971) and Miltimore et al. (1975) for Canada. Table 3, in which data have been taken from the above published studies, indicates the variable selenium content of animal feed ingredients.

BIOLOGICAL AVAILABILITY

There have been several published studies illustrating differences in the biological availability of selenium occurring in various feedstuffs. Mathias et al. (1965) found that selenium in alfalfa was comparable to sodium selenite for the prevention of liver necrosis in the rat. The effectiveness of the alfalfa selenium in preventing exudative diathesis in the chick was markedly reduced by a high level of sulfur. Mathias et al. (1967) observed that the selenium present in milk had higher potency than that in sodium selenite for prevention of exudative diathesis, although the two sources of selenium had equal effectiveness in preventing liver necrosis in the rat.

Miller et al. (1972) reported a study in which selenium retention by chicks was compared when the element was derived from fish meal, fish solubles, selenite, or selenomethionine. Selenium from selenomethionine was retained better than that from selenite; and compared to selenomethionine, the fishery products were only 31 percent as effective.

Cantor et al. (1975a) found that selenomethionine was much more potent than either selenite or selenocystine for preventing pancreatic fibrosis in the chick. The selenium in seleniferous wheat was highly effective for preventing both pancreatic fibrosis and exudative diathesis, possibly due to the high percentage of selenomethionine (Olson et al., 1970). In another study, Cantor et al. (1975b) determined the biological availability of selenium in various feedstuffs for the prevention of exudative diathesis. Selenium potency in most of the feedstuffs of plant origin, in comparison to selenite selenium, was highly available, ranging from 60 to 90 percent, but was less than 25 percent available in animal products. Scott (1973) has reported the biological availability of selenium in a number of natural feedstuffs for protection against exudative diathesis as follows: alfalfa meal, 140 percent (vs. selenite selenium); brewers' grains, 89 percent; brewers' yeast, 81 percent; wheat, 110 percent; corn, 83 percent; soybean meal, 64 percent; cottonseed meal, 78 percent; menhaden fish meal, 35 percent; meat and bone meal, 36 per

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cent; poultry by-product meal, 33 percent; tuna meal, 33 percent; and rock phosphate (Curacao), 50 percent. However, Gabrielsen and Opstvedt (1980) suggested that the assay conditions used by Scott and his associates were not valid and published quite different relationships for the bioavailability of selenium in plant and animal products. Relative to selenium in sodium selenite (100 percent), the effectiveness of selenium in fish meals was 32 to 60 percent, in soybean meal was 18 percent, and in corn gluten meal was 26 percent for restoration of serum gluathione peroxidase activity in selenium-depleted chicks.

TABLE 3 Variation of Selenium Concentrations in Various Feed Ingredients (as-fed basis)

	Selenium (ppm)	
Ingredient	United States	Canada
Alfalfa meal	0.01–2.00	0.02–0.27
Barley	0.05–0.50	0.02–0.99
Bentonite	1.00–20.00	—
Blood meal	—	0.50–1.20
Brewers' grains	0.15–1.00	0.29–1.10
Corn	0.01–1.00	0.01–0.33
Dicalcium phosphate	0.15–1.00	0.39–1.00
Feather meal	—	0.60–1.20
Fish meals	1.00–5.00	1.30–3.40
Gluten feed	0.15–0.50	0.12–0.25
Gluten meal	0.10–1.50	0.20–0.57
Linseed meal	0.50–1.20	0.70–1.50
Meat meal	0.08–0.50	0.20–0.81
Oats	0.01–1.00	0.01–1.10
Poultry by-product	0.50–1.00	—
Rapeseed meal	—	0.46–1.90
Soybean meal	0.06–1.00	0.04–0.78
Whole soybeans	0.07–0.90	—
Wheat	0.01–3.00	0.02–1.50
Wheat middlings	0.15–1.00	0.41–0.89
Wheat bran	0.10–3.00	0.24–1.30

SOURCES: Williams et al. (1941), Thompson and Scott (1968), Patrias and Olson (1969), Scott and Thompson (1971), NRC (1971), and Wauchope (1978) for the United States; and Arthur (1971) and Miltimore et al. (1975) for Canada.

Very few studies have been carried out to determine the bioavailability to humans of selenium from various foods (Levander, 1983). Alexander (1982) and Douglass et al. (1981) used animal models and found that the

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availability of selenium from tuna to previously depleted rats was only about half as great as that for selenium from selenite for elevation of hepatic glutathione peroxidase activity. Selenium from beef kidney or various products made from seleniferous wheat were roughly equivalent to selenite. A recent bioavailability trial conducted on Finnish men of low-selenium status who were supplemented with different forms of selenium indicated that a comprehensive assessment of selenium bioavailability requires the determination of several parameters. These include a short-term platelet glutathione peroxidase activity measurement to determine immediate availability, a medium-term plasma selenium measurement to estimate retention, and a long-term platelet glutathione peroxidase measurement after discontinuation of supplements to determine the convertibility of tissue selenium stores to biologically active selenium (Levander et al., 1983).

SELENIUM IN WATER

DRINKING WATER, SPRINGS, AND WELLS

Various aspects of selenium in water have been recently reviewed (NRC, 1980b). Selenium occurs as a minor constituent in drinking water in a concentration range of 0.1 to 100 μg/liter (Davis and De Wiest, 1966). The U.S. Department of Health, Education and Welfare (1962) has set the upper limit for selenium in drinking water to be 10 μg/liter. It would appear from published data that one rarely finds surface waters containing toxic concentrations of the element or even levels that would provide a significant fraction of the nutritional requirements of animals (NRC, 1971). In surveys conducted by the U.S. Department of Health, Education, and Welfare (1959-1962) on the selenium content of waters from the major watersheds, only two samples contained more than 10 μg selenium/liter. In analyzing 194 public water-supply sources, Taylor (1963) found that selenium was barely detectable in most samples; only a few samples averaged as high as 8 μg/liter. In a seleniferous area of South Dakota, Smith and Westfall (1937) could not detect any selenium in drinking water from 34 of 44 wells; the other 10 wells contained 50 to 300 μg selenium/liter. Beath has reported a few instances where appreciable amounts of selenium occur in springs and wells in seleniferous areas. In one instance an Indian family near Ignacio, Colorado, had well water containing 9,000 μg/liter (Beath, 1962). Cannon (1964) reported 5,800 μg/liter in spring water from a uranium-mineralized area in Utah. The selenium content of well water in seleniferous areas is highly variable; however, the vast majority of samples have contained well below the limit of 10 μg/liter (Cooper et al., 1970).

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Byers (1935, 1936) has reported that in seleniferous areas, water in deep wells contains very little selenium. Hadjimarkos and Bonhorst (1961) analyzed well water from farms located in three Oregon counties. They found that most samples contained between 2 μg and less than 1 μ g/liter.

RIVERS, LAKES, AND IRRIGATION WATER

In the extensive surveys conducted on the major watersheds in the United States, only two samples had selenium contents equal to or above 10 μ g/ liter (U.S. Department of Health, Education, and Welfare, 1959-1962). These were a sample from the Animas River at Cedar Hill, New Mexico (10 μ g/liter), and a sample from the Missouri River at St. Louis (14 μg/liter). Using a more sensitive analytical method, Scott and Voegeli (1961) found the selenium content of Animas River samples to contain 1 to 40 μg/liter, averaging close to 1 μg/liter. These authors observed that higher selenium levels in Colorado surface waters were correlated with higher water pH values. There have been reports of high selenium values in river waters where irrigation drainage from seleniferous soils has contained as much as 2,680 μg/liter (Williams and Byers, 1935a; Byers et al., 1938). Rivers at the point of entering the Colorado River have contained up to 400 μg/liter. Water in lakes, including those in seleniferous areas, has been found to contain very little selenium (Beath et al., 1935). These low levels have been explained by the precipitation of selenite with oxides of such metals as iron and manganese (Goldschmidt and Strock, 1935; Byers et al., 1938). Selenium has been detected in a number of deep sea deposits (Goldschmidt and Strock, 1935; Williams and Byers, 1935b; Moxon et al., 1939; Edgington and Byers, 1942) suggesting further that the element can be removed from water by precipitation.

OCEANS

In extensive studies, Schutz and Turekian (1965) found an average of 0.090 μg/liter for selenium in the major oceans. Others have found values of 6 μg/liter or less for ocean waters collected in various locations (Goldschmidt and Strock, 1935; Strock, 1935; Byers et al., 1938; Ishibashi, 1953). The low levels of selenium in most ocean waters have been attributed to its precipitation, under certain conditions, with metal oxides (Strock, 1935; Williams and Byers, 1936; Olson, 1939; Olson and Jensen, 1940).

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SELENIUM IN HUMAN FOODS

DISTRIBUTION BY FOOD GROUPS

The amount of selenium in a plant-derived food varies largely with its protein content and with the area of the country in which it is grown (Levander, 1976a). The concentration of selenium in the milk, eggs, and meat of animals is influenced by the level of selenium in the plant material they consume (Allaway, 1978). In North American diets, cereals are the dominant food of plant origin for supplying selenium, with much of the cereal consumption in the form of bread. The United States and Canadian wheat crops are produced primarily in selenium-adequate regions, and this results in moderately high average concentrations of the element in wheat-related foods in both countries (NRC, 1976b). Meat and fish also are good sources of selenium for humans, whereas most fruits and vegetables provide little selenium. Higgs et al. (1972) concluded that ordinary cooking techniques did not appear to result in major losses of selenium from most foods. Little or no loss of selenium occurred as a result of broiling meat, baking seafoods, frying eggs, or boiling cereals. Ganapathy et al. (1977) found that food preparation methods did not affect the selenium content of legumes and vegetables. Ferretti and Levander (1976) found that although some soybean meat extenders contain comparable or higher selenium levels than the beef or chicken they replace, others have much lower levels. Ferretti and Levander (1974, 1975) also found that small losses of selenium occur during the manufacturing of breakfast cereals, with the lost selenium appearing in the by-products destined for livestock feeding.

CONCENTRATIONS IN SELENIFEROUS REGIONS

Smith and Westfall (1937) reported the selenium content of some foods produced on seleniferous farms in South Dakota, finding 0.16 to 1.27 ppm selenium in milk, 0.25 to 1.0 ppm in bread made from local flour, 0.25 to 9.14 ppm in eggs, and 1.17 to 8.0 ppm (dry basis) in meat. Williams et al. (1941) found 0.1 to 0.5 ppm selenium in bread milled from wheat grown in seleniferous areas of the United States. On analyzing 951 samples of wheat from 8 states in the more seleniferous regions of the United States, Lakin and Byers (1941) found that only 7.5 percent of their samples contained over 4 ppm selenium. The other samples contained 1 ppm or less. Of the 66 samples of flour milled in the regions, only 5 contained more than 1 ppm selenium. Williams et al. (1941) found most samples of mustard seed and dry beans obtained from seleniferous areas contained less than 3 ppm and

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1 ppm, respectively. Anderson et al. (1961) have reported that because many of the most seleniferous areas have been retired from farming, it is likely that there are very few locations today having the high concentration of selenium in foods that was found by Smith and Westfall (1937) and others.

CONCENTRATIONS IN NONSELENIFEROUS REGIONS

There are relatively few reports on the concentration of selenium in foods representative of normal diets in the United States and elsewhere. Some analyses have shown lower levels of selenium in foods produced in low-selenium areas. Characteristically, there are large differences in selenium levels for the same food item among different investigators. One of the main factors contributing to these differences is undoubtedly the use of a small number of samples from a few localized areas. Problems in analytical precision sometimes appear, particularly at low selenium levels (Schroeder et al., 1970).

Nevertheless, despite the variability, the data show at least in a relative way which foods are likely to provide a lower or higher dietary intake of selenium. Information on the nutritional availability of selenium in various foods for humans is meager and is largely inferred from experiments with livestock, poultry, and laboratory animals.

The data subsequently described on selenium levels in various foods are on a fresh-weight basis unless otherwise stated.

DAIRY PRODUCTS AND EGGS

Levels of selenium in milk reflect the level of naturally occurring selenium in the diet. Mathias et al. (1967) found dried skim milk from cows fed either low- or high-selenium diets to contain 0.06 and 0.28 ppm selenium, respectively. Allaway et al. (1968) reported that milk obtained from South Dakota, a relatively high-selenium area, contained 0.05 ppm, whereas a sample from Bend, Oregon, a low-selenium area, contained 0.02 ppm. Other analyses for whole milk sampled in the United States include average values of 0.012 ppm (Morris and Levander, 1970), 0.010 ppm (Schrauzer and White, 1978), and 0.021 ppm (Hadjimarkos, 1963). Values obtained in other countries for cows' milk averaged: Germany, 0.09 ppm (dry basis, Kiermeier and Wigand, 1969); Denmark, 0.2 ppm (dry basis, Bisbjerg et al., 1970); Japan, 0.030 ppm (Sakurai and Tsuchiya, 1975); Canada, 0.015 ppm (Arthur, 1972); USSR, 0.013 ppm (Suchkov, 1971); Great Britain, 0.010 ppm (Thorn et al., 1978); and New Zealand, 0.006 ppm (Millar and Sheppard, 1972).

When selenium supplements have been provided to lactating dairy cows

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there has been very little increase in milk selenium level (Conrad and Moxon, 1979; Maus et al., 1980).

Of other dairy products analyzed, butter and cream (Morris and Levander, 1970; Arthur, 1972) had the lowest concentration of selenium (0.003 to 0.006 ppm) and cheese (Morris and Levander, 1970; Arthur, 1972) the most (0.010 to 0.123 ppm). Whey selenium concentrations generally reflect regional differences in natural selenium levels in feeds consumed by dairy cows (Hitchcock et al., 1975).

In Oregon the selenium concentrations (dry basis) of whole egg samples averaged 0.317 ppm (Hadjimarkos and Bonhorst, 1961). Other values reported for whole eggs have been 0.39 ppm (Arthur, 1972), 0.20 ppm (Schrauzer and White, 1978), and 0.52 ppm (Higgs et al., 1972).

CEREAL PRODUCTS

Levander (1976a) has presented in tabular form much of the reported data on the selenium concentration of various grain products and breakfast cereals. Arthur (1972) reported that the selenium concentration of breakfast foods can vary widely with species of grain and geographical origin. Products made from corn grown in Ontario, Canada, or in the midwestern United States had the lowest values, averaging 0.07 ppm, whereas those made from Canadian western wheat contained the highest amount of selenium, averaging 0.56 ppm. Puffed wheat products made from western Canada durum wheat had an average selenium concentration of 1.27 ppm. Breakfast cereals from rice grown in the southern United States varied in selenium concentration from 0.01 to 0.24 ppm. Analyses for the United States show a wide variation among various breakfast cereals: 0.024 to 0.451 ppm (Morris and Levander, 1970); 0.032 to 0.51 ppm (Higgs et al., 1972); and 0.201 to 1.26 ppm (dry basis, Ganapathy et al., 1977). Bread appears to be a relatively good source of selenium ranging from 0.28 to 0.68 ppm in various reports (Levander, 1976a), with whole wheat bread containing more selenium than white bread (Morris and Levander, 1970; Arthur, 1972; Schrauzer and White, 1978).

MEAT, POULTRY, AND FISH AND OTHER SEAFOODS

Meats are a good source of selenium. It is apparent from the results of many studies that levels in animal tissues tend to be reflections of the concentrations of available "natural" selenium in the diets (Hoffman et al., 1973; Jenkins et al., 1974), although when supplements of inorganic selenium are added to the diets, the tissue levels of selenium may not be increased appreciably (NRC, 1971). Ku et al. (1972) reported that the sele

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nium concentrations of longissimus muscle (loin) of swine fed typical diets in various states ranged from 0.034 ppm (Virginia) to 0.521 ppm (South Dakota) and were linearly correlated ($r > 0.9$) with dietary selenium concentrations. Reports from various countries on the selenium concentration of selected meats and fish products have been summarized by Levander (1976a). Morris and Levander (1970) found the average selenium value for steak, ground beef, chicken, pork chops, and lamb chops was 0.22 ppm, a value similar to that obtained by others for beef, pork, and poultry meats (Arthur, 1972; Schrauzer and White, 1978). Kidneys were found by Morris and Levander (1970) to contain the highest concentrations of selenium (1.4 to 3 ppm) in animal tissues, followed by liver (0.20 to 0.85 ppm). Fish and other seafoods are good sources of selenium; Arthur (1972) reported trout to contain 0.36 ppm and shrimp to contain 2 ppm. Other workers (Morris and Levander, 1970) found an average value of 0.63 ppm in cod and flounder fillets and 0.63 ppm for various shellfish.

FRUITS AND VEGETABLES

Fruits and vegetables are recognized as poor dietary sources of selenium (Levander, 1976a). Many have less than 0.01 ppm (Morris and Levander, 1970; Arthur, 1972; Ganapathy et al., 1977; Schrauzer and White, 1978; Thorn et al., 1978). Cucumbers, carrots, cabbages, onions, and radishes had slightly higher values, 0.015 to 0.140 ppm, and mushrooms and garlic between 0.060 and 0.249 ppm selenium.

BABY FOODS

The average values for processed meats, cereals, fruits, and vegetables followed those previously described except that they were considerably lower than fresh, unprocessed samples (Morris and Levander, 1970; Arthur, 1972; Levander, 1976a; Thorn et al., 1978).

DIETARY SELENIUM LEVELS IN VARIOUS COUNTRIES

An indication of the selenium concentration of certain selected foods for various countries is presented in Table 4.

It is evident that in each country there are wide differences in the selenium level in foods, depending on the kind of food and location where it was produced. In the United States, because diets have a varied nature and the ingredients a varied origin, it is unlikely except under unusual circumstances that an excess or inadequacy of dietary selenium would arise. Individual intakes of selenium will vary with the amounts of selenium-rich foods eaten. Those consuming more of the high-selenium cereal products, seafoods, and animal organs such as kidneys and liver would have higher dietary selenium levels. However, the intake of most Americans would fall within the suggested safe and adequate range of approximately 50 to 200 μg selenium/day (NRC, 1980a).

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TABLE 4 Selenium Content of Selected Foods of Various Countries[a]

	Average Selenium Content and/or Range (ppm, wet basis [b])					
Food	United States	Canada	Germany	Britain	UKSSR	Japan
Meats (no kidney, liver)	0.22 (0.12–0.43)	0.14 (0.03–0.35)	0.27	0.06	0.292	0.01–0.05
Kidney	1.62	2.77	—	1.39	—	—
Liver	0.43	0.43	0.44	0.13	—	—
Seafoods (excluding fish)	0.53 (0.34–0.66)	1.25	—	—	—	—
Fish	0.38	1.08	1.54	0.37	—	—
Whole milk	0.012	0.015	0.14	<0.01	0.100	—
Butter, cream	0.006	0.003	—	<0.01	—	—
Cheese	0.082 (0.052–0.105)	0.080	—	0.12	0.298	—
Eggs	0.098	0.039	1.01	0.11	0.022	0.12–0.26
Cereal products	0.38 (0.03–0.67)	0.52	—	0.11	0.278	0.02–0.87
Vegetables	0.010 (0.004–0.039)	0.027 (0.001–0.12)	0.03 to	<0.01	0.125	—
Fruits	0.006	0.007	0.30 (both)[c]	<0.01	0.004	—

[a]Derived from: Morris and Levander, 1970, United States; Arthur, 1972, Canada; Oelschläger and Menke, 1969, Germany; Thorn et al., 1978, Britain; Suchkov, 1971, Ukrainian Soviet Socialist Republic; Suzuki et al., 1970, Japan.

[b]Food analyses for Germany expressed on a dry basis.

[c]Range for vegetables and fruits combined.

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The average daily intakes of selenium by humans in various countries have been reported by several investigators (Table 5; Levander, 1976a). Watkinson (1974) calculated that the per capita dietary intake was 56 μg/ day in New Zealand; 132 μg/day in Maryland, USA; and 151 μ g/day in Ontario, Canada. Thompson et al. (1975) found a range of 98 to 224 μg/ day in the diet of Canadians. Sakurai and Tsuchiya (1975) found that a typical Japanese diet provided about 88 μ g/day. Mondragon and Jaffe (1971) estimated the average daily intake by Venezuelans as 326 μg. Other investigators have reported average daily selenium intakes for humans as: Great Britain, 60 μg (Thorn et al., 1978); New Zealand, 28 to 32 μg (Thomson and Robinson, 1980); Sweden, 23 to 210 μg (Boström and Wester, 1968; Wester, 1971, 1974); northeastern United States, 60 to 150 μ g (Schroeder et al., 1970); and Finland, 30 μg (Koivistoinen, 1980). Welsh et al. (1981) determined by analysis the actual selenium intakes of Maryland, USA, residents consuming self-selected diets as 81 ± 41 μ g/ day.

Analyses of market basket samples collected in four different regions of the United States have not revealed appreciable differences in selenium intake (U.S. Department of Health, Education, and Welfare, 1974). However, great extremes in the dietary intake of selenium have been reported in the People's Republic of China, ranging from 11 μg/day in Keshan disease areas to 5 mg/day in areas of endemic selenosis (G. Q. Yang, personal communication).

CONTRIBUTIONS OF WATER

Present U.S. standards for drinking water suggest 10 μ g selenium/liter as the acceptable upper limit (U.S. Department of Health, Education, and Welfare, 1962). Drinking water rarely contains selenium at levels above a few micrograms per liter. Therefore, this source of selenium is unlikely to be significant from either a nutritional or a toxicological standpoint, a conclusion that is in accord with a recently published report (NRC, 1980b).

SELENIUM CYCLING IN NATURE

Several proposals have been made for the cycling of selenium in nature. An early scheme developed by Moxon et al. (1939) described a geological cycling of selenium in which plants and animals had a role. In 1964 a biological selenium cycle was postulated, involving the oxidation and reduction of the element by plants, fungi, and bacteria (Shrift, 1964). Later, Lakin and Davidson (1967) summarized knowledge of the geochemical cycling of selenium, and the cycling of low and high levels of the element in soils, plants, and animals was reviewed by Allaway et al. (1967) and Olson (1967), respectively. Recent versions of the cycling of selenium in nature are shown in Figure 3 (NRC, 1976b) and Figure 4 (Frost, 1973).

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TABLE 5 Estimated Human Daily Intake of Selenium from Dietary Sources (µg/day)a

Food	New Zealand[b]	United States[b]	Canada[b]	Canada[c] Toronto-1	Canada[c] Toronto-2	Canada[c] Winnipeg	Canada[c] Halifax	Japan[d]	Venezuela[e]
Plant									
Vegetables, fruit, sugars	5.8	5.4	6.9	5.1	1.3	9.1	7.4	6.5	14.6
Cereals	4.3	44.5	74.4	62.0	111.8	79.8	105.0	23.9	88.2
Animal									
Dairy products	8.4	13.5	23.4	6.5	5.0	27.6	21.8	2.3	70.4
Meat, fish	37.7	68.6	46.0	24.7	30.4	64.3	90.0	55.6	152.6
Total	56.2	132.0	150.7	98.3	148.5	180.8	224.2	88.3	325.8

[a]From review by Levander, 1976.
[b]Watkinson, 1974.
[c]Thompson et al., 1975.
[d]Sakurai and Tsuchiya, 1975.
[e]Mondragon and Jaffe, 1971.

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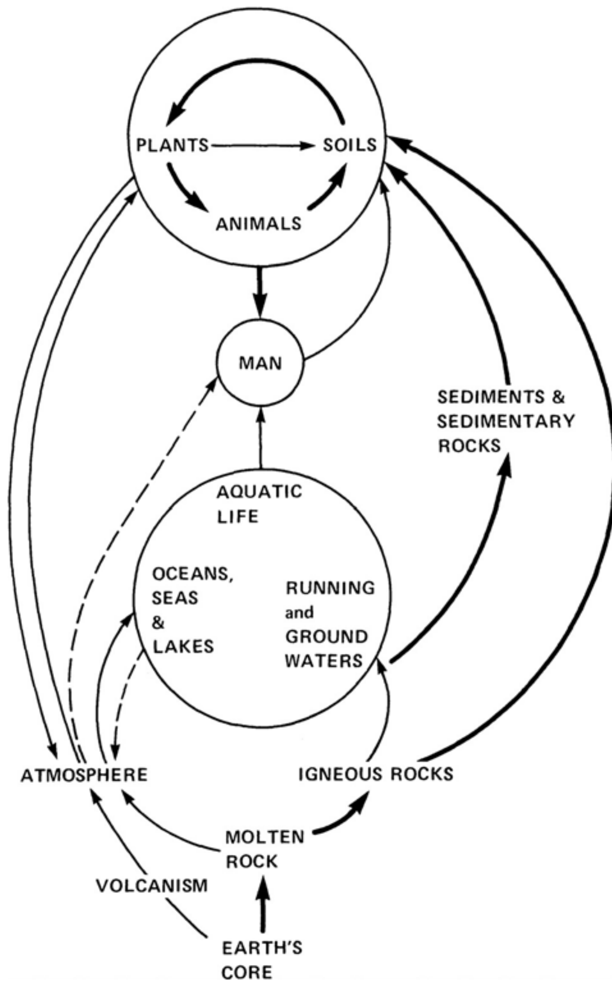

FIGURE 3 Cycling of selenium in nature. From NRC, 1976b.

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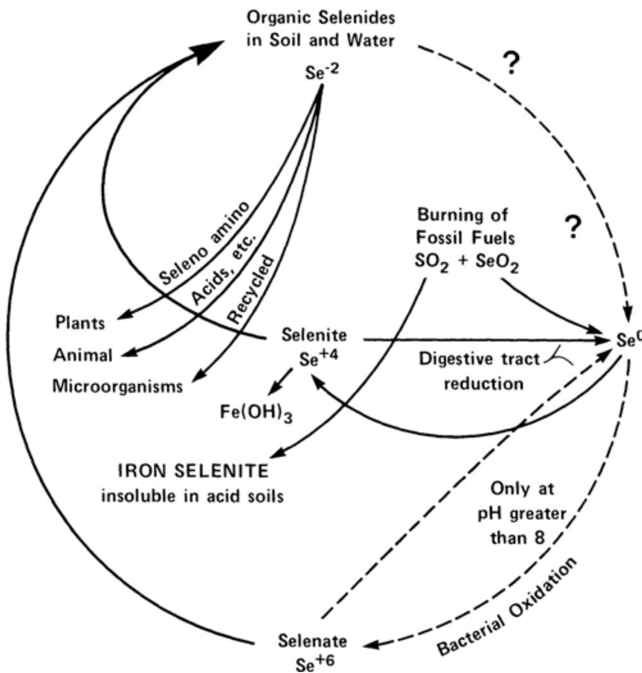

FIGURE 4 Some possibilities of biological cycling of selenium. From Frost, 1973.

Quantitative information on each of the cycling processes, involving rocks, water, air, soils, plants, and animals, is meager. However, it is possible to describe each of the cycle components in a general way. Selenium is transported from the core to the surface of the earth through igneous extrusion and volcanic gases. Soils may obtain selenium from the rocks that form the parent material, from volcanism, from industrial airborne wastes, from irrigation water, and from fertilizers. Geological processes such as wind erosion, glaciation, water erosion, and leaching all affect the selenium content of soils. Although selenium in sedimentary rocks is insoluble and unavailable to plants, chemical weathering and plant and microbial action transform much of it to soluble and available forms. The soil pH can have a marked influence on the selenium content of the plants. Chemical oxidation in alkaline soils produces selenate, which is available to plants; in acid soils the forms of selenium are much less available. The concentration of selenium in feed and food plants is governed largely by the amount and availability of the element in the soils. The levels of selenium in milk, eggs, and meats reflect the concentration of the element in the plant material fed to the

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livestock and poultry producing the food. Plant and animal wastes return selenium to the soil.

Oceans, seas, and lakes obtain selenium from inflowing waters, with some of the element deposited in the sediments. Selenium is transported in running water to lowlands and poorly drained areas.

The atmosphere is supplied with selenium via soil dust, volcanoes, burning of fossil fuels, industrial emissions, and volatile products produced by plants and animals. Some of the airborne element returns to the land and water as solid particles or in water precipitation.

In the biological cycling of selenium, selenite and selenate are taken up by the plant roots with much selenium subsequently reduced within the plant to the −2 oxidation state. Monogastric animals consume food containing selenium compounds in the −2 oxidation state and appear to reduce dietary selenite and selenate. The trimethyl selenonium ion is excreted in the urine (Palmer et al., 1970), and primarily elemental selenium and metal selenides are excreted in the feces (Peterson and Spedding, 1963). Thus, animal feces return the element to the soil in relatively insoluble, inert forms. Some soil bacteria can convert the elemental selenium to selenite and selenate forms, thereby making it available to plants (Sarathchandra and Watkinson, 1981). In addition to the biological processes in the soil, chemical oxidation of selenium compounds may increase the availability of the element to plants.

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4

Biochemical Functions

Klaus Schwarz (1965), in whose laboratory the essentiality of selenium in animals was discovered (Schwarz and Foltz, 1957), postulated that selenium functioned as an essential cofactor at specific sites of intermediary metabolism. Currently, the known biochemical functions of selenium are as a component of the enzyme glutathione peroxidase, found in animals, and of several bacterial enzymes. The selenium deficiency signs observed in animals can be partially explained by a lack of glutathione peroxidase (GSH-Px) (Hoekstra, 1975), but this does not eliminate the possibility of other roles for selenium in animals (see "Other Functions of Selenium," page 49). For example, Burk and Gregory (1982) have recently reported a selenium-binding protein of unknown function in rat liver and plasma that has properties quite distinct from those of GSH-Px. In contrast to animals, microorganisms generally grow and reproduce well in the absence of selenium, a lack of certain selenium-containing enzymes being the only sign of selenium deficiency in bacteria.

In 1954, Pinsent reported that selenium (and molybdenum) were necessary for the appearance of formate dehydrogenase activity in *E. coli.* At about the same time that Rotruck et al. (1973) reported that GSH-Px in the rat was a selenoenzyme, the microbial enzymes formate dehydrogenase (Andreesen and Ljungdahl, 1973) and protein A of glycine reductase (Turner and Stadtman, 1973) were shown to be selenoenzymes. These two enzymes are inhibited by iodoacetamide (Turner and Stadtman, 1973; Enoch and Lester, 1975), and the form of selenium in reduced glycine reductase and formate dehydrogenase has been reported to be selenocysteine (Cone et al.,

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1976, 1977; Jones et al., 1979). Two other bacterial enzyme activities, nicotinic acid hydroxylase (Imhoff and Andreesen, 1979) and xanthine dehydrogenase (Wagner and Andreesen, 1979) have been reported recently to require the presence of selenium. A fifth possible selenoprotein, thiolase, isolated from two bacterial species grown in the presence of selenium, has been reported to contain selenium (Hartmanis, 1980). In animals, GSH-Px is presently the only known selenoenzyme, and thus knowledge of the chemistry and biochemistry of GSH-Px is an important part of our current understanding of the biochemical function of selenium in animals.

NATURE AND PROPERTIES OF GLUTATHIONE PEROXIDASE

Glutathione peroxidase (glutathione: H_2O_2 oxidoreductase, E.C. 1.11.1.9) was discovered by Mills (1957), who found that this enzyme in the presence of reduced glutathione would protect erythrocytes against H_2O_2-induced and ascorbate-induced hemoglobin oxidation and hemolysis. The addition of glucose to the incubation medium was shown to protect the erythrocyte at least in part by maintaining the concentration of reduced glutathione (Mills and Randall, 1958; Cohen and Hochstein, 1963). Vitamin E, added to the diet or to the incubation medium, protected erythrocytes against hemolysis (Dam, 1957), but dietary selenium was usually reported not to prevent hemolysis (Christensen et al., 1958; Gitler et al., 1958). Rotruck et al. (1971, 1972a) integrated these facts and demonstrated that dietary selenium protected erythrocytes from ascorbic acid-induced hemolysis only if glucose was included in the incubation medium. The ability of vitamin E to prevent hemolysis was not affected by glucose, and glucose had no protective effect if the erythrocytes were from selenium-deficient rats. Glutathione levels were higher in erythrocytes from selenium-deficient rats than from selenium-adequate rats, suggesting that the defect in selenium deficiency was not in the maintenance of glutathione levels, but rather in its utilization. Rotruck et al. (1972b, 1973) then focused on GSH-Px and discovered that it was a selenoenzyme.

Glutathione peroxidase has been purified from the tissues of cattle, humans, swine, sheep, and rats, and shown to be an approximately 80,000-dalton enzyme consisting of four apparently identical subunits (Ganther et al., 1976). Determination of GSH-Px molecular weight by sedimentation-equilibrium indicates that the molecular weight of GSH-Px differs from species to species: 76,000 ± 1,000 for rat liver (Nakamura et al., 1974), 83,800 ± 1,200 for bovine erythrocytes (Flohé et al., 1971a), 95,000 ± 3,000 for human erythrocytes (Awasthi et al., 1975). The size of GSH-Px can vary also from tissue to tissue in the same species (Awasthi et al., 1975, 1979;

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Sunde et al., 1978). Oh et al. (1974) and Flohé et al. (1973) independently demonstrated that GSH-Px from ovine and bovine erythrocytes contained 4 g-atoms of selenium per mole of GSH-Px. This value has been confirmed by Nakamura et al. (1974) and Awasthi et al. (1975) for rat liver and human erythrocytes. Glutathione peroxidase contains no heme or flavin, in contrast to other peroxidases (Flohé et al., 1971c), and neutron activation analysis has indicated that no metals other than selenium are present in GSH-Px (Flohé et al., 1973).

Following the demonstration that the selenium in protein A of reduced microbial glycine reductase was selenocysteine (Cone et al., 1976, 1977), Forstrom et al. (1978) and Wendel et al. (1978) reported that the selenium in reduced GSH-Px is present also as selenocysteine. These workers alkylated the reduced form of purified GSH-Px with iodoacetate or chloroacetate and then hydrolyzed the enzyme in hydrochloric acid. The alkylated derivatives were separated from the other amino acid residues by standard amino acid analysis procedures. The selenium-containing peak co-chromatographed with authentic carboxymethylselenocysteine, indicating that the selenium in the reduced form of GSH-Px is present as selenocysteine. Sequential Edman degradation was used to demonstrate that the selenocysteine is incorporated into the peptide backbone of GSH-Px (Zakowski et al., 1978).

The amino acid composition of rat liver GSH-Px was determined by Nakamura et al. (1974). Each subunit was reported to contain two cysteine and three methionine residues out of a total of 153 amino acids. The amino acid composition of bovine erythrocyte GSH-Px is similar; it contains 178 amino acid residues, and a tentative amino acid sequence has been published (Ladenstein et al., 1979).

Bovine erythrocyte GSH-Px has been crystallized, and the three dimensional structure at 2.8 Å resolution has been determined (Ladenstein and Wendel, 1976; Ladenstein et al., 1979). The subunits are nearly spherical, with a radius of 18.7 Å; the subunits are identical or at least very similar, with one Se atom per subunit. The GSH-Px tetramer, with dimensions of 90.4 × 109.5 × 58.6 Å, appears to be an almost flat, planar arrangement of two dimers. Each active site consists of regions from both subunits of a dimer. The selenium atoms are located on the surface of the enzyme; the selenium atoms in a dimer are 21 Å apart, suggesting that only one selenium atom is present per active site. The number of active sites per tetramer has not been established nor has whether all four selenium atoms are active catalytically. The selenium atom appears as a "protrusion of the main chain density," and Ladenstein et al. (1979) concluded that a selenocysteine or selenocysteine derivative satisfactorily fits this density.

Thiols other than glutathione are poor substrates for GSH-Px (Mills, 1959). Flohé et al. (1971b) studied the donor substrate specificity in detail

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and found no other substrate with more than 30 percent of the activity of glutathione. In contrast to catalase, GSH-Px will destroy a variety of organic hydroperoxides at rates similar to those of H_2O_2 destruction (Little and O'Brien, 1968). Various lipid hydroperoxides, steroid hydroperoxides, thymine hydroperoxide, nucleic acid hydroperoxides, prostaglandin hydroperoxides, and presumably vitamin K hydroperoxide have been shown to be acceptor substrates for GSH-Px (Christophersen, 1969; Günzler et al., 1972; Little, 1972; Nugteren and Hazelhof, 1973; Larson and Suttie, 1978). On the other hand, cholesterol-25- and cholesterol-7α-hydroperoxide have been reported to be poor substrates (Little, 1972) and the enzyme cannot reduce fatty acid peroxides esterified in phospholipids (McCay et al., 1981). Because several peroxide substrates elicit similar maximal velocities, a peroxide-enzyme complex is most likely not formed during catalysis.

Flohé and co-workers (Flohé et al., 1972; Günzler et al., 1972; Flohé and Günzler, 1974) have studied extensively the kinetics of GSH-Px. They concluded that the reaction mechanism is a ter uni ping-pong mechanism: the first step is an oxidation of the enzyme by the peroxide substrate followed by release of the corresponding alcohol. This is followed by two successive additions of reduced glutathione (GSH) to the enzyme, and then release of oxidized glutathione (GSSG). This mechanism takes into account the inability to saturate the enzyme with either substrate and the similar V_{max} for most peroxide substrates. Formation of ternary or quaternary complexes is not predicted during catalysis. The mechanism is best described as a series of three bimolecular steps.

Ganther et al. (1976) proposed that the selenium in GSH-Px cycles between a selenol (E-SeH) and a selenenic acid (E-SeOH), or between a selenenic acid and a seleninic acid (E-SeOOH). X-ray photoelectron spectroscopy (Wendel et al., 1975; Chiu et al., 1977) and x-ray crystallographic studies (Ladenstein et al., 1979) have provided some evidence for different oxo-derivatives of selenium during catalysis, but have not conclusively identified these several oxidation states.

Purified GSH-Px not exposed to GSH is irreversibly inhibited by cyanide; reduction of the enzyme with GSH, dithiothreitol, or dithionite prevents this inhibition by cyanide (Prohaska et al., 1977b). However, reduced GSH-Px is irreversibly inhibited by iodoacetate (Flohé and Günzler, 1974). Flohé and Günzler (1974) were unable to detect bound GSH when excess GSH was used, but Kraus et al. (1980) have demonstrated that GSH can bind to a form of GSH-Px different from the fully reduced and fully oxidized forms of the enzyme. These results suggest that GSH binds to an intermediate form of GSH-Px by a selenyl-sulfide (E-Se-SG) or seleninyl-sulfide (E-Se(O)SG) linkage. Thus chemical reactivity can be used to identify the various oxidation states of GSH-Px that

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seemingly correspond to the intermediate forms of the enzyme proposed by the kinetic data of Flohé et al. (1972), and to those of the proposed molecular mechanism of Ganther et al. (1976).

Glutathione peroxidase has been assayed either by direct measurement of the disappearance of GSH (Mills, 1959; Flohé, 1971; Hafeman et al., 1974) or by the use of an excess of glutathione reductase (NAD(P)H:GSSG oxidoreductase EC 1.6.4.2), which couples the utilization of GSH to the disappearance of NADPH (Paglia and Valentine, 1967). Because the apparent K_m for each substrate is dependent on the concentration of the other substrate, the assay is usually conducted with a fixed initial level of GSH and a concentration of peroxide far above the apparent K_m for the peroxide. Sodium azide, and not cyanide, should be used to inhibit catalase, because of cyanide inhibition of GSH-Px (Prohaska et al., 1977b). Because H_2O_2 reacts faster spontaneously with GSH than do organic hydroperoxides, causing a higher background, several workers have suggested that cumene hydroperoxide or t-butyl hydroperoxide be used for assaying GSH-Px. However, with the discovery that the GSH-S-tranferases have GSH-Px activity with organic hydroperoxide substrates but not H_2O_2 (Prohaska and Ganther 1977), these substrates are not recommended for the determination of Se-dependent GSH-Px activity unless the absence of GSH-S-transferase activity has been confirmed chromatographically. Another pitfall encountered in GSH-Px activity determination is that hemoglobin will catalyze the oxidation of GSH by H_2O_2. Paglia and Valentine (1967) suggested that the conversion of methemoglobin to cyanomethemoglobin would eliminate this problem, but Flohé and Brand (1970) reported that this treatment did not completely eliminate hemoglobin-induced peroxidase activity when H_2O_2 was used as a substrate. Günzler et al. (1974) found that non-GSH-Px catalysis of GSH oxidation was completely eliminated by cyanomethemoglobin formation if one of the organic hydroperoxide substrates was used and the cyanomethemoglobin conversion was performed on freshly drawn blood. Provided that GSH-S-transferase activity is not present, this method should be adequate for the determination of GSH-Px in low activity samples, such as human blood. However, some investigators have found that this technique does not compensate satisfactorily for peroxidase activity associated with human hemoglobin (Burk et al., 1981; Butler et al., 1982).

GLUTATHIONE PEROXIDASE ACTIVITY IN ANIMALS

The distribution of GSH-Px activity in animal tissues has been reviewed thoroughly by Ganther et al. (1976). In the selenium-adequate rat the highest GSH-Px activity is found in the liver and erythrocytes; moderate

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activity in the heart, kidney, lung, and adrenal glands; and low activity in the brain, testis, and lens (Lawrence et al., 1974). In the selenium-adequate chick, GSH-Px activity is high in the liver and moderately low in erythrocytes (Omaye and Tappel, 1974). In the selenium-adequate lamb, GSH-Px activity is very high in erythrocytes and low in the liver (Oh et al., 1976a,b). The guinea pig has been reported to have very low levels of liver GSH-Px (Lawrence and Burk, 1978). These reports demonstrate that the tissue distribution of GSH-Px varies from species to species.

Approximately 60 percent of the GSH-Px activity in rat liver is cytosolic and 30 percent mitochondrial (Green and O'Brien, 1970; Flohé and Schlegel, 1971). At least 60 percent of rat liver mitochondrial Se is associated with GSH-Px (Levander et al., 1974). Between 75 and 100 percent of ovine erythrocyte selenium is accounted for by selenium incorporated into GSH-Px (Oh et al., 1974), but as little as 10 percent of the selenium in livers from selenium-adequate sheep was reported to be accounted for by GSH-Px (Sunde et al., 1978). These differences may reflect the presence of other specific selenoproteins, or they may simply indicate that in tissue with low GSH-Px activity, a large proportion of the selenium is incorporated into or bound nonspecifically to proteins in general.

Selenium supplementation has been shown to increase tissue GSH-Px activity above that of unsupplemented animals in rats (Chow and Tappel, 1974; Hafeman et al., 1974; Lawrence et al., 1974; Reddy and Tappel, 1974; Smith et al., 1974;), chicks (Noguchi et al., 1973; Omaye and Tappel, 1974; Cantor et al., 1975b), sheep (Godwin et al., 1975; Oh et al., 1976a,b; Whanger et al., 1977, 1978b), cattle (Anderson et al., 1978), mice (Revis et al., 1979), horses (Caple et al., 1978), swine (Sivertsen et al., 1977; Hakkarainen et al., 1978), Japanese quail (Kling and Soares, 1978) deer (Brady et al., 1978b), and salmon (Poston et al., 1976). In humans, strong correlations between blood selenium and GSH-Px activity have been observed in individuals consuming low levels of selenium (Thomson et al., 1977b; McKenzie et al., 1978), but Schmidt and Heller (1976) and Schrauzer and White (1978) have reported a lack of correlation between blood GSH-Px activity and blood levels of selenium in individuals consuming adequate or high levels of selenium. This is most likely due to the non-specific incorporation of selenomethionine into blood proteins, as described below. In addition, blood selenium and GSH-Px were not correlated in blood of pregnant women (Butler et al., 1980, 1982), indicating other factors may be involved.

Of the various body components studied, liver and plasma GSH-Px activities decrease most rapidly during selenium depletion and increase most rapidly during selenium repletion (Noguchi et al., 1973; Chow and Tappel, 1974; Hafeman et al., 1974; Lawrence et al., 1974; Omaye and Tappel,

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1974, Reddy and Tappel, 1974; Smith et al., 1974; Oh et al., 1976a,b). Tissue GSH-Px activity has been reported by several workers to also increase with the log of the dietary selenium concentration (Omaye and Tappel, 1974; Smith et al., 1974), yet other workers (Hafeman et al., 1974; Oh et al., 1976a,b) have reported that tissue GSH-Px activity plateaus at approximately 0.1 ppm dietary selenium for all tissues except erythrocytes and pancreas. This leveling off of GSH-Px activity, but not selenium content, with increasing selenium supplementation suggests that tissue GSH-Px activity may be a better indicator of effective selenium status than is tissue selenium content.

Direct comparison of the biopotency of various selenium compounds for GSH-Px synthesis has shown that, in selenium-deficient chicks fed diets supplemented with less than 0.1 ppm selenium, selenite was twice as effective as selenomethionine in increasing plasma, liver, and heart GSH-Px (Noguchi et al., 1973), but that with higher levels of selenium supplementation or a longer supplementation period, selenite and selenomethionine had equal biopotency (Omaye and Tappel, 1974; Cantor et al., 1975b). Pierce and Tappel (1977) found that a single large oral dose of selenite or selenomethionine (300 μg Se/90 g rat) given to selenium-deficient rats resulted in similar increases in liver, kidney, small intestine, and stomach GSH-Px activity 48 hours after selenium administration. However, Sunde et al. (1981) found that with dietary selenium supplementation to selenium-deficient rats the increase in liver, plasma, and heart GSH-Px due to selenite supplementation was not affected by the level of dietary methionine, but that suboptimal dietary methionine impaired the biopotency of selenomethionine below 0.5 ppm selenium. Additional dietary methionine resulted in a selenomethionine biopotency equivalent to selenite biopotency.

Selenomethionine degradation has been thought to follow the usual methionine degradation pathways (Schwarz, 1965). McConnell and coworkers (McConnell and Cho, 1965, 1967; Hoffman et al., 1970; McConnell and Hoffman, 1972a,b) have shown that selenomethionine can readily replace methionine in intestinal uptake, acylation of methionine-tRNA, and incorporation into general body proteins. Clearly, selenomethionine follows the metabolic pathways of intact methionine, and thus when methionine is limiting, selenomethionine will be incorporated into general body proteins in place of methionine, where it will be unavailable for GSH-Px synthesis until these proteins turn over. This can explain the observations of Sunde et al. (1981) that selenomethionine biopotency is impaired when dietary methionine is limiting.

Hawkes et al. (1979) have indicated that selenocysteine may be incorporated directly into the peptide backbone of GSH-Px via a specific seleno

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cysteine-tRNA, but Sunde and Hoekstra (1980) have shown with isotope dilution experiments that selenite and selenide are more readily metabolized than is selenocysteine to a form of selenium that can be incorporated into GSH-Px. These workers have suggested that a form of selenium other than free selenocysteine is incorporated posttranslationally into an amino acid residue (such as serine) already incorporated in the pre-GSH-Px protein.

Germain and Arneson (1977) demonstrated that selenate did not provide selenium for GSH-Px synthesis in mouse neuroblastoma cells, whereas selenite very effectively increased GSH-Px activity, indicating that selenate is not the form used for GSH-Px synthesis, and that selenate reduction to selenite is impaired in these cells. Selenocystine and selenite had equivalent biopotency in this in vitro system (Germain and Arneson, 1979). White and Hoekstra (1979) demonstrated that selenium from selenite was much more readily incorporated into GSH-Px than was selenium from selenomethionine. Because animals are unable to synthesize selenomethionine from inorganic selenium (Cummins and Martin, 1967; Jenkins, 1968) and are able to synthesize selenocysteine from inorganic selenium only to a minimal extent (Olson and Palmer, 1976), these results further indicate that another inorganic form of selenium serves as the immediate precursor used for selenium incorporation into GSH-Px. Further experiments will be necessary to establish the pathways of selenium metabolism leading to the immediate selenium precursor and the mechanism of selenium incorporation into GSH-Px.

GLUTATHIONE-S-TRANSFERASE

In 1976 it was discovered that selenium-deficient rat liver had a non-selenium-dependent GSH-Px activity (Lawrence and Burk, 1976; Prohaska and Ganther, 1976). This activity is catalyzed by one or more of the GSH-S-transferases (EC 2.5.1.18) (Prohaska and Ganther, 1977). These enzymes have no catalytic ability to destroy H_2O_2 but will reduce cumene hydroperoxide and t-butyl hydroperoxide. This peroxidase activity shows zero-order kinetics with respect to GSH, in contrast to GSH-Px kinetics (Prohaska and Ganther, 1977; Lawrence et al., 1978). Sephadex G-150 chromatography separates these two enzymes; the molecular weight of the rat liver GSH-S-transferases is 39,000. After chromatography to tissue preparations of rat erythrocytes, skin, skeletal muscle, spleen, heart, lung, thymus, and intestine, Lawrence and Burk (1978) reported no detectable peroxidase activity due to the presence of GSH-S-transferase. Liver and adrenals had the highest activity. Approximately 90 percent of the total activity determined with cumene hydroperoxide was accounted for by

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GSH-S-transferase in the testis of selenium-adequate rats, but only 35 percent of the total in liver, kidney, and adrenal. GSH-S-transferase accounted for 43 percent of the total activity determined with cumene hydroperoxide in hamster liver; 70 to 85 percent of the activity in livers from pigs, sheep, chickens and humans; and 100 percent of the activity in guinea pig liver. This does not demonstrate, however, that guinea pigs do not have selenium-dependent GSH-Px or a selenium requirement, because preliminary data indicate that GSH-Px can account for at least 15 percent of the total activity in guinea pig liver and 100 percent in erythrocytes (Sunde and Hoekstra, unpublished).

FUNCTION OF GLUTATHIONE PEROXIDASE

The discovery that hydroperoxides were substrates for GSH-Px (Little and O'Brien, 1968) provided an important clue to the biochemical function of GSH-Px, and thus of selenium. The erythrocyte possesses both catalase and GSH-Px activity. From kinetic data and GSH levels present in the erythrocyte, Flohé et al. (1972) have calculated that the rate of H_2O_2 reduction per heme or per selenium, respectively, is nearly identical for these two enzymes in the erythrocyte. Catalase would therefore seem to be far more important than GSH-Px for H_2O_2 destruction because of the higher concentrations of catalase in the red cell. However, GSH-Px-deficient erythrocytes are susceptible to hemolysis when exposed to oxidizing agents, indicating that the ability to reduce hydroperoxides is of critical importance in the erythrocyte.

Except in degenerate cells like the mammalian erythrocyte, catalase and GSH-Px are often localized in distinct compartments (catalase in the peroxisomes and GSH-Px in the cytosol and mitochondrial matrix space), such that there is little direct overlap in the competition for H_2O_2 (Flohé et al., 1976). In human and guinea pig leukocytes, catalase activity is low and GSH-Px activity is high (Higgins et al., 1978), further demonstrating that these two protective enzymes are generally not in direct competition for H_2O_2.

Decreases in tissue GSH-Px activity and the development of selenium-deficiency signs in animals are well correlated. In weanling rats fed a selenium-deficient diet, liver GSH-Px activity falls to undetectable levels at about the time liver necrosis develops (Hafeman et al., 1974). In chicks, depressed plasma GSH-Px activity and the development of exudative diathesis are well correlated (Noguchi et al., 1973; Cantor et al., 1975b). These diseases are prevented either by dietary selenium or vitamin E, suggesting that selenium and vitamin E have overlapping roles in the protection of cells.

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Liver perfusion experiments have helped to substantiate the role of GSH-Px in protecting the liver against peroxidation. Isolated perfused rat liver was shown to destroy H_2O_2 or organic hydroperoxides added to the perfusate and to release GSSG into the perfusate (Sies et al., 1972; Sies and Summer, 1975). Burk et al. (1978) demonstrated that GSSG was not released when livers from selenium-deficient rats were perfused with H_2O_2, indicating that GSH-Px was the catalytic source of the GSSG. Under rather unphysiological conditions (i.e., perfusion of liver with high levels of organic hydroperoxide), GSH-S-transferase destroyed the organic hydroperoxides added to the perfusate and released GSSG into the perfusate. This indicates that the peroxidase activity of GSH-S-transferase may have some physiological significance. Chance et al. (1978) have shown that exposure of perfused liver to hyperbaric oxygen will cause the release of GSSG into the perfusate; GSSG release is especially increased in the vitamin E-deficient liver. These perfusion experiments demonstrate that GSH-Px, vitamin E, and possibly GSH-S-transferase can function in the cell to protect against peroxidation.

OTHER FUNCTIONS OF SELENIUM

Selenium may have other biochemical functions in higher animals that are not a result of the ability of GSH-Px to serve as a biological antioxidant. It is unlikely that GSH-Px acts directly on fatty acid hydroperoxides in lipid membranes, but it may function by catalyzing the destruction of cytosolic hydrogen peroxide (McCay et al., 1981). A mammalian selenium-binding protein clearly different from GSH-Px was reported to be present in selenium-adequate lambs but absent in lambs suffering from nutritional muscular dystrophy (Pedersen et al., 1972). This 10,000-dalton protein has proved difficult to purify and characterize (Whanger et al., 1973; Black et al., 1978) and so the claim that it is a selenoprotein must remain tentative until the protein is characterized and the selenium stoichiometry determined.

A selenium-binding protein of 15,000 to 20,000 daltons has been observed in bovine and rat spermatozoa. Calvin (1978) reported a 17,000-dalton selenium-binding protein located in the midpiece of rat sperm. Pallini and Bacci (1979) found a 20,000-dalton selenium-binding protein in bovine sperm mitochondria, and McConnell et al. (1979b) have reported a 15,000-dalton selenium-binding protein from rat testis cytosol. Spermatozoa from selenium-deficient rats have been reported to show decreased mobility and increased midpiece breakage (Brown and Burk, 1973; Wu et al., 1973, 1979). Thus, spermatozoa may possess a specific selenoprotein that serves as a mitochondrial structural protein or as an enzyme, although

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the possibility that this protein is a GSH-Px subunit or its derivative has not been eliminated.

It would seem unlikely that only one or two selenoproteins arising from selenite administration are present in animals, yet GSH-Px appears to be the only substantial ^{75}Se-labeled peak present in chromatograms of cytosol of liver and most other tissues, except at early time points, following (^{75} Se)selenite administration. Several other ^{75}Se-binding proteins have been observed in various tissues, but have not been characterized (Chen et al., 1975; Prohaska et al., 1977a; Herrman, 1977; Gasiewicz and Smith, 1978). Additional selenoproteins may be present in the particulate fractions as well as the soluble fractions of animal tissues.

Burk et al. (1974) reported that selenium-deficient rats accumulate three times as much injected ^{75}Se in the microsomal fraction of rat liver as do rats supplemented with 0.5 ppm dietary selenium. Burk and Correia (1978) further demonstrated that with selenium deficiency, the rate of heme degradation is increased following phenobarbital injection, suggesting that selenium may have a role in the regulation of heme catabolism. These reports suggest that additional biochemical roles for selenium as a component of membrane-bound proteins may be discovered.

Hoffman and McConnell (1974) and Chen and Stadtman (1980) have reported that selenium can be incorporated into the purine and pyrimidine bases of RNA in bacteria grown in presence of selenite. Hawkes et al. (1979) have reported ^{75}Se-labeled, acylated tRNAs isolated from rat liver, which may contain selenium in the RNA portion of the molecule. Thus, selenium may have a specific role in rare purine or pyrimidine bases.

Selenium deficiency, in combination with vitamin E deficiency, has been shown to decrease the ability of ducks to resist infection (Yarrington et al., 1973). The microbicidal activity, but not phagocytizing ability, of neutrophils from selenium-deficient rats and cattle is also impaired (Serfass and Ganther, 1975, 1976; Boyne and Arthur, 1978). Neutrophil GSH-Px activity was depressed in selenium-deficient animals, so the effect of selenium deficiency on the immune response may or may not involve GSH-Px.

Glutathione peroxidase may have a specific role in prostaglandin synthesis (Nugteren and Hazelhof, 1973; Van Dorp, 1975); but prostaglandin endoperoxide synthetases also have peroxidase activity, so GSH-Px may not be essential for prostaglandin metabolism (Christ-Hazelhof and Nugteren, 1978). Bryant and Bailey (1980) have noted altered metabolism of arachidonic acid via the lipoxygenase pathway in platelets from selenium-deficient rats and have suggested that this may be the first example of a specific function for selenium as a required component in the normal metabolism of an essential fatty acid.

Burk et al. (1980) recently reported that the toxicity of diquat, a herbi

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cide similar to paraquat, was reduced, but not eliminated, in selenium-deficient rats by injection of a physiological dose of selenite 6 to 10 hours before diquat administration. These workers suggested that this protection was due to a biochemical function of selenium other than that of GSH-Px because tissue GSH-Px activities were not significantly increased 10 hours after the selenium injection. This report offers strong evidence for an additional role of selenium in animals, although the effect could possibly be mediated by localized increases in GSH-Px activity not detectable in whole tissue homogenates.

NUTRITIONAL AND METABOLIC INTERRELATIONSHIPS

With the first demonstration of the essentiality of selenium—that selenium was the integral part of Factor 3 and prevented liver necrosis in rats—it was clear that the biochemistry of selenium is interrelated with other nutritional factors. Of these other factors, the biochemical function of vitamin E seems most complementary with that of selenium. As discussed more completely in other parts of this report, selenium and vitamin E deficiencies in animals cause degenerative lesions; the nature and tissue location depends on the species and the status of other nutritional factors. For example, in rats a combined deficiency of vitamin E and selenium results in liver necrosis (Schwarz and Foltz, 1957). Vitamin E deficiency alone causes fetal death and resorption (Evans and Bishop, 1922), and selenium deficiency alone results in poor growth and failure to reproduce in rat pups born to selenium-deficient dams and raised on a selenium-deficient diet (McCoy and Weswig, 1969). Chicks develop muscular dystrophy, encephalomalacia, exudative diathesis, or pancreatic degeneration, depending on the presence or absence of vitamin E, selenium, sulfur amino acids, and excess dietary unsaturated fatty acids (Scott, 1978).

The effects of vitamin E and of selenium deficiency have been postulated to result from the destruction of cellular membranes or of critical cellular proteins and thus of cellular integrity. Addition of polyunsaturated fatty acids to the diet tends to exacerbate these deficiency defects, whereas synthetic antioxidants in many cases will alleviate the signs of vitamin E and selenium deficiency. Tappel (1962) suggested a basis for these observations by postulating that the biochemical role of vitamin E is as a lipid antioxidant. Selenium was also classified as an antioxidant because of its ability to prevent a number of vitamin E deficiency diseases. Green and Bunyan (1969) attacked this hypothesis because they felt there was no direct evidence showing that lipid peroxidation occurred in vivo, that vitamin E was chemically involved in the protection against lipid peroxidation, or that selenium had antioxidant properties in vivo.

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In the 1970s, however, several new discoveries strongly suggested that activated-oxygen and free-radical attack of cellular components occurs, and that generation of hydroperoxides occurs in vivo. As discussed above, GSH-Px was shown to contain selenium, demonstrating that selenium does have antioxidant properties in animals. Superoxide dismutase was identified as a scavenger of superoxide (McCord and Fridovich, 1969); together, superoxide dismutase and GSH-Px may prevent the reaction of superoxide with hydrogen peroxide to form hydroxy radical (Fridovich, 1975). Ethane and pentane evolution in the breath of rats due to the peroxidative breakdown of unsaturated fatty acids also demonstrated that lipid peroxidation does occur in vivo and that such lipid peroxidation is minimized by vitamin E and dietary selenium (Dillard et al., 1977; Hafeman and Hoekstra, 1977a,b). Thus selenium, as a component of GSH-Px, and vitamin E both can serve as biological antioxidants; these findings do not eliminate the possibility of other biochemical roles for either of these nutrients.

Hydrogen peroxide, hydroperoxides, superoxide, various radicals including hydroxy radical, and possibly singlet oxygen are formed as products of necessary reactions in cells or by further chemical reaction of these products, and so protective systems have evolved to contain and ultimately destroy these reactive species before they damage cells. These protective systems are compartmentalized and thus complement one another. As a lipid-soluble antioxidant, vitamin E scavenges free radicals and possibly singlet oxygen (McCay et al., 1978) before they can attack cellular and intracellular membranes. Glutathione peroxidase destroys H_2O_2 and hydroperoxides in the cytosol and mitochondrial matrix space. Catalase degrades H_2O_2 in the peroxisome. Superoxide dismutase detoxifies superoxide in the cytosol and mitochondria before superoxide can react with H_2O_2 to form hydroxy radical.

In deficiency diseases that can be prevented by either vitamin E or selenium, such as liver necrosis in the rat, the cells seemingly have vitamin E and GSH-Px organized in a serial arrangement; the origin of the prooxidant species is presumably in the soluble portion of the cell, but the molecular target is in the membrane. If GSH-Px does not destroy the peroxides, then vitamin E can still protect the membrane. Although lipid hydroperoxides are excellent substrates for GSH-Px, this soluble enzyme has been reported not to reduce lipid hydroperoxides within membranes to the corresponding alcohols in vitro. Instead, GSH-Px may protect the cell by destroying hydrogen peroxide and thus preventing the formation of hydroxy radical (McCay et al., 1976).

In deficiency diseases that can be prevented by dietary selenium but not by vitamin E, such as pancreatic degeneration in the chick (Cantor et al., 1975a), aqueous prooxidant species are seemingly formed that can then

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damage critical soluble proteins without initial destruction of the membrane. Analogous to the relationship between selenium and vitamin E deficiency and pancreatic degeneration, the toxicity of paraquat and nitrofurantoin is reported to be increased by selenium deficiency but not by vitamin E deficiency in the chick (Combs and Peterson, 1979, 1980). These water-soluble herbicides most likely catalyze the production of superoxide, which could lead to hydroxy radical formation if GSH-Px, as well as superoxide dismutase, is not present. Apparently in the chick the target of the toxic species, presumably hydroxy radical, is in the cytosol and thus is not protected by lipid-soluble vitamin E. In the rat, however, both selenium and vitamin E deficiencies are reported to increase paraquat toxicity (Bus et al., 1975), suggesting a difference in the relative roles of vitamin E and GSH-Px in these two species.

In deficiency diseases that can be prevented by vitamin E but not by selenium, such as encephalomalacia in the chick, presumably both the origin and the target of the activated species lie within the hydrophobic regions of the cell. The different abilities of various antioxidants to replace vitamin E and prevent deficiency diseases has been related to their different abilities to quench these species and to their differential solubilities in hydrophobic regions of tissues such as membrane and adipose tissue.

Nutritional muscular dystrophy in lambs can often be prevented by selenium supplementation alone (Muth et al., 1958), although dietary unsaturated fatty acid supplementation will produce a nutritional muscular dystrophy that is not prevented by selenium (Blaxter, 1962; Whanger et al., 1977). A high-polyunsaturated-fat diet also accelerates the development of encephalomalacia in vitamin E-deficient chicks. Apparently the increased unsaturated fatty acid content in the diet causes an increased susceptibility of the membrane to peroxidation that cannot be prevented by soluble GSH-Px.

The addition of sulfur amino acids to the diet delays the onset of liver necrosis in rats fed selenium- and vitamin E-deficient diets. This effect is not due solely to contamination of the sulfur amino acids by selenium (Schwarz, 1965). The torula yeast-based diets commonly used in such experiments are limiting in the sulfur amino acids; the addition of methionine to the diet has been shown to increase the hepatic GSH concentration (Seligson and Rotruck, 1979). A higher GSH level increases the apparent V_{max} of GSH-Px (Flohé et al., 1972) and thus may explain the ability of methionine to delay the onset of liver necrosis. Alternatively, supplemental sulfur amino acids may improve the availability of selenomethionine present in the torula yeast (Sunde et al., 1981). Schwarz (1965) reported that the addition of various methyl donors such as choline or betaine to the diet exacerbates the development of liver necrosis and may be due to a decreased degradation of

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selenomethionine as well as of methionine. These results suggest that adequate dietary methionine, or dietary sulfur in ruminants, is important for maximal selenium biopotency in livestock because a major form of selenium in most feedstuffs of plant origin is selenomethionine (Allaway et al., 1967; Olson et al., 1970). Additionally, selenomethionine present in general body proteins may be an important source of selenium as these proteins turn over.

Tissue GSH-Px activity can be induced or repressed by various factors. Increased tissue GSH-Px activity is observed under conditions of increased oxidant stress, such as exposure to ozone or the inclusion of autooxidized lipids in the diet (Chow and Tappel, 1974; Reddy and Tappel, 1974). Revis et al. (1979) reported increased GSH-Px activity in the muscles from genetically dystrophic mice as compared to control mice, suggesting either GSH-Px induction or a selective advantage of higher GSH-Px in these genetically dystrophic mice. Excess dietary vitamin E has been shown to decrease tissue GSH-Px in rats (Yang and Desai, 1978), further suggesting that a relative decrease in oxidant stress will lower the need for GSH-Px.

The deficiency of several required nutrients not previously mentioned—iron deficiency in humans and rabbits (Macdougall, 1972; Rodvien et al., 1974), riboflavin deficiency in pigs (Brady et al., 1979), vitamin B_6 deficiency in rats (Yasumoto et al., 1979), and copper deficiency in rats (Jenkinson et al., 1980)—have been reported to decrease tissue GSH-Px activities, but the mechanisms are not understood.

Several toxic agents have been shown to decrease tissue GSH-Px activity. Silver acetate decreased liver GSH-Px activity in rats supplemented with 0.5 ppm selenite (Wagner et al., 1975), and 0.2 percent tri-o-cresyl phosphate reduced liver and erythrocyte GSH-Px activity by altering selenium metabolism (Swanson, 1975). Silver may precipitate selenide and thus make it unavailable for GSH-Px synthesis; tri-o-cresyl phosphate decreases tissue selenium levels, apparently by increasing selenium excretion. Doxorubicin, an anticancer drug that is very cardiotoxic, has been reported to reduce heart GSH-Px activity within 4 hours after injection into rabbits. It is unclear whether this reduction is due to specific antagonism of selenium or GSH-Px metabolism, or to general toxicity to the heart (Revis and Marusic, 1978; Doroshaw et al., 1980).

Selenium has been shown to reduce the toxicity of cadmium, inorganic and methyl mercury, thallium, and silver. Selenium apparently decreases the rate of excretion of these toxic substances and changes the distribution of these elements within the body (Parizek et al., 1974). Recently Gasiewicz and Smith (1978) identified a specific protein in plasma that binds both cadmium and selenium; either element alone will not result in the formation of this relatively stable complex, suggesting that this complex

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is a possible biochemical mechanism for the decreased toxicity and metabolic changes observed within the body when selenium and cadmium are administered concurrently. Ganther et al. (1972) demonstrated that selenium also protects against methylmercury toxicity and suggested that the presence of selenium may lessen the toxicity of the mercury in tuna. The observation that vitamin E and the synthetic lipid soluble antioxidant N,N′-diphenyl-p-phenylene-diamine (DPPD) protected against methylmercury poisoning in rats (Welsh, 1979) led to the suggestion that methylmercury may exert part of its toxic action by generating free radicals (Gan

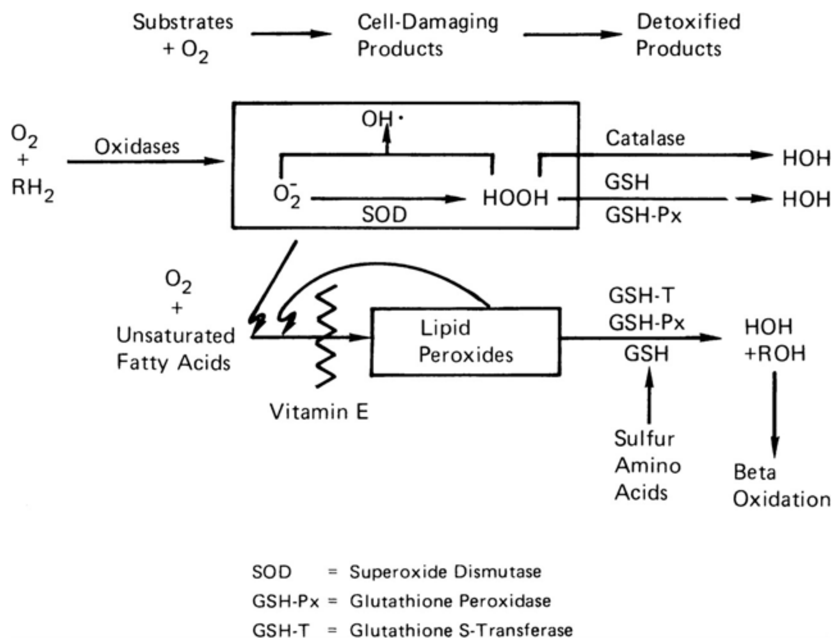

FIGURE 5 Interrelationships of selenium, vitamin E, and sulfur amino acids. In oxidative metabolism, highly reactive forms of oxygen are produced, such as superoxide ion, hydroxy radical, and hydrogen peroxide (upper box). Catalase and glutathione peroxidase (a selenoenzyme) decompose hydrogen peroxide. Unsaturated fatty acids react with oxygen to form lipid hydroperoxides. This process is stimulated by free radicals (curved arrows) and inhibited by radical scavengers such as vitamin E. Reduction of organic peroxides by glutathione is catalyzed by glutathione peroxidase and also by various GSH transferases (sometimes called GSH peroxidase II). Glutathione peroxidase helps prevent the formation of lipid peroxides (by destroying hydrogen peroxide) and may also help eliminate those peroxides that are formed. (Prepared by H. E. Ganther, University of Wisconsin, Madison.)

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ther, 1980). Reports that lead (Bell et al., 1978) and copper (Godwin et al., 1978) are more toxic to selenium-deficient animals and that copper pretreatment will decrease the toxicity of selenium (Stowe and Brady, 1978; Stowe, 1980) suggest that the metabolism of several other elements is interrelated with that of selenium. Characterization of the biochemical interactions of these elements awaits further experimentation.

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5

Metabolism

DIETARY FORMS

A number of organic selenium compounds have been identified in plants or plant products. These compounds include selenocystine, selenocysteine, Se-methylselenocysteine, selenohomocystine, selenomethionine, Se-methyl-selenomethionine, selenomethionine selenoxide, selenocystathionine, and dimethyl diselenide (Shrift, 1969). There is some evidence for the presence of selenite and selenate in plants (Butler and Peterson, 1967; Olson et al., 1970). Selenocystine, selenocysteine, selenomethionine, and Se-methylselenomethionine, however, appear to be the major selenium compounds in seeds or forages commonly consumed by livestock (Peterson and Butler, 1962; Shrift, 1969; and Olson et al., 1970). Thus, organic selenium is the major form for animals consuming natural feeds.

Feeds and forages grown in certain areas of North America, however, do not contain enough selenium to meet livestock requirements (see the section, "Regional Distribution in Crops"). One way to correct this deficiency has been to mix grains grown in high-selenium areas with selenium-deficient feeds (Ullrey et al., 1977). Approval has now been given to add inorganic selenium to feeds deficient in this element, and the most common forms used are sodium selenite or selenate. Selenized yeast tablets, containing primarily organic selenium, are available as human supplements and have been shown to increase blood selenium levels (Schrauzer and White, 1978).

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ABSORPTION

The absorption of selenium is significantly lower in ruminants than in monogastric animals. The retention of selenium taken orally as selenite was found to be 77 percent in swine as compared to only 29 percent for sheep (Wright and Bell, 1966). Essentially, no absorption of selenium occurred in the rumen and abomasum, and the greatest absorption of selenium occurred in the small intestine and the cecum of sheep. In swine, no absorption occurred in the stomach and the first part of the small intestine, but the greatest absorption occurred in the last part of the small intestine, the cecum, and the colon. Similar observations have been noted for rats. The greatest absorption of selenomethionine and selenite occurred in the duodenum, followed in decreasing amounts by the jejunum and ileum, with essentially no absorption in the stomach (Whanger et al., 1976). By use of the everted intestinal sacs of hamsters, McConnell and Cho (1965) found that selenomethionine was transported against a concentration gradient, whereas selenite and selenocystine were not. The transport of selenomethionine was inhibited by methionine, but the transport of selenite and selenocystine was not inhibited by their respective sulfur analogues.

Some differences in the absorption of selenium incorporated into protein, as compared to the unbound form, have been found. The intestinal absorption of ^{75}Se from a kidney homogenate of rabbits dosed with ^{75}Se-selenomethionine was 87 percent, as compared to 91 percent for selenomethionine mixed with unlabeled rabbit kidney homogenates (Thomson et al., 1975). ^{75}Se-selenite or ^{75}Se-selenomethionine was injected into the coelomic cavity of fish, and their muscle removed, homogenized, and fed in diets to rats. The intestinal absorption of ^{75}Se given as labeled fish was less complete than that of ^{75}Se mixed with unlabeled fish (Richold et al., 1977). In a short-term human study, selenite was almost as well absorbed as selenomethionine in young women (Thomson et al., 1978a). In a prolonged study, three individuals were given different treatments. One was given 100 μg selenium as selenomethionine, the second was given 100 μg selenium as selenite, and the third was given 65 μg selenium in mackeral daily for 4 to 10 weeks (Robinson et al., 1978a). Selenite-Se was not absorbed (45 percent) as well as selenomethionine (75 percent) or fish-Se (66 percent). Thus, different dietary forms of selenium may have an influence on absorption in humans.

VASCULAR TRANSPORT

From 75 to 85 percent of the selenium in ovine erythrocytes is associated with glutathione peroxidase (GSH-Px)(Oh et al., 1974). Essentially all of

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the selenium in erythrocytes of rats is associated with GSH-Px, but only about 10 percent of the selenium is associated with this enzyme in human erythrocytes (Behne and Wolters, 1979). Even less of the selenium (1.5 percent) in human plasma is associated with this enzyme. Patterns similar to those in humans have been noted for the rhesus monkey (Whanger, unpublished observations). Thus, the major proportion of selenium is associated with GSH-Px in rat or sheep erythrocytes, but not in primate erythrocytes.

Even though there are differences in the amount of selenium associated with GSH-Px between primates and other animals, the metabolism of selenite by blood in vitro is similar. The uptake and release of selenite by bovine (Jenkins and Hidiroglou, 1972) or human erythrocytes (Lee et al., 1969) involve sulfydryl groups, and the binding of selenite to plasma proteins is dependent upon the presence of erythrocytes (Lee et al., 1969; Sandholm, 1974, 1975). This binding of selenium to plasma proteins is not energy dependent and does not require protein synthesis (Porter et al., 1979). These relationships have been clarified further with studies on rat erythrocytes (Gasiewicz and Smith, 1978). The uptake and subsequent metabolism of selenite are dependent upon the reduced glutathione concentrations in the erythrocytes. The results indicate that H_2Se or a similar product of GSSeSG reduction by glutathione reductase was the final product of selenite metabolism by rat erythrocytes.

In mice plasma the protein-bound selenium is mainly located in albumin, with smaller amounts possibly situated with the α- and β-globulins (Sandholm, 1974). In contrast, the important selenium-binding proteins in plasma of humans appear to be the lipoproteins. When human blood was incubated with ^{75}Se-selenite in vitro, the most heavily labeled proteins in the plasma were the α-lipoproteins and an unidentified fraction located electrophoretically between the α_1- and β_2-globulin fractions (Sandholm, 1975). This is consistent with the findings of Burk (1974), who showed that up to 16 percent of the plasma ^{75}Se was found in very low density lipoproteins after the administration of ^{75}Se-selenite to patients. The ^{75}Se bound to human plasma proteins is absorbed by lymphocytes in preference to selenite, suggesting that plasma proteins function as carriers of selenium to these lymphocytes (Porter et al., 1979).

BODY RETENTION AND TISSUE DISTRIBUTION

The tissue distribution of selenium in various animals using either ^{75}Se or stable selenium has been reported by several investigators. With required dietary selenium intake, the kidney contains the highest concentration of selenium, followed by the liver and other glandular tissues such as the

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spleen and pancreas. Intestinal and lung tissues can have relatively high concentrations. Cardiac muscle contains appreciably more than skeletal muscle. Wool and hair may have relatively high concentrations, but nervous tissue has low concentrations. Selenium concentrations in muscle, liver, and kidney for sheep, cattle, and swine and in muscle, liver, and eggs for poultry fed various levels of dietary selenium are shown in Table 6. Some typical values for selenium in tissues in addition to those shown in Table 6 are (in ppm wet weight) cardiac muscle, 0.15 to 0.20; pancreas, 0.34 to 0.44; ovary, 0.19 to 0.25; cerebrum, 0.07 to 0.09; and wool, 0.21 to 0.49.

Not only is the tissue content of selenium dependent upon the level in the diet, but also upon the chemical form. In general, selenium is deposited in tissues at higher concentrations when present in diets as organic rather than as inorganic selenium. A possible exception to this involves using as a selenium source fish meal, in which heavy metals are thought to complex the selenium (Mahan and Moxon, 1978). Ullrey et al. (1977) fed sheep and cattle diets composed of low-selenium ingredients from Michigan and added selenite selenium to make the diets contain 0.20 and 0.30 ppm selenium, respectively. These workers then used grains from South Dakota to formulate diets containing similar levels of selenium. In both sheep and cattle the selenium content in muscle, liver, kidney, and plasma was higher when the South Dakota diets were fed than when the same amount of selenium as selenite was fed in the Michigan diets. Likewise in pigs the selenium content in muscle, liver, and kidney was higher when the diet containing 0.45 ppm selenium was composed of ingredients from South Dakota than when the same level of selenium, predominantly as selenite, was fed in diets composed of ingredients from Michigan (Ku et al., 1973). Also, the selenium in various grain products for swine must be considered. Inorganic and organic selenium contributed from brewers' grains or distillers' grains and solubles were shown to result in similar weekly serum selenium response curves within each selenium level with 4-week-old weanling swine, while selenium contributed by fish meal had lower levels (Mahan and Moxon, 1978). At 0.4 ppm dietary selenium intake, muscular tissue selenium levels were greater, compared to the selenite source, when fish meal or brewers' grains were fed, whereas nonmuscular tissue (liver, kidney, and testes) had similar selenium concentrations for all groups. Fish meal provided the poorest selenium retention of all test products evaluated. This difference in response to various organic selenium sources has also been demonstrated with poultry. Selenium given as selenomethionine results in higher content in muscle than when given as selenite or selenocystine (Osman and Latshaw, 1976). Latshaw and Biggert (1981) also showed that dietary selenomethionine results in higher egg selenium con

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centrations than does dietary selenite. Selenium given as selenomethionine or as seleniferous wheat resulted in more selenium in eggs than when selenium was given as selenocystine, *Astragalus* selenium, or fish meal (Latshaw and Osman, 1975). Consistent with tissue data on sheep, cattle, and swine, when selenium is supplied as a natural feed ingredient (0.42 ppm) for hens, it causes higher muscle, liver, and egg selenium content than when the same amount is supplied predominantly as selenite (Latshaw, 1975). Furthermore, the availability of selenium must be taken into consideration. For example, using chicks as the test animals, the availability of selenium from plant sources was found to be higher (60 to 210 percent) than from animal sources (8 to 25 percent), as compared to sodium selenite (Cantor et al., 1975b).

In lambs suffering from white muscle disease (WMD), levels of selenium less than 0.05 ppm in muscle and less than 0.1 ppm in liver (dry basis) have been observed (Allaway et al., 1966). When the dietary intake of selenium is very low, the kidney of lambs has a higher concentration of selenium than does the liver, but when the dietary intake of selenium is increased, the liver usually has a higher concentration of selenium than does the kidney (Ewan et al., 1968c; Oh et al., 1976b). These workers fed lambs an artificial milk composed of torula yeast, glucose, stripped lard, vitamins, and minerals. Tissue selenium levels were very low in unsupplemented lambs (less than 0.02 in muscle, less than 0.08 in liver, and less than 0.2 ppm in kidney). Supplementation with selenium as selenite up to 1.0 ppm caused the greatest increase of selenium content in the liver. In work with practical diets (Paulson et al., 1968a; Oh et al., 1976a) various levels of selenium as selenite (up to 0.52 ppm) were added to deficient diets, and muscle, liver, and kidney levels increased respectively from 0.02, 0.05, and 0.5 to 0.1, 0.9, and 3.8 ppm. Paulson et al. (1968a) determined the selenium content of lambs fed “commercial” diets at several state agricultural experiment stations. These diets contained 0.16 to 0.52 ppm selenium; the selenium in skeletal muscle ranged from 0.2 to 1.6 ppm, in the livers from 0.61 to 2.5 ppm, in the kidneys from 3.8 to 7.5 ppm (dry basis), and in blood from 0.23 to 0.61 ppm. These workers also reported that the blood reached 0.71 ppm in sheep grazing native grasses containing 1.15 ppm selenium. Ullrey et al. (1978) and Paulson et al. (1968a) determined the tissue selenium residue of lambs fed up to 264 ppm selenium in salt. At this highest level of selenium intake in salt the muscle, liver, blood, and kidney contained, respectively, 0.57, 6.5, 0.36, and 4.8 ppm selenium (dry-weight basis).

At high levels of selenium intake the livers and kidneys of cattle and sheep have been found to contain 5 to 25 ppm of selenium (fresh-weight basis). Moxon et al. (1944) reported 5.6 ppm selenium in liver and 3.0 ppm in muscle (both fresh-weight basis) of

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TABLE 6 Concentrations of Selenium in Animal Tissues in Relation to Level of Dietary Selenium

Animal	Diet and Selenium Content (ppm)	Major Form of Selenium	Range in Tissue Se Content (ppm)			Plasma Se (ppb)	References and Tissue Se Basis
			Muscle	Liver	Kidney		
Lambs (6 wk)	Dams fed hay and oats (0.01–0.04 Se)	Organic	0.02–0.04	0.04– 0.10	0.52– 0.83		Allaway et al. (1966) dry weight
	Dams fed hay and oats (0.47–2.70 Se)	Organic	0.80–2.40	4.00–14.70	3.28– 7.70		
Lambs (4–8 wk)	Torula yeast-glucose artificial milk (0.01 Se)	Organic	0.02–0.20	0.05– 0.45	0.20	15	Ewan et al. (1968b), Oh et al. (1976b)[a] dry weight
	Plus 0.10 Se (selenite)	Inorganic	0.04–0.16	0.06– 0.70	1.80	99	
	Plus 0.50 Se (selenite)	Inorganic	0.27	1.80	3.30	151	
	Plus 1.00 Se (selenite)	Inorganic	0.29–0.46	3.00– 3.60	—		
Lambs (17–18 wk)	Legume-grass silage, and hay and grain (0.02 Se)	Organic	0.08–0.10	0.15– 0.19	1.90– 2.40		Paulson et al. (1968a), Oh et al. (1976a)[a] dry weight
	Plus 0.05–0.09 Se (selenite)	Inorganic	0.10–0.14	0.30– 0.50	2.90– 3.40		
	Plus 0.12–0.50 Se (selenite)	Inorganic	0.18–0.30	0.60– 1.90	3.60– 4.20		
	0.16 Se	Organic	0.36	0.90	3.80		
	0.23–0.52 Se	Organic	0.62–1.56	0.92– 2.54	5.90– 7.60		
Lambs (17–22 wk)	Deficient diet composed of hay and grain	Organic	0.11–0.24	0.48– 1.40	3.87– 4.50	53 (30)	Paulson et al. (1968a), Ullrey et al. (1978) dry weight
	Plus 26–30 Se (selenite in salt)	Inorganic	0.22–0.25	0.93– 1.60	4.35– 4.50	88 (180)	
	Plus 65–170 Se (selenite in salt)	Inorganic	0.27–0.38	1.44– 2.60	4.34– 5.11	112–125 (290)	
	Plus 264 Se (selenite in salt)	Inorganic	0.57	6.50	4.80	(360)	
	Hay and grain diets ranging (0.19–0.78 Se)	Organic	0.92	2.14	5.38	124	Ullrey et al. (1978) dry weight
	Plus 30 Se (selenite in salt)		0.93	2.10	4.89	127	
	Plus 65 Se (selenite in salt)		0.68	2.02	4.63	150	
	Plus 170 Se (selenite in salt)		1.13	2.71	4.60	137	

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Lambs (46 kg)	Complete roughage and grain (0.060 Se)	Organic	0.06	0.19	0.99	32[b]	Ullrey et al. (1977) wet weight
	Plus 30 Se (selenite in salt)	Inorganic	0.07	0.27	1.24	78[b]	
	Complete roughage and grain						
	(0.20 Se)	Inorganic	0.09	0.38	1.26	114[b]	
	(0.20 Se)	Organic	0.17	0.62	1.30	156[b]	
	(0.30 Se)	Inorganic	0.11	0.53	1.22	134[b]	
	(0.30 Se)	Organic	0.16	0.66	1.35	164[b]	
Yearling ewes	Hay and grain high protein diet (Se?)	Organic		0.75	0.50		Rosenfeld and Beath[c] (1945) wet weight
	Plus dosing with total of 360 to 860 mg Se for up to 64 d	Inorganic	0.00–0.80	1.33– 9.10	1.47– 6.87		
	Plus dosing with total of 1,922 mg Se for up to 116 d	Inorganic	0.80	29.21	3.95		
Ewes (2 yr)	Hay and grain (Se?)	Organic	0.20	0.80	1.40		Maag and Glenn (1967) wet weight
	Plus dosing 37.5 mg Se/d/93 d	Inorganic	0.50–0.60	17.50–28.00	4.50– 6.90		
	Plus dosing 50 mg Se/d/93 d	Inorganic	0.90	24.70	6.20		
Calves (20 wk)	Mostly grain practical diet (0.3 Se)	Organic	0.50	0.91	2.70	(110)	Kincaid et al. (1977) lyophilized weight
	Plus 0.1 Se (selenite)	Inorganic	0.46	0.89	2.78	(110)	
	Plus 1.0 Se (selenite)	Inorganic	0.84	2.66	3.76	(180)	
Calves (8 mo)	Roughage and concentrate	Organic	0.03	0.09	1.01	21	Ammerman et al. (1980) wet weight
	Plus 0.1 Se (selenite)	Inorganic	0.04	0.11	1.22	22	
	Plus 0.2 Se (selenite)	Inorganic	0.04	0.11	1.29	24	
Steers (470 kg)	Complete roughage and grain						
	(0.20 Se)	Inorganic	0.086	0.38	1.37	65[b]	Ullrey et al. (1977) wet weight
	(0.20 Se)	Organic	0.14	0.50	1.46	76[b]	
	(0.30 Se)	Inorganic	0.10	0.44	1.37	73[b]	
	(0.30 Se)	Organic	0.14	0.50	1.58	91[b]	
Steers (246 kg)	Base diet of grain and hay (0.11 Se)	Organic	0.07–0.11	1.13– 1.20	1.08– 1.32		Maag and Glenn (1967) wet weight
	Plus 0.55 to 1.10 mg Se/kg wt daily for 18 wk	Inorganic	0.10–0.70	5.00–12.30	2.55– 4.37		

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Steers (4 yr)	Grazed pastures of 4–13 Se for 3 summers	Organic	3.03	5.60	3.95	(2100)	Moxon et al. (1944) wet weight
Pigs (76 d)	Purified diet with torula yeast (0.01 Se), glucose, vitamins and minerals	Organic	0.07	0.08	1.25		Ewan (1971) lyophilized weight
	Plus 0.50 Se (selenite)	Inorganic	0.30	1.38	7.50		
Pigs (11 wk)	16% crude protein, corn-soy diet (0.052 Se)	Organic	0.055	0.17	1.51	(62)	(62) Groce et al. (1973b) wet weight
	Plus 0.05 Se (selenite)	Inorganic	0.075	0.36	1.88	(139)	
	Plus 0.10 Se (selenite)	Inorganic	0.091	0.40	1.82	(145)	
	Plus 0.20 Se (selenite)		0.093	0.41	1.80	(154)	
Pigs (50 kg)	16% crude protein, corn-soy diet (0.04 Se)	Inorganic	0.12	0.61	2.14		Ku et al. (1973) wet weight
	Plus 0.40 Se (selenite)	Organic	0.48	0.84	2.17		
	Crude basal (0.45 Se)	Organic	0.45	0.92	2.33		
	Plus 0.10 Se (selenite)						
Pigs (10 wk)	Corn-soybean meal (0.07 Se)	Organic	0.04	0.05	0.36	13[b]	Mahan and Moxon (1978) wet weight
	Plus 0.12 Se (selenite)	Inorganic	0.07	0.23	1.05	63[b]	
	Fish meal (0.18 Se)	Organic	0.07	0.15	0.75	50[b]	
	Brewers' grains (0.16 Se)	Organic	0.09	0.20	0.90	56[b]	
	Distillers' grains (0.16 Se)	Organic	0.07	0.18	0.83	54[b]	
Pigs (91 kg)	Starter and grower ration (0.46–0.78 Se)	Organic	1.70–2.10[d]	3.20	10.44	(350)	Jenkins and Winter (1973) dry weight
	Plus 0.10 Se (selenate) to starter ration		1.60–2.20[d]	3.38	10.84	(360)	
	Plus 0.10 Se (selenate) to starter and grower ration until 57 kg		1.60–1.90[d]	3.16	10.36	(280)	
	Plus 0.10 Se (selenate) to starter and grower ration until 91 kg		1.60–2.00[d]	3.17	11.01	(300)	

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Turkeys (14–20 wk)	Practical diets (0.13–0.20 Se)	Organic	0.17–0.22[e]	0.62– 0.70		(181-200)	Cantor and Scott (1975) wet weight
	Plus 0.10 Se (selenite)		0.17–0.22[e]	0.65– 0.67		(184-188)	
	Plus 0.20 Se (selenite)		0.18–0.22[e]	0.64– 0.68		(192-196)	
				0.62– 0.70			
Chicks (4 wk)	Corn-torula yeast based (0.030 Se)	Organic	0.05	0.15	0.18		Osman and Latshaw (1976) lyophilized weight
		Inorganic	0.14	0.78	1.33		
	Plus 0.06 Se (selenite)	Organic	0.19	0.68	1.18		
	Plus 0.06 Se (Se-methionine)	Organic	0.13	0.77	1.45		
	Plus 0.06 Se (Se-cysteine)						
Hens (laying)	Corn-soybean based (0.10 Se)	Organic	0.33	0.43	0.32[f]		Latshaw (1975) dry weight
	Plus 0.32 Se (selenite)	Inorganic	0.42	0.82	(0.40)[f]		
	Corn-soybean based (0.42 Se)	Organic	1.18	1.92	0.74[f]		
					(0.51)[f]		
					1.23[f]		
					(2.47)[f]		
Hens (35 wk)	Corn-soybean based (0.05 Se)	Organic	0.25[g]	0.26[h]			Latshaw and Osman (1975) dry weight
	Plus 0.10 Se (Se-cysteine)	Organic	0.34[g]	0.48[h]			
	Plus 0.10 Se (Se-methionine)	Organic	0.65[g]	0.39[h]			
	Plus 0.10 Se (selenite)	Inorganic	0.32[g]	0.44[h]			
	Plus 0.20 Se (selenite)	Inorganic	0.40[g]	0.62[h]			
	Plus *Astragalus* Se (0.10 Se)	Organic	0.26[g]	0.37[h]			
	Plus Selenif wheat (0.10 Se)	Organic	0.49[g]	0.42[h]			
	Plus fish meal (0.10 Se)	Organic	0.26[g]	0.24[h]			
	Corn-soybean based (0.30 Se)	Organic	1.53[g]	0.63[h]			

[a]Data converted to dry-matter basis assuming 30 percent dry matter.
[b]Equals serum Se levels. Parentheses indicate whole blood Se levels, otherwise values are for plasma.
[c]Presumably wet-weight basis but not indicated by authors.
[d]Equals the concentration range for ham, shoulder, and loin.
[e]Equals the concentration range for leg and breast muscle.
[f]Equals the concentration in eggs. Numbers in parentheses are the amount in the egg white.
[g]Equals the concentration in egg white.
[h]Equals the concentration in egg yolk.

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steers that had been pastured on seleniferous rangeland for 3 years. Maag and Glenn (1967) fed selenite at levels up to 12 to 24 mg selenium/kg body weight to steers until 6 out of 8 animals died from selenium poisoning. The selenium content of the muscles of these animals ranged from 0.10 to 0.73 ppm and the livers contained 5.0 to 12.3 ppm (fresh-weight basis). When levels of up to 0.3 ppm selenium in diets were fed to cattle, muscle, liver, and kidneys contained, respectively, 0.14, 0.50, and 1.58 ppm selenium (wet-weight basis; Ullrey et al., 1977).

Addition of up to 0.2 ppm selenium as selenite to diets for pigs containing high levels of natural selenium does not significantly increase the tissue selenium content (Groce et al., 1973b; Jenkins and Winter, 1973; and Ku et al., 1973). Concentrations of up to 2.2, 3.38, and 11.0 ppm (wet-weight basis) were obtained, respectively, for muscle, liver, and kidney when natural dietary selenium levels were 0.8 to 0.9 ppm. Whole-blood values ranged up to 0.35 ppm (Jenkins and Winter, 1973). The concentrations of selenium in muscle, liver, and kidney in deficient pigs appear to be 0.07, 0.08, and 1.2 ppm, respectively (dry-matter basis; Ewan, 1971).

Feeding practical diets (0.13 to 0.2 ppm Se) to turkeys resulted in 0.17 to 0.22 ppm and 0.62 to 0.70 ppm selenium (fresh weight), respectively, in muscle and liver (Cantor and Scott, 1975). The addition of up to 0.2 ppm selenium as selenite to this diet did not result in significant increases of selenium in these tissues. The addition of 0.06 ppm selenium in various forms to torula yeast-based diets (0.03 ppm Se) for chicks resulted in up to 0.9, 0.78, and 1.4 ppm selenium (lyophilized tissues), respectively, in muscle, liver, and kidney (Osman and Latshaw, 1976). Addition of 0.32 ppm selenium as selenite to a corn-soybean basal diet (0.10 ppm Se) resulted in 0.42, 0.82, and 0.74 ppm selenium (dry-weight basis), respectively, in muscle, liver, and eggs of laying hens (Latshaw, 1975). The selenium content of eggs can also be influenced by dietary selenium. Various levels of selenium and different chemical forms of this element were added to a corn-soybean meal basal diet (0.05 ppm Se) for laying hens, and concentrations of up to 1.5 and 0.63 ppm selenium (dry weight) were obtained for egg white and egg yolk, respectively (Latshaw and Osman, 1975). However, the relative selenium concentrations found in egg whites and egg yolks may sometimes be reversed (Arthur, 1972).

The selenium content of human tissues appears to show patterns similar to tissues from animals fed diets with required levels of selenium. The mean selenium content (wet-weight basis) was highest in kidney (1.09 ppm) followed by the liver (0.54 ppm), spleen (0.34 ppm), and testes and pancreas (0.30 ppm), with the lowest content in brain (0.13 ppm) for humans ranging from 9 months to 68 years of age (Schroeder et al., 1970).

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The mean selenium content of hair was found to be about 0.57 ppm, which is similar to that from rats fed control diets. This is significantly higher than the hair values (0.047 to 0.088 ppm) reported for people living in a selenium-deficient area of mainland China (Keshan Disease Research Group, 1979a). The calculated human body burden of selenium for Americans was about 15 mg (Schroeder et al., 1970). This is two to three times more than that calculated for New Zealanders (4.7 to 10 mg), which is not surprising since the selenium status of the latter is known to be low.

As with animals, the blood selenium levels in humans are apparently influenced by dietary intake. The blood selenium in people of New Zealand averaged about 0.07 ppm, which is low in comparison to the values reported for people (as summarized by Griffiths and Thomson, 1974) living in the United Kingdom (0.32 ppm), Sweden (0.12 ppm), Canada (0.18 ppm), or the United States (0.22 ppm). The blood selenium levels in people arriving in New Zealand from the United States have been shown to gradually decrease from 0.20 ppm to 0.07 ppm within about 200 days. The lowest blood values reported thus far are 0.01 to 0.03 ppm for humans suffering from Keshan disease in mainland China (Keshan Disease Research Group, 1979b). McKenzie et al. (1978) have summarized the blood selenium levels in children living in various countries; the levels range from a low of 0.04 ppm in New Zealand to a high of 0.81 ppm in Venezuela.

The peak of selenium retention on a whole-body basis (Muth et al., 1967) and in tissues such as blood, liver, muscle, kidney, spleen, and lung (Brown and Burk, 1973) is reached within hours (up to 24) after the injection of ^{75}Se as SeO_3^{2-} . In tissues like brain and thymus, however, the maximum is not reached until about 2 days after injection (Brown and Burk, 1973). The kidney retains the greatest amount of selenium (percent of dose) for short time periods (48 hours) followed by the liver, pancreas, heart, and muscle in decreasing order (Kincaid et al., 1977). The small intestine, however, may retain a large amount (up to 8.5 percent of dose) of the ^{75}Se.

The importance of selenium in male reproduction is indicated by the incorporation of ^{75}Se as SeO_3^{2-} in the reproductive organs. In contrast to other tissues, the maximum incorporation of selenium in testes and epididymis of rats was reached 2 to 3 weeks after injection (Brown and Burk, 1973; and McConnell et al., 1979b). As an indication of the accumulation of selenium in male reproductive organs, about 40 percent of the total body ^{75}Se was found in testes plus epididymis of rats 3 weeks after injection (Brown and Burk, 1973). Within the sperm, ^{75}Se became associated primarily with the midpiece of the sperm tail. Calvin (1978) extended these studies with rat sperm and found the selenium to be primarily in the tail keratin, a disulfide-stabilized fraction obtained by extracting isolated tails

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with sodium dodecyl sulfate. The name *selenoflagellin* was proposed for this selenium-binding polypeptide of 17,000 molecular weight (MW) in sperm. Calvin suggested that this molecule may be essential for proper assembly of the rat sperm tail. In bulls, the peak in accumulation of ^{75}Se in whole semen was reached 40 days after injection (Smith et al., 1979), which is similar to results with a ram in which the maximum incorporation of ^{75}Se in sperm was reached 49 days after injection (Tripp et al., 1979). In the bull the epididymis and testis retained the greatest amount of ^{75}Se (CPM/g basis), except for the kidney, 23 days after injection. Among the accessory glands, the prostate and seminal vesicles contained the highest levels of ^{75}Se. Some studies on the binding of ^{75}Se to proteins in testes have been done (McConnell et al., 1979b). ^{75}Se is bound to three proteins with molecular weights of 57,000, 45,000, and 15,000. The two higher molecular-weight compounds predominate at short labeling times (1 to 24 hours), whereas the 15,000 molecular-weight compound predominates after longer labeling periods (1 or more weeks).

METABOLISM

There are many factors that influence the metabolism of selenium. Among these are the chemical forms of selenium, sulfur, arsenic, metals, microorganisms, and vitamin E, and previous selenium intake.

INORGANIC SELENIUM

There is very little doubt concerning the ability of animal tissues to convert inorganic selenium to organic forms. This is demonstrated by the incorporation of ^{75}Se from selenite into dimethyl selenide (Hsieh and Ganther, 1975), into GSH-Px (Oh et al., 1974; Forstrom et al., 1978), and into selenoamino acids (Godwin and Fuss, 1972; Olson and Palmer, 1976). The selenium residue in glutathione peroxidase has been indicated to be selenocysteine (Forstrom et al., 1978). A small amount of selenocystine was found in tissues of rabbits after administration of ^{75}Se-selenite (Godwin and Fuss, 1972). Evidence was also obtained for some other unidentified selenoamino compounds. Similarly, a selenocysteine derivative was found in pronase digests of acetone powders of liver and kidney tissues from rats given selenite (Olson and Palmer, 1976). These workers found no selenomethionine under the conditions of study. Thus, the conversion of selenite to selenomethionine in tissues has not as yet been demonstrated. Godwin et al. (1971) isolated ^{75} Se-selenomethionine from ewe milk protein following the intraruminal administration of ^{75}Se-selenite, but this could be due

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to the actions of the rumen microorganisms as discussed elsewhere (see the section, "Rumen Microorganisms").

Although the pathways for reduction of selenite to selenide have been fairly well established (Ganther, 1979), the pathways for conversion of selenide to selenoamino acids have not been fully delineated. Since selenocysteine is one of the forms of selenium identified in animal tissues, most of the work has been done on its incorporation into proteins. Evidence has been presented for a specific transfer RNA in rat liver for selenocysteine (Hawkes et al., 1979). By this mechanism the selenocysteine could be incorporated during translation via the action of this tRNA and its charging enzymes. An alternative mechanism is that the selenocysteine is formed in situ from some previously incorporated amino acid such as cysteine or serine, which would be susceptible to a posttranslational modification. This type of reaction could occur similarly to the cysteine synthase reaction, which can produce cysteine from serine and sulfide if selenide or its equivalent is substituted for the sulfide (Olson and Palmer, 1976).

ORGANIC SELENIUM

In contrast to sulfur, selenium compounds tend to undergo reductive pathways in tissues. However, reduced selenium compounds can be metabolized by animal tissues. Some evidence has been presented for formation of selenocystathionine, selenoglutathione, selenotaurine, and selenocysteic acid in tissue homogenates of chicks and mice injected with ^{75}Se-selenomethionine (Martin and Gerlach, 1972). However, differences in either the metabolism of various selenium compounds or their biopotency have been observed. In both rats (Millar et al., 1973) and sheep (Jacobsson, 1966) greater retention of radioactivity was found in the pancreas after the injection of ^{75}Se-selenoamino acids than after the injection of selenite or selenate. Selenomethionine was found to be four times as effective as either selenite or selenocystine in prevention of pancreatic degeneration in chicks (Cantor et al., 1975a). In contrast, selenite, selenate, or selenocystine were more effective than selenomethionine in the prevention of exudative diathesis in chicks, which was highly correlated with plasma GSH-Px activity (Cantor et al., 1975b). Other differences in selenium compounds have also been noted in chicks. Feeding selenomethionine to hens resulted in more selenium in egg white than in egg yolk, whereas feeding selenite or selenocystine resulted in more selenium in egg yolk than egg white (Latshaw and Osman, 1975). A higher concentration of selenium was found in the pancreas and breast muscle (Osman and Latshaw, 1976) of chicks fed selenomethionine than when fed either selenite or selenocystine. These authors concluded that selenocystine is not incorporated into protein but is metab

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olized like inorganic selenium compounds. In work by others, marked differences were found in the biopotency of various organic selenium compounds in the prevention of dietary liver necrosis in rats (Schwarz and Fredga, 1975). Thus the data of these different investigators suggest that the various organic selenium compounds are not metabolized to common intermediates.

REDUCTION OF SELENIUM

Evidence has been obtained for the formation of hydrogen selenide from selenite in tissues (Diplock et al., 1973; Hsieh and Ganther, 1975). There are some formidable problems, however, involved in studying the production of hydrogen selenide. Oxygen must be rigorously excluded in order to prevent oxidation of H_2Se to Se^0. The volatile selenium is readily deposited on glass, nylon, and polypropylene and plastic surfaces. Polystyrene and polyethylene are more satisfactory (Ganther, 1979). Carrier gas, rate of gas delivery, and types of trapping agents used are other critical factors (Diplock et al., 1973). Identification of H_2 Se as the acid-volatile product is usually based on its trapping behavior, in which silver nitrate or sodium arsenite are very effective. Nitric acid, however, is a poor trapping agent for this gas. McConnell and Portman (1952a) identified dimethyl selenide in the exhaled gases of rats given ^{75}Se-labeled inorganic selenium. Dimethyl selenide can be trapped in soluble form by using nitric acid trapping solutions.

Ganther (1979) has provided the basic information on the mechanism for reduction of selenite to selenide. A specific requirement for GSH, anaerobic conditions (for best activity), and NADPH are essential for this reduction. Reduction of selenite to selenide occurs by a series of reactions involving initially the nonenzymic reaction of selenite with GSH to form an intermediate in which selenium is joined to GSH in the S-Se-S linkage (reaction 1). This is followed by NADPH-linked reduction of this intermediate ions 2 and 3):

Both the microsomal and the cytoplasmic fractions catalyze the methylation of selenium, apparently by methyltransferases acting upon the hydrogen selenide (Hsieh and Ganther, 1977). The microsomal enzyme system is quite labile and is exceedingly sensitive to arsenite. The activity of the liver microsomal system can be increased four-fold by feeding rats a stock diet rather than a purified diet (Hsieh and Ganther, 1976). The cyto

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solic Se-methyltransferase can be readily purified from rat liver or kidney and is not nearly as sensitive to arsenite as the microsomal one. S-adenosylmethionine is an effective methyl donor in either system. McConnell and Portman (1952b) reported that rodents tolerated rather large amounts of dimethyl selenide (the LD_{50} at 24 hours was 1.3 g selenium or 1.8 g dimethyl selenide/kg of body weight for rats), suggesting that it is a detoxification product of selenium metabolism. While these data have not been confirmed by others, Obermeyer et al. (1971) found that the intraperitoneal injection of male albino rats (Sprague-Dawley) raised on a commercial rat chow with up to 0.8 g Se (1.1 g dimethyl selenide)/kg of body weight caused no deaths in 5 animals 24 hours after injection. Parizek et al. (1976) reported 90 percent mortality in 24 hours after intraperitoneal injection of adult male rats with only 2.2 mg dimethyl selenide/kg of body weight, which is about 400 times lower than the LD_{50} reported by the previous workers. There is no obvious explanation for this large difference, but some of it could be due to a sex-linked difference in lethality of this compound (Parizek et al., 1976). The selenium status of the animal could also have had an effect. No mortality was observed in dimethyl selenide-injected rats that had been drinking water containing 1.0 ppm selenium, whereas up to 90 percent mortality occurred in rats injected with this compound without prior treatment with selenium (Parizek et al., 1976). Thus, the reason rats used by McConnell and Portman (1952b) were more resistant to dimethyl selenide may be due to previous exposures to higher levels of selenium.

PREVIOUS SELENIUM INTAKE

The degree to which the tissues have been previously saturated by dietary selenium greatly influences the retention of a subsequent dose. Supplementation of diets for rats with various levels of selenium up to 5.0 ppm caused a progressive drop in retention of ^{75}Se-selenite from more than 50 percent to less than 20 percent of the dose (Hopkins, 1962). Marked increases in the urinary excretion of ^{75}Se accounted for much of the decreased retention. An inverse relationship between the selenium status of sheep and the retention of a dose of ^{75}Se-selenite has been observed (Muth et al., 1967; Lopez et al., 1969). This is also reflected in the uptake of selenite by erythrocytes. Erythrocytes from selenium-deficient sheep will take up a larger amount of radioactive selenium during in vitro incubation than will those from animals with adequate selenium (Wright and Bell, 1963; Weswig et al., 1965). This test has been suggested as a possible useful diagnostic procedure in anticipating selenium-responsive diseases. Furthermore, the fixation of ^{75}Se into rumen bacteria in vitro is inversely

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proportional to the previous dietary intake of selenium by the host sheep (Hidiroglou et al., 1968). The selenium status also appears to influence the number of selenium-binding proteins in plasma. Two peaks of protein-bound ^{75}Se were seen on gel filtration chromatography of plasma from rats fed a selenium-adequate diet, whereas only one peak was present from rats fed a selenium-deficient diet (Burk, 1973).

RUMEN MICROORGANISMS

The rumen microorganisms are probably responsible for the lower absorption of selenium in ruminants than in nonruminants. Much of the dietary selenium is reduced to insoluble forms by rumen microbes (Cousins and Cairney, 1961; Peterson and Spedding, 1963; Whanger et al., 1968). A greater percentage of inorganic than organic selenium is converted into these insoluble forms, and a high-carbohydrate diet is more favorable to selenium conversion into insoluble forms than a high-roughage diet (Whanger et al., 1968).

Even though rumen microbes convert a portion of the selenium into insoluble forms, they also incorporate selenium into their proteins. Selenomethionine was shown to be incorporated into bacterial protein when rumen fluid was incubated in vitro with this compound (Paulson et al., 1968b). Characterization of the ^{75}Se-containing compounds in rumen microbes revealed the presence of ^{75}Se-selenomethionine after incubation with ^{75}Se-selenite in vitro (Hidiroglou et al., 1968). Thus, rumen microbes appear to be able to convert inorganic selenium to organic selenium compounds, as well as to incorporate organic selenium compounds into bacterial proteins.

INFLUENCE OF SULFUR

The sulfur analogues of selenium compounds appear to have the greatest influence on selenium metabolism. This is demonstrated by nearly a three-fold increase in urinary excretion of selenium following a parenteral dose of sodium selenate when rats were given sulfate either parenterally or in the diet. Sulfate had only slight effects on the urinary excretion of selenium that was administered in the form of selenite (Ganther and Baumann, 1962a). Rather high levels of selenium and sulfur were used in these experiments. Although sulfur has been implicated in promoting selenium deficiency problems, there are no consistent reports on the influence of this element on selenium metabolism. Paulson et al. (1966) found little difference in the selenium uptake by tissues when lactating ewes, fed diets containing either 0.28 or 0.62 percent sulfur, were dosed intraruminally with ^{75} Se-selenate. When ^{75}Se was injected into the rumen, Pope et al. (1979) found that wethers fed a low-sulfur diet (0.05 percent) maintained higher

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blood selenium levels and excreted less selenium in urine than animals fed higher levels of sulfur (0.11 to 0.2 percent). This is consistent with research by others (White and Somers, 1977), which showed that sheep fed a low-sulfur diet (0.07 percent) had significantly higher plasma and wool selenium levels when given selenomethionine. Hence, the alteration of selenium metabolism appears to be the greatest with sulfur-deficient animals.

INFLUENCE OF ARSENIC

The beneficial effect of arsenic on selenium poisoning was noted in the 1930s when 5 ppm of sodium arsenite in the drinking water was found to give full protection against liver damage in rats fed diets containing 15 ppm selenium (Moxon and Rhian, 1943). Several chemical forms of arsenic, including some organic arsenicals, are effective against selenium toxicity (Levander, 1977). Even though arsenic counteracts selenium toxicity, it was found to inhibit expiration of dimethyl selenide. This apparent paradox was elucidated by data showing that arsenic increases the biliary excretion of selenium, resulting in decreased tissue levels (Levander, 1977). In the reverse situation, selenium has also been shown to increase the biliary excretion of arsenic. Arsenic, however, cannot substitute for the metabolic functions of selenium; all attempts either to promote or prevent selenium deficiency diseases in animals by feeding arsenic have been unsuccessful.

INFLUENCE OF OTHER ELEMENTS

The toxicity of selenium can be reversed by such metals as copper, mercury, and cadmium when given at high dietary levels (Hill, 1974), suggesting that metals can influence the metabolism of selenium. Cadmium is equal to or superior to arsenite as an inhibitor of selenium volatilization in rats (Ganther and Bauman, 1962b), providing further evidence that metals can alter selenium metabolism. Some evidence is available to indicate that even tellurium will induce selenium and vitamin E deficiency in ducklings (Van Vleet, 1977b). Other elements, such as thallium, silver, lead, and cobalt, have been shown to affect selenium metabolism, as was discussed in a review by Diplock, (1976). For a more detailed discussion on metal-selenium interaction, see the section, “Nutritional and Metabolic Interrelationships.”

EFFECTS OF VITAMIN E

Although a metabolic interrelationship between selenium and vitamin E has definitely been established (Hoekstra, 1975), moderate levels of vitamin E do not affect selenium metabolism,. The distribution and excretion

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of selenium in young rats depleted of selenium and vitamin E were no different from that in animals receiving protective amounts of vitamin E in the diet (Hopkins, 1962). Massive doses of vitamin E, however, apparently decrease selenium volatilization in rats and increase selenium retention in the liver and carcass. Since selenium requirements have been shown to be dependent upon the vitamin E status of animals (Thompson and Scott, 1969), moderate levels of this vitamin must be influencing the effectiveness of selenium. Furthermore, the vitamin E status of animals apparently affects the oxidation state of tissue selenium, since the proportion of selenium that was acid-volatile was significantly less in vitamin E-deficient rats than in vitamin E-supplemented ones (Diplock et al., 1973).

MISCELLANEOUS FACTORS

A number of other factors will influence the metabolism of selenium, as discussed in various reviews (Ganther, 1965; Levander, 1972; Diplock, 1976). These include the quantity and nature of protein in diets, previous adaptations of the animal to selenium, and the presence of BAL (2,3-dimercaptopropanol), penicillamine, sodium dehydrocholate, linseed meal, bromobenzene, and phosphates. Some of the protective factors in linseed meal have been recently identified. These include two newly identified cyanogenic glycosides, linustatin and neolinustatin, which have been shown to provide significant protection against growth depression due to selenium toxicity (Palmer et al., 1980). These respective compounds were found to be present in linseed meal at concentrations of 0.17 to 0.19 percent. Along similar lines, potassium cyanide dosing to ewes was reported to increase the incidence of white muscle disease in their lambs (Rudert and Lewis, 1978). Moreover, cyanide protects partially against selenium toxicity in rats (Palmer and Olson, 1979). However, attempts to induce selenium deficiency by adding cyanide to water for rats had little effect (Palmer and Olson, 1981). Other examples of the possible influence of dietary components are comparisons of crude diets (commercial) to purified ones. Two to three times as much volatile selenium was exhaled when ^{75}Se-selenite was injected into rats that had been fed certain crude diets than when it was injected into those that had been fed purified basal diets that permitted good growth rates. Not all crude diets, however, possessed this ability to promote exhalation of volatile selenium (Ganther, 1965).

EXCRETION

The primary route of excretion of selenium is in the urine of monogastric animals, regardless of whether it is given orally or injected (Hopkins, 1962;

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Burk et al., 1972); but the urinary route in ruminants is dependent upon the method of administration. When selenium is administered orally to ruminants, most is excreted with feces (Cousins and Cairney, 1961; Peterson and Spedding, 1963; Paulson et al., 1966; Lopez et al., 1969). In contrast, when selenium was injected either intravenously or subcutaneously in ruminants, more was excreted in urine than in feces (Wright and Bell, 1966). There is also an age effect, as indicated by the work of Ewan et al. (1968c). ^{75}Se given orally to young lambs (8 to 10 weeks of age) fed a synthetic liquid diet was recovered to the extent of 66 to 75 percent in urine and 34 to 27 percent in feces. The rumen microbes no doubt contribute to this age effect, since they are present in greatest numbers in fully developed ruminants.

The peak of urinary excretion occurs 2 to 3 days after administration of the dose (Muth et al., 1967; Burk et al., 1972). The size of dose, as well as the selenium status of the animal, influences the speed of excretion and the relative amounts that may be excreted via urine. In lambs (Lopez et al., 1969), calves (Kincaid et al., 1977), and rats (Burk et al., 1972), urinary excretion of selenium was found to be directly proportional to the selenium status of the animals.

Essentially all of the selenium excreted in feces of ruminants is in insoluble forms, and very little is available for uptake by plants (Cousins and Cairney, 1961; Peterson and Spedding, 1963). The poor availability is evident by data showing that less than 0.3 percent of ^{75}Se was taken up by three common pasture species of plants growing for 75 days on feces from sheep dosed orally with Se-selenite. Trimethyl selenide is the major urinary metabolite of selenium (Byard, 1969; Palmer et al., 1969). This compound is essentially unavailable nutritionally as a source of selenium for the prevention of liver necrosis in rats (Tsay et al., 1970), suggesting it to be a detoxification product of selenium. Mortality and survival time were not significantly affected by 0.15 or 1.5 ppm selenium added as trimethyl selenide, but 0.15 ppm selenium added as sodium selenite gave complete protection. An injection of ^{75}Se-labeled trimethyl selenite was rapidly excreted in unchanged form in the urine (70 percent in the first 12 hours).

Excretion of selenium by humans is very similar to patterns for mono-gastric animals. From 43 to 86 percent of an oral dose of selenium appears in the urine of humans (Thomson, 1972; van Rij et al., 1979). The daily urinary loss for patients was less for those with lower blood and plasma selenium concentrations (van Rij et al., 1979), indicating the body can conserve this element. In patients given ^{75}Se-selenite, there were only trace amounts of radioactivity expired in air, and no dermal losses were detected (Thomson and Stewart, 1974). Peak excretion of ^{75}Se occurred 4 to 5 days after dosing. Subsequent studies from this same laboratory were con

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ducted with ^{75}Se-selenomethionine in women (Griffiths et al., 1976). As with selenite, very few respiratory or dermal losses of selenium occurred after administration of selenomethionine, but the urinary excretion was about half that observed for selenite. Based on balance studies with New Zealand women, the minimum dietary requirement of selenium for maintenance of normal human health was estimated to be probably not more than 20 μg/day (Stewart et al.,1978).

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6

Nutritional Aspects

DIETARY REQUIREMENTS OF ANIMALS FOR SELENIUM

A detailed discussion of the interactions of selenium with other dietary constituents has been presented in the chapters, "Biochemical Functions" and "Metabolism." In summarizing quantitative estimates of dietary selenium requirements, it is important to note that the need for this element depends upon these interactions and, particularly, upon the dietary supply of vitamin E. In addition, the criteria chosen as measures of adequacy may vary appreciably in their sensitivity. For example, in young swine there may be no measurable differences in weight gain between pigs receiving diets containing 0.04 or 0.14 ppm selenium, but the former may result in mortality of 15 to 20 percent (Ullrey, 1974). Other criteria may give different answers. Based upon plasma and liver selenium concentrations and GSH-Px activities, Meyer et al. (1981) have concluded that the weanling pig requires at least 0.3 mg selenium/kg of diet.

Another issue that influences estimates of selenium need is that of biological availability (see pp. 26–28). The required concentration of selenium in the diet may need to be twice as great in a situation in which bioavailability is only 50 percent that of a more useful selenium source.

The consequence of these considerations is to render doubtful a single statement of the selenium requirement for any species. Based on the references cited in this publication, it is probable that selenium requirements for most of the animals studied fall in the range of 0.05 to 0.3 ppm in the dry diet.

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Supplemental selenium levels approved by the United States Food and Drug Administration are 0.1 ppm for cattle, sheep, swine (0.3 ppm in prestarter and starter diets), chickens, and ducks, and 0.2 ppm for turkeys (U.S. Department of Health, Education, and Welfare, Food and Drug Administration, 1974, 1979; U.S. Department of Health and Human Services, Food and Drug Administration, 1981a, 1981b, 1982).

MEETING SELENIUM REQUIREMENTS FOR ANIMALS

If selenium is present in adequate concentrations in natural feedstuffs, as is frequently the case in the Dakotas, there is no need for supplemental selenium. In regions that are demonstrably deficient, use of feedstuffs from selenium-adequate areas or use of selenium supplements may be necessary. Selenium supplements that have proved satisfactory include sodium selenite or sodium selenate. Use of the former is most common. It may be incorporated in the complete diet or mixed at higher concentrations in free-choice supplements such as salt (Rotruck et al., 1969; Ullrey et al., 1977, 1978; Whanger et al., 1978b). To ensure continued bioavailability, the carriers should have minimum reducing activity. Otherwise, a significant proportion of selenite may be reduced to elemental selenium, which may be less well used (Groce et al., 1973a). However, Olson et al. (1973) found the stability of sodium selenite and potassium selenate was satisfactory for poultry when premixed with glucose monohydrate, wheat bran, corn, linseed meal, soybean meal, or soybean protein as a carrier and kept reasonably cool and dry.

A selenium pellet (elemental selenium and powdered iron) of high specific gravity has been devised (Kuchel and Buckley, 1969) that will be retained in the reticulum of ruminants and will slowly release selenium in amounts consistent with daily need (Handreck and Godwin, 1970; Whanger et al., 1978b). This form of selenium is particularly convenient for supplementing grazing ruminants that are not provided other concentrate feeds. Unfortunately, this product is not yet approved for use in the United States.

Aqueous selenium solutions have also been successfully used as a periodic oral drench or as an intramuscular or subcutaneous injection (Young et al., 1961; Muth, 1963; Julien et al., 1976b; Whanger et al., 1978b).

DEFICIENCY SIGNS IN ANIMALS

RATS

The first evidence for the essentiality of selenium was obtained with rats (Schwarz and Foltz, 1957). A deficiency of both selenium and vitamin E

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for rats results in necrotic liver degeneration, which is produced by feeding a semipurified diet containing torula yeast as the major protein source. This diet is very low in vitamin E and sulfur amino acids, and the early work showed that the addition of either vitamin E, cystine, or selenium, referred to by Schwarz as Factor 3, prevented this liver necrosis. Subsequent work, however, indicated that the effectiveness of cystine was related to the incidental selenium content of this amino acid (Schwarz et al., 1959). The time required for signs to occur (usually 3 to 6 weeks) depends on the strain used and probably on the initial content of selenium and vitamin E in tissues of the rats. Changes in the cytoplasm and mitochondria can be detected by electron microscopy before gross signs of liver necrosis appear. Death results in a few days after the microscopic appearance of liver necrosis. Even though either vitamin E or selenium prevents liver necrosis in rats, supplements of dietary selenium do not prevent other signs of vitamin E deficiency, such as peroxidation and discoloration of body fat, brown discoloration of the uterus, depigmentation of incisors, in vitro hemolysis of erythrocytes in the absence of glucose, and impaired reproductive capacity of females (Christensen et al., 1958; Harris et al., 1958).

McCoy and Weswig (1969) were first to observe the effects of selenium deficiency in rats in the presence of dietary vitamin E. This was accomplished by raising and maintaining weanling female rats on a low-selenium diet (18 ppb Se) containing torula yeast as the protein source, supplemented with vitamin E (60 mg d-α-tocopheryl acetate/kg diet). These animals grew and reproduced normally. However, their offspring had sparse hair coats, grew poorly, had discoloration of the eyes, and failed to reproduce. Selenium supplementation restored the hair coat, growth, and reproductive ability. The discoloration of the eyes was due to cataracts (Whanger and Weswig, 1975), and selenium appeared to be most effective among several dietary variables tested in reversing this condition. The motility of spermatozoa from deficient male rats was found to be very poor and the majority of the sperm cells showed breakage near the principal piece of the tail (Wu et al., 1973), thus presumably contributing to sterility. Essentiality of selenium for the rat in the presence of dietary vitamin E has been confirmed by other workers. Hurt et al. (1971) depleted rats of selenium in one of two ways: by feeding a basal purified diet containing amino acids as the only nitrogen source or by feeding females through pregnancy on a torula yeast diet (12 ppb Se) and using the young as experimental subjects. In either case, selenium supplementation stimulated growth of the young rats. In addition to the deficiency signs mentioned above, Ewan (1976a) found the total growth hormone to be reduced in the pituitary and feed efficiency to be lower in vitamin E-supplemented selenium-deficient rats.

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Just as the rat was used to develop the first evidence for the essentiality of selenium, it was also used to define the first biochemical function for selenium. Thus, the rat has played a significant role in research into both the nutritional and biochemical aspects of selenium. Erythrocytes in the presence of glucose from selenium-deficient rats were found to be very susceptible to hemolysis in vitro, whereas those from selenium-supplemented rats were very resistant to this condition (Rotruck et al., 1971). This led to studies dealing with the relationship of selenium to the activity of glutathione peroxidase (Rotruck et al., 1972b). Subsequently it was shown that GSH-Px was indeed a selenoenzyme (Rotruck et al., 1973), providing an enzymatic means to evaluate the selenium status of animals. The activity of GSH-Px in rat tissues has been shown to increase when dietary selenium was supplied either as selenite (Hafeman et al., 1974) or as selenomethionine (Chow and Tappel, 1974). Liver GSH-Px was found to fall to undetectable levels within 24 days after weanling rats were fed a selenium-deficient diet, whereas erythrocyte GSH-Px activity decreased more slowly, with 21 percent of the initial activity remaining after 66 days (Hafeman et al., 1974). A corresponding increase of both liver and erythrocyte GSH-Px was found to occur with increased levels of dietary selenium, ranging from 0.05 to 5.0 ppm. Other metabolic changes that have been found to occur because of selenium deficiency in rats are altered hepatic heme metabolism (Correlia and Burk, 1976) and altered fatty acid and glucose metabolism (Fischer and Whanger, 1977).

MICE

Much less work has been done on selenium deficiency in mice, but the available evidence indicates that these animals should respond similarly to rats. Multiple necrotic degeneration of tissues is observed in mice fed a selenium- and vitamin E-deficient torula yeast diet similar to that used for rats (De Witt and Schwarz, 1958). Liver and kidney necrosis are evident, and there may be pancreatic dystrophy and degeneration of both the skeletal and heart muscle. All of these conditions induced by feeding a torula yeast diet can be prevented by either vitamin E or selenium. Since GSH-Px activity has been found in tissues of mice (Wada et al., 1976; Su et al., 1979), these animals would presumably have a selenium requirement. In other work, selenium-deficient mice have been shown to be more susceptible to foreign compounds. Selenium-deficient mice treated with paraquat (a broad-spectrum herbicide) had significantly elevated plasma glutamic-pyruvic transaminase activity, longer hexobarbital sleeping times, and slower clearance of indocyanine green than paraquat-treated selenium-supplemented mice (Cagen and Gibson, 1977).

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HAMSTERS

A clear selenium deficiency has not been demonstrated in hamsters. Vitamin E deficiency in this animal causes sterility and degeneration of liver and muscle tissues that is not prevented by selenium (Bieri and Evarts, 1974). Of the seven species of animals examined, hamsters had the highest activity of GSH-Px in liver (Lawrence and Burk, 1978). These animals had been fed stock diets, and the selenium content was not indicated. Thus, the hamster would appear to have a selenium requirement.

GUINEA PIGS

Myopathy produced in guinea pigs by feeding a diet low in vitamin E was not prevented by supplementing the diet with selenium (Seidel and Harper, 1960; Bonetti and Stirpe, 1963). The selenium content of the basal diets used in these studies was not indicated. Guinea pigs did not develop dystrophy when they consumed hay that caused dystrophy in lambs (Tripp, unpublished data, Oregon State University). Although early work (Lawrence and Burk, 1978) did not find any GSH-Px activity in livers of guinea pigs fed a stock diet, subsequent work (Burk et al., 1981) showed the existence of the enzyme in liver and blood, and thus a presumed selenium requirement in this species.

RABBITS

Rabbits fed a diet deficient in vitamin E develop muscular weakness, which leads to death in 4 to 6 weeks. Selenium is completely ineffective in preventing or retarding this nutritional disease (Draper, 1957; Hove et al., 1958). No dystrophy occurred in rabbits consuming low-selenium hay that caused dystrophy in lambs and calves consuming it (Jenkins et al., 1970). When 1 percent linoleic acid was incorporated into the diet for rabbits, severe muscle degeneration developed within 4 to 6 weeks; selenium was completely ineffective in preventing the disorder. In contrast, oral administration of linoleic acid to calves or lambs did not promote a higher incidence of dystrophy or inhibit the protective effects of selenium. Thus, as in the guinea pig, there are etiological differences between the development of myopathy in domesticated ruminants and rabbits. Total GSH-Px activity has been found in rabbit tissues at comparable levels to that in rat tissues (Cheeke and Whanger, 1976; Lee et al., 1979). However, both the percentage of total GSH-Px activity that was not dependent upon selenium and the absolute non-selenium-dependent enzyme activity was higher in

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liver and kidney of rabbits than of rats (Lee et al., 1979); the authors suggested that this may partly explain the lack of response of rabbits to dietary selenium deficiency.

NONHUMAN PRIMATES

When adult squirrel monkeys were fed a selenium-deficient diet containing vitamin E (60 mg/kg), with torula yeast as the source of protein, for 9 months, their hair became sparse, they lost weight, and they became listless (Muth et al., 1971). When 40 μg selenium as sodium selenite was injected biweekly into some of the monkeys, a rapid change in vitality occurred, body weight increased within 2 weeks, and normal hair coats were restored 4 weeks after the first selenium injection. Those monkeys that were not treated with selenium became moribund or died. Examination of tissue revealed hepatic necrosis, cardiac and skeletal muscle degeneration, and nephrosis. Although some of these disorders are characteristic of vitamin E deficiency, no changes in plasma tocopherol levels occurred as selenium deficiency progressed.

Rhesus monkeys appear to be much more resistant than squirrel monkeys to selenium deficiency. When pregnant rhesus monkeys were fed selenium-deficient diets (15 to 30 ppb) containing vitamin E, no changes characteristic of selenium deficiency occurred in either the adults after 18 months or the young after 14 months (Butler et al., 1980). As expected, blood selenium levels and erythrocyte and plasma GSH-Px activities were significantly higher in the selenium-supplemented than in the seleniumdeficient animals. No differences, however, in the activities of plasma creatine phosphokinase, lactic dehydrogenase, glutamic oxaloacetic transaminase, or ornithine carbamyl transferase, or in plasma tocopherol levels, have been found between selenium-deficient and selenium-supplemented animals. In other work, the amount of selenium associated with GSH-Px in erythrocytes of squirrel monkeys was found to be similar to that associated with rats, lambs, and calves; whereas the amount of selenium associated with this enzyme in erythrocytes of the rhesus monkey was similar to that associated with humans (P. D. Whanger, unpublished observations). This may be the reason these two species of primates respond in a markedly different manner to selenium deficiency. Thus, the selenium requirements among different primates may vary widely.

FISH

Poston et al. (1976) demonstrated a nutritional requirement for selenium in the Atlantic salmon (*Salmo salar*). They found that selenium deficiency,

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either uncomplicated or combined with vitamin E deficiency, reduced survival of the growing fish. Fish deficient in both nutrients showed severe muscular dystrophy, which was prevented by dietary supplementation with the combination of selenium and vitamin E, but not with either nutrient alone. Selenium-deficient fish showed depressed activities of GSH-Px in plasma. Further work (Poston and Combs, 1979) showed that dietary supplementation of L-ascorbic acid produced increased activities of GSH-Px in plasma and improved the growth responses of selenium-deficient Atlantic salmon to supplemental selenium. Hilton et al. (1980), using an assay procedure that would not distinguish between selenium-dependent glutathione peroxidase and glutathione-S-transferase, found an increase in plasma GSH-Px activity in rainbow trout when a low-selenium, adequate vitamin E diet was supplemented with selenium.

CHICKENS

The chick shows three selenium-deficiency diseases: exudative diathesis, nutritional muscular dystrophy, and nutritional pancreatic dystrophy. Exudative diathesis and nutritional pancreatic dystrophy can be completely prevented by dietary selenium, whereas nutritional muscular dystrophy depends upon adequate dietary levels of vitamin E or sulfur-containing amino acids for its complete prevention. Like nutritional muscular dystrophy, exudative diathesis is also prevented by vitamin E. The only disease that is presently recognized to result from uncomplicated selenium deficiency in chicks is nutritional pancreatic atrophy.

Exudative diathesis was first observed by Dam and Glavind (1938). It occurs in the selenium- and vitamin E-deficient chick and is characterized by severe subcutaneous edema, particularly on the breast and abdomen. The condition results from abnormally increased permeability of capillaries and, in advanced stages, involves hemorrhage in tissues in edematous areas. The breakdown of hemoglobin results in a green-blue discoloration of affected areas of the skin that is readily identifiable as a sign of the deficiency. The chick with exudative diathesis is thus anemic and hypoproteinemic and shows reduced growth. These signs are apparent at 2 to 3 weeks of age when chicks are fed a diet deficient in both selenium and vitamin E. However, if the dam was also deficient with respect to these nutrients, chicks will show exudative diathesis by 6 to 10 days of age. If selenium or vitamin E is not provided, exudative diathesis leads to death by 3 to 4 weeks in chicks from normal dams, or by 10 to 14 days in second generation depleted animals. Exudative diathesis is prevented by diets containing at least 0.1 ppm available selenium in the absence of vitamin E, or by diets containing at least 100 IU vitamin E/kg in the absence of appre

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ciable selenium (less than 0.02 ppm). Selenium and vitamin E are mutually sparing for prevention of exudative diathesis (e.g., the deficiency disease is prevented with a diet containing 0.04 ppm available selenium and 5 IU vitamin E/kg). This interrelationship is thought to be due to their complementary functions in the protection of capillary cell membranes from lipid peroxidation (Noguchi et al., 1973). Chicks with exudative diathesis show low activities of vitamin E and selenium-dependent GSH-Px in most tissues, but increased levels of reduced glutathione, which result from inability to use its reducing equivalents in peroxide metabolism.

Nutritional muscular dystrophy occurs in chicks fed diets low in selenium, vitamin E, and sulfur-containing amino acids (Calvert et al., 1962). The disease is characterized by dystrophy of the skeletal muscles and is especially prominent in the *M. pectorales,* which show white striations parallel to the longitudinal direction of the muscle fibers that are visible through the skin. The disease involves Zenker's degeneration of the muscle fibers, with perivascular infiltration of eosinophils, lymphocytes, and histiocytes. These cells are responsible for a large increase in lysosomal enzymes in the degenerating muscle (Desai et al., 1964). The pathogenesis of nutritional muscular dystrophy can be followed with rises in glutamicoxaloacetic transaminase activity in plasma. Dystrophic muscles have concentrations of reduced glutathione approaching twice normal levels, whereas livers from the same animals show significantly depressed GSH concentrations. Nutritional muscular dystrophy is prevented by dietary vitamin E. It is not prevented by dietary selenium in the absence of vitamin E; however, selenium markedly reduces the amount of vitamin E required to prevent the disease (Calvert and Scott, 1963). Whereas 20 IU vitamin E/kg are required to prevent the myopathy in the selenium-deficient chick, only 10 IU vitamin E/kg are required in the presence of 0.1 ppm selenium, and as little as 2.5 IU vitamin E/kg are required in diets containing 1 ppm selenium (Scott, 1974). Nutritional muscular dystrophy is also prevented by the sulfur-containing amino acids (Dam et al., 1952; Machlin and Shalkop, 1956; Jenkins et al., 1962; Hathcock et al., 1968a). Cysteine is much more effective than methionine in preventing this disease, because the conversion of methionine to cysteine appears to be impaired in the vitamin E-deficient chick (Hathcock et al., 1968b).

The chick has a specific requirement for selenium for maintenance of pancreatic exocrine function. In chicks deficient in selenium per se, pancreatic acinar cells undergo vacuolation and hyaline body formation, followed by cytoplasmic shrinkage and infiltration with fibroblasts and macrophages (Gries and Scott, 1972). These histological changes are accompanied by a progressive loss of production of pancreatic lipase and proteases (Noguchi et al., 1973). Lipase insufficiency and the consequent

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impairment of fat digestion result in impaired micellar solubilization of lipids and, thus, impaired absorption of lipids including vitamin E (Thompson and Scott, 1970). Therefore, secondary vitamin E deficiency is a normal consequence of primary selenium deficiency in the chick with pancreatic atrophy. This consequence may be prevented by supplementing the diet with high levels of vitamin E and by adding micelle-promoting substances to the diet. Second generation selenium-deficient chicks show histological signs of nutritional pancreatic atrophy by 4 to 5 days of age, severe pancreatic fibrosis and depressed growth by 14 to 16 days, and high mortality after 21 days of age. The disease is prevented by adding less than 50 ppb available selenium to low-selenium (less than 15 ppb) purified diets; the selenoamino acid selenomethionine has been shown to be a particularly effective source of selenium for prevention of nutritional pancreatic atrophy (Cantor et al., 1975a). Bunk and Combs (1980) showed that the growth depression associated with severe uncomplicated selenium deficiency is due in part to a depression in appetite. They found that forced feeding of selenium-deficient chicks overcame two-thirds of the growth depression but did not prevent the atrophic degeneration of the pancreas. More recent work (Bunk and Combs, 1981a) indicates that a major portion of the balance of the growth effect of severe selenium deficiency is due to an impairment in metabolic conversion of methionine to cysteine (i.e., the severe selenium deficiency in the chick results in a metabolic cysteine deficiency). The complication, however, does not appear to be a factor in the etiology of nutritional pancreatic atrophy, because that lesion does not respond to dietary cystine. These recent studies suggest roles for selenium in the regulation of feed intake and in the metabolism of the sulfur-containing amino acids that are distinct from those of selenium in the maintenance of pancreatic exocrine function and which may involve biochemical functions other than that of the selenium-dependent GSH-Px. Further, Bunk and Combs (1981b) have found that selenium-dependent GSH-Px activity may not differ among chicks with variable susceptibility to nutritional pancreatic atrophy and have suggested that an additional non-selenium-dependent GSH-Px related factor may be involved in protecting chicks from this lesion.

The dietary requirement for selenium of the laying hen appears to be no more than 0.05 ppm in practical-type diets, even when those diets are not supplemented with vitamin E or synthetic antioxidants. Laying Single Comb White leghorn hens fed corn-soy based diets of lower selenium content (less than about 0.03 ppm) without supplemental vitamin E show reduced rates of egg production (Cantor and Scott, 1974; Latshaw et al., 1977). Selenium needs are greater for breeding hens than for laying hens, as levels of about 0.10 ppm in practical diets are required to sustain maxi

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mal embryonic survival (Cantor and Scott, 1974; Combs and Scott, 1979). Selenium-deficient breeder hens show low levels of selenium-dependent GSH-Px, as do their progeny at hatching. Progeny of selenium-deficient hens show substantially increased immediate needs for dietary selenium (Combs and Scott, 1979), and have been observed in New Zealand with congenital muscular dystrophy (Salisbury et al., 1962).

TURKEYS

Turkey poults show two types of selenium deficiency diseases: a mild and intermittent form of exudative diathesis and muscular dystrophy. Combined selenium- and vitamin E-deficiency in the poult results in an exudative diathesis that is much less severe than that manifested by the chick (Creech et al., 1957; Rahman et al., 1960). This condition is sometimes associated with hydropericardium and hemorrhages (particularly on the thighs) of varying severity (Walter and Jensen, 1964).

The most characteristic sign of selenium deficiency in the poult is myopathy of the gizzard, which shows severe hyaline degeneration of the muscular tissues, thus assuming a pale appearance. Whereas the gizzard lesion is manifested by almost all selenium-deficient poults, individual cardiac or skeletal myopathies are found in only 25 percent or 25 to 50 percent, respectively, of all cases. Poults with muscular dystrophy show hypoalbuminemia, markedly elevated levels of glutamic-oxaloacetic transaminase in plasma, and depressed GSH-Px in plasma. They grow poorly and have poor liveability (Cantor et al., 1982).

In contrast to the nutritional muscular dystrophy of the chicken, the nutritional myopathies of the poult are not influenced by the levels of sulfur-containing amino acids in the diet, and they are completely prevented by selenium. Whereas the exudative diathesis of the poult is prevented by either selenium or vitamin E, the nutritional myopathies of the poult appear to be primarily related to selenium deficiency. Vitamin E potentiates the protective effect of selenium against these myopathies; however, vitamin E is insufficient to completely prevent gizzard myopathy in the absence of selenium (Walter and Jensen, 1964; Scott et al., 1967). Therefore, the dietary requirement of the poult for selenium varies according to the levels of vitamin E and perhaps of other antioxidants in the diet; Scott et al. (1967) found that 0.18 ppm selenium (as Na_2SeO_3) was required to prevent gizzard myopathy in the presence of adequate vitamin E but that 0.28 ppm selenium was required for equal protection of the gizzard in the absence of vitamin E.

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DUCKS

Growing ducks fed diets deficient in both selenium and vitamin E develop lesions in gizzard and intestinal smooth muscle, in cardiac muscle, and in skeletal muscle (Pappenheimer and Goettsch, 1934; Yarrington et al., 1973; Moran et al., 1975; Hulsteart et al., 1976; Van Vleet, 1977a). The pathogenesis of these myopathies has been described by Van Vleet and Ferrans (1977a,b) as resulting from initial damage within mitochondria that results in their disruption and consequent mineralization. These changes were observed to be accompanied by ultrastructural alterations of myofilaments and focal sarcoplasmic mineralization. These myopathies are associated with depressed growth; however, the latter effect is prevented by dietary vitamin E (Dean and Combs, 1981). Van Vleet et al. (1981) were able to induce lesions characteristic of selenium-vitamin E deficiency in ducklings fed diets adequate in these two nutrients by providing excesses of silver, copper, cobalt, tellurium, cadmium, or zinc. Exudative diathesis has also been reported in the selenium-deficient duckling (Jagar, 1972; Moran et al., 1975). Selenium-deficient ducks show low selenium-dependent GSH-Px activities in plasma. These activities respond quickly to dietary supplementation with sodium selenite or vitamin E. Supplemental selenium supports optimal growth in the absence of vitamin E when added to the diet to provide 0.10 to 0.15 ppm total selenium.

JAPANESE QUAIL

Selenium-deficient Japanese quail (*Coturnix coturnix japonica*) show severely depressed growth, with poor feathering and poor survival (Scott and Thompson, 1968). Japanese quail that are also deficient in vitamin E occasionally show exudative diathesis. When they are reared to maturity on such a diet, egg production and fertility are normal; however, embryonic survival and viability of laying females is reduced (Jensen, 1968). Progeny of selenium- and vitamin E-deficient females are extremely weak at hatching, and frequently assume prostrate positions. Jensen (1968) observed a high incidence of gizzard myopathy in second generation selenium- and vitamin E-depleted quail.

SWINE

Studies of the essentiality of selenium for swine and its interrelationship with vitamin E are quite recent compared to studies of vitamin E alone. More than 50 years have passed since vitamin E deficiency was described

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in rats, but the first controlled study of vitamin E deficiency in swine was apparently that of Adamstone et al. (1949). These workers reported a decline in reproductive efficiency and signs of locomotor incoordination and muscular necrosis. Four years later, Obel (1953) described a naturally occurring dietary disease in vitamin E-deficient swine that was characterized by hepatic necrosis, fibrinoid degeneration of blood vessel walls, and muscular dystrophy. Shortly thereafter, selenium was established as an essential nutrient for rats (Schwarz and Foltz, 1957); and Eggert et al. (1957), Grant and Thafvelin (1958), and Pellegrini (1958) reported a relationship between selenium deficiency and the lesions in swine cited above. Soon after, Grant (1961) discovered the close relationship between mulberry heart disease and vitamin E-responsive lesions, which, until that time, had been thought to be unrelated. Mulberry heart disease developed when swine were fed diets containing high levels of unsaturated fats and was accompanied by muscular dystrophy and hepatosis dietetica. The administration of selenium and vitamin E prevented mulberry heart disease and hepatosis dietetica, and vitamin E prevented muscular dystrophy. (It should be noted that, while Thomlinson and Buxton (1963) indicated that anaphylaxis could precipitate mulberry heart disease, this was not confirmed by Tiege and Nordstoga (1977) who consider this a multifactorial entity; the latter workers observed a red mottled myocardium, which on histological examination revealed hyperemia but no microthrombosis or other pathognomonic signs.)

It was clear that liberal amounts of unsaturated fat promoted the development of this disease, and Lannek commented in 1967 that “muscular dystrophy as a field disease in pigs seems essentially to be a Scandinavian problem.” However, two years later, Michel et al. (1969) reported field cases in U.S. swine fed corn-soybean meal diets in which muscular dystrophy was prevented by supplemental vitamin E. The deficiency appeared to involve a shortage of both selenium and vitamin E, but at that time supplemental selenium could not legally be provided. Trapp et al. (1970) pursued the problem further and published a thorough description of the pathology seen in naturally occurring cases. These workers reported sudden death in feeder pigs (20 to 40 kg) and lesions of hepatic necrosis, icterus, edema, hyalinization of the walls of arterioles, and skeletal and cardiac muscular degeneration. Occasionally, a pig was observed with clinical signs of icterus, edema in the ventral cervical region, dyspnea, difficult locomotion, reluctance to move, and weakness. Edema was prominent in most tissues but especially in the mesentery of the spiral colon, lungs, subcutaneous tissues, and submucosa of the stomach. Esophagogastric ulcers were common, as observed earlier by Obel (1953) in association with hepatosis dietetica. Dietary supplements of vitamin E or intramuscular injections of

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selenium and vitamin E stopped the acute death losses. In addition, the incidence of the mastitis-metritis-agalactia complex (MMA), of spraddle-legged newborn pigs, and of impaired fertility appeared to be reduced. Ringarp (1960) had previously observed that sows exhibiting agalactia often showed degenerative muscle changes suggestive of selenium-vitamin E deficiency. Ullrey et al. (1971) supplemented a corn-soybean meal diet with 0.2 ppm selenium, 22 IU vitamin E/kg, and 880 mg choline chloride/ kg and reduced ($P < 0.05$) the incidence of MMA from 39 to 24 percent in two studies involving 191 farrowings. In both studies, these supplements tended to increase the number of live pigs born per litter. In one study, but not the second, there was an increase ($P < 0.05$) of 1.1 pigs per litter at 3 weeks.

Although Wu et al. (1973) demonstrated that selenium is necessary for the production of morphologically normal spermatozoa in rats, Segerson et al. (1981) found no impairment of sperm morphology or viability in boars fed a diet containing 0.025 ppm selenium and 33 IU vitamin E/kg from about 77 to 250 days of age. Tiege and Nafstad (1978) conducted electron microscopical examinations of the spiral colon epithelium of pigs that were either deficient in or supplemented with selenium and vitamin E. Deficient pigs had a decreased contrast of intracellular membranes, fewer microvilli (and those that were present were short and irregular in appearance), numerous swollen mitochondria with vacuolation, and intercellular edema.

Bengtsson et al. (1978a) fed a semipurified diet containing 0.008 ppm selenium and 1.4 mg α-tocopherol/kg. The earliest clinical signs noted were cutaneous maculae associated with a microangiopathy. The maculae were round-angular, up to 15 to 20 mm in diameter, and resulted in slightly thickened skin. The most frequent locations were the perineum, the ventral abdomen close to the midline and around the umbilicus, and on the ears. Common sites included the posterior thighs and ventral throat. In the acute stage the maculae were bright red, changing to a deep red and eventually to a bluish tone. In later stages the center of the lesions was sometimes covered by a thin, brownish red crust. Incidence and severity were reduced by supplemental vitamin E, but supplemental selenium appeared only to delay lesion development (Bengtsson et al., 1978b).

Anemia has been reported in vitamin E-deficient swine by a number of workers (Obel, 1953; Grant, 1961; Nafstad, 1965; Nafstad and Nafstad, 1968; Baustad and Nafstad, 1972). Nafstad (1965) described hematologic and bone marrow changes including anemia, leukocytosis, multinucleation of erythrocyte precursors, and increased numbers of megakaryocytes. However, anemia was not observed in selenium- and vitamin E-deficient swine by Michel et al. (1969), and Fontaine et al. (1977a,b) concluded that

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vitamin E did not significantly influence erythropoiesis in growing pigs. This conclusion was supported by the work of Niyo et al. (1980), who studied pigs deficient in selenium and vitamin E and found neither anemia nor any morphological abnormalities in circulating erthrocytes or leukocytes, although multinucleated erythroblasts were observed in bone marrow smears. Likewise, erythrocyte Δ-aminolevulinic dehydratase activity, viscosity of whole blood, and plasma protein and fibrinogen concentrations were unaffected.

Tolerance to Iron

Researchers in Britain (Patterson et al., 1967, 1969, 1971; Patterson and Allen, 1972) and Scandinavia (Lannek et al., 1962) have demonstrated a low tolerance of selenium- and vitamin E-deficient baby pigs to intramuscular injections of iron-dextrose for the prevention of anemia. The studies of Tollerz and Lannek (1964) indicated that pretreatment with selenium, vitamin E, or ethoxyquin was protective. However, Michigan workers (Miller et al., 1973) were unable to produce mortality or muscle lesions in pigs from sows fed corn-soybean meal diets unsupplemented with selenium and vitamin E when the pigs were fed 600 ppm iron from ferrous sulfate or injected intramuscularly with 1,000 mg of iron from iron-dextran. When 5 percent aerated cod liver oil was incorporated into the gestation diet and offspring were orally dosed with 5 to 10 ml aerated cod liver oil daily, an intraperitoneal injection of 750 mg iron from iron-dextran/kg of body weight produced myopathy in two of eight 8-day-old pigs (Cook, 1974). This myopathy was histologically identical with selenium-vitamin E deficiency.

Blood Enzymes

Certain enzymes in blood plasma can be sensitive indicators of tissue damage and may provide evidence of the tissue affected. Plasma activity of these enzymes is dependent on the equilibrium between rate of release from damaged cells and rate of inactivation or removal from the bloodstream. This information may be helpful in the diagnosis of animal disease and has been used in studies of selenium-vitamin E deficiency in swine. Orstadius (1961) reported that plasma aspartate aminotransferase (AspAT) or glutamic-oxalacetic transaminase (GOT) and ornithine carbamyl transferase (OCT) were useful indicators of muscular dystrophy and liver necrosis, respectively, in field cases of vitamin E deficiency in pigs. None of the enzymes is organ-specific, but their concentration in different tissues varies (Wretlind et al., 1959).

Average AspAT and alanine aminotransferase (AlaAT) or glutamic-

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pyruvic transaminase (GPT) activities in swine myocardium, liver, and skeletal muscle are shown in Table 7 (Tollersrud, 1973). Myocardium has the highest activity of both transferases. Liver is also high in AspAT but rather low in AlaAT. When myocardial lesions such as mulberry heart disease predominate, elevated plasma levels of both transferases may be found. Pigs suffering mainly from hepatic injury (hepatosis dietetica) should exhibit elevated plasma AspAT but only moderate increases in AlaAT. Isocitrate dehydrogenase (ICD) is present in all tissues but tends to be more liver specific. Thus, liver damage will induce a substantial rise in plasma ICD activity, while myopathies produce a lesser effect.

Tollersrud (1973) reported that plasma activities of AspAT, AlaAT, and ICD reflect necropsy findings in pigs fed semipurified diets low in selenium and vitamin E. Hepatosis dietetica was the predominant lesion when plasma AspAT and ICD activities were very high and AlaAT activity was only moderately increased. When activities of all three enzymes were significantly elevated, lesions were found in myocardium and/or skeletal muscle, as well as in liver. The usefulness of this technique in diagnosing a simple selenium deficiency may be limited, however. Supplements of 0.25 ppm selenium from sodium selenite did not prevent these enzyme anomalies, while daily supplements of 100 mg D,L-α-tocopheryl acetate did. Likewise, Bengtsson et al. (1978b) found that selenium additions to a vitamin E-deficient diet did not decrease the incidence of abnormal elevation of plasma AspAT activity. Hyldgaard-Jensen (1973) contended that plasma increases in the isozymes LDH_1 and LDH_5 are indicative of lesions in myocardium and skeletal muscle, respectively, while increases in glutamate dehydrogenase (GDH), sorbate dehydrogenase, and OCT strongly indicate liver damage. Unfortunately, this possibility has not been tested in a case of simple selenium or vitamin E deficiency.

Interpretation of plasma enzyme activities may be complicated by other factors. Tollersrud (1970) found that the activities of AspAT, AlaAT, and lactate dehydrogenase (LDH) were increased in the liver as the level of pro

TABLE 7 Average Enzyme Concentrations in Wet Swine Tissue (Reitman-Frankel Units/Gram)

Tissue	Asparate Amino-transferase × 10^4	Alanine Amino-transferase × 10^4
Myocardium	5.63	0.65
Liver	4.10	0.18
Skeletal muscle	1.47	0.28

SOURCE: Tollersrud (1973)

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tein in the diet was increased. Thus, moderate increases in plasma activities of these enzymes could appear in response to changes in diet composition and protein need, independent of morphological damage. Increases in certain plasma enzymes have also been reported in pigs after physical exercise, apparently related to increased permeability of muscle cell membranes (Hyldgaard-Jensen, 1971). Such increases are generally greater in the vitamin E-deficient subject, presumably because of a decline in membrane stability. As a consequence of the limitations cited above and their own findings of low correlations (0.19 and 0.01, respectively) between plasma selenium and AspAT and AlaAt, Simesen et al. (1979) concluded that plasma AspAT and AlaAT activities are of no value in diagnosing selenium and vitamin E deficiency in swine. In contrast, Fontaine et al. (1977a) found that elevated serum creatine phosphokinase activity was a useful indicator of subclinical muscular dystrophy in vitamin E- and/or selenium-deficient swine; and vitamin E deficiency increased red cell lipid peroxide concentration, while selenium deficiency did not (Fontaine and Valli, 1977).

Gross Pathology and Histopathology

Signs at necropsy do not usually differentiate between deficiencies of selenium and vitamin E, although Trapp et al. (1970) have attempted to distinguish between selenium-vitamin E deficiency and other diseases such as polyserositis, eperythrozoonosis, edema disease, and coal-tar pitch poisoning. The most commonly seen gross lesion of selenium-vitamin E deficiency was bilateral paleness of skeletal muscles. This was particularly evident in the quadriceps, femoris, gracilis, adductor, psoas, and longissimus dorsi muscles. Sometimes it was difficult to judge whether the paleness represented pathology, and lesions had to be confirmed microscopically. Occasionally, quite obvious chalky white areas were evident. The most striking gross change involved the liver, which frequently was swollen and pale with focal color variations in all lobes. Most often these foci were dark red, but sometimes they were tan to yellowish tan, ranging in diameter from 2 mm to 1 cm. Usually, these foci were raised above the surrounding surface, but sometimes they were depressed, the total effect imparting a roughened appearance to the liver. About half the pigs were icteric and edematous. Edema was prominent in the mesentery of the spiral colon, lungs, subcutis, and gastric submucosa. An occasional pig showed mottling of the myocardium.

Histologically, the most consistent lesions in skeletal muscle were loss of striations, vacuolization, and fragmentation of individual or groups of fibers. Sometimes there was edema between muscle fibers. In a few pigs

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there was mineral deposition in individual fibers, while in other pigs, muscle changes were progressive, from Zenker's necrosis to loss of many individual fibers and an increase in mononuclear cells between the remainder. Scattered through the liver were lobules that had degenerated and necrosed, while adjacent lobules appeared normal. The degeneration was characterized progressively by condensation of the perinuclear cytoplasm, dense and strongly eosinophilic cytoplasm with pyknosis, karyorrhexis or karyolysis and lysis of hepatic cells, and dilatation of sinusoids with blood, giving the impression of massive intralobular hemorrhage. In depressed areas of the liver there was an increase in interlobular connective tissue and a disappearance of hepatic lobules. The depression resulted either from contraction of connective tissue or decreased volume due to necrosis and disappearance of hepatic cells. Edema that had been seen grossly was prominent in the lungs and in the submucosa and serosa of the gastrointestinal tract. Myocardial changes were not consistent, but occasionally there were foci with loss of striations, increased intensity of staining of fibers, pyknosis of nuclei, necrosis and, in some areas, mineralization of fibers. Microangiopathy was commonly observed in the submucosa of the gastrointestinal tract, in skeletal and cardiac muscles, and occasionally in the central nervous system. Hyalinization of the arteriolar walls was predominant, with these lesions most common in pigs with extensive edema or marked muscle necrosis.

Similar lesions, plus a cutaneous microangiopathy producing the maculae previously mentioned, were described by Bengtsson et al. (1978a). The capillary and arteriolar changes were mainly confined to the dermis but sometimes occurred in the subcutis. It may be significant that these workers observed hepatosis dietetica, mulberry heart, skeletal muscle degeneration, cutaneous microangiopathy, gastric ulcers, and gastric parakeratosis in pigs fed a diet containing 0.008 ppm selenium and 1.4 mg α-tocopherol/kg supplemented with 15 mg D, L-α-tocopheryl acetate/kg. Forty-five milligrams of D, L-α-tocopheryl acetate/kg prevented the development of these lesions. However, supplements of 0.135 ppm selenium from sodium selenite, without supplemental vitamin E, did not (Bengtsson et al., 1978b).

Ultrastructural changes in skeletal muscle and myocardium of selenium- and vitamin-E deficient pigs have been described by Van Vleet et al. (1976, 1977a, 1977b). The earliest lesions in skeletal muscles that could be visualized by electron microscopy were myofibrillar lysis and disruption of mitochondria, sarcoplasmic reticulum, and plasma membranes. The basal lamina of the sarcolemma persisted after destruction of the enclosed sarcoplasm and provided a framework of subsequent regeneration. The myocardium exhibited similar changes in the myofibrils, but there was no

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regeneration associated with the persistance of basal lamina. Vascular lesions developed independently of myofibrillar alterations, with primary damage to the endothelium. Insudation of blood proteins and blood cells into the subjacent vascular wall produced hyaline masses of fibrinoid and secondary damage to smooth muscle cells.

CATTLE AND SHEEP

The occurrence of selenium deficiency in the diets of domesticated ruminants is associated largely with muscular degeneration or weakness. Most prominent among the conditions is nutritional muscular dystrophy, a metabolic disease that has occurred most widely in sheep (Muth, 1963), but also occurs in cattle. It appears that certain reproductive problems in cattle and sheep are related to the muscular incompetence resulting from selenium deficiency (Segerson et al., 1977).

Nutritional Myopathy

This disease appeared as a prominent economic condition in the improved grazing areas of the United States and Canada after World War II (Muth, 1955, 1963). Its association with selenium deficiency came immediately after the discovery of the nutritional importance of selenium (Hogue, 1958; Muth et al., 1958).

Changing grazing systems are thought to be a factor in the growing incidence of white muscle disease. The system of low-yielding hays and grasses for foraging, supplemented with grain and protein concentrates, was replaced with intensified high-yield-grass production and rearing and marketing lambs with minimum concentrates. The much higher levels of protein in improved grasses meant protein concentrates, normal carriers of organic sources of selenium, were eliminated from the feeding cycle of sheep (Muth, 1963). Also, more dependence on ruminal synthesis of protein exposes plant proteins to the reducing action of rumen microflora (Cousins and Cairney, 1961; Whanger et al., 1978a), a problem enhanced by the longer residence time of grasses in the rumen (Van Soest, 1965).

Nutritional muscular dystrophy and other selenium-responsive diseases are widespread in areas where the feeds consumed contain between 20 and 30 ppb selenium in dry matter. Supplements of selenite, selenate, and selenium-rich protein have been used successfully to correct deficiencies. Apparently, maintaining the dietary intake at 100 ppb selenium in dry feed given ewes will eliminate the signs in lambs (Muth, 1963). Less dietary selenium is needed when contained in the natural proteins because a greater proportion is absorbed. The incidence of dystrophy in lambs has

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been reduced in a number of experiments by administering low levels of selenium, orally or parenterally, to pregnant ewes (Muth et al., 1958; Young et al., 1961; Setchell, 1962; Setchell et al., 1962; Hamdy et al., 1963; Oksanen, 1965; Ewan et al., 1968b) or to lambs. Mortality may be as high as 65 percent in the first neonatal days in extremely deficient flocks. Oral or parenteral administration of 1 mg selenium as selenite to mildly dystrophic lambs will produce improvement within 24 hours.

There are fewer studies on white muscle disease in cattle than in sheep, possibly because the disease is not as common in the former. Selenium has effectively prevented the disease when administered to young cattle (Hartley and Grant, 1961) or to pregnant cows (Oksanen, 1965).

Examples of the forms of the disease seen on farms are described by Hartley and Grant (1961) and Andrews et al. (1968). Lambs affected with the congenital form are either born dead or die suddenly after physical exertion a few days following birth. Myocardial, liver, and body cavity lesions are observed, but skeletal musculature is rarely affected. The “delayed” form occurs mostly between 3 and 8 weeks of age. The predominant sign is muscular weakness. The lambs walk with a stiff gait and arched back, avoid movement, lose condition, and die. Those with severe heart involvement die suddenly. Skeletal muscles show dystrophy, but cardiac lesions are not always present. Cawley and Bradley (1978) reported that 2-month-old calves on four different farms died suddenly after a period of excitement. Histopathological examination revealed acute myocardial degeneration. Biochemical examination of other animals in the herd showed selenium deficiency. Selenium injections and feeding corrected the problem.

Lesions of nutritional myopathy in cattle and sheep are primarily calcification and degeneration of skeletal muscle and myocardium (Bonucci and Sadun, 1973). The affected areas are the left ventricular wall and the interventricular septum of the heart. The most active skeletal muscles having the greatest work requirement are the common sites of lesions. On the other hand the abductors of the thigh are commonly involved in the neonate and the longissimus dorsi and triceps are affected in the 3- to 8-week-old lamb.

The activities of lactic dehydrogenase, creatine phosphokinase, 5 ′-nucleotidase, and glutamic, oxalic, and pyruvic transaminases in the serum or plasma are increased (Buchanan-Smith et al., 1969; Whanger et al., 1976). Glutathione peroxidase is low and serum selenium concentration is less than 20 ppb (Whanger et al., 1977). Hoffman et al. (1973) concluded that selenium levels below 5 ppm in kidney cortex dry matter and 0.5 ppm in muscles of calves and lambs might be used as an indication of selenium deficiency in ruminants, although lower muscle selenium concentrations

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have been observed in apparently normal calves and lambs (Ullrey et al., 1977).

Nutritional myopathy is a multietiological problem, and this is manifested in the histopathology of the sarcomere. The initial histological lesions seen in dystrophic animals are microscopic deposits of calcium midway between the Z-bands of the sarcomere (Muth, 1966). In Canada, treatments with both vitamin E and selenite were most successful (Hoffman et al., 1973). In northern Europe, α-tocopherol has been considered the most effective component of the selenium-vitamin E mixture in preventing nutritional muscular dystrophy. In these countries, the problem is associated with poor curing of lightly fertilized grass forages and with an alteration of the unsaturated fat components in the cured hays. As a result the primary lesion of the sarcomere is degeneration, and calcification is secondary if seen at all (Oksanen, 1967).

Reproduction and Retained Placenta

Selenium deficiency has been related to reproductive failures in ruminants (Hartley and Grant, 1961; Andrews et al., 1968; Buchanan-Smith et al., 1969). Vitamin E appears to be an important complementary factor (Buchanan-Smith et al., 1969).

Selenium additions (1 ppm) to diluted semen increased motility and oxygen consumption in 13 of 15 ejaculates of sperm (Julien and Murray, 1977; Pratt, 1978).

During the course of an experiment to develop improved laboratory methods for ova culture and transfer, impaired fertility of ova was noted in a group of cows after transferring them from Green County to Wayne County, Ohio (Segerson et al., 1977). Chemical profiles of the diets consumed indicated that protein, energy, vitamin A, and selenium were below requirements. Subsequently, the effect of combined selenium and vitamin E injections upon the fertilization of ova was evaluated in superovulated beef cows maintained on either an adequate or inadequate plane of nutrition. Optimum fertilization (100 percent) of ova occurred in those taken from females receiving supplemental selenium and vitamin E and maintained on adequate nutrition. Other groups were only 40 percent fertilized. Segerson and Ganapathy (1979) obtained a similar result in sheep at normal estrus. Muscular contractions of the uterus were stronger in ewes receiving selenium. They theorized that stronger uterine contractions in selenium-supplemented ewes increased the number of sperm successfully reaching the ova.

One of the most important selenium-responsive diseases in dairy cows is

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retained placenta. This disorder results from the failure of the fetal placenta to separate from the maternal crypts in the caruncles, a process that normally occurs within 2 to 8 hours postpartum. Thus, retentions refer to placentas that remain attached to the uterus for more than 12 hours. Placental retentions occur in about 10 percent of the parturient dairy cows (Black et al., 1953). Placental retentions increased incidence of uterine infection to 54 percent in affected animals, compared to 10 percent for cows with normal calvings (Callahan, 1969). Since nearly 25 percent of the professionally treated diseases of dairy cattle are associated with genital infections, the economic significance of retained placenta should not be underestimated (Erb et al., 1958; Wetherhill; 1965).

The importance of prepartal nutrition in the etiology of retained placenta has been reported (Guieero, 1959; Wetherhill, 1965). Recently, selenium deficiency has surfaced as a major factor in the onset of this disease. In Great Britain, Trinder et al. (1969) first observed higher retention rates for placentas in herds with correspondingly greater problems of nutritional muscular dystrophy and were able to reduce incidence through supplementation of selenium and vitamin E (Trinder et al., 1973).

Effective experimental prevention of retained placenta in the United States was accomplished by Julien et al. (1976a) with injections of 50 mg selenium per cow in high-incidence herds. The feeds contained only 20 to 40 ng selenium/g of dry matter. The optimum time for dosing was between 1 and 3 weeks prepartum, since the biological half-life of selenium is about 10 days and clearance is accelerated in the immediate prepartum period (Conrad and Moxon, 1979). The injection of a single dose of 50 mg selenium as sodium selenite with 680 IU α-tocopherol reduced the incidence of retained placenta from 51 percent to 9 percent in 113 cows (Julien et al., 1976b). Fifty milligrams of selenium were required to maintain plasma concentrations between 50 and 100 ng/ml. The importance of vitamin E in the etiology of retained placenta is not known, but the small amounts of tocopherol in many silages (Schingoethe et al., 1978) and its necessity as a complement to selenium in other reproductive diseases suggests that its role needs to be determined. With some Ohio diets supplemented with sodium selenite, oral intakes of 1 mg/day eliminated retained placenta (Julien et al., 1976a). Negative results from selenium administration have been reported from South Dakota, a selenium-adequate area, and Maryland (Williams et al., 1977).

Increased use of corn silage and low-tocopherol hay silage as major ingredients replacing hay in beef and dairy cattle and sheep diets in the eastern corn belt may bring about more cases of selenium deficiencies because of the low selenium and vitamin E content of corn silage. Many samples

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collected in Ohio are in the range of 20 ng selenium/g of dry matter (Moxon and Olson, 1974). A total diet of legume-silage increased the plasma clearance of selenium in dairy cows (Reinhardt et al., 1978).

Other Selenium-Related Diseases

Unthriftiness in both cattle and sheep (characterized by loss of condition and diarrhea that can lead to death) has responded to selenium (Andrews et al., 1968). Periodontal disease, “camel-back” in ewes, pneumonia in lambs, and nonspecific diarrhea in calves are diseases that respond to selenium therapy (Kendall, 1960; Lagacé, 1961; Hamdy et al., 1963; Andrews et al., 1968; Mosier et al., 1978).

Supplemental dietary selenium may improve weight gains (McLean et al., 1959; Oldfield et al., 1960; Robertson and During, 1961; Andrews et al., 1968; Ewan et al., 1968b; Paulson et al., 1968a; Rotruck et al., 1969) but not under all conditions (Shirley et al., 1966).

A possible mechanism by which selenium counters unthriftiness in sheep and cattle and improves weight gains is through protection of the immune system. There is strong evidence that selenium functions biochemically in neutrophils of steers (Boyne and Arthur, 1979). There was no detectable GSH-Px activity in selenium-deficient neutrophils, whereas activity was systematically detected in the selenium-adequate group. On the other hand, selenium deficiency in steers does not affect the ability of neutrophils to phagocytize bacterial cells. The deficiency does cause a significant reduction in the ability of the phagocytic neutrophils to kill ingested bacteria. A similar decrease in antimicrobial activity has also been reported in the neutrophils of selenium-deficient rats (Serfass and Ganther, 1975). Alterations of microtubular function in GSH-Px-deficient polymorphonuclear leucocytes have been reported by McCallister et al. (1980), which may explain why selenium deficiency impairs the killing ability of phagocytic cells.

HORSES

Jones and Reed (1948) and Dodd et al. (1960) have described a muscular dystrophy in horses that is consistent with selenium deficiency. In the latter study, affected foals were 3 days to 5 months of age, but most were 1 to 2 months old. They were reluctant to move, had a stiff gait, and exhibited marked swelling and hardness of the nuchal crest. Difficulty in suckling was noted, and pathology of lingual, masseter, and neck muscles was involved. Muscle degeneration was bilaterally symmetrical. Steatitis was also evident. At one horse farm where four cases of myodegeneration had been

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identified previously, no cases were observed following intramuscular injections of 1.1 to 1.7 mg selenium from sodium selenate. However, no negative controls were used.

Stowe (1967) surveyed the serum selenium concentrations of standardbreds and thoroughbreds in Kentucky and at Aqueduct Raceway, Long Island, New York. Suckling foals consumed mostly mare's milk and had serum selenium concentrations of 0.070 ppm, although a few were as low as 0.027. Weanlings, yearlings, adult mares, adult stallions, and horses in training were fed bluegrass pasture or good quality legume-grass hay plus a concentrate containing mostly oats. Respective serum selenium concentrations were 0.147, 0.131, 0.127, 0.121, and 0.124 ppm. When orphaned foals were fed a semipurified diet unsupplemented with vitamin A, vitamin E, or selenium, serum selenium values after 60 days were 0.037 ppm, compared to 0.142 to 0.167 ppm in serum of foals supplemented with 0.5, 1.0, or 2.0 ppm selenium. Serum glutamic-oxaloacetic transaminase (GOT) activity increased during selenium depletion. When a single intramuscular injection of 0.11 mg selenium/kg of body weight was given, serum GOT activity returned to normal, but the response was unexpectedly slow. Stowe suggested that this slow response should be considered when anticipating responses to selenium therapy for the tying-up (transient myotonia) syndrome (Hill, 1962). Bergsten et al. (1970) conducted a similar study, and Gabbedy and Richards (1970) speculated about the role of selenium deficiency in white muscle disease in a foal. Schongaard et al. (1972) have linked deficiencies of vitamin E and selenium with myodegeneration in young foals, and Lannek (1973) has proposed that it is a common problem.

Wilson et al. (1976) communicated with all the provincial veterinary diagnostic laboratories in Canada concerning myodegeneration and suspected selenium-vitamin E deficiency in horses. The clinical, macroscopic, and microscopic features of 10 isolated cases were compared. Muscle weakness, reluctance to move, difficulty in nursing, and death within 10 days of birth were common. At necropsy, diffuse paleness and linear pale streaks were seen in skeletal and cardiac muscle. Granular and hyaline degeneration with early mineralization of swollen muscle fibers was seen histologically. Subcutaneous edema and pulmonary and hepatic congestion were also evident. Selenium (ppm) and vitamin E (IU/kg) concentrations in the dry matter of feedstuffs from one farm where myodegeneration was diagnosed were as follows: hay, 0.027 and 8.4; oats, 0.039 and 6.6; pasture grass, 0.092 and 23.2.

Owen et al. (1977b) have associated selenium-vitamin E deficiency with skeletal myopathy in adult horses, and Blackmore et al. (1979) have suggested that selenium deficiency may be associated with poor racing performance. Exercise-induced myopathies in the horse bear considerable simi

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larity to capture myopathy of wild species, including the zebra (Basson and Hofmeyr, 1973). Jarrett et al. (1964) considered the lesions to be morphologically identical with vitamin E deficiency. The primary etiology is not clear, however, and Harthoorn and Young (1974) described a bicarbonate-responsive metabolic acidosis during the acute phase of capture myopathy in zebra.

Brady et al. (1977, 1978a) explored the effects of exercise in the horse on the erythocyte glutathione system. Indicators of tissue damage, such as plasma creatine phosphokinase, GOT, and lactate dehydrogenase, increased in activity slightly, but no clinical signs of myopathy were seen. Nevertheless, erythrocyte malondialdehyde concentration increased, and it was evident that exercise induced some increase in peroxidation. Erythrocyte-reduced glutathione concentration was unchanged or increased slightly. Erythrocyte GSH-Px activity decreased, and total glutathione reductase activity increased after exercise. Active glutathione reductase activity, as a percentage of total glutathione reductase activity, declined with exercise in that study (Brady et al., 1977), in which blood lactate concentrations were markedly increased. The total glutathione reductase activity increase could have been a response to insufficient absolute concentrations of reduced nicotinamide adenine dinucleotide phosphate (NADPH) or a response to apparent insufficiency induced by declining blood pH, which could increase the glutathione reductase K_m for NADPH. Selenium supplementation, as compared to unsupplemented controls, did not influence the measured parameters, but plasma selenium concentrations of unsupplemented horses were 0.16 ppm and were probably adequate. In a review of the trace element requirements of horses, Schwarz and Kirchgessner (1979) have concluded that the dry diets should contain 0.1 to 0.2 ppm selenium.

DOGS

The first suggestion that selenium deficiency may be associated with a myopathy in dogs was published by Manktelow (1963). The diet of these dogs was principally mutton from an area of New Zealand where selenium-responsive diseases of sheep were noted. A fatal, myocardial necrosis was seen in young pups and a skeletal myodegeneration in an adult dog. Renal mineralization was also noted. Two bitches that had lost litters during previous perinatal periods were dosed with selenium during pregnancy and subsequently whelped normal litters.

Beagles, which were initially 5 to 8 weeks old, developed clinical signs of vitamin E-selenium deficiency after 40 to 60 days of consuming an unsupplemented semisynthetic diet (Van Vleet, 1975). Generalized muscular weakness progressed from unsteadiness to prostration and coma. Pitting

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and subcutaneous edema were observed in the limbs, ventral abdomen, ventral neck, and submandibular area. Anorexia and depression were evident late in the disease. Plasma glutamic-oxaloacetic transaminase and creatine phosphokinase activities were markedly increased and were associated with a severe myopathy and renal mineralization. These signs were prevented by supplements of 1.0 ppm selenium as sodium selenite or by 30 IU α-tocopherol/kg of diet. Intestinal lipofuscinosis was prominent in dogs fed unsupplemented or selenium-supplemented diets and was moderately severe in the vitamin E-supplemented dogs. Hepatic selenium concentration at necropsy was 0.10 ppm (wet basis).

WILD ANIMALS

A muscular dystrophy following mechanical capture of wild Hunter's antelope (*Damaliscus hunteri*) was described by Jarrett et al. (1964) as indistinguishable from white muscle disease in cattle suffering from vitamin E deficiency. Pale areas in skeletal muscle showed hyaline degeneration with loss of striations. Transverse breaks were seen in some muscle fibers, and totally degenerated fibers showed marked proliferation of the sarcolemmal sheaths. A similar condition, referred to as muscle necrosis, was described by Young (1966) in red hartebeest (*Alcelaphus buselaphus*) in which lesions in heart and skeletal muscle, as well as degenerative changes in liver and kidney, were found. Leg paralysis and skeletal and cardiac muscle necrosis have been observed in the greater (*Phoenicopterus ruber roseus*) and lesser (*P. minor*) flamingo (Young, 1967).

Young and Bronkhorst (1971) referred to the condition as over-straining disease in wild animals. Ebedes (1969) described the condition in oryx (*Oryx gazella gazella*) and Basson et al. (1971) observed it in a number of wild species. Basson and Hofmeyr (1973) named the syndrome “capture myopathy” and described it in red hartebeest, oryx, springbok (*Antidorcas marsupialis*), eland (*Taurotragus oryx*), roan antelope (*Hippotragus equinus*), sable antelope (*H. niger*), kudu (*Tragelaphus strepsiceros*), nyala (*T. angasi*), Burchell's zebra (*Equus burchelli*), mountain zebra (*E. zebra hartmannae*), giraffe (*Giraffa camelopardalis*), buffalo (*Syncerus caffer*), black rhinoceros (*Diceros bicornis*), and elephant (*Loxodonta africana*).

McConnell et al. (1974) described pain, stiffness, muscle dysfunction, paresis, labored respiration, and histological signs of white muscle disease in young baboons. White muscle disease has also been described by Herbert and Cowan (1971) in live-trapped mountain goats (*Creamnos americanus*) and by Young (1972) in tsessebe (*Damaliscus lunatus*) and oribi (*Ourebia ourebi*).

The primary etiology of capture myopathy is not known. The above re

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ports provide no information on selenium and vitamin E status of the wild species. Injections of a variety of medicaments, including selenium and vitamin E, were not effective once clinical signs were seen. However, Harthoorn and Young (1974) found that zebra that were pursued intensely for 2 km became acidemic and, if untreated, died within 12 hours. If an intravenous infusion including 1000 mEq of sodium bicarbonate were administered by 30 minutes after capture, the zebra survived. At necropsy, untreated animals exhibited extensive, generally bilateral areas of pale, degenerated muscle interspersed with hemorrhages. The kidneys and liver were pale and swollen; there were pale, apparently necrotic areas in the heart; and the lungs were congested and edematous. Captive wild animals also exhibit white muscle disease. While etiology is frequently unknown, R. M. Sauer, pathologist at the National Zoological Park, Washington, D.C., reported in 1971 (personal communication) that selenium-vitamin E deficiency had been diagnosed in reindeer, dorcas gazelle, greater kudu, and dik-diks. Clinical signs included failure to conceive, stillbirths, neonatal deaths (up to 10 to 12 weeks), low birth weights and retarded growth, and transient and shifting lameness in both juveniles and adults. Serum creatine phosphokinase activity was elevated, and necropsy lesions included muscular dystrophy and hepatic necrosis. Concern over possible selenium deficiency in infant wild animals reared on commercial milk replacers led to publication (Gray, 1974) of selenium concentrations in 13 products, many of which were found to be quite low.

Stuht et al. (1971) reported mortality and bilateral skeletal muscular dystrophy in captive white-tailed fawns (*Odocoileus virginianus*) from does fed defined diets containing 0.15 ppm selenium and 5 IU vitamin E/kg. Subsequently, Brady et al. (1978b) studied 32 adult white-tailed does and their fawns over a 2-year period when receiving a basal diet containing 0.04 ppm selenium and 5.5 IU vitamin E/kg or this diet plus 0.2 ppm selenium, 45 IU vitamin E/kg, or both. Dietary selenium supplements had a significant effect on plasma selenium concentration and erythrocyte GSH-Px activity in both does and fawns. Time-dependent and hydrogen peroxide-dependent erythrocyte hemolysis in vitro was reduced in the does by supplemental vitamin E. White muscle disease and mortality were seen only in fawns, invariably following capture for blood collection. Only supplemental vitamin E significantly reduced mortality. However, both selenium and vitamin E decreased blood malondialdehyde concentration, and selenium alone decreased liver malondialdehyde concentration.

SELENIUM IN HUMAN NUTRITION

The preceding discussion amply demonstrates the nutritional need for selenium in a wide variety of animal species. Accumulating evidence sug

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gests that selenium may be required by humans also. For example, the stoichiometry of selenium in human erythrocyte GSH-Px is similar to that of the enzyme derived from various animal sources (Awasthi et al., 1975). Also, blood selenium levels are low in children with kwashiorkor (Burk et al., 1967; Levine and Olson, 1970), and administration of selenium has been reported to result in growth (Schwarz, 1961) and reticulocyte (Hopkins and Majaj, 1967) responses in kwashiorkor patients. Moreover, the growth of human fibroblasts in cell culture is enhanced by selenium (McKeehan et al., 1976). Finally, recent reports from New Zealand and the People's Republic of China (discussed below) indicate that selenium supplementation may be of value in persons consuming very low levels of the element.

In 1980 the U.S. National Research Council recommended a safe and adequate dietary selenium intake for adults of 50 to 200 μg/day with correspondingly lower intakes for younger age groups (NRC, 1980a). This recommendation was based primarily on extrapolation from animal experiments, since few data with human subjects were available at that time. A recent balance study estimated that a daily selenium intake of about 70 μg was needed to replace excretory losses and maintain body stores of healthy young North American males (Levander et al., 1981). That experimentally derived figure falls well within the safe and adequate range of the National Research Council but is considerably in excess of the 20 μ g/day needed to maintain balance in young New Zealand women (Stewart et al., 1978). This difference in the amount of selenium needed for balance in North Americans and New Zealanders is probably due to the greater total body pool of selenium in Americans.

The role of selenium in human nutrition is supported by the work of van Rij et al. (1979), who described a New Zealand patient on total parenteral nutrition (TPN) because of complications that developed following abdominal surgery. Previous to surgery the patient had lived in an area of the country known to have low levels of selenium in its soils. Immediately prior to TPN the plasma selenium level of the patient was 25 ng/ml. Thirty days after starting TPN, the patient suffered from increasing bilateral muscular discomfort in her quadriceps and hamstring muscles. Walking aggravated the muscle pain and mobility was severely impaired. The upper limb girdle was not affected. At this point the plasma selenium level of the patient had dropped to 9 ng/ml. Daily supplementation with 100 μg selenium as selenomethionine added to the TPN solution caused the disappearance of all muscle symptoms within a week, and there was a return to full mobility. The low plasma selenium levels seen in this patient, along with the favorable response to selenium treatment, suggest the essential role of selenium in human nutrition.

Another case of apparent selenium deficiency during TPN was described

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by Johnson et al. (1981) as a 43-year-old man who lived in the northeastern United States. The patient had been on TPN for 2 years and had a poor selenium status, as suggested by low erythrocyte and heart (post mortem) selenium levels and depressed GSH-Px activities. The patient had a dilated cardiomyopathy similar to that of Keshan disease (see below). It was concluded that the patient suffered from selenium deficiency due to long-term TPN complicated by a draining fistula and malabsorption.

In contrast to the above two reports, Kay and Knight (1981) found no signs or symptoms of selenium deficiency in 43 adults from the north island of New Zealand during medium- or long-term TPN, even though these patients had very low selenium levels. These differing responses of patients to low selenium intake indicate that more research is required to determine the role of selenium in TPN.

Additional evidence of the role of selenium nutrition in human health problems concerns recent reports from the People's Republic of China regarding Keshan disease (Keshan Disease Research Group, 1979a,b). This is an endemic cardiomyopathy distributed in a region running from northeastern China to the southwest. The disease primarily affects children from 1 to 9 years of age and is characterized by gallop rhythm, heart failure, cardiogenic shock, abnormal electrocardiograms, and heart enlargement.

The Chinese workers first showed that the average selenium content of human hair in areas affected by Keshan disease was generally below 0.12 μg/g, whereas in areas removed from the affected region, hair selenium content ranged from 0.25 to 0.6 μg/g. Hair selenium levels in unaffected areas near the affected region were between 0.12 and 0.2 μg/g. The selenium content of several staple foods was found to be lower in affected than in unaffected areas. Also, the concentration of selenium in the blood of persons living in the affected areas often dropped below 0.010 μg/ml, while the lowest value in areas unaffected by Keshan disease was about 0.040 μg/ml. Results from urinary selenium-loading tests and whole-blood GSH-Px assays were said to indicate poor selenium status in the affected areas.

Because of these manifold relationships between selenium and Keshan disease, an intervention trial with sodium selenite was conducted with children 1 to 9 years old who lived in an affected area. A group of 4,510 children was treated with sodium selenite in the 1974 trial and 3,985 children received a placebo. The dose of sodium selenite was 0.5 mg/week in 1- to 5-year-olds and 1.0 mg/week in 6- to 9-year-olds. The morbidity rate due to Keshan disease was 0.22 percent (10/4,510) and 1.35 percent (54/3,985) in the treated and placebo groups, respectively. A significant effect of selenium was also seen in the 1975 trial, so the placebo groups were discontinued in the 1976 and 1977 trials. The case rate dropped markedly in those

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years, although one case was observed in a group of 212 children who failed to take the selenium treatment in 1976. No untoward side effects due to sodium selenite were noted in these trials, except for some isolated instances of nausea that could be eliminated by postprandial dosing. Continuous ingestion of the selenium tablets for 3 or 4 years produced no hepatic damage as assessed by physical examinations and liver function tests.

Although the positive prophylactic response obtained with selenium and the multitude of relationships revealed between selenium and Keshan disease indicate a role for selenium in the disease, the Chinese workers interpreted their data cautiously and concluded that a deficiency of selenium was probably not the only cause of the disease. Certain epidemiological characteristics, such as seasonal variability or differential response in rural and urban areas, were not explicable solely in terms of selenium deficiency. Therefore, it was suggested that a lack of selenium was only one component in the causality of the disease and that other predisposing environmental conditions would have to be met before Keshan disease would occur. One possible environmental condition that might play a role in the etiology of Keshan disease is viral infection, since selenium-deficient mice were less resistant than control mice to the cardiotoxic effects of a coxsackie B_4 virus that had been isolated from a Keshan disease patient (Bai et al., 1980).

As the Chinese studies point out, infants and children appear to be most at risk with regard to selenium deficiency, presumably because of their increased metabolic requirements and faster growth rates. Certainly, most animal studies show that it is the young of any given species that bear the most severe consequences of ingesting a selenium-deficient diet. Premature infants constitute a group that might be particularly vulnerable to selenium deficiency because of their almost total reliance on human milk during their first 12 weeks of life. Gross (1976) studied a group of premature infants whose vitamin E status was adequate as judged by serum vitamin E levels but whose GSH-Px activities and plasma selenium levels declined from 4.2 units/g hemoglobin and 0.080 μg/ml at 1 week of age, respectively, to 2.7 units/g hemoglobin and 0.035 μg/ml at 7 weeks of age. A subgroup of prematures fed a formula based on cow's milk that also contained a high level of polyunsaturated fat and supplemental iron suffered decreased hemoglobin levels and increased reticulocyte counts that were thought to be the result of the oxidative stress of the formula in conjunction with the poor selenium status of the infants.

Another group of infants and children who might be especially prone to developing selenium deficiency are those who suffer from certain metabolic diseases such as phenylketonuria (PKU) and maple syrup urine disease (MSUD) and who must consume only special synthetic diets that are

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very low in selenium. McKenzie et al. (1978) described one such 13-year-old child in New Zealand whose whole blood and plasma selenium levels were 0.016 and 0.009 μg/ml, respectively, and yet the child was clinically in good health. In West Germany the serum selenium levels of children with PKU or MSUD range between 0.007 and 0.028 μg/ml (Lombeck et al. 1978), and their erythrocyte GSH-Px activities were depressed compared to values of normal children (4.6 vs. 8.8 units/g hemoglobin). The average hair selenium levels were lower in the patients (0.062 μg/g) than in healthy children (0.429 μg/g) and indeed were in the range of values reported from areas with Keshan disease in China. And yet all the patients in West Germany thrived well. Also, their red cells showed no increased rate of hemolysis or oxidation of hemoglobin to methemoglobin after incubation with sodium azide. Such comparisons of data from different countries reinforce the original conclusion of the Chinese investigators that selenium may be only one of the agents involved in the etiology of Keshan disease and that other predisposing environmental conditions may be necessary for the disease to occur.

The elderly may also be in danger of suboptimal selenium status since this age group in New Zealand had lower blood-selenium levels and erythrocyte GSH-Px activities than young adult controls (Thomson et al., 1977b). It was not possible to establish whether these differences were due to poor dietary habits or were an integral part of the aging process. Pooled dietary composites of Swedish pensioners furnished only an average of 31 μ g selenium/day (Abdulla et al., 1979), which is less than the safe and adequate range for adults (NRC, 1980a).

In conclusion, selenium deficiency has been reported in humans as indicated by reduced blood-selenium levels, decreased erythrocyte GSH-Px activities, and favorable responses to selenium treatment or prophylaxis. In some instances, however, the deficiency signs observed are not consistent (total parenteral nutrition) or other factors may be involved (Keshan disease). Nevertheless, nutritionists and medical health personnel should be alerted to the possible occurrence of suboptimal selenium status in persons at risk because of their geographical location (e.g., New Zealand, Scandinavia, areas of the People's Republic of China), their age (infants or elderly people), their exposure to predisposing environmental factors (possibly viruses, heavy metals, or prooxidants), their status with regard to related nutrients (e.g., vitamin E), or the restricted nature of their diet (patients consuming special medical diets or undergoing total parenteral nutrition, or individuals of low economic status subsisting on just a few staple foods).

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7

Effects of Excess Selenium

The poisonous nature of many selenium compounds remained more or less a laboratory curiosity until the 1930s, when it was discovered that selenium was the active principle in forages and grains that caused alkali disease in livestock raised in certain areas of the American great plains. The practical nature of this problem stimulated a great deal of research on both chronic and acute selenosis (reviewed by Moxon and Rhian [1943] and Rosenfeld and Beath [1964]). This chapter deals with general aspects of the toxicity of selenium compounds to animals and humans.

SELENIUM TOXICITY IN LABORATORY ANIMALS

ACUTE TOXICITY

The minimum lethal dose of selenium as sodium selenite or selenate in rabbits, rats, and cats was 1.5 to 3.0 mg/kg body weight regardless of whether the salts were given orally, subcutaneously, intraperitoneally, or intravenously (Smith et al., 1937). Animals receiving such acute doses of selenium compounds develop a garlicky breath odor because of the exhalation of volatile methylated selenium metabolites. Dimethyl selenide, the primary volatile metabolite, and trimethylselenonium ion, a urinary metabolite, have relatively low orders of toxicity, their LD_{50} in rats being 1,600 mg and 49.4 mg selenium/kg, respectively (McConnell and Portman, 1952b; Obermeyer et al., 1971). However, these compounds should not be regarded as innocuous, since they can have strong synergistic toxici

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ties with mercuric chloride (Parizek et al., 1971) and sodium arsenite (Obermeyer et al., 1971). Also, male rats have been reported to be much more sensitive to dimethyl selenide than female rats (Parizek et al., 1971), and male rats fed diets low in selenium apparently are extremely sensitive to the toxicity of dimethyl selenide (Parizek et al., 1980). This susceptibility to dimethyl selenide toxicity can be largely eliminated by pretreating the male rats with small injected doses of selenite or by increasing the prior oral intake of dietary selenite. Elemental selenium is quite nontoxic, since its oral LD_{50} in rats is 6,700 mg/kg (Cummins and Kimura, 1971).

Aside from garlicky breath odor, animals acutely poisoned with selenium exhibit vomiting, dyspnea, tetanic spasms, and death from respiratory failure (Franke and Moxon, 1936). Pathological changes include congestion of the liver, with areas of focal necrosis; congestion of the kidney; endocarditis; myocarditis; petechial hemorrhages of the epicardium; atony of the smooth muscles of the gastrointestinal tract, gallbladder, and urinary bladder; and erosion of the long bones, especially the tibia.

CHRONIC TOXICITY

Dietary selenium levels of 4 to 5 ppm are sufficient to cause growth inhibition in animals fed a normal diet (NRC, 1976b). However, the resistance or susceptibility of animals to chronic selenium poisoning can be markedly altered by a number of factors. For example, Harr et al. (1967) found that rats fed a commercial “laboratory chow” diet were two to three times more resistant to chronic selenium toxicity than rats fed a semipurified diet. On the other hand, diets low in protein quality or quantity potentiated chronic selenosis (Gortner, 1940; Lewis et al., 1940). The growth rate of vitamin E-deficient rats was depressed by only 1 mg selenium as sodium selenite/kg of diet (Witting and Horwitt, 1964), and swine deficient in vitamin E and selenium were shown to be more susceptible to acute selenium toxicity than pigs fed diets supplemented with vitamin E and selenium (Van Vleet et al., 1974). Weanling rats are more susceptible to selenium toxicity than older rats (Halverson et al., 1966), and rabbits are more sensitive to selenium poisoning than rats (Pletnikova, 1970). Jaffe and Mondragon (1969) obtained evidence suggesting that rats can adapt somewhat to a chronic selenium intake, since chronically poisoned rats from mothers previously exposed to selenium stored less of the element in their livers than rats from mothers fed a nonseleniferous stock diet.

Another factor that can influence the interpretation of chronic selenium toxicity experiments is the criterion used to assess the degree of response to a given dose of selenium. As indicated above, the most commonly used criteria in the past were growth inhibition and mortality. Other criteria

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used include liver damage, splenomegaly, pancreatic enlargement, anemia, and elevated serum bilirubin levels (e.g., see Halverson et al., 1966). Jaffe et al. (1972b) reported that excess selenium intake in rats decreased fibrinogen levels and prothrombin activities and elevated serum alkaline phosphatase and glutamic-pyruvic or glutamic-oxaloacetic transaminase activities. However, all these effects were observed only at selenium intakes that also depressed growth rate.

Pletnikova (1970) measured various biochemical indices in rabbits and rats that were given low doses of sodium selenite in aqueous solution for long periods of time. In this experiment, 32 rabbits and 16 rats were divided into 4 groups and given daily peroral doses of 0, 5.0, 0.5, and 0.05 μg selenium/kg body weight for 7½ months and 6 months, respectively. There was a significant increase in the concentration of oxidized glutathione in the blood of the rabbits given 5 μg/kg for 2 months, and hepatic sulfobromophthalein excretion and succinic dehydrogenase activity decreased after 7 months. Fewer and less-pronounced changes were caused by 0.5 μg/kg, while 0.05 μg/kg weakened the capacity for forming new conditioned reflexes. Although these responses were considered harmful effects of selenium, the level of selenium given perorally to rats at a dose of 5 μg/kg is roughly equivalent to the intake provided by a diet containing 0.063 ppm. Since this level of dietary selenium intake is clearly within the nutritional range, the interpretation of this experiment is open to question. Most biologists would regard responses to selenium in the doses used by Pletnikova (1970) as physiological rather than pharmacological or toxicological effects.

SELENIUM TOXICITY IN FARM ANIMALS

Rosenfeld and Beath (1964) classified three distinct forms of selenium poisoning in livestock: (a) acute, (b) chronic of the blind-staggers type, and (c) chronic of the alkali-disease type.

In the field, acute selenium poisoning is caused by the ingestion of a large quantity of highly seleniferous accumulator plants in a short period of time. The experimental or accidental administration of selenium compounds has also produced acute poisoning in farm animals (NRC, 1976b). Signs of severe distress include labored breathing, abnormal movement and posture, and prostration and diarrhea, and are followed by death in a few hours. Acute selenosis is generally not a practical problem because livestock usually avoid the accumulator plants except when other pasture is not available.

Rosenfeld and Beath (1964) stated that blind staggers occurs in animals that consume a limited amount of selenium accumulator plants over a pe

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riod of weeks or months, but this disease has not been produced in animals by the administration of pure selenium compounds. However, blind staggers can be mimicked experimentally by giving aqueous extracts of accumulator plants, so Maag and Glenn (1967) and Van Kampen and James (1978) suggested that alkaloids or other toxic substances in the accumulators may play a role in this syndrome. The affected animals have impaired vision, and they wander, stumble, and finally succumb to respiratory failure.

Animals that consume grains containing 5 to 40 mg selenium/kg over a period of several weeks or months suffer from chronic selenosis, known as alkali disease. Signs include liver cirrhosis, lameness, hoof malformations, loss of hair, and emaciation. Although Maag and Glenn (1967) were not able to demonstrate alkali disease experimentally in cattle given inorganic selenium, Olson (1978) cited several studies indicating that the disease is associated with the consumption of seleniferous grains or grasses and could be produced experimentally by feeding inorganic selenium salts.

There is no effective way to counteract selenium toxicity in livestock except to remove the animals from the areas with high selenium soils and close these areas to livestock production. Grains or grasses grown in these areas, however, can still be used if they are blended with crops from areas with lower selenium soils.

SELENIUM OVEREXPOSURE IN HUMANS

The public health aspects of excess selenium exposure first became of concern after the discovery that selenium caused alkali disease in livestock, since it was quickly realized that selenium from grains or vegetables grown on seleniferous soils could also enter the human food chain. Smith et al. (1936) surveyed rural farming and ranching families living in the Great Plains area of the United States known to have a history of alkali disease in livestock. No symptoms pathognomonic of human selenium poisoning were found, and no serious illness definitely attributable to selenium toxicity was observed. Vague symptoms of anorexia, indigestion, general pallor, and malnutrition were reported, and more pronounced disease states such as bad teeth, yellowish discoloration of the skin, skin eruptions, chronic arthritis, diseased nails, and subcutaneous edema were seen.

Since the results of this preliminary study were not clear, a second, more complete survey was carried out to delineate more exactly the symptomatology of human selenosis and its possible relationship to urinary selenium excretion (Smith and Westfall, 1937). To increase the probability of detecting effects of selenium overexposure, 100 subjects were selected from the earlier survey who had high levels of selenium in their urine. Once again it was concluded that none of the symptoms observed could be con

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sidered specific for selenium poisoning. However, numerous complaints of gastrointestinal disturbance were considered significant, and a high incidence of icteroid skin discoloration was thought perhaps to be related to liver dysfunction possibly caused by selenium ingestion. Bad teeth were also seen in 27 percent of the individuals surveyed. Other symptoms were reported so rarely that they did not appear to be associated with selenium.

Jaffe (1976) conducted a survey in Venezuela and compared children from a high-selenium region (Villa Bruzual) with those from Caracas. Average hemoglobin and hematocrit values were depressed in Villa Bruzual, but no correlation between blood and urine selenium levels and hemoglobin or hematocrit values was observed in specific individuals. Any differences in hemoglobin were thought to be more likely due to differences in nutritional or parasitological status rather than to differences in selenium intake (Jaffe et al., 1972a). Prothrombin and serum alkaline phosphatase and transaminase activities were normal in all children, and no correlation with blood selenium levels was found. Dermatitis, loose hair, and pathological nails were more common in children from the high-selenium region, and the clinical signs of nausea and pathological nails seemed to correlate with serum and urine selenium levels. But it was doubted that selenium was responsible for the increased incidence of those clinical signs since no differences attributable to selenium were seen in the various biochemical tests carried out (Jaffe et al., 1972a).

Nine cases of acute selenium intoxication were described by Kerdel-Vegas (1966) in persons who had consumed nuts of the “Coco de Mono tree” (*Lecythys ollaria*) from a seleniferous area in Venezuela. In most cases, nausea, vomiting, and diarrhea occurred a few hours after eating the nuts, followed by hair loss and nail changes a few weeks after the initial episode. Most patients appeared to make a satisfactory recovery, with eventual regrowth of hair and nails; but a 2-year-old boy died due to severe dehydration. Samples of Brazil nuts marketed in Great Britain contained an average of 22 ppm of selenium (Thorn et al., 1978), and Chavez (1966) reported signs of selenium toxicity in rats fed diets that included defatted Brazil nut flour containing 51 ppm of selenium. Brazil nuts marketed in the United States also are high in selenium, with 6 percent of one sample containing 100 ppm or more (Palmer et al., 1982).

Although data from industrial exposure to selenium are limited, Glover (1976) has stated that “there have been no deaths or cases of irreversible pathological conditions due to selenium or its compounds being absorbed from industrial processes.”

A detailed description of an episode of endemic human selenosis was recently reported from the People's Republic of China (Yang et al., 1983). The morbidity due to selenium intoxication was almost half of 248 inhabit

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ants from the 5 most heavily affected villages during the years of peak prevalence (1961 to 1964). Loss of hair and nails was the most common sign of the poisoning, but lesions of the skin, nervous system, and possibly teeth may have been involved in the areas of high incidence. The mean urinary selenium level found in this area of China with selenosis (2.68μg/ml) was greater than even the maximum value (1.98 μg/ml) reported by Smith and Westfall (1937). The average blood selenium level in this high-selenium region of China (3.2 μg/ml) substantially exceeded the level that Jaffe et al. (1972a) concluded was hazardous to children (0.813 μg/ml). The selenium content of vegetable, cereal, hair, blood, and urine samples from the selenosis area was up to three orders of magnitude higher than that of corresponding samples from Keshan disease (selenium-deficiency) areas. The selenium entered the food chain from soils that had been contaminated by weathered coal of a very high selenium content (average greater than 300 μg/g).

Thus, with the exception of the Chinese experience, it has not been possible to identify any specific, definitive long-term human health problem due to selenium overexposure. This seems rather remarkable in light of the great inherent toxicity of selenium. However, it should be pointed out that others felt that human selenium poisoning is common, widespread, and in certain localities of importance to public health (Lemley, 1943). Kilness (1973) decried the fact that no subsequent systematic survey with appropriate controls has been made in South Dakota since the first surveys done over 30 years earlier. Moreover, Smith and Westfall (1937) were surprised by the absence of definite evidence of serious injury, especially in those subjects whose urinary selenium concentrations were markedly elevated.

Because of the lack of any well-documented selenium intake data during excess selenium exposure, a precise figure for an intake that would be harmful to humans cannot be given. Most of the subjects of Smith and Westfall (1937) were thought to be absorbing between 10 and 100 μg/kg body weight per day. This would be equivalent to a dietary selenium intake of 700 to 7,000 μg/day by a 70 kg man, if it can be assumed that all of the ingested selenium was absorbed. Tsongas and Ferguson (1977) could find no difference in the health status of two populations that drank water containing 50 to 125 μg selenium/liter or 1 to 16 μg selenium/liter, respectively. It was not possible to estimate the daily dietary intake of selenium in the endemic-selenosis area of China during the period of peak prevalence, but the dietary intake some time after the peak prevalence had subsided averaged 4.99 mg/day with a range of 3.20 to 6.69 mg/day (Yang et al., 1983). A tentative maximum acceptable daily selenium intake for the protection of human health of 500 μg was proposed by Sakurai and Tsuchiya (1975). This intake was arrived at by first estimating that the usual average

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selenium intake by humans ranged between 50 and 150 μg/day. Intakes of 10 to 200 times normal were thought acceptable as an estimated range for the safety margin within which most persons could tolerate selenium. Multiplying the lower of both estimates gave the lowest level of potentially dangerous selenium intake, i.e., 50 × 10 or 500 μg/day.

Obviously, progress in selenium toxicology would be greatly enhanced if a more specific and sensitive test of selenium overexposure could be developed. Perhaps with the discovery of the role of selenium in GSH-Px (see Chapter 4) and the newly found inhibition of protein synthesis by selenodiglutathione (Vernie et al., 1979) such tests will be forthcoming in the future.

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8

Selenium and Human Health

Since both selenium toxicities and deficiencies have been demonstrated in animals under practical conditions, concerns have been expressed about the possible impact on human health of either excessive selenium exposure or suboptimal selenium intake. This chapter discusses various attempts that have been made to link human health problems with either too high an exposure or too low an intake of selenium, either by extrapolating results from animal models to man or by making statistical associations between the presumed selenium status of the general population and the incidence of various human diseases.

HIGH SELENIUM EXPOSURE

CANCER

The concept that high levels of selenium might be carcinogenic was derived from early work by Nelson et al. (1943), who fed groups of 18 female rats a low-protein diet supplemented with 0, 5, 7, or 10 ppm selenium as seleniferous corn or wheat or 10 mg selenium/kg as a mixed inorganic selenide containing ammonium potassium selenide and ammonium potassium sulfide. Of the 73 selenium-treated rats that died or were killed before 18 months, none had any tumors or advanced adenomatoid hyperplasia. Of the 53 selenium-treated rats that lived 18 to 24 months, 43 developed cirrhosis and 11 had liver cell adenoma or low-grade carcinoma without metastasis in cirrhotic livers. No tumors appeared in any of the 18- to 24-

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month old rats that had no cirrhosis. The incidence of spontaneous hepatic adenoma and low-grade carcinoma was low in the nonexposed control rats, and the incidence of spontaneous hepatic tumors in the rat colony was less than 1 percent in rats 18 to 24 months of age. The interpretation of this experiment is complicated by the fact that hepatic tumors were observed only in the presence of liver cirrhosis, and histological differentation between neoplasia and possible regenerative hyperplasia in sections of such damaged organs is difficult.

Klug and Hendrick (1954) fed 35 young adult male rats a diet containing 19 ppm of selenium as seleniferous wheat for 16 months. A group of 15 control rats received the same diet, except that nonseleniferous wheat was substituted for the seleniferous wheat. No evidence of lung tumors due to selenium was obtained in this experiment. These rats were not examined for liver tumors.

Preliminary studies by Volgarev and Tscherkes (1967) suggested that feeding 4.3 mg selenium as sodium selenate/kg in a low-protein diet caused an increased incidence of tumors in rats, but follow-up experiments did not reproduce these results. Also, the experimental design used in this work was flawed in that control rats not exposed to added selenium were not included.

An increased incidence of tumors was reported in rats given 2 ppm selenium as sodium selenate in drinking water for 52 weeks, followed by 3 ppm until death (Schroeder and Mitchener, 1971). However, the increased tumor incidence in the selenate-treated rats may have been due to the longer life span of the exposed animals. Moreover, this study is difficult to evaluate because there appeared to be no systematic histological search of the organs and tissues of the experimental animals.

Schroeder and Mitchener (1972) carried out two experiments in which mice were given either 0 or 3 ppm selenium as either sodium selenite or selenate in drinking water during their entire lifetime. Sections were prepared from 119 of 180 control mice and 88 of 176 selenium-exposed mice autopsied from both experiments. Of the controls sectioned, tumors were found in 23 (19 percent), and 10 (43 percent) of the tumors were malignant. Of the selenium-exposed mice sectioned, tumors were found in 13 (15 percent) and all tumors were malignant. It was concluded that selenium as selenite or selenate had little tumorigenic or carcinogenic effect in mice, but when tumors did appear they were all malignant.

Tinsley et al. (1967) and Harr et al. (1967) reported on an extensive study in which 1,437 rats were fed either a commercial laboratory chow-type diet or a semipurified diet containing either 12 or 22 percent casein. These diets were supplemented with 0 to 16 mg selenium/kg fed as sodium selenite or sodium selenate. Most of the rats fed the semipurified

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diets supplemented with more than 2 mg/kg were dead within 100 days, and almost all died before 2 years. However, no hepatic tumors were seen in the 71 rats fed 0.5 to 2.0 mg/kg that survived 2 years or more.

Three studies have shown carcinogenic effects that seem due more to an effect of a particular compound that contains selenium than to an effect of selenium per se. For example, Seifter et al. (1946) found adenomatous hepatic hyperplasia and multiple thyroid adenomas in rats fed 0.05 percent bis-4-acetamino-phenyl-selenium dihydroxide for 105 days. Innes et al. (1969) demonstrated an increased incidence of hepatomas, lymphomas, and pulmonary tumors in mice given the maximal tolerated dose of selenium diethyldithiocarbamate (ethyl selenac) for 82 weeks. The dose used was 10 mg/kg body weight via stomach tube starting at 1 week of age, followed by 26 mg mixed directly into each kilogram of diet after 4 weeks of age.

A recent study carried out under contract for the National Cancer Institute Carcinogenesis Testing Program indicates that high levels of selenium sulfide, the active component of certain antidandruff shampoos, is carcinogenic for rats and mice (NCI, 1979). Groups of 100 rats or mice (50 males and 50 females) were given one of four treatments for 103 weeks: untreated control, vehicle control (received volumes of 0.5 percent aqueous carboxymethylcellulose equal to those of the test solutions administered), and low- or high-dose groups (received stated dose of selenium sulfide suspended in 0.5 percent aqueous carboxymethylcellulose). The dosing schedule for the rats was 3 and 15 mg selenium sulfide/kg of body weight given 5 days per week by gavage in the low- and high-dose groups, respectively, whereas the mice received 20 and 100 mg/kg of body weight by the same route and schedule in the low- and high-dose groups. These doses were chosen on the basis of preliminary subchronic toxicity studies, which indicated the highest dose of selenium sulfide that these animals would be likely to tolerate in long-term experiments. The incidence of hepatocellular carcinomas in the rats was 29 and 42 percent in the high-dose males and females, respectively, while none of the other treatment groups exhibited a tumor incidence greater than 2 percent. In the mouse study the high-dose females had a 45 percent incidence of hepatocellular carcinoma, in contrast to 4 percent or less in any other female treatment group. The high-dose females also had an elevated incidence of alveolar/bronchiolar carcinomas. The response of the male mice was less clear, perhaps because of a higher rate of spontaneous tumor formation or a greater resistance to the effects of the test chemical. The increased incidence of liver tumors in rats and mice given selenium sulfide differs from the studies with selenium compounds discussed above in that the hepatic tumors were seen in animals that had not developed cirrhotic livers.

There are few studies that have specifically investigated any possible

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relationship between overexposure to selenium and the increased incidence of cancer in humans. However, Glover (1967) commented that the death rate due to malignant neoplasms observed among workers in a selenium rectifier plant in West England was about the same as that expected for the general population of England and Wales. Moreover, studies that have compared death rates due to cancer in different geographical areas with blood selenium levels in the general population are not consistent with the concept that high selenium intakes contribute to an overall increased human cancer mortality (see the section on cancer under the heading, "Low Selenium Exposure").

It was concluded for regulatory purposes that selenium can cause hepatomas, but only in the presence of severe hepatotoxic phenomena. As a result it was felt that selenium could not properly be classified as carcinogenic because of its capacity to induce liver damage (and consequent hepatomas) when abused by being consumed at high levels (Gardner, 1973). However, this concept may have to be reexamined in light of the fact that selenium sulfide can cause liver cancer in rats without producing liver damage (NCI, 1979). On the other hand, van Houweling (1979) concluded that there must be a no-effect level for carcinogenicity for an essential trace nutrient such as selenium.

DENTAL CARIES

As discussed in Chapter 7, poor dental health was observed in persons living in seleniferous areas of South Dakota (Smith et al., 1937) or in children residing in seleniferous zones of Venezuela (Jaffe, 1976). Attempts to produce caries experimentally in laboratory animals with high levels of selenium have generally failed if the selenium was given posteruptively (reviewed by Shearer and Johnson, 1980). On the other hand, if high levels of selenium were given during tooth development, some effect on dental caries was obtained. For example, Buttner (1963) fed a caries-susceptible strain of female rats a cariogenic diet and gave 0, 5, or 10 ppm sodium selenite in the drinking water during mating, pregnancy, and lactation. These high levels of selenium impaired reproduction so that the number of pups born in these groups was 31, 20, and 7, respectively. The pups were continued on the same levels of sodium selenite in the water for 120 days. The mean number of carious lesions was increased by 36 and 62 percent in the groups receiving 5 and 10 ppm selenite in their water, respectively, but growth was significantly depressed in both these groups. Bowen (1972) fed monkeys a cariogenic diet and gave one group 2 mg selenium as sodium selenate/liter of drinking water for 15 months, followed by 1 mg/liter for another 45 months. The dose of selenium had to be reduced because of

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greenish malodorous stools in the selenium-treated animals. Selenium treatment had no effect on the first permanent molars, which had already formed before the start of the experiment, but the second permanent molars had a yellow chalky appearance in the selenium-treated monkeys and carious lesions developed more rapidly in these teeth in the selenium-exposed group. Britton et al. (1980) gave 10-day pregnant rats either distilled drinking water or water containing 0.8 or 2.4 ppm selenium as sodium selenite or selenomethionine until the pups were weaned at 19 days of age. The weaned pups received a high sucrose diet and oral inoculations of *Streptococcus mutans*. No change in caries status was seen in the groups receiving 2.4 ppm in the water, but there was a significantly reduced incidence of caries in the groups getting 0.8 ppm. Thus, under certain conditions high levels of selenium in the drinking water can increase caries when administered preeruptively to experimental animals, whereas moderately high selenium levels appear to have some cariostatic effect (cariostatic effect confirmed by Johnson and Shearer, 1981). At any rate no studies have been carried out which indicate that selenium has any cariogenic activity when given to animals at the lower levels likely to be encountered by people.

Several epidemiological studies have been conducted by Hadjimarkos and associates who noted a relationship between the prevalence of dental caries and the intake of selenium as reflected by its urinary excretion (Hadjimarkos et al., 1952; Hadjimarkos and Bonhorst, 1958). On the other hand, a survey undertaken by Ludwig and Bibby (1969) to determine geographic variations in the prevalence of dental caries in the United States indicated that caries prevalence in high-selenium areas was the same or less than it was in New England, which is known to be a selenium-deficient area. Cadell and Cousins (1960) also found no relationship between urinary selenium and dental caries in children in New Zealand, but Hadjimarkos (1960) argued that these urinary selenium levels were too low to expect any elevation in dental caries. Schwarz (1967) criticized the work of Hadjimarkos by pointing out that various socioeconomic factors that might influence caries incidence were ignored and that, at any rate, the amounts of selenium excreted into the urine were well within the limits of those seen in normal people not exposed to excessive selenium. Suchkov et al. (1973) reported that people living in a mountainous region of the Ukraine had a high level of selenium in their teeth and a high incidence of caries, while people living in a forest-steppe area had a low level of selenium in their teeth and a low incidence of caries. But the drinking water in the mountainous region was softer and contained lower levels of fluoride, so these possible confounding factors cannot be ruled out. Curzon (1981) analyzed 362 samples of enamel prepared from first permanent maxillary premolars from 12- to 19-year-old lifelong residents

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from various parts of the United States and New Zealand and found a weak but significant negative relationship between individual enamel selenium levels and individual caries scores. A recent evaluation of the relationship between dental caries and human selenium intake (NRC, 1976a) concluded that there seems no reason to suspect that selenium is important to cariogenesis in man, and this subcommittee uncovered no new evidence to contradict that view.

REPRODUCTION

Sublethal doses of sodium selenite caused no embryonic malformations when injected into pregnant hamsters (Holmberg and Ferm, 1969). In fact, sodium selenite protected partially against the teratogenic effect of injected sodium arsenate or cadmium sulfate. On the other hand, selenium compounds have long been known to cause embryonic abnormalities when injected into the eggs of chickens (Palmer et al., 1973).

Old anecdotal reports from Colombia, South America, claimed that women living in seleniferous areas gave birth to malformed infants (Rosenfeld and Beath, 1964). More recently, one probable and four certain pregnancies among six women formulating microbiological media containing sodium selenite were reported to terminate in abortions, except one, which was born with bilateral club foot (Robertson, 1970). However, a survey of other laboratories doing similar work revealed no pattern of such trouble, and no difference in urinary selenium levels was noted between the affected group of women and a control group residing nearby. On the basis of published health statistics, no correlation could be seen between the incidence of infant mortality due to congenital malformations and the level of selenium in the urine of school children in different states of Venezuela (Jaffe and Valez, 1973). Jaffe (1973) concluded that no modern evidence has been presented for the teratogenicity of dietary selenium in humans. A preliminary report that urinary selenium excretion was related to miscarriage (Tsongas and Ferguson, 1977) was not confirmed (T. A. Tsongas, University of Pennsylvania, Philadelphia, personal communication, 1978).

AMYOTROPHIC LATERAL SCLEROSIS

Kilness and Hochberg (1977) suggested that selenium might be an environmental factor predisposing to amyotrophic lateral sclerosis (ALS) since they observed an unusual cluster of four cases of this disease in male farmers residing in a seleniferous area. But Schwarz (1977) pointed out that the frequency of ALS is as high if not higher in low-selenium areas as in moderate- or high-selenium areas. Norris and Sang (1978) concluded

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that exposure to selenium is not related to ALS, since 19 of 20 cases had urinary selenium levels lower than the mean for unexposed persons. Kurland (1977) maintained that the cluster observed by Kilness and Hochberg (1977) was probably due to chance rather than a new etiologic clue in ALS.

CONCLUSIONS

Certain specific compounds containing selenium, i.e., bis-4-acetaminophenyl-selenium dihydroxide, selenium diethyldithiocarbamate, and selenium sulfide, are capable of causing cancer in rats when administered at high levels for prolonged periods. However, it is not possible on the basis of these results to generalize about the carcinogenicity of different selenium compounds. For example, attempts to produce cancer in rodents by giving oxyanions of selenium such as selenite or selenate, the forms of selenium currently used as additives to animal feeds, were either unsuccessful or seriously flawed in experimental design.

An early report, which started the controversy regarding the carcinogenicity of selenium compounds, used either seleniferous grain or a mixed inorganic selenide as a source for feeding high levels of selenium to rats. Histological evaluation suggested that these forms of selenium produced hepatic tumors, but the interpretation of the results was complicated by the fact that tumors occurred only in those rats that developed liver cirrhosis. A later study in which rats were fed high levels of selenium as seleniferous wheat did not find any lung tumors due to the selenium exposure.

Aside from the two above reports involving seleniferous grain, there have been no animal studies that have investigated the carcinogenic potential of the forms of selenium that occur naturally in human foods. However, a comparison of public health statistics from various parts of the United States reveals that, if anything, the cancer death rate is lower in those areas of the country in which consumption of locally produced foods could result in an increased dietary selenium intake.

A limited number of observations on workers industrially exposed to selenium gives no indication that cancer rates are any higher in such workers than in the general population.

Although preeruptive administration of high levels of selenium can cause an increased incidence of dental caries in experimental animals, there is no evidence to suggest that typical levels of exposure result in increased caries in humans.

In contrast to old anecdotal reports, recent analyses of public health data indicate no correlation between congenital malformations in infants and excessive exposure to selenium.

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The notion that amyotrophic lateral sclerosis is related to selenium overexposure has not been substantiated.

LOW SELENIUM EXPOSURE

CANCER

Clayton and Baumann (1949) first observed that high levels of dietary selenium had a protective effect against chemically-induced cancer in rats. These workers fed two groups of 15 rats a basal diet containing 0.064 percent 3 ′methyl-4-dimethylaminoazobenzene for 4 weeks. During the next 4 weeks neither group received the azo dye, but one group was fed the basal diet supplemented with 5 mg/kg selenium as sodium selenite. Then both groups were given the basal diet plus 0.048 percent of the azo dye but no supplemental selenium for another 4 weeks. Finally, the rats were given the basal diet with neither azo dye nor selenium for an additional 8 weeks. Of 9 surviving rats that were given selenium, 2 developed liver tumors, whereas 4 of 10 survivors in the unsupplemented group had liver tumors. In a repeat experiment, the incidence of liver tumors was 4 of 13 and 8 of 13 in the selenium-supplemented and unsupplemented groups, respectively. Similar results were obtained more recently by Griffin and Jacobs (1977) who fed three groups of 15 rats 0.05 percent 3 ′-methyl-4-dimethylaminoazobenzene in a basal diet of laboratory chow and gave the supplemented groups either 6 mg selenium as sodium selenite/liter of drinking water or 6 mg selenium as high-selenium yeast/kg of diet. The incidence of liver tumors in the surviving rats was 11 of 12, 7 of 15, and 9 of 14 in the unsupplemented, selenite-supplemented, and selenium yeast-supplemented groups, respectively. Shamberger (1970) showed that selenium applied dermally or given in the diet decreased the number of papillomas in mice painted with various carcinogenic polycyclic hydrocarbons. For example, the incidence of papillomas was 87 percent in mice painted daily with 0.25 ml of a solution containing 0.01 percent 3-methylcholanthrene for 19 weeks and 68 percent in mice painted with the same solution containing 0.0005 percent sodium selenide. In groups of mice fed a torula yeast diet supplemented with 0, 0.1, or 1.0 mg selenium as sodium selenite/kg, the incidence of papillomas in mice painted with 0.25 ml of 0.03 percent [α] pyrene for 27 weeks was 14 of 35, 22 of 36, and 8 of 33, respectively.

Jacobs et al. (1977) injected two groups of 15 young male rats with 20 mg sym,-dimethylhydrazine dihydrochloride/kg of body weight weekly for 18 weeks. The incidence of colon tumors was 6 of 15 in a group receiving 4 ppm selenium as sodium selenite in the drinking water, whereas the incidence was 13 of 15 in rats not treated with selenium. The total number of

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colon tumors was 11 and 39 in the selenium-treated and untreated groups, respectively.

Harr et al. (1972) fed four groups of 20 weanling female rats a torula yeast diet that contained 150 mg 2-acetylaminofluorene (AAF)/kg and was supplemented with various levels of selenium as sodium selenite. The number of rats that had developed either hepatic or mammary cancer after 200 days was 12, 12, 2, and 0 in the groups fed the torula diet supplemented with 0, 0.1, 0.5, and 1.0 mg selenium/kg, respectively. However, by the end of the experiment (320 days) the number of tumors was similar in all groups, so these workers felt that it was not possible to conclude "whether the observed effects of added selenite represented a prevention of carcinogenesis or a modification of the rate of induction." Two subsequent trials failed to confirm the protective effects of selenite against AAF-induced tumors (P. D. Whanger, Oregon State University, Corvallis, personal communication, 1980). This discrepancy may be explained on the basis of the degree of depletion of selenium in the rats. The original experiment used rats that were depleted of selenium through two generations for the groups receiving 0 or 0.1 ppm supplemental selenium, whereas the follow-up studies used rats depleted only through a single generation. Marshall et al. (1979) fed two groups of 15 adult male rats a laboratory chow diet that contained 0.03 percent AAF for 14 weeks followed by 5 weeks of carcinogen-free diet. One group received 4 ppm of selenium as sodium selenite in the drinking water, which was started 1 week prior to carcinogen feeding and continued throughout the experiment. The incidence of liver tumors was 4 of 14 and 9 of 13 in the selenium-treated and untreated groups, respectively.

Ip and Sinha (1981) have recently shown that selenium-deficient rats fed a high polyunsaturated fat diet (25 percent corn oil) had a greater incidence of mammary tumors following treatment with dimethylbenz (α) anthracene than did rats fed the same diet supplemented with 0.1 ppm selenium. On the other hand, no difference in tumor incidence was observed between the selenium-deficient and selenium-supplemented groups if the diets were either low fat (1 percent or 5 percent corn oil) or high in saturated fat (1 percent corn oil plus 24 percent coconut oil).

The mechanism(s) by which selenium diminishes the potency of these various carcinogens is not known. However, Marshall et al. (1979) found that liver microsomes prepared from 3-methylcholanthrene-induced rats supplemented with 4 ppm selenium as sodium selenite in their drinking water produced less of the highly carcinogenic metabolite, N-hydroxy-2-acetylaminofluorene (N-OH-AAF), than did microsomes from unsupplemented rats. Thus, at least in this case, selenium presumably could act by shifting carcinogen metabolism toward detoxification pathways. In other

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experiments, pretreatment of rats with 4 ppm selenium as sodium selenite in the water increased hepatic N-OH-AAF glucoronyl transferase activity and decreased p-nitrophenol-sulfotransferase activity but had no effect on AAF-deacylase activity (Daoud and Griffin, 1978). Such selenium pretreatment also lowered hepatic levels of AAF and N-OH-AAF and decreased the binding of these carcinogens or their metabolites to hepatic DNA and tRNA. Griffin (1979) has also suggested that the inhibition of carcinogenesis by selenium may be due to protection of cellular membranes against aberrant oxidations via its role in GSH-Px (see Chapter 5).

But whatever the mechanism by which selenium acts, it does not appear to be effective against all types of chemical carcinogenesis, since dietary selenium had no effect on the induction of tracheal cancer by 1-methyl-1-nitrosourea (MNU) in hamsters (Thompson and Becci, 1979). In this study, groups of 35 hamsters were fed a torula yeast diet supplemented with 0, 1, or 5 ppm selenium as sodium selenite/kg for 2 weeks. Then they were continued on the diets and given weekly intratracheal instillations with a 0.5 percent MNU solution for 12 weeks. All hamsters were killed 195 days after the first instillation, and the incidence of tracheal carcinomas was 9 of 34, 8 of 33 and 10 of 31 in the groups receiving 0, 1, and 5 ppm dietary selenium, respectively. If selenium is an anticarcinogen by virtue of its effects in altering the metabolism of carcinogens, then no effect of selenium against MNU would be expected since it is a direct alkylating agent and does not require metabolic activation for its carcinogenic properties to be exerted.

High levels of selenium have also been shown to have a protective effect against the development of spontaneous mammary tumors in certain strains of mice normally having an elevated incidence of spontaneous mammary adenocarcinomas that are thought to be of viral origin. Schrauzer and Ishmael (1974) fed two groups of 30 virgin 4- to 6-week-old female C_3H/St mice a basal diet containing 0.15 ppm selenium. After 16 months, the incidence of mammary adenocarcinoma in a group that received 2 mg selenium as selenium dioxide/liter of drinking water was 10 percent, whereas 82 percent of the mice given drinking water without added selenium had tumors. In another experiment, four groups of 30 female C_3H/St mice were fed a basal diet that contained 0.45 ppm selenium and were given 0, 0.1, 0.5, or 1.0 mg selenium/liter of drinking water. The incidence of spontaneous mammary tumors in these groups was 42, 25, 19, and 10 percent, respectively (Schrauzer et al., 1978). Medina and Shepherd (1980) found that 2 and 6 mg selenium as selenium dioxide/liter of drinking water decreased the incidence of mammary tumors in BALB/cfC3H mice fed a laboratory chow-type diet from 82 percent in the untreated controls to 48 percent and 12 percent, respectively. However, similar levels of selenium in the water

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had no effect on the growth rate of primary tumors transplanted subcutaneously into BALB/c mice, and 4 mg of selenium as selenium dioxide/liter of water had no effect on the rate of tumor formation in three of four different preneoplastic mammary outgrowth lines transplanted into the mammary gland-free fat pads of syngeneic mice. Schrauzer and Ishmael (1974) also reported that selenium did not inhibit the growth of advanced spontaneous or transplanted mammary tumors. Thus, selenium may act by inhibiting chemical or viral transformation of normal cells or by inhibiting expression of initially transformed cells. On the other hand, Poirier and Milner (1979) found that intraperitoneal injection of 1 mg selenium as sodium selenite/kg of body weight inhibited tumor development in mice previously inoculated with Ehrlich ascites tumor cells.

Shamberger and Frost (1969) first called attention to an inverse relationship between blood selenium levels of the general population and cancer death rates in various areas of the United States. Later work indicated that there was a particularly low mortality due to gastrointestinal and urogenital types of cancer in those states located in high-selenium regions of the country (Shamberger and Willis, 1971; Shamberger et al., 1976). However, Allaway (1972) has criticized these associations between cancer mortality and the geographic distribution of selenium as lacking strength, consistency, and selectivity.

Based on food consumption data from 17 countries, Schrauzer (1976) concluded that the mortality due to cancer of the large intestine, rectum, and breast was directly correlated with the intake of meat, eggs, milk, fat, and sugar and was inversely correlated with the intake of high-selenium foods such as cereals and fish. Just the opposite correlations were found for hepatic and gastric cancer. The apparent dietary selenium intake, calculated assuming that the same average concentration of selenium was present in the foods consumed in all countries, was highest in those countries that had the lowest mortality due to cancer of the large intestine, rectum, and breast (Schrauzer et al., 1977). However, Jansson et al. (1978) pointed out that the same statistical associations that suggested a protective effect of dietary selenium against colon, rectal, and breast cancer also suggested an increased risk of hepatic and gastric cancer due to selenium.

Blood selenium levels lower than normal were reported in patients with colon or gastric cancer, but normal levels were seen in patients with rectal and breast cancer (Shamberger et al., 1973). In fact, Capel and Williams (1979) showed that erythrocyte selenium levels and GSH-Px activities were higher in breast cancer patients than in controls, although plasma selenium levels were depressed (the latter was also observed by McConnell et al., 1979a). Thus, patients with rectal and breast cancer, supposedly related to low selenium intake, had normal if not elevated blood or erythro

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cyte selenium levels, whereas patients with gastric cancer, thought to be linked to a high selenium intake, had subnormal blood selenium levels. Broghamer et al. (1979) noted that wide variation was encountered in serum selenium concentrations of carcinoma patients, and there appeared to be an apparent relationship between the serum concentration and the extent of tumor involvement in terms of metastasis, patient survival time, the incidence of tumor recurrence, and the occurrence of multiple primary neoplasms. No difference in the blood selenium levels of New Zealand surgical patients with and without cancer was observed by Robinson et al. (1978a) or van Rij et al. (1978). Although these findings might be partially explained by the generally low selenium levels seen in that country, the selenium levels in the patients studied were all influenced by their nutritional status, age, and severity and duration of disease, and lowered selenium levels were not characteristic for the cancer patients. Therefore, it was suggested that the low-selenium status of cancer patients was more likely a consequence of their illness rather than the cause of the cancer.

CARDIOVASCULAR DISEASE

Swine fed diets deficient in both selenium and vitamin E develop a characteristic cardiomyopathy (Van Vleet et al., 1977a,b; see also Chapter 6), and rats and lambs fed diets deficient in selenium and vitamin E develop electrocardiographic changes that can be prevented by selenium supplementation (Godwin, 1965; Godwin and Fraser, 1966). Using an approach similar to that outlined above for cancer, Shamberger et al. (1975, 1978, 1979) concluded that age-specific heart disease mortality was lower in those states of the United States or countries of the world with high selenium intakes than in those states or countries with low selenium intakes. However, Masironi and Parr (1976) reported no difference in tissue selenium concentrations between patients who died with or without myocardial infarction. Westermarck (1977) found that blood selenium levels of patients with acute myocardial infarction were lower than those of healthy adults, but no difference was observed in heart or liver selenium levels of patients who died of myocardial infarction and those who died from other diseases. Shamberger (1978) found no difference in the kidney selenium levels of autopsy specimens taken from patients who died from atherosclerosis and hypertension, compared to those who died from a variety of other diseases. Thomson et al. (1978b) showed that blood selenium concentrations of New Zealand hypertensives, with or without atheroma, were no lower than those of normotensives. On the other hand, a recent epidemiological study from Finland suggests that low serum-selenium levels may be

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associated with an increased risk of cardiovascular death and myocardial infarction (Salonen et al., 1982).

Since human blood platelets were reported to contain high levels of selenium, Kasperek et al. (1979) suggested that low selenium intake might increase the risk of thrombotic episodes, and indeed the GSH-Px activity of platelets was shown to be depressed in patients with acute myocardial infarction (Wang et al., 1981). Platelet GSH-Px activity is decreased in selenium-deficient rats (Bryant and Bailey, 1980). A biochemical rationale for a possible role of selenium in heart disease is provided by the recent observation that prostacyclin synthesis is decreased in aortic rings from selenium-deficient rats (Bult et al., 1981). Fatty acid hydroperoxides inhibit prostacyclin synthetase (Moncada and Vane, 1979), so it is possible that selenium deficiency, via depressed GSH-Px activity, could inhibit the production of prostacyclin, the arachidonic acid metabolite that decreases platelet aggregation (Gryglewski, 1980). Despite the inability of some workers to relate the selenium concentrations of human tissues to the incidence of cardiovascular disease, the recent report from the People's Republic of China describing a cardiomyopathy in children severely deficient in selenium (so-called Keshan disease, see Chapter 6) suggests that selenium may have a role in proper heart function at very low levels of dietary intake. However, the amount of dietary selenium needed to prevent cardiomyopathy in humans apparently is very small, since blood selenium levels in children with Keshan disease were only about one-sixth of those reported in New Zealand, a country of known low selenium intake, and only about one-twentieth of those observed in the United States. It should also be emphasized that the pathology of Keshan disease is totally different from that characteristic of the degenerative heart conditions typical in the West.

REPRODUCTION AND NEONATAL HEALTH

Selenium deficiency causes decreased sperm motility in rats (Wu et al., 1979), and a variety of reproductive problems have been associated with selenium deficiency in animals (see Chapter 6). Also, selenium has been shown to be associated with a number of incompletely characterized proteins found in testicular cytosol (McConnell and Burton, 1981) or spermatozoa (Calvin et al., 1981). Using an approach similar to that employed by Shamberger to relate selenium status to cancer or cardiovascular disease, Cowgill (1976) found that the birthrate in the continental United States is lower in those regions where the selenium concentration in forage crops is low than in those where the concentration of selenium is high. Shamberger (1971) noted higher neonatal death rates on a population basis in low-sele

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nium areas of the United States than in high-selenium areas, but Cowgill (1976), concerned that couples in low-selenium areas were taking selenium to prevent neonatal death, pointed out that comparisons of neonatal death rates should be made on the basis of live births. When expressed on this basis, no differences in neonatal death rates were observed between high-and low-selenium regions. Money (1970) suggested that selenium may play a role in the etiology of the sudden infant death syndrome (SIDS), but Rhead et al. (1972) found no difference in the blood or plasma selenium levels between normal infants and those that had died of SIDS. In a later paper, Money (1978) suggested that somewhat elevated iron intake might precipitate SIDS in infants of marginal selenium and vitamin E status, but no definitive role for any of these nutrients has been established in this condition.

INFECTIOUS DISEASES

Mice fed a chow diet supplemented with 0.7 ppm and 2.8 ppm selenium as sodium selenite had approximately 7 times and 30 times greater antibody titers, respectively, after challenge with sheep red blood cells than did mice fed the unsupplemented chow diet (Spallholz et al., 1973). The primary immune response to sheep red blood cells can also be increased by injecting mice intraperitoneally with 3 μg to 5 μg of selenium as sodium selenite, although the increase is greatest when the selenium is given prior to or simultaneously with the antigen (Spallholz et al., 1975). Toxic levels of dietary selenium decreased the immune response of mice to sheep red blood cells (Spallholz et al., 1973) and increased the susceptibility of chicks to infection with *Salmonella gallinarum* (Hill, 1979). Although the mechanism by which selenium enhances the immune response is not known (Martin and Spallholz, 1976), the lipid peroxide-destroying activity of GSH-Px may be involved, since vitamin E and synthetic antioxidants also stimulate the immune response under certain conditions (Nockels, 1979).

DeWitt et al. (1957a,b) found that torula yeast-based diets deficient in selenium, vitamin E, and cystine decreased the resistance of mice to *Schistosomiasis mansoni.* However, the deficient torula diet produced an unfavorable in vivo growth environment for the parasites, since somatic development was markedly impaired and, although more worms were present, they did not attain sexual maturity. Thus, the underdeveloped worms did not produce eggs, which in the normal infection are the major cause of pathology.

Serfass and Ganther (1975) showed that the ability of peripheral polymorphonuclear neutrophils from selenium-deficient rats to kill *Candida*

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albicans was markedly decreased, although ingestive activity was not impaired. Peritoneal exudate polymorphonuclear neutrophils from selenium-deficient rats also tended to have decreased fungicidal activity, although the changes were not statistically significant. The authors stated that to their knowledge this was the first demonstration of impaired phagocytic microbicidal capacity due to the deficiency of a specific nutrient. Later work indicated that selenium deficiency in rats caused declines in the GSH-Px activities of peritoneal exudate polymorphonuclear neutrophils and pulmonary alveolar and peritoneal exudate macrophages (Serfass and Ganther, 1976).

Chen and Anderson (1979) reported that the selenium concentrations in the sera of 17 patients acutely ill with Legionnaire's disease were lower than in their paired convalescent-phase sera. Such a trend was not seen in 10 similarly matched samples of serum from control patients with pneumonia. Although the mechanism of this effect is not known, Jaquess et al. (1980) reported that rather high concentrations of sodium selenate (50 μg/ ml) stimulated the growth of *Legionella pneumophila* when grown on agar cultures.

CYSTIC FIBROSIS

Research on cystic fibrosis in humans has been hampered by the lack of a suitable animal model of the disease. The histopathology of the pancreatic lesions seen in selenium-deficient chickens (discussed in Chapter 6) in some ways resembles that of cystic fibrosis in humans, but the similarities are superficial and are not considered to be the result of the same underlying causes. Wallach (1978) noted that the histopathological changes he observed in one sick rhesus monkey were reminiscent of certain pathological features of cystic fibrosis in humans. This monkey had been fed a pelleted diet that had been soaked in “a commercial long chain polyunsaturated oil supplement” in order to correct a hair coat problem. It was suggested that the sickness of the monkey was due to the prooxidant stress of the elevated intake of polyunsaturated fatty acids coupled with a presumed marginal deficiency of selenium and/or vitamin E, but no analytical values for these latter two nutrients in the tissues of the monkey were available. On this basis, Wallach postulated that selenium deficiency may play a key causative role in human cystic fibrosis, although marginal intakes of other nutrients, including vitamin E, zinc, copper, and riboflavin, as well as an excessive intake of polyunsaturated fat, were also thought to be involved.

To support his hypothesis, Wallach and Garmaise (1979) presented limited analytical data on the selenium content of blood and tissues from patients with cystic fibrosis. An acute case had a whole-blood selenium level

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of 0.08 μg/ml (the units in Wallach's original paper were μg/dl, but μg/ml almost certainly was intended; the fluorometric analytical technique used for selenium determination would not be sensitive enough to measure hundredths of micrograms per deciliter of blood). Although this value is somewhat low in comparison to usual levels in the United States, the concentration is certainly higher than that of most native New Zealanders, who have no known predisposition to develop cystic fibrosis. In fact, Wallach's (1978) own figures show that the rate of cystic fibrosis in New Zealand is only one-fifth to one-half that in the United States; the rate in Sweden, another country thought to have rather low selenium intakes, is only one-tenth to one-fourth that in the United States. Analysis of stabilized cases (Wallach and Garmaise, 1979) revealed whole-blood selenium values of 0.12 to 0.30 μg/ml, well within the typical range in the United States. Analysis of tissues from two deceased infants aged 4 and 7 months that had cystic fibrosis revealed liver and kidney values of 0.19 and 0.25 μg per gram and 0.54 and 0.50 μg/g, respectively. Although these values were stated to be only one-tenth normal levels, this is incorrect; Wallach's analyses were expressed on a wet-weight basis whereas the values he used for comparison were on a dry-weight basis. Also, the data Wallach used for comparative purposes were obtained from tissues taken from middle-aged or elderly adults, and since the selenium level in tissues may vary considerably with age, it is improper to compare data from infants with that from adults. Unfortunately, data on selenium levels of tissues from infants are even more limited than those available from adults, but Schroeder et al. (1970) found that the level of selenium in the liver and kidney of a 9-month-old male infant was 0.33 and 0.70 μg/g, respectively—values which are not that far removed from Wallach's figures. It should also be pointed out that the levels found by Wallach in the tissues of his cystic fibrosis patients are not particularly low in light of the levels that are found in selenium-deficient animals and would not be considered indicative of selenium deficiency in animals (see Chapter 6). Selenium levels in serum or whole blood of cystic fibrosis patients were not considered deficient, and whole-blood GSH-Px activity was in the normal range (Lloyd-Still and Ganther, 1980; Castillo et al., 1981; B. A. Underwood, Massachusetts Institute of Technology, Cambridge, personal communication, 1980).

SELENIUM SUPPLEMENTS

As is readily apparent from the above discussion, numerous attempts have now been made to associate low or suboptimal selenium intakes with a wide variety of human diseases. For example, one investigator has questioned whether the optimal levels of dietary selenium for the postulated

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nutritional requirement are the same as those needed for cancer prevention (Griffin, 1979). Some workers have called for an increase in dietary selenium intakes to protect against cancer, either by consuming selenium-rich foods or by taking selenium supplements (Schrauzer and White, 1978). Griffin (1979), however, has stated that supplementation of selenium in humans is not warranted at this time and that in fact there are reasonable doubts that selenium may have any practical value in the prevention of cancer in humans. It was concluded there must be proof that selenium indeed is of value against human cancer before selenium supplementation can be advocated in humans.

Other workers have suggested that selenium deficiency may play a role in the etiology of heart disease (Frost and Ingvoldstad, 1975) but, again, the usefulness of selenium supplements in such conditions must be questioned. Cardiomyopathy is seen only in animals deficient both in vitamin E and selenium, and heart damage is not observed in uncomplicated selenium deficiency. The relationship between selenium levels in human tissues and various types of heart disease remains controversial. While it is true that a cardiomyopathy in children that was thought to be related to low selenium intake has recently been reported in the People's Republic of China, it must be emphasized that the amounts of dietary selenium needed to prevent this condition are very small. The Chinese noted that this disease did not occur in areas where the daily dietary intake of selenium was 30 μg or more. There is no evidence that any intake greater than this is of any benefit against such heart disease. To suggest otherwise is to fall into the common “if a little is good, then more must be better” trap of faulty reasoning about nutritional supplementation. Also, it must again be emphasized that the pathology of Keshan disease is quite different from that of cardiovascular disease commonly seen in Western cultures.

Because of the wide coverage given the hypothesis that selenium deficiency may play a role in cystic fibrosis in the popular press and various lay nutrition publications (see, for example, Shaw, 1979), it has been estimated that several hundred cystic fibrosis patients in the United States may presently be following a high-selenium diet and/or taking selenium supplements (M. Adams, Center for Disease Control, Atlanta, personal communication, 1979). While it was claimed that supplementation with selenium reversed a positive sweat test in one infant diagnosed as having cystic fibrosis (Wallach and Garmaise, 1979), the child later died after a short period on selenium supplements (Hubbard et al., 1980). An editorial recommending against the use of selenium supplements for cystic fibrosis patients has recently appeared (Hubbard et al., 1980). Thomson and Robinson (1980) were unable to find any association between any human disease and the low selenium intake characteristic of New Zealand and

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concluded that supplementation of the general population was not justified at present.

As was discussed in Chapter 7, the amount of selenium needed to cause toxicity can be decreased in certain situations. Also, selenium has peculiar metabolic interactions with other compounds; e.g., methylated selenium metabolites that occur naturally in the body have a pronounced synergistic toxicity with mercuric chloride and inorganic arsenic compounds. An interrelationship of particular interest in the present context is the finding of Jacobs and Griffin (1979) that combined supplementation of 1,2-dimethylhydrazine-treated rats with vitamin C in the diet and selenium in the drinking water led to an increased incidence of colon tumors as compared to unsupplemented rats or rats supplemented with selenium or vitamin C alone. This observation is of importance to human health because those persons taking selenium supplements may also be taking vitamin C supplements for other reasons. Therefore, in light of the inherent toxicity of selenium and the inability to predict many of its metabolic interrelationships with other dietary constituents, its use as a human dietary supplement cannot be encouraged at this time.

CONCLUSIONS

Experiments with rodents have shown under a wide variety of conditions that selenium has a protective effect against certain chemically induced and spontaneous, presumably virally induced, tumors.

Associations have been made between the presumed selenium status of various populations and their incidence of cancer, but such correlations have been criticized because of their lack of strength, consistency, and selectivity. Although low blood selenium levels are sometimes observed in cancer patients, depressed blood selenium levels are not uniquely characteristic of such patients and may rather reflect their lack of well being or poor nutritional status.

Animals deficient in both vitamin E and selenium develop cardiomyopathy, but such a condition is not found in animals suffering from an uncomplicated selenium deficiency.

As in the case of cancer, associations have been drawn between presumed human selenium status and the rate of heart disease but, again, these associations are lacking strength, consistency, and selectivity.

Although a cardiomyopathy in children (Keshan disease) that is thought to be at least partially caused by selenium deficiency has been recently reported in the People's Republic of China, the disease is found only in populations severely deficient in selenium.

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There is no evidence to suggest that inadequate selenium intake plays any role in human reproductive failure.

Selenium at levels in excess of nutritional requirements improves the immune response in mice, and selenium deficiency decreases the microbicidal activity of phagocytes in rats. However, there is no evidence indicating that suboptimal selenium intake contributes to impaired resistance to infectious diseases in humans.

The hypothesis that cystic fibrosis is a conditioned selenium-deficiency disease has not been substantiated.

In well-nourished populations there is no evidence to indicate that selenium supplements have any prophylactic or therapeutic benefit against human diseases such as cancer, cardiovascular disease, or cystic fibrosis. Selenium supplements were reported to be of benefit against Keshan disease, a juvenile cardiomyopathy found in certain areas of the People's Republic of China, but this condition was not observed in any area where the daily dietary intake of selenium exceeded 30 μg/day. In most parts of the world, human diets readily furnish this quantity, and there seems little justification at this time for the general use of human selenium supplements.

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Summary

Selenium was identified in 1818 by Berzelius. It has both metallic and nonmetallic properties and occurs in four oxidation states of biological significance: as selenide (Se^{-2}), elemental selenium (Se^{0}), selenite (Se^{+4}), and selenate (Se^{+6}). Although the chemistry of selenium is similar to that of sulfur, biological systems tend to reduce selenium compounds and to oxidize sulfur compounds. Selenium is most commonly analyzed in biological samples by digestion with nitric and perchloric acids, reaction with diaminonaphthalene to form a piazselenol, extraction with cyclohexane, and quantitation by fluorometry.

Selenium is widely but variably distributed in the earth's crust, with an average abundance of about 0.09 ppm. That entering commerce is derived primarily from the electrolytic refining of copper. The selenium concentration of most surface soils lies between 0.1 and 2.0 ppm, even in some that support growth of toxic plants. Toxic seleniferous soils are usually alkaline and occur in regions of low rainfall in extensive areas of Alberta, Saskatchewan, Manitoba, South Dakota, Wyoming, Montana, North Dakota, Nebraska, Kansas, Colorado, Utah, Arizona, and New Mexico. Nontoxic seleniferous soils are found in Hawaii and Puerto Rico, are acid (pH 4.5 to 6.5), have a zone of iron and aluminum compounds that bind selenium, and developed under humid conditions. Low-selenium soils are found in the Pacific Northwest, northern and eastern Canada, the northeastern United States, the South Atlantic seaboard, and in a border region of Arizona and New Mexico. In alkaline, well-aerated soils, selenium tends to form selenates that are quite available to plants and may lead to toxic con

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centrations, particularly in accumulator plants such as species of *Astragalus, Machaeranthera, Haplopappus,* and *Stanleya.* In acid soils, a ferric hydroxide-selenite complex is formed that is only slightly available to plants. Plants growing on such soils frequently contain inadequate concentrations of selenium (< 0.1 ppm dry basis) for animals that consume them. Selenium concentrations in surface or well water in the United States are generally less than 10 μg/liter. Daily selenium intakes of humans in the United States and Canada are probably in the range of 50 to 250 μg.

The essentiality of selenium for animals was discovered in 1957. The biochemical functions of selenium that are currently recognized include its role as a component of glutathione peroxidase (GSH-Px) in animals and of several bacterial enzymes. Other functions are under active investigation. GSH-Px is a protein with a molecular weight of about 80,000 daltons and with 4 subunits and 4 g-atoms of selenium per mole. Tissue concentrations of this enzyme differ from species to species, with localization demonstrated in the cytosol and mitochondrial matrix space of the liver. This enzyme appears to protect tissues against peroxidation by destroying H_2O_2 or organic hydroperoxides. The metabolic interrelationship of GSH-Px with vitamin E is particularly evident in deficiency diseases that can be prevented either by vitamin E or selenium. Liver cells seemingly have vitamin E and GSH-Px organized in a serial fashion, with vitamin E found in the lipophilic cell membrane. Prooxidants presumably originate in the hydrophilic portions of the cell, and their molecular target is the membrane. If GSH-Px does not destroy the peroxides, then vitamin E can still protect the membrane by serving as a free-radical trapper.

The major selenium compounds in seeds or forages consumed by livestock appear to be selenocystine, selenocysteine, selenomethionine, and selenium-methylselenomethionine. Supplements to deficient animal diets are most commonly sodium selenite. Ruminants absorb less selenium than monogastric animals, with the primary absorption sites in both groups being the small intestine, cecum, and colon. Vascular transport varies with species, with evidence of binding via sulfhydryl groups to erythrocytes and to plasma proteins. Tissue concentrations tend to be highest in kidney, followed by liver, pancreas, and spleen. Cardiac muscle has higher concentrations than skeletal muscle. Wool and hair may be relatively high, but nervous and adipose tissue are low. In general, selenium is deposited in tissues at higher concentrations when present in the diet in organic rather than inorganic form. Various organic selenium compounds are not necessarily metabolized to common intermediates; e.g., selenomethionine is more effective than selenocystine in prevention of pancreatic degeneration in chicks but is less effective in preventing exudative diathesis. Animal tis

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sues convert inorganic selenium to organic forms, and the pathways for conversion of selenite to selenide have been fairly well established. However, the means by which selenide is incorporated into selenocysteine have not been fully delineated. Within limits, absorbed selenium in excess of need is excreted, primarily via the urine.

Signs of selenium deficiency are frequently indistinguishable from those of vitamin E deficiency and include hepatic necrosis, icterus, edema, hyalinization of the walls of arterioles, abnormal sperm morphology, and skeletal and cardiac muscular degeneration. Pancreatic dystrophy in chicks can result from an uncomplicated selenium deficiency. Plasma activity of certain enzymes, such as aspartate aminotransferase, ornithine carbamyl transferase, alanine aminotransferase, isocitrate dehydrogenase, lactate dehydrogenase, and sorbate dehydrogenase may increase in response to different types of tissue damage. A variety of stresses in animals tends to increase the incidence of lesions that are morphologically similar to lesions caused by a deficiency of selenium or vitamin E. Such stresses include forced exercise, infectious disease, high levels of dietary fat, and exposure to unusual amounts of prooxidants. Levels of selenium above minimum requirements do not appear to be protective against these stresses. An endemic cardiomyopathy (Keshan disease), which is responsive to selenium supplementation, has been observed in humans in the People's Republic of China. Dietary requirements of most animals for selenium appear to fall in the range of 0.05 to 0.3 mg/kg dry matter. The safe and adequate range of daily intakes recommended by the Food and Nutrition Board (NRC, 1980a) for adult humans is 50 to 200 μg.

Acute selenium toxicity results in garlic breath, vomiting, dyspnea, tetanic spasms, and death from respiratory failure. Chronic toxicity results in growth failure. Depending on the species, liver damage, splenomegaly, pancreatic enlargement, anemia, elevated serum bilirubin levels, dermatitis, hair loss, and abnormal hooves and nails may also be seen. Maximum tolerable dietary concentrations proposed for animals are 2 mg/kg dry matter.

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