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I hereby recommend that the thesis prepared under my supervision by Ralph Woodworth Haswell

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INDUSTRIAL CADMIUM POISONING

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by

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CHAPTER I

INTRODUCTION

A. The Early History of Cadmium

Cadmium and zinc occur together in nature, but zinc is 200 times as abundant as cadmium. No distinction was made between them until 1817 when Stromeyer attributed the yellow tinge of a sample of iron-free zinc carbonate to the presence of a new element which he succeeded in isolating. For the new element, Stromeyer proposed the name cadmium, a variant of "cadmia" which name had previously been applied to the flue dust of smelting furnaces. This name had, in turn, been derived from Cadmos, the first to introduce the use of zinciferous earth at Thebes in Greece. The oxide of zinc, formed during the sublimation of zinc, in the course of its purification, attached itself to the chimneys of the furnaces where it formed grayish incrustations known in commerce as "tutty" or "cadmia of furnaces" (71).

The earliest written reference to the effects of cadmium on man is found in the 13th century manuscripts of the Scholae Salerni. Included among the list of drugs which were said to produce moderate vomiting was "cadmia", impure zinc oxide (226).

As early as 1656, Stockhausen (247) gave what is perhaps the first description of industrial poisoning among smelters in alluding to a purgative action following the ingestion of "cadmia" (132). A damaging action of the dusts of "cadmia" on the lungs was mentioned by Ramazzini (202) in 1713 (197). In 1822 Burdach (27) is said to have

developed nausea and vomiting after he had, in an experiment, ingested one-half grain (33 mgms.) of cadmium sulfate (262). A death from ingestion of cadmium chloride was reported by Hinder and Palmer (109) in 1866, and ten years later Wheeler (271) reported two cases of poisoning from cadmium bromide.

Marme (1867) attempted to distinguish between the toxic symptoms due to cadmium and those caused by zinc (163). Tracinski (258) (1888) and later Seiffert (225) (1897) described symptoms similar to those of "zinc ague" when cadmium was inhaled in the form of hot fumes. Poisoning by the inhalation of a dust of cadmium carbonate used in polishing silverware has also been mentioned (240).

B. Properties of Cadmium

1. Physical Properties

The metal cadmium has an atomic number of 48 and an atomic weight of 112.41. It is silver-white in color with a bluish tinge, and possesses a bright luster which soon dulls on exposure to moist air. It is capable of taking a high polish, and is resistant to corrosion and rust. Although harder than tin, it is flexible and, like tin, emits a crackling noise when bent. It is soft enough to be cut easily with a knife. Its ductility and malleability enable it to be drawn into wires or beaten into plates. Its electrical conductivity compares favorably with that of zinc.

Cadmium produces a metallic streak on paper. It shows a distinct fibrous structure when broken. The cast metal is crystalline with a closely packed hexagonal lattice. Distillation in a current of hydrogen may produce regular octahedral crystals and other forms of the cubic system. Cadmium becomes brittle at 80° C., the change appearing to be due to a crystalline transition, and it can then be powdered by rubbing it in a mortar.

The specific gravity is 8.642 at 20° C. Cadmium melts at 321° C. and vaporizes appreciably at that temperature. Its boiling point is 767° C. The vapor of cadmium is orange-yellow or yellow-brown, and odorless. It is monoatomic, and is approximately four times as heavy as air (167).

2. Chemical Properties

The chemical properties of cadmium, a bivalent element of Subgroup IIB of the Periodic Table, closely resemble those of zinc. When zinc, which occupies a higher position in the electromotive series, is added to a solution of cadmium salts it dissolves, thus precipitating the cadmium.

Upon exposure to air metallic cadmium undergoes a slow, superficial oxidation. It remains bright in dry oxygen or dry air at ordinary temperatures, but if moisture is present the hydroxide is formed. If the air contains carbon dioxide as well, some basic carbonate is produced as a compact, tenacious, gray film which impedes the oxidation of the subjacent metal. Cadmium does not decompose water at ordinary temperatures. When water vapor is passed over cadmium at a dull red heat, hydrogen gas is liberated, and small crystals of oxide are deposited on the metal.

Neither dry chlorine gas nor liquid chlorine attacks cadmium at ordinary temperatures. The gaseous hydrogen halides and their aqueous solutions readily attack cadmium with the evolution of hydrogen and the formation of the corresponding soluble, cadmium halide. Cadmium salts give a yellow precipitate of cadmium sulfide with hydrogen sulfide in acid solution.

When heated, cadmium volatilizes, and the vapor burns readily in air with a bright flame, evolving a brown fume of cadmium oxide (167).

In the organism, cadmium combines with certain lipids as phosphatides, lecithin and sphingomyelin (39) (276).

3. Solubility of Cadmium

Cadmium is insoluble in water and resistant to attack by alkalis, but is attacked by almost all acids, both weak and strong (83) (172). In investigations on the action of various foods on solders containing cadmium, it was found that the metal is readily dissolved, especially by foods containing such organic acids as acetic, tartaric, citric and lactic (69) (147) (209). Plum marmalade and boiling jam, as well as a solution of dilute acetic acid (0.25-2.5%), readily attack cadmium-plated articles (17) (94). Cadmium salts of organic acids have the following solubilities in water: lactate - 10.11%, succinate - 0.37%, citrate - 0.23%, tartrate - 0.1%, and oxalate - 0.009% (70).

4. Radio-active properties of cadmium

There are 16 known isotopes of cadmium, including 8 stable, naturally occurring ones and 8 artificially produced radioactive ones. Several of the latter are available for tracer studies. The relative abundance of the cadmium isotopes has been determined (128) (146).

C. Important Commercial Compounds

Some of the common compounds of cadmium used in commerce are: cadmium sulfide, oxide, hydroxide, sulfate, carbonate, fluoride, chloride, bromide and iodide.

Cadmium sulfide is manufactured in two shades; bright citron yellow and orange yellow. The former is made by precipitating cadmium from a slightly acid solution with hydrogen sulfide, and the latter is

obtained by precipitation from a strongly acid solution (198). Cadmium sulfide becomes paler when exposed to light in moist air due to its oxidation to the sulfate, but in dry air it is not changed (167). Mixtures of cadmium sulfide and white lead are known in commerce as "jaune brilliant". This color is inclined to darken with the formation of black lead sulfide (198).

CdS Cadmium sulfide has a hexagonal structure, melts at 1750° C. (100 atmospheres pressure) and its specific gravity is 4.82. It is slightly soluble in water, soluble in acids, and in hot water forms a colloidal solution (100).

The production of cadmium sulfide in the United States for use as a pigment amounted to 3,118,413 lbs. in 1951 (29).

CdO Cadmium oxide is brown in color and readily dissolves in acids with the production of the corresponding salts. Cadmium oxide is insoluble in hot or cold water. Its specific gravity is 8.15 in the cubic form and 6.95 in the amorphous state. It volatilizes below 1000° C.(100) (167).

The manufacture of cadmium oxide is similar to that of cadmium up to the point of distillation, but there the cadmium vapors are burned instead of being condensed. The oxide formed is collected in bags attached to the discharge end of the ventilating system of the blue powder furnaces. The color of the powder varies from a yellowish-brown to a brownish-red, purple-red, dark brown or bluish-black (198).

The gross weight of the cadmium oxide produced in the United States in 1951 was 616,369 lbs.(29).

$Cd(OH)_2$ Cadmium hydroxide is trigonal or amorphous, white and exists in the colloidal (gelatinous) state. Its solubility in water is 2.6×10^{-4} grams per 100 cc. at 25°C. It has a specific gravity of 4.79 and decomposes at 300°C. (100). It can be prepared by adding potassium hydroxide to a solution of a cadmium salt.

$CdSO_4$ Cadmium sulfate, the most common salt of cadmium, is a rhombic, white solid with a specific gravity of 4.7, a melting point of 1000°C. and a solubility of 75.5 grams in 100 cc. of water at 0°C. (100). Its tetrahydrate is a very soluble salt prepared by dissolving cadmium oxide or carbonate in sulfuric acid.

$CdCo_3$ Cadmium carbonate is insoluble in water but soluble in acids. It is trigonal in structure and white in color. Its specific gravity is 4.26 at 4°C. It decomposes under 500°C.

CdF_2 Cadmium fluoride in its cubic form is white with a specific gravity of 6.64, melting point of 1100°C., boiling point of 1758°C., and a solubility in water of 4.35 grams per 100 cc. at 25°C. It may be prepared by the evaporation of a solution of cadmium in hydrofluoric acid.

$CdCl_2$ Cadmium chloride occurs generally in the crystalline form with $2\frac{1}{2}$ molecules of water. This hydrate has a specific gravity of 3.33. It loses its water at 34°C. Anyhdrous cadmium chloride is colorless, hexagonal, and has a specific gravity of 4.05 at 25°C., a melting point of 568°C., a boiling point of 960°C., and a solubility of 140 grams in 100 cc. of water at 20°C. Molten cadmium chloride forms a white mass with a metallic luster, but, if prepared by passing

chlorine over molten cadmium, the color is red, possibly due to the presence of the colloidal metal (167). It may be obtained by evaporating a solution of the metal or oxide in hydrochloric acid (198).

$CdBr_2$ Cadmium bromide is a yellow crystalline powder with the specific gravity of 5.2, which melts at 567°C. and boils at 963°C. It is soluble in water to the extent of 57 grams in 100 cc. at 10°C. It is often associated with 4 molecules of water which it loses at 36°C. It can be prepared more conveniently by dissolving cadmium oxide in bromine water than by passing the vapor of bromine over heated cadmium (167). On sublimation cadmium bromide yields white plates with a mother-of-pearl luster.

CdI_2 Cadmium iodide, alpha form, may be obtained by digesting one part of the metal with two parts of iodine in water. On evaporation it crystallizes in large, brownish, transparent hexagonal tablets which are soluble in water and alcohol (198). It has a specific gravity of 5.67 at 30°C., a melting point of 388°C., a boiling point of 713°C. and a solubility of 79.8 grams in 100 cc. of water at 0°C. (100).

CHAPTER II.

MANUFACTURE

A. Production

For many years most of the world's cadmium was produced in Silesia (198). In the United States, production began in 1906, when the Graselli Chemical Company extracted cadmium from "blue powder", and steadily increased until after the first World War, when the United States held first place in the world's production. This was 160,000 lbs. in 1914, 1,400,000 lbs. in 1930, 7,412,000 lbs. in 1937, and 12,504,000 lbs. in 1950 (28) (187). In 1950 the production in the United States comprised primary metallic cadmium 8,865,393 lbs., primary cadmium compounds 340,704 lbs., and secondary metal and compounds 513,198 lbs., totalling 9,719,295 lbs. (28).

Net exports of metallic cadmium from the United States totalled 516,168 lbs. in 1951, a reversal of the position from 1950 when there was a net import balance of 277,182 lbs. In 1951 a total of 1,606,775 lbs. of flue dust was imported from Mexico for metallic cadmium extraction here. The market price for commercial sticks of cadmium was 2.55 dollars per pound in 1951 (29). Seventy percent of the total production of cadmium in the United States comes from Denver, Colorado. A list of the plants producing cadmium metal in the United States in 1950 follows: Primary metallic cadmium - Denver, Colorado; Bradley and Kellogg, Idaho; Depue and E. St. Louis, Illinois; Great Falls, Montana; Bartlesville and Henryetta, Oklahoma; Donora, Josephtown and

Palmerton, Pennsylvania; C. Cristi and Dumas, Texas. Secondary metallic cadmium - Jonesboro, Arkansas (29).

B. Sources

Cadmium does not occur free in nature and only one mineral, greenockite or cadmium sulfide, is known to contain it in any considerable quantity (77.8 percent) (28). This occurs in the form of a yellow powder or stain on the mineral sphalerite or zinc blende. In a relatively small concentration it is almost always associated with zinc ores, but it may also be found to a lesser extent in ores of lead and copper that contain zinc mineralization.

The principal commercial sources of cadmium are the zinc ores, blende (ZnS containing up to 3 percent of cadmium sulfide as isomorphous greenockite), sphalerite, wurzite, smithsonite and calamine (here it exists as cadmium carbonate) (214). Some zinc concentrates have been reported to contain as much as 1 percent of cadmium. In general, however, the cadmium content seldom exceeds 0.5 percent (28). Cadmium-containing ores in association with zinc ores are found in Greenock and Bishopton in Scotland, in Bohemia, and in Pennsylvania, Missouri, Arkansas, and Colorado in the United States (198). Zinc concentrates from the Tri-State district average 0.35 percent of cadmium, but concentrates from mines in the Rocky Mountain region and Far West rarely yield more than 0.2 percent cadmium (28).

Cadmium is never present in adequate quantities in the ores to support profitable mining for itself alone. The entire domestic supply of primary cadmium is recovered as a by-product concurrently with the

treatment of ores of other metals. It is obtained from zinc dust collected in the early stages of distillation in zinc retorts and from the flue dusts of zinc-blende roasting furnaces and lead blast furnaces, as well as from the high-cadmium precipitate obtained in purifying zinc at electrolytic zinc plants (28). Flue dust from gas purification has the following composition: Pb - 36-45 percent, Zn - 10-20 percent, Cd - 7-14 percent, Cl - 2-8 percent, S - 4-9 percent, As - 0.8-2.0 percent, Tl - 0.3-1.0 percent, Cu - 0.5 percent and Fe - 0.2-0.8 percent (54). A small quantity of secondary metal is recovered from old bearings and other alloys, but this constitutes no great portion of the total supply (29).

C. Extraction

Cadmium is extracted from zinc ores, zinciferous residues and by-products, following roasting by dry methods, as direct distillation, or by wet methods involving solution and either electrolytic or chemical precipitation (197). When cadmiferous zinc ores are roasted, a certain amount of cadmium is lost either by volatilization of the oxide or by reduction of the oxide and volatilization of the metal (244). Such losses may amount to nearly 62 percent (118).

In the dry method roasted cadmiferous zinc ore, in which cadmium is present as the oxide, is mixed with an equal volume of coal and charged into a number of small clay or carborundum retorts capable of holding from 35-100 lbs. of recoverable metal. When heated by natural producer gas to a temperature of from 1200-1400°C., the metallic oxides

are reduced to metals and in vaporized form are swept out of the retorts along with carbon dioxide. The more volatile cadmium passes over first, and advantage is taken of this fact for the isolation of the metal. The less volatile metallic vapors are condensed in clay vessels, and a secondary metal canister catches a powdery material called "blue powder" which contains 1.5-4 percent of cadmium, the remainder being zinc and small amounts of arsenic and lead. The "blue powder" serves as the raw material for cadmium production. It is recharged with coal into a retort where it is subjected to fractional distillation at 800°C. (198). On repeated distillation, cadmium metal of over 99.5 percent purity may be obtained (167).

In the wet method first used by Stromeyer, the ore is dissolved in sulfuric acid and then treated with metallic zinc which displaces the cadmium from its sulfate, depositing it in the sludge or "heavy metal residues" along with lead and other heavy metals (249). There are two methods of extracting cadmium from these residues. In the first, treatment with sulfuric acid dissolves cadmium, cobalt, and nickel, and leaves copper. The cadmium is electrically precipitated from this solution on the cathodes. The deposit is molded by hand into briquettes roughly 6" by 8", melted under oil, and cast into sticks or slabs. In the second method the "heavy metal residues" may be purified by resolution in concentrated sulfuric acid and reprecipitated by zinc until there has been obtained a precipitate containing about 60 percent of cadmium with lead, zinc, etc. These "secondary residues" are stored away to dry for 1-8 months in piles, sometimes covered, some-

times uncovered. The "dry residue" is distilled in the blue powder retorts, and the cadmium vapors are condensed and cast into finger molds (198).

D. Purification

To eliminate the last traces of zinc, the crude cadmium metal is dissolved in hydrochloric acid, then diluted and precipitated as a sulfide by a current of hydrogen sulfide. The sulfide is then dissolved in concentrated hydrochloric acid and the subsequent addition of sodium carbonate precipitates cadmium carbonate, which is reduced to the oxide upon ignition. The pure oxide, thus obtained, may then be reduced to the metallic form by distillation with charcoal.

Another method of purification is that of heating the cadmium powder in a stream of purified hydrogen for a long time and then distilling it in vacuo. The sixth distillate is spectroscopically free from impurities (174).

CHAPTER III.

CONSUMPTION AND USES

A. Consumption

The consumption of primary cadmium in all forms apparently totalled 9,625,768 pounds in 1950. This figure reflected a 29 percent increase over the quantity apparently consumed in 1949. In 1950, as in the previous two years, cadmium metal was purchased by the Federal Government for the national stockpile (28).

In 1951 the amount of cadmium used was approximately 25 percent less than in 1950, owing largely to the restrictions placed on end uses of cadmium by the National Production Authority in order to enable supplies to meet all military and essential civilian requirements despite a 10 percent decrease in primary production. The reduction in consumption more than offset the decrease in production and, as a result, stocks increased substantially. Governmental regulations have since been relaxed to permit increased use of cadmium in a wide range of military and civilian products (29).

B. Uses

In the past century cadmium was used occasionally for alloys of low melting point, but after the first World War it came into extensive use in electroplating (49) (96) (250). It's application as a slow neutron absorber greatly increased United States production (100) (239). Cadmium is also used as a catalyst in hydrogenation (133).

About 95 percent of the available cadmium is used in electroplating, bearing alloys and pigments. The remaining 5 percent goes into miscellaneous alloys, laboratory reagents, atomic piles and photographic chemicals (29).

1. Electroplating

Cadium plating of iron and steel, on which there are many patents (111,153,275,277), is in extensive use because of the rust preventing properties of cadmium which, in some respects, surpass those of nickel and other metals (29). The metal also offers excellent protection for copper and brass, taking a high polish permanent in air (172). In comparison with zinc, cadmium offers the following advantages as an electroplating medium: 1. Thinner coatings provide equal protection; 2. the rate of deposition for a given quantity of electric current is larger, hence costs are reduced; 3. cadmium retains its metallic luster longer; 4. plated parts are more easily soldered; 5. cadmium has a greater resistance to atmospheric corrosion; 6. it is superior in throwing power, or ability to deposit uniformly in recesses; and 7. corrosion by galvanic action is more effectively minimized (29).

Although there has been an overall increase in the use of cadmium for plating, there has recently been a tendency to restrict its use somewhat. This is due not only to the high cost of cadmium, but also to a questioning of its efficacy as a protective coating (29) (30). Some have found zinc superior at least for some purposes (172). Cadmium stands between iron and zinc in the electromotive

series, being only slightly anodic to iron with a potential difference of less than 0.1 volt, and it is possible that it may be cathodic to some kinds of iron or steel plate, thus allowing the latter, where exposed, to become corroded (172).

Cadmium plating solutions consist, in general, of cadmium carbonate or other cadmium salts dissolved in a solution of sodium cyanide, along with some substance, such as milk, cheese, casein, or glucose, which favors a more uniform deposition of cadmium on the articles (28). The cadmium content of plating solutions varies from 0.2 to 4.3 percent, with 0.2 to 7.1 percent of sodium cyanide (236). The cadmium coating can also be applied by a spraying process, but the high cost of cadmium wire has retarded the development of this method (29). The usual thickness of the coating on iron and steel is from one to two ten-thousandths of an inch, corresponding to about 200 to 400 milligrams per square decimeter of surface. This is a heavier coating than that of tin on ordinary tin plate. In the course of time cadmium diffuses to some extent into the iron of the plate forming a layer of Cd-Fe alloy. Steel plate is often coated electrolytically with a zinc-cadmium alloy containing about 9 percent cadmium, and also with a tertiary zinc-tin-cadmium alloy (172).

Items commonly electroplated with cadmium include nails, screws, rivets, bolts, nuts, washers, fasteners, and miscellaneous parts for a wide variety of products used in aircraft, ordnance and automobiles (29). Means for the coloration of cadmium-coated articles have been developed (278).

2. Bearing alloys

Cadmium-base bearing metals are used as a substitute for tin in anti-friction and anti-fatigue metals, principally in automobile internal combustion engines that operate at high speed and temperature (140). The bearing alloys are generally of two types, the Cd-Ni bearing, composed of 98.5 percent or more of cadmium and 1.2 percent of nickel, and the Cd-Ag bearing, composed of 98.3 percent or more of cadmium, 0.7 percent of silver and 0.6 percent of copper. "Graphalloy", a cadmium-impregnated graphite containing 30 to 35 percent of cadmium, is used in oilless bearings, bushing linings, and contacts for controller switches (29).

A process has been developed for coating nickel or copper bearings by exposing them to cadmium vapor under non-oxidizing conditions. The temperature is maintained at 900-1200°F. for a time not exceeding ten hours to impregnate the surface with cadmium by diffusion, giving anti-friction properties, while leaving the surface devoid of a cadmium layer of appreciable thickness. The cadmium penetrates from the surface into the interior of the bearing with a proportionate drop in cadmium concentration from the surface to the core (201).

3. Solders and other alloys

A minor use of metallic cadmium is in the manufacture of low melting alloys for soldering and brazing, fusible alloys for sprinkler apparatus, fire detector systems, and valve seats for high-pressure gas

containers (29). One alloy in particular, containing 90.8 percent of lead, 7.8 percent of cadmium, and 1.4 percent of zinc, is superior for general soldering purposes which involve the use of iron (250). Its presence in alloys, sometimes in suprisingly small amounts, gives qualities of great practical value to the alloy. In copper wire it adds strength with but small reduction in the electrical conductivity (140). Alloys containing cadmium are employed in making electrical conductors, jewelry, ceramic products, plating pigment, marine hardware, alkaline storage batteries, standard cells (as Cd-Hg alloy), high temperature resistors, and cadmium vapor lamps (25). Cadmium amalgam was once used for filling teeth (167). It also finds uses in photography and process engraving (49) (96).

4. Compounds

Cadmium sulfide is used as a paint pigment because of its great resistance to heat, light and humidity (168). The pigment known as cadmium lithipone is obtained by precipitating cadmium sulfide and barium sulfate (25). The cadmium yellows, when mixed with ultramarine blues, give brilliant and very stable greens (112). Cadmium selenide is a red fixative. Cadmium sulfide is used in the manufacture of cadmium sulfoselenide, which, with cadmium sulfide, is intimately admixed with barium sulfate to produce cadmolith primrose, lemon and golden, and cadmolith red (45). These colors are used in paint, soap, rubber, ceramics, paper, printing ink, and other products.

Virtually all of the cadmium carbonate, oxide, hydroxide and

chloride produced is used in cadmium plating solutions. Cadmium chloride has also been used for dyeing. The bromide, chloride and iodide are used in photographic films, process engraving and lithographing (29). Cadmium nitrate is used for coloring glass and porcelains (250). The tungstate is used for fluorescent paints (250) and phonograph records (33). Cadmium oleate exhibits greater resistance to hydrolysis than zinc oleate and may attain greater industrial use as an impregnating material for porous ceramic articles and for waterproofing textiles (197). Cadmium salts have been used as denaturants for alcohol (221).

5. Medical Uses

Although cadmium salts have been investigated in the past for the treatment of pulmonary tuberculosis (44) (48) (105) (156) (157) (203) (210) (267), syphilis (131) (78) (141) (154), malaria (206), dementia praecox (205), leprosy (48) and neoplasms (21), they have no practical importance as therapeutic or bactericidal agents (159).

Effective clinical response and practicability in the institutional use of cadmium chloride aerosol for the treatment of epidermophytosis and bromidrosis has been reported (269).

CHAPTER IV.

ANALYSIS

A. Collection of dust and fume

As an air contaminant, cadmium occurs usually as the oxide in the form of a dust or fume and may be collected in the impinger with water as the medium or with an electrostatic precipitator (92). A high efficiency in collecting cadmium fumes in the field was found using the filter paper method. The electrostatic precipitator proved reliable but bulky and expensive. The impinger showed a low efficiency. The sampling rates were 1 to 2.5 cubic feet per minute (125) (234).

B. Detection and determination

Many delicate and discriminating spot tests have been developed, but few micro-quantitative methods for the estimation of the element have been published.

1. Spot tests

The most sensitive test known for cadmium is a very selective spot test based upon the formation of a red precipitate with a reagent prepared from alpha, alpha'-dipyridyl, ferrous sulfate and potassium iodide. So little as 0.05 microgram, present in a concentration of $1:10^6$, may be detected. Feigl (65) has described a method for detecting as little as 0.002 per cent of cadmium in zinc ores and

0.0002 percent of cadmium in powdered glass.

Sensitive colorimetric methods for the detection of traces of cadmium have been published by Mahr and Ohle (160), and by Dwyer (52). The sensitivity has been given as $1:3\times10^{8}$ (5).

In a method for the microscopic detection of cadmium oxide particles in the lung, "oxine" combines with cadmium to form cadmium - "oxine" - dihydrate which gives a green fluorescence under ultra-violet light (255).

In a useful, rough qualitative test dilute hydrochloric acid (or acetic acid) is dropped along with a drop of sodium or ammonium sulfide solution on the suspected metal; if cadmium is present cadmium sulfide is formed, giving a canary yellow color. A white color indicates zinc (41) (216).

2. Quantitative determination

The polarographic method is the most convenient for the analysis of occasional samples; it is capable of detecting 1.5 to 500 micrograms or more of cadmium per three millimeters of solution with excellent specificity (35). It offers the advantage of relative freedom from interferences, provides a photographic record of the analysis and permits two or more toxic metals to be determined simultaneously (149). Details of the procedure have been given by Levine (149), Silverman (235) and by Feicht (62).

The colorimetric methods are laborious and time-consuming, and require careful attention to details if contamination by zinc is to be avoided. They provide a reliable means for the determination of cadmium

when polarographic or spectrographic equipment is not available (35). A colorimetric sulfide method, using intensification of color under ultra-violet light, reported by Fairhall (58), has been found by Cholak (35) to lack sensitivity. The formation of cadmium sulfide in ammoniacal solution, containing gelatin as a protective colloid, was proposed (123), but the precipitation of cadmium selenide was considered a more delicate test by Krumholz (138), who gave details of the sensitivity and the interference by other metals. The use of colloid stabilizers may decrease the intensity of the coloration by 65 to 70 percent. A method which avoids a stabilizer and in which the brightness is measured by means of a selenium photocell, improves the procedure (95). A number of organic reagents develop colors with cadmium which in the absence of interfering metals may be useful for colorimetric determination. Dithizone has been used by several workers, (35) (38) (66) (67) (129) (147) (213) (227) (231) (248). Other reagents proposed have been diphenylcarbazide (63), quinaldinic acid (204) and hydroxyquinoline ("oxine") (270).

As little as 0.4 microgram can be determined spectrographically and the method is said to be the most rapid and economical of those available, when many samples must be analyzed routinely (35) (184). Electrolysis before spectroanalysis has been recommended (33).

Other methods include the following. Titration of cadmium, precipitated with beta-naphthoquinoline in the presence of potassium iodide, with standard potassium iodate, in the presence of 10 percent potassium cyanide, has been proposed (15) (106). This could be applied

to the determination of 1 to 75 milligrams of cadmium oxide suspended in air (16). Determination of cadmium with brucine and potassium iodide, based upon titration of iodide has been published (57) (134) (179) (256). Electrometric titration with sodium sulfide, using the platinum-tungsten electrode, has been developed (233). Gravimetric methods also exist (134) (241). The cadmium content of tin-rich alloys was determined through the loss of weight obtained by raising the temperature and volatilizing the cadmium from the alloy (101). A procedure for determining the thickness of cadmium deposited on steel has been published (40).

CHAPTER V.

METABOLISM

A. Occurrence and Sources of Cadmium in Animal Tissues

The occurrence of cadmium in living tissues was first demonstrated spectroscopically by Fox and Ramage in 1931 (72) (73) (229).

Cadmium does not occur naturally in food in quantities detectable by common analytical methods, although small amounts may be found by special methods (64) (259). Canned oysters contained 1.21 parts per million. It has been found to the extent of 0.12 and 0.21 parts per million in hog and rabbit kidneys, respectively, and in greater amounts, 0.56 and 0.66 parts per million in beef kidneys. The kidneys of other animals contained smaller amounts. No significant amounts were found in rabbit, beef or hog livers (129).

Ground water had quantities ranging from 0 to 0.55 milligrams of cadmium per liter (126). Two mine waters from the Mississippi zinc region had 0.02 percent and 0.09 percent of cadmium, respectively, and a spring on Shoal Creek, Missouri had 0.10 percent (167).

In soils, amounts of the order of 1.7×10^{-4} percent to 4.5×10^{-3} percent have been found polarographically. In human organs, cadmium was found in the kidneys of a victim of lead poisoning to the extent of 3.3×10^{-3} percent (3.3 mgms. percent) and in the kidneys of a man who died with heart disease to the extent of 3.8×10^{-4} (0.38 mgms. %). It was also found in the spleen, lungs and other organs (161).

B. Absorption and Distribution

1. Absorption

Soluble cadmium salts administered orally to animals or taken accidentally by man in sufficient dosage, are absorbed by the gastro-intestinal tract in quantities sufficient to cause severe toxic symptoms and signs. Cadmiol injected intramascularly into rabbits was very slowly resorbed from the place of injection. Analysis showed that 50 percent remained at the site of injection after two weeks, and 20 percent after eight weeks (108). Absorption of the metal or its ordinary compounds through the unbroken skin does not occur to any practically important extent (197). No cadmium was found in the urine of a man upon whose forearm had been rubbed an alcoholic solution of cadmium chloride and who wore for 40 hours an undershirt that contained 50 milligrams of cadmium (as $CdCl_2$) distributed over its entire surface. No cutaneous damage or other effects were noted (221).

Cadmium fumes and dusts inhaled and retained in the lung are absorbed in varying amounts depending upon the compound involved. The use of a radio-active technique demonstrated that most of the cadmium retained ($CdCl_2$ aerosol) in the lungs of rats had already passed the lung barrier by the end of a 30 minute exposure. For twelve hours after exposure the cadmium content of the lung continued to fall, then remained constant indefinitely; at that time the unabsorbed cadmium was believed to have become fixed in the lung (194). In

experiments in which dogs inhaled cadmium containing dusts, less cadmium was absorbed from the lungs and distributed in the tissues when the dust consisted of CdS than when the oxide was used, perhaps because the former was less soluble (196). Seventy percent of the total amount of cadmium found in the tissues one week after exposure to cadmium sulfide dust was found in the lungs (199).

The progressive tendency toward the storage of cadmium in the body under suitable conditions proves that it may be absorbed more rapidly than it can be excreted. After periods of feeding cadmium to cats, there seemed to be a loss of the stored cadmium during a period of feeding a cadmium free diet (194). Thirty-eight percent of the injected dose of cadmium was recovered from the organs of a dog killed four weeks after intravenous administration of 20 milligrams of cadmium as a soluble salt. Eight weeks after an intramuscular injection of cadmium, 70 percent of the total amount injected was recovered from the body (108).

2. Distribution

Chemical analysis of the viscera of cats fed on diets containing cadmium chloride, carbonate or phosphate demonstrated that the main distribution of cadmium was in the liver and kidneys, the kidneys generally containing relatively much more than the liver (194) (199). Prolonged feeding deposited cadmium in the bone (199). Injected cadmium is highly concentrated in the liver and kidney (108) (194). Chemical analysis of the organs after intravenous injection of cadmium chloride

showed that the liver contained 13 to 21 times the average body concentration, the kidneys 4 to 6 times and the lung one-half (194). Eight weeks after the intramuscular injection of cadmium, 4 milligrams of cadmium was found in the liver of a rabbit, 2.6 milligrams in the kidneys and 0.3 milligrams in one-half of the intestinal tract (108).

Shortly after the inhalation of cadmium oxide and chloride, cadmium is found mainly in the lungs, liver and kidneys; later it is found chiefly in the liver, kidneys and lungs, with lesser amounts stored in the bones and teeth (194) (196) (199). After a year's exposure to cadmium sulfide, the cadmium concentration is always higher in the lung than in any other organ. In general, the concentration of cadmium found in the kidney was much greater than that found in the liver (196).

After subcutaneous injection of tagged cadmium sulfate into rabbits, the distribution of the metal in the various organs could be demonstrated by means of radio-autographs. Quantitatively, the cortex of the kidney contained 4 to 6 times as much cadmium as the medulla. Densitometric readings showed that the periphery of the lobules in the liver contained approximately twice as much cadmium as the inner half (77). By means of the dithizone method, in which the metal is made visible as brilliant red granula, it was found concentrated in the mitochrondia surrounding the nucleus of the liver cells (9). Moderate amounts of cadmium were found in the glandular tissue of the pancreas, but only small amounts were found in the connective tissue septa.

No appreciable difference in cadmium concentration was found in the islets of Langerhans as compared with the acini. Cadmium was uniformly distributed in the lymph follicles, and the spleen. The Geiger-Muller tube counting technique failed to show the presence of cadmium in plasma although a relatively high concentration of cadmium occurred in the whole blood (77).

C. Excretion

The excretion of cadmium following any route of administration is slow and mainly through the intestinal tract, and only relatively small amounts are excreted in the urine (108) (154) (194). After dogs were given $CdCl_2$ intravenously, the blood level dropped progressively so as in one hour to equal that in the bile, after which both fell in parallel. Investigation of isolated portions of the intestinal tract, with the bile duct ligated, showed excretion of cadmium at all levels of the small intestine and in the stomach. The inhalation of soluble salts of cadmium by mice resulted in a maximum value of cadmium in the gut at two hours, and in the gut wash at six hours (194).

CHAPTER VI.

TOXICITY OF CADMIUM

A. General

The toxic action of cadmium has long been recognized, and much experimental work has been carried out to show its physiological and pathological effects. These bear some resemblance both to those of zinc and of mercury (17) (130) (131) (198) (221). It is much more toxic than zinc and less toxic than mercury (69).

Protozoa (131), fungi (116), insects (especially the larval stage) (91) and fish (164) are killed by cadmium in relatively moderate concentration. Stimulation of plant growth has been observed (86) (215). Contradictory evidence has been presented concerning the action of cadmium upon bacteria (43) (107) (131) (152) (158) (159) (170) (217) (265) (266) (267) (279) (280).

Cadmium was found to inhibit the oxidases tyrosinase (20) and succinoxidase (13) (238), rennin (87), papain (137), invertase (242) and reductase (135). Phosphatase from the prostate was activated (10) (183). The enzymes carboxylase (151), catalase (281) and amylase (88) were activated in low concentrations and inhibited by high concentrations of cadmium. Cadmium inhibited lactic fermentation of colon bacilli (6).

Local application of concentrated solutions of all soluble cadmium compounds cause a caustic or astringent action (131) (163),

and, when placed on red meat a visible whitening appeared (221). This has also been observed after hypodermic (260), subcutaneous (163) and intramuscular (206) injection. Protein precipitation may also occur in blood vessels after intravenous injection (221).

Cadmium salts give a burning sensation in the mouth (163), and the immediate irritant effect upon the nerve endings in the gastric mucosa may induce vomiting (221) (261).

In fatal poisoning of experimental animals, cadmium exerts a toxic action upon the central nervous system, paralyzing the respiratory center and the vasomotor system (6) (8) (47) (186). The heart is arrested in diastole (8) (189) (201) (212). First the reflexes are abolished and then the sensation of pain. Somnolence develops and death ensues in asphyxia associated with pulmonary edema but unaccompanied by convulsions. The effect on the nervous system has been thought to be exerted first on the anterior horn cells of the spinal cord, then on the cells of the medulla and to a smaller extent upon the brain (55) (56). A reversible inhibition of nerve excitability has been noted (34).

B. Lethal Dosages

The lethal dose of cadmium administered by way of the gastrointestinal tract is said to range from 300 to 600 milligrams for rabbits weighing 1500 to 1800 grams, and from 150 to 300 grams per kilogram of body weight for dogs (130) (163). The ingestion of approximately 8.9 grams of cadmium chloride resulted in the death of a fourteen

year old boy one and one-half hours later (109). The intravenous injection of 10 cubic centimeters of a 2 percent cadmium chloride solution caused the death of an eighteen year old man (124). Cyanosis and marked edema of the face were mentioned. The lethal intravenous dose for dogs is 30 milligrams, for cats 16 milligrams, and for rabbits 10 to 20 milligrams per kilogram of weight (163). Twice or three times the intravenous dosage is required to produce the same effects by subcutaneous administration (163) (228). Pigeons were killed by 15 milligrams of cadmium injected subcutaneously and the $L.D._{50}$ for rabbits after subcutaneous injection of cadmium sulfate was 6.3 milligrams of cadmium per kilogram of body weight (75) (76) (163). The lethal dose for man is not known (19).

The relative toxicity of solutions of cadmium salts when given intravenously to cats and rabbits decreases in the following order: nitrate, sulfate, bromide, chloride and iodide. The concentration of the cadmium ion yielded by the above salts (most active to least active) was nitrate, chloride, sulfate, bromide, and iodide. Thus it appears that their pharmacological activity, except that of the chloride, is in direct proportion to the concentration of the cadmium ion (224).

Barrett, Irwin and Semmons exposed animals for ten to thirty minutes to cadmium oxide in the form of particles ranging in size from 0.3 to 0.5 micron and in concentrations ranging from 10 to 1000 milligrams per cubic meter (11). The estimated $L.D._{50}$ for rats was 500 minute-milligrams of cadmium oxide per cubic meter of air, for mice less than 700, for rabbits 2500, for guinea pigs 3500, for dogs 4000, and for

monkeys 15,000. The fumes were twice as toxic as phosgene for the rat, but only one-tenth as toxic as phosgene for the monkey. Cadmium oxide generated by the annealing of cadmium-plated rivets was only one-half as toxic for these animals as the arc-produced fumes (11). The $L.D._{50}$ of cadmium aerosol for mice was 0.045 milligrams per liter, and 0.02 milligrams per liter was apparently a threshold concentration (263).

C. Signs and Symptoms

Toxic doses of cadmium, regardless of the manner of their introduction into the organism, caused such reactions as loss of appetite, vomiting, diarrhea, loss of energy, and death. Small doses of soluble cadmium salts given over a longer period of time resulted in chronic poisoning evidenced by gastro-enteritis and progressive loss of weight (163).

The most delicate criterion of chronic cadmium poisoning of male albino rats was the production of bleached incisors. There was a definite degree of bleaching at 16 parts of cadmium (as $CdCl_2$) per million parts of food low in fluoride content (68) (273). Cadmium has been found in the maxillary bone and the hard tissue of the tooth following experimental feeding of cadmium (122). The use of drinking water containing 40 parts of cadmium (as $CdCl_2$) per million by rats, after their teeth had become calcified, was followed by an increase in the incidence of caries (68) (90) (145). Reduction of food consumption was noted when the food contained 25 parts of cadmium

(as $CdCo_3$) per million (221). Chronic feeding of 62 parts of cadmium (as $CdCl_2$) per million in the diet of albino rats resulted in stunting of growth, cardiac hypertrophy, and an anemia without a proportionally lowered red blood cell count (68) (119) (272). Growth was resumed and the anemia was believed to have disappeared on resumption of the control diet, for the eyes returned to their normally pink color. With a dosage of 0.56 milligrams of cadmium (as $CdCl_2$) in the diet per day, no cumulative action was observed in rats. The minimum emetic dose of cadmium chloride for cats, when given in solid food, was found to be 4.11 milligrams of cadmium per kilogram of food, which represented the daily intake when the concentration in the food was 150 parts per million. The average mean emetic concentration lay between 200 and 250 parts per million. The maximum amount of cadmium that was tolerated without producing emesis was 22.7 milligrams of cadmium per kilogram of body weight, and the actual concentration was 400 parts per million. No evidences of systemic cumulative effect or of habituation in cats were observed. Vomiting occurred earlier with a liquid diet and with a larger amount of food ingested (221). Prodan noted that vomiting was preceded by abundant salivation which persisted after the vomiting (199).

Exposure of cats to massive concentrations of cadmium oxide fume caused abundant salivation and panting after 10 minutes. After 30 minutes salivation continued and respiration involved the accessory muscles. Exposure to lower concentrations resulted in salivation and panting in about 12 hours. The animals refused to eat or

drink and appeared to be sluggish. After 24 hours of exposure they were still salivating and developed dyspnea (199). Upon exposure to cadmium chloride aerosol, salivation, retching and vomiting were immediate. The respirations were rapid and labored, with a prolonged expiratory phase and occasional wheezing suggesting bronchial obstruction. The heart rate was slowed at first. Later the rate increased, the blood pressure fell, and the respiratory rate increased (103). With the onset of pulmonary edema, the plasma volume lessened, resulting in rapidly developing hemoconcentration but, due to the less efficient diffusion of oxygen across the edematous alveolar membrane, the arterial oxygen saturation decreased despite the increased oxygen-carrying capacity of the blood. When pulmonary edema developed more slowly the hemoconcentration was less marked, and the arterial oxygen saturation fell somewhat less quickly, but eventually went to a much lower level. In even more chronic courses, there was a slow decrease in the arterial saturation which remained at about 50 percent for four or more days and then slowly rose. During this time, the animals were prostrate, extremely dyspneic and anorectic (103).

Pulmonary edema occurred within two or three hours after the inhalation of large amounts of CdO fumes, CdO dust, CdS dust and $CdCl_2$. An eosinophilic precipitate appeared in the pulmonary fluid within 9 hours, increasing its protein content. Within 24 hours histological examination showed desquamation of the epithelium as far distally as the terminal bronchioles, and edema of the walls of the alveolar ducts and bronchioles (103) (199).

Examination of animals that survived the acute pulmonary edema revealed that the edema quickly receded but the lung did not revert to normal in one to three days, passing into a second state of "proliferative interstitial pneumonitis" or bronchopneumonia (185) (190). The mortality in this stage was about equal to that which occurred during the acute stage of pulmonary edema (190). This stage of proliferation is not peculiar to animals but has also been observed in man after the inhalation of large amounts of cadmium oxide (26). Fibroblastic proliferation in the air passages resulted in thick, eosinophilic, hyaline membranes lining the respiratory bronchioles and alveolar ducts and obstructing the openings of the atria and alveolae (103). Also fibroblastic proliferation in the interalveolar tissues resulted in thickening of the alveolar walls, increasing the alveolar barrier to diffusion of alveolar gases into the circulation (199). Hyperplasia was present with regeneration by pseudo-stratified, columnar, non-ciliated epithelial cells in the bronchi, bronchioles and alveolar ducts, frequently lining the adjacent atria and alveolae (103). The nuclei were plump, with some evidence of mitoses, and the cells projected into the alveolar spaces, especially near the terminal air passages. The epithelial hyperplasia disappeared in about ten days, but the fibroblastic proliferation continued into a third stage in animals with permanent pulmonary changes evident after about a month (130) (190). Granulation was followed by organization and obstruction of the bronchioles. Widespread patchy fibrosis was seen, especially about the air passages and blood vessels, as well as thickening and

fibrosis of the alveolar walls (190) (199). Atelectasis and moderate emphysema were present (103) (199).

About 25 percent of the animals which survived exposure to cadmium fumes in sufficient concentrations to cause symptoms, showed a significant degree of residual pulmonary fibrosis (190).

Princi observed no significant change in the sedimentation rate, hemoglobin, hematocrit, red blood cell count, white blood cell count, or the myelocytic/erythrocytic ratio in the bone marrow of dogs exposed to CdO and CdS dust for 12 to 15 months (196).

D. Pathology after feeding

The following effects have been observed following the administration of cadmium by various routes:

Kidney - Fatty degeneration after oral administration of cadmium carbonate and after the introduction of cadmium phosphate into the diet of cats for two months (199). Intense necrosis in the convoluted tubules, epithelial casts and occasional calcified casts in some of the tubules, and cadmium deposits in the kidneys of rabbits, after subcutaneous injection of cadmium chloride (228).

Liver - Generalized granulation of the liver cells or, more severely, pronounced fatty infiltration, principally about the central vein (163) (199). Focal necrosis with some inflammatory reaction and fibrous tissue proliferation following the addition of cadmium chloride to the diet of albino rats (273). Cirrhosis after subcutaneous injections of cadmium sulfate on six days per week over the period of

six months (76).

Lung - Some infiltration with polymorphonuclear leucocytes following the oral administration of large amounts of cadmium salts (199). Congestion and pulmonary infarction in acute poisoning (130) (163). Hemorrhage (124) (191).

Gastro-intestinal tract - Swelling and redness of the gastric mucosa (130) (163) (191) (221) (228).

Heart - Fatty degeneration in chronic poisoning (163) (191).

Pancreas - Marked atrophy and inflammation (273).

Spleen - Hyperplasia (75) (273).

Teeth - Bleaching (273).

Bone Marrow - Hyperplasia with almost complete absence of fat cells; myeloid cells about twice as abundant as in controls (273).

Peripheral Blood - hypoglobia, leucopenia, granulocytopenia and thrombocytopenia after subcutaneous injection into rabbits (24) (68). Leucocytosis with a relative increase in polymorphonuclear cells (199) (221), reticulocytosis and late eosinophilia after feeding (68) (273). Increased (7) (131) or decreased (131) (268) tendency toward hemolysis depending upon the concentration of the cadmium ion (237).

E. Mechanism of Action

The toxic action of cadmium was postulated by Tepperman (254) to be a combination of cadmium with the sulfhydryl groups (238) of numerous important enzymes, thereby inhibiting their activity (13) (254). The evidence in favor of this hypothesis was provided by the

demonstration that this inhibition could be reversed by thiols unless the cadmium had been added in excessive concentrations (13).

CHAPTER VII.

CADMIUM "FOOD" POISONING

Prior to January 1, 1941, only 20 cases of poisoning from the use of cadmium-coated vessels for food or drink had been recorded, but within five years thereafter, 639 more cases of poisoning were reported (61). There is little doubt that additional cases have occurred but were not diagnosed, and it is equally certain that many were so diagnosed in error. It is often difficult to trace the origin of such gastro-intestinal upsets (61). The United States Public Health Service (200) reviewed the literature prior to April 24, 1942 and listed the cases of poisoning followed by the ingestion of cadmium. Other cases have occurred since (31) (82) (117) (155) (173) (216) (252).

Woodward* noted the illness of at least 32 persons who had eaten cottage cheese which had been stored in cadmium-lined cans. Concentrations of cadmium ranging from 197 to 490 parts per million were found in samples of the cheese. Cangelosi (32) noted that the drinking of lemonade containing 15 parts of cadmium per million induced mild symptoms of poisoning, and Jenner (117) reported that the dose of 56 milligrams of cadmium in highly acid grapefruit juice caused very severe poisoning. However, Griebel and Weiss (93) noted that an intake of even 330 milligrams had been tolerated without permanent injury.

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The diagnosis of cadmium "food" poisoning is made on the following criteria:

1. History. Nausea, vomiting, abdominal pain, diarrhea (less if there has been vomiting), and weakness occurred, following the ingestion of contaminated food or beverages. Vertigo, sensory disturbances of the hands and arms, and even convulsions, may be observed in severe cases. Any of these symptoms may become evident within from ten minutes up to five hours after the intake of contaminated food, the interval depending somewhat upon its nature. It may be said that acute poisoning by cadmium is distinguished from bacterial food poisoning, except when preformed toxins are present, by the quickness of the onset of symptoms and by the relatively mild diarrhea (32) (172).

2. Detection of cadmium in the food, drink or vomitus. Yellow cadmium sulfide is precipitated when hydrogen sulfide is passed through a slightly acid wet-ashed solution (115).

3. Rapid recovery. However, the patients may remain unable to carry on normal duties for several days (261).

The treatment of acute poisoning following the ingestion of cadmium is entirely symptomatic and supportive (197). Shock is not an infrequent complication, and violent acute gastritis is common. The acid-base balance and fluid loss should be restored, and care should be taken not to aggravate the gastro-enteritis (197). Lufkin (155) advanced the idea that because sodium bicarbonate solution precipitates cadmium salts it is the solution of choice for gastric lavage in first-aid treatment.

Chronic poisoning has not been observed to result from the consumption of contaminated food (172). Laboratory experiments indicate that the use of cadmium-lined utensils involves risks (173), but Princi (197) noted no symptoms in persons who drank water containing 0.047 milligrams of cadmium per liter over long periods with analytical evidence of long-continued absorption. The chronic toxicity of cadmium sulfide and sulfoselenide pigments was studied by Gabby (81). He concluded from animal experiments that if a baby consumed all the paint from the inside of a crib once every six months over a period of several years, the effects of ingesting the pigment might be considered negligible. From the work on animals he believed that if a child ate an entire stick of chalk containing 33.3 percent of one of the cadmium pigments every day he attended school over a period of several years, no ill effects would be noted, although if the pigment contained selenium there might be a slight depression of appetite. He knew of no known instance of intoxication that had been encountered in the manufacture or use of the pigments. Truffert (259) suggested that the maximum concentration of cadmium permitted in most foods should be limited to 1 milligram per kilogram. In crustacea and mollusca, cheese and sugar products, he would allow up to 5 milligrams per kilogram, but in milk, beer, and other beverages, he would permit only 0.5 milligrams.

CHAPTER VIII.

ACUTE INDUSTRIAL POISONING

A. Exposure

The United States Public Health Service has estimated from the data on 15 States that were surveyed from 1936 to 1939, that the number of workers in the United States exposed to cadmium was 30,927, almost two-thirds of them being in the non-ferrous metal industries. The iron and steel industry accounted for only 10 to 15 percent of the total. Of the surveyed workmen, 33 percent had the benefit of local exhaust ventilation, 8 percent were provided with masks, 6.7 percent were employed in an enclosed process, 2.5 percent were given respirators (not air-line), and 1.8 percent worked with wet methods. Fourteen and one-half percent of the workmen enjoyed general exhaust ventilation; 13.5 percent of the systems were of a type involving negative pressure, and 1 percent were positive. Data were not tabulated as to whether the protective respiratory devices in operation were of an approved type (18).

More than 1200 types of exposure to cadmium were present in the environment of the following Ohio workers: Cadmium alloy makers, workers with cadmium and cadmium compounds, cadmium platers, cadmium vapor lamp makers, calico printers, storage battery makers, chargers (zinc smelting), color makers, solderers, welders, chemical process men, glass blowers, cupulo tenders, painters, and polishers. Super-

visors, foremen, technical workers and maintenance men were exposed, as well as laborers (50) (181).

The industries of Ohio which were found to provide exposure to cadmium include glass and auto factories, foundries, those where welding, forging and heat-treating processes are carried on, machine shops, brass factories, electroplating, printing and publishing, and those which manufacture chemicals, electrical machinery, gas and electric fixtures, toys and novelties. Other types of exposures were noted in "other metal industries" (182). Exposure to cadmium fume occurs in the tool and dye industry where an alloy wire containing cadmium is used in brazing cutting tools. Air samples collected by means of an electrostatic precipitator showed concentrations in excess of the maximum allowable concentration (114). The rubber industry has been investigated (46).

The greatest hazards are present in the manufacture of cadmium and in the handling of its compounds. Some of the most significant are encountered in the following operations:

1. The roasting of zinc ores containing cadmium.
2. The smelting of the ores.
3. The condensation of the "blue powder".
4. The collection in filter bags.
5. The handling of "blue powder" and cadmium oxide.
6. The handling of the "metal residues".
7. The making and handling of cadmium sulfide and lithopone.
8. The spraying of CdS paint.

9. The welding of cadmium.

10. The melting of cadmium.

The diagnosis of industrial cadmium poisoning is made on the following criteria:

1. History. Exposure to the fumes of cadmium oxide. The presence of cadmium must be demonstrated in the material to the vapor of which the workman has been exposed. The estimated concentration of cadmium must be sufficient to have caused poisoning. The contribution of other toxic agents must be taken into consideration.

2. Detection of significant quantities of cadmium in the blood, urine, or tissues.

3. Presence of typical signs and symptoms.

4. Clinical course of the patient.

The symptoms of poisoning may be divided into early and delayed types. Early symptoms may occur almost immediately after the exposure begins or so late as 4 to 8 hours after it has ended, depending somewhat upon the nature and degree of exposure. They include dryness and irritation of the throat, headache, cough and tightness and oppression or constriction of the chest. More severe exposure may result in giddiness and loss of consciousness (148). Delayed symptoms may appear 3 to 4 hours, or even 20 to 36 hours, after the exposure. They are: weakness, nausea and vomiting (depending somewhat upon the amount of cadmium ingested), respiratory distress with shortness of breath, pain in the chest and abdomen, and occasionally chills.

Signs of poisoning may be classified as those observed in workmen exposed to moderate amounts and those exposed to massive amounts.

Moderate exposure results in the appearance of few signs. The patient is pale, given to retching and dyspneic on exertion. The pharynx is injected. No adventitious signs are heard in the chest. There is usually some epigastric tenderness on palpation. All other physical signs are normal.

Severe exposure may induce prostration, nausea and vomiting (almost always present), severe abdominal pain and tenderness on palpation, orthopnea and cyanosis (occasionally), and fever (infrequently). Physical signs include an increase in the pulse and respiratory rates. Pulmonary edema, pneumonitis or bronchopneumonia may or may not be demonstrated by radiological means.

Laboratory investigation has demonstrated leucocytosis with a relative increase in polymorphonuclear leucocytes. An increase in the erythrocyte count without a proportionate increase in the hemoglobin concentration was observed (110) (120). An increase in the sedimentation rate of the erythrocytes has been mentioned (85). Albumin has been found in the urine (120).

A survey of 59 cases established the mortality rate as 15 percent. Deaths occurred between the 5th and 7th day, and recovery within 7 to 11 days after exposure (243).

The vast majority of those who recovered following illness from acute inhalation were found to have no detectable disease attributable to cadmium upon examination some months after apparent recovery (182) (243). However, Ross reported that several workmen were off duty for periods of one to two months following recovery. Some complained of

nausea, anorexia, weakness of the legs, slight shortness of breath on exertion, and epigastric tenderness two months after apparent recovery (211).

It is not known how great a hazard there may be in the process of cadmium plating after the cadmium is in solution. There are reports of the skin having turned black after coming into contact with the solution (198). Hamilton and Hardy (99) mentioned that cyanogen may be given off from the open plating tanks. Skin irritation from cyanide has been observed (121). When powdered zinc has been added to acid solution to replace cadmium, workers have been poisoned by arsine. Another dangerous procedure observed was the addition of hydrogen sulfide to a sample from the tank to test for the presence of cadmium (113).

Cadmium is in the moderately hazardous group of materials, with reference to the explosibility of metal-powder dust clouds (104). The fire hazard in connection with the "blue powder" and cadmium sulfide should be noted (198).

In the Donora episode it was concluded that the contribution of the cadmium plant to the atmospheric pollution was not significant (219). Cadmium has not been found, under ordinary conditions, in the atmosphere of Cincinnati in concentrations sufficient to justify apprehension as to its hygienic effect upon the population (127). The average quantity of cadmium in the atmosphere of Cincinnati was 0.22 micograms per cubic meter (36) (37).

B. Poisoning

Industrial cadmium poisoning has resulted only after the exposure of workmen to cadmium heated sufficiently to give off the oxide in yellowish-brown fumes (165).

Over 110 cases, with 15 deaths, have been described (3) (22) (23) (42) (59) (79) (80) (84) (85) (97) (110) (114) (120) (144) (148) (175) (180) (182) (188) (193) (208) (220) (223) (240) (253) (264). Bulmer, Rothwell and Frankish described an incident in which the annealing of cadmium plated rivets caused the illness of 14 men, two of whom died (26). Analysis of the dried lungs of fatally poisoned persons showed an average concentration of 1.75 milligrams of cadmium per 100 grams. An indirect calculation, in an attempt at the reconstruction of the exposure, indicated that the lethal dosage may have been 2500 to 2900 minute-milligrams of cadmium oxide per cubic meter of air. The particle size was less than 0.3 micron. Spolyar et al reported five cases, including one death, due to the heating of cadmium plated pipes (243). Merewether (169) noted seven and Ross (211) twenty-three cases that occurred after the ignition of cadmium dust, but in the instance reported by Ross, wood and canvas filter frames were also burnt. Shiels (230) reported one death in fourteen cases of poisoning among firemen exposed to the fumes of cadmium oxide and sulfonated castor oil. The fatality resulted after 20 minutes of exposure to an estimated concentration of 140 milligrams of cadmium per cubic meter of air. The lungs contained 4 milligrams of cadmium by spectroanalysis.

C. Treatment

The early diagnosis of cadmium poisoning and the recognition that the pulmonary reaction may be delayed are very important. Except where exposure had been slight and brief, cessation from work and complete rest in bed for 48 hours must be insisted upon in order to lessen the amount of work performed by the heart should pulmonary edema occur. In severe cases, longer restriction in bed is indicated. Oxygen therapy should be started at once, even though the patient appears to have been subjected to only moderate concentrations of fumes, in order to combat pulmonary edema. Thus the same therapeutic needs must be met as in cases of exposure to phosgene, oxides of nitrogen, or methyl bromide.

Symptomatic treatment carried out according to general medical principles should be instituted. Appropriate sedatives should be given for cough and gastric disturbance (243). Suitable antibacterial therapy may be employed if secondary invaders are suspected (197).

Daily doses of 100 to 150 milligrams of B.A.L. (2,3 dimercaptopropanol) have been advocated for the treatment of acute cadmium poisoning, but the clinical use of this substance has not been reported (89). In experimental cadmium poisoning, the excretion of cadmium is increased and is shifted in the direction of the kidney in the first 24 hours after the administration of B.A.L. (254) (257). The urinary excretion is increased to 10 times its value in controls

and becomes equally as significant as the intestinal excretion (89) (194). In such experiments renal insufficiency has developed (254). Stocken (246) postulated that this resulted from tubular readsorption and consequent concentration of the metallo-organic complex (cadmium mercaptide) in the epithelium of the renal tubules causing an intoxication due to the subsequent release by intracellular oxidation of toxic amounts of cadmium ions (254).

Treatment with B.A.L.-glucoside resulted in less severe renal damage in surviving animals than that observed after therapy with B.A.L. The concentration of cadmium found in the kidneys of rabbits treated with B.A.L.-glucoside was about the same as in the controls and much lower than that observed following B.A.L. therapy, despite the fact that more cadmium was excreted in the urine of animals treated with B.A.L.-glucoside than in that of those given B.A.L. B.A.L.-glucoside forms, in vivo, mercaptides of low dissociation which remain extracellular and are not resorbed in the tubules to the extent evidenced by the Cd-B.A.L. complex. The entire increase in the loss of cadmium after B.A.L.-glucoside therapy is almost completely accounted for by the enhanced urinary excretion (257).

Other therapeutic agents investigated include other thiols. There is an increasing efficiency and toxicity with an increase in the number of sulphydryl groups in the molecule when thiols are compared in regard to their ability to reverse the inhibition of succinic dehydrogenase by cadmium chloride. Of the thiols tested, B.A.L. is itself the least toxic, and best satisfies the requirements

for counteracting the cadmium poisoning (238). A number of non-thiols were examined, though less extensively than B.A.L., as potential therapeutic agents. One of these substances, selenium as SeO_2, is effective prophylactically as well as therapeutically.

Amounts of B.A.L. approaching the maximum tolerated dose are required for therapy (257). The therapeutic effectiveness of B.A.L. administered after respiratory exposure to cadmium (as well as its deleterious action when administered prior to exposure), can be understood in terms of a decreased (or increased) concentration of cadmium ions in lung tissue, with, presumably, correspondingly less damage to critical enzyme systems (194) (238). When given therapeutically, B.A.L. neither accelerates nor delays cadmium loss from the lung, but when used in prophylaxis B.A.L. fixes the cadmium in the lung (257).

D. Prevention

Recognition of the potential hazard of the presence of cadmium in industrial materials, use and maintenance of closed operating systems, use of protective devices for workmen, adequate removal of cadmium fumes at the source, thorough housekeeping, and special medical control are necessary for the prevention of industrial poisoning (176).

Acute industrial poisoning usually results from the lack of recognition that cadmium plated articles are being processed. Cadmium

is frequently substituted for zinc plate, and some platers add cadmium to the zinc used in electro-galvanizing. The difference between zinc-coated and cadmium-coated steel is apparent only after some experience, although at first glance they appear similar. In general, cadmium-plated articles usually give a smoother, non-crystalline appearance. There has been some agitation for the labeling of cadmium-coated metals. While this would be effective, no doubt, in relation to large pieces, it would be somewhat difficult to enforce in its application to small objects so coated (61). A contractor engaged in plating should voluntarily affix an appropriate warning tag to all articles leaving his shop which are either cadmium-plated or which contain cadmium in the plating. A descriptive bulletin on cadmium poisoning should be enclosed with the bill of sale submitted by the plater (114).

The use of spot tests by skilled observers to determine the presence of cadmium in or on industrial materials has been suggested. One procedure is to apply a drop of concentrated hydrochloric acid on the metal surface, allow a few seconds for the acid to dissolve some of the coating, and then add to the spot a drop of ammonium hydroxide which has been saturated with hydrogen sulfide. A bright yellow precipitate will indicate that the coating is cadmium, while a white precipitate will indicate zinc. The oxide of cadmium formed when it is heated in air is brown and the oxide of zinc is white. A cadmium-plated object forms a yellow-gold film when heated gently with a welding torch, but zinc-coated articles turn smoky-dark gray (193).

Provision must be made for masks or respirators to be worn for short periods and for emergency use. One type of mask and one type of respirator were tested against the fume of cadmium oxide and against cadmium chloride mixed with hydrochloric acid vapor. The use of a simple respirator is recommended when the percentage of cadmium contained in the material is small. A soda-lime cartridge should be attached to the respirator when acid fume is also present in the atmosphere. A canister mask should be used in all cases where the cadmium content is high (198). Positive pressure masks have also been recommended. A list of respiratory protective devices has been published (218).

Specially designed local exhaust systems, similar to those used in chrome plating, must be used when cadmium plating is performed, in order to provide adequate removal of mists at their source.

The criteria of safe occupational exposure to cadmium have thus far been lacking. Cotter and Cotter presented a series of five cases in which exposed workers had cadmium in the blood and urine, but did not present the classic clinical picture of cadmium poisoning (45). Studies of their blood chemistry indicated evidences of injury to the liver, kidney and bone marrow. They recommended that careful studies of the blood chemistry of workers exposed to cadmium should be done whenever possible. Princi (196) observed no correlation between the severity of prolonged exposure to cadmium oxide and the amounts of cadmium recovered from the blood and spot samples of the urine of dogs. The level of cadmium found in the blood was not

related to the concentration in spot samples of urine. Friberg urged that special effort be made to detect any evidence of pulmonary and renal dysfunction during yearly examinations of the cadmium workers (76). Chest x-ray, sedimentation rate, and tests for the detection of protein in the urine should be routine. Pulmonary function tests, to show any effect of cadmium, should be done at intervals. The records of preplacement examinations should include the results of all such tests for the purposes of comparison. Efficient housekeeping should be maintained and rules to prevent the ingestion of cadmium should be enforced.

CHAPTER IX.

CHRONIC INDUSTRIAL POISONING

Although cases of acute cadmium poisoning caused by the inhalation of the fumes of cadmium oxide are well known, cases of chronic cadmium poisoning have not been observed in the United States, but have been reported by investigators in European countries. It seems likely that the disparity of the reports involves differences in materials and processes.

Inflammation of the pharynx and nose with ulcerations of the cartilaginous part of the nasal septum but without perforation, was described in Italy among platers. Mancioli (162) thought that the changes were to be attributed to the chronic absorption of cadmium.

The earliest sign of the chronic absorption of cadmium is a band of yellow pigmentation of the vestibular surface of the incisors (14) (142) (143) (195). No subjective complaints can be elicited from the workmen (14) (195). The coloration is greatest at the gingival margin and extends part of the way to the free edge of the tooth (14) (195). Much greater exposure could occur without apparent injury (14). Baader (9) mentioned Valetas's observation of the band of pigmentation of the teeth of workmen after exposure of only two to four months duration. This pigmentation could not be removed and was thought to be deep in the enamel and dentine without involvement of the pulp, but Princi was unable to explain in which part of the

dental structure the cadmium was stored after thorough animal experimentation (142) (143) (196). Workmen who had never used nicotine in any form developed the band, and smoking concealed it in some instances (76). Although the tartar was impregnated with the color, the gums were not colored nor inflamed. (14) (195). LeBourg thought that the intensity of the pigmentation was proportional to the severity of exposure, but Barthelemy observed no relationship. Disappearance of the band took longer than its appearance (14) (143). Mouth breathing, increasing direct contact with the fumes of cadmium oxide, and an alkaline condition of the mouth, forming sulfocyanate saliva, were thought to favor the coloration, but Princi (196) stated that it is unknown how the cadmium is deposited in the teeth (9). Cadmium was present in the teeth of exposed workmen only, but no radiological changes were detected (14) (195). There were no changes in the color of the teeth of dogs after prolonged inhalation of cadmium (196).

Nicaud, Lafitte and Gros reported a disabling disease syndrome in workmen, which they interpreted as chronic cadmium poisoning. These workmen had been exposed for eight to ten years to cadmium fumes and dust in an accumulator battery plant, and suffered from weight loss, vague motor disturbances, impairment of locomotion, in association with severe lancinating pains without specific localization in the lower limbs, pelvis and lumbar region. Physical examination yielded essentially negative results. Radiological investigation revealed the presence of certain abnormalities in the skeletons of

some of the workmen. Osseous striae or fissures, usually transverse and multiple and often symmetrical, involve the entire skeleton in some instances, but especially the upper part of the femur. The striae gave the appearance of spontaneous fractures, but no calluses or displacements were observed. The calcium, phosphorous and phosphatase levels were normal and there was only a slight anemia (178).

Barthelemy (14) divided the syndrome into four periods which follow:

1. Latent Period. If the exposure is discontinued before the appearance of symptoms, none occur later, even after three to five years. Barthelemy advised calcium gluconate therapy from the beginning of exposure, and limited the exposure to six months in each year.

2. Alarm Period. The yellow band appears on the teeth after two years exposure. Twelve injections of calcium gluconate should be given every four months to prevent any progression.

3. Painful Period. Asthesia develops about the fourth year and is followed by pain.

4. Radiological Period. Milkman's (171) syndrome appears after eight years of exposure. Three of the six patients with radiological changes returned to work after three months of treatment with vitamin D, calcium gluconate and parathyroid injections.

Proteinuria, impaired renal function, anosmia, increased erythrocytic sedimentation rate, and pulmonary emphysema associated

with low working capacity have been reported among workers in European battery plants (9) (76). Their incidence was greater in exposed than in unexposed groups (76). Weight loss, fatigue, gastro-intestinal symptoms, cough and shortness of breath were mentioned (76). Electrophoretic and ultracentrifugal investigations revealed that the principal component of the proteins in the urine had a probable molecular weight of twenty to thirty thousand. Electrophoretic examination of the blood of five workmen showed the presence of a protein with abnormally low molecular weight.

Since the workmen referred to above were exposed to nickel as well as to cadmium dust, Friberg (76) exposed rabbits to the actual factory dust for three hours per day over periods of seven to nine months. After six months of exposure precipitation tests on centrifuged urine revealed the presence of protein in the urine of most of the animals. The proteinuria was thought to be due to cadmium, and the emphysema to be due mainly to cadmium and perhaps partly to nickel. Friberg reported the death of three workmen during the three year interval of his continued observation and felt that two of the three fatalities were attributable to the prolonged exposure to cadmium. The results of air analysis were reported to vary from three to fifteen milligrams of cadmium per cubic meter of air. Post mortem examination showed right ventricular hypertrophy in both workmen, and pulmonary emphysema was noted in one. Spectrographic determination showed the concentration of 3.9 milli-

grams of cadmium in 100 grams of splenic and pancreatic tissue, 3.6 milligrams percent in the vertebrae, 1.5 to 3.1 milligrams percent in the liver, 2.0 to 2.4 milligrams percent in the kidney, and 0.6 milligrams percent in the lung.

Baader (9) referred to a German workman who died four years after discontinuance of exposure to cadmium. Spectroanalysis showed 11.7 to 17.5 milligrams and 9.5 to 14.3 milligrams of cadmium in 100 grams of kidney and liver tissue respectively. Microscopic examination revealed intramural plexus lesions in areas of segmental dilatation of the esophagus and jejunum.

Stephens (245) noted a cadmium concentration as high as 13 milligrams percent in the liver of a spelter worker.

In contrast to the above disabling conditions which have been observed in European workmen, there are no references to similar experiences in the United States. Hardy and Skinner examined eight men who had been employed four to eight years in the manufacture of cadmium-faced steel bearings by dipping them in molten Cd at 800 to 850 °F. (102). Atmospheric concentrations varied from 0.06 to 0.68 milligrams of cadmium per cubic meter of air the average being 0.1 milligram per cubic meter. Cadmium was detected in the urine of all of the workmen. The symptoms noted were fatigue, dental trouble, and gastro-intestinal and respiratory complaints. Two of the men had low hemoglobin values, and chest x-rays were normal.

Princi surveyed a cadmium smelter over a period of three months, and carefully examined twenty workmen exposed six months

to twenty-two years to cadmium fumes and dusts (195). Average atmospheric concentrations as high as 31.30 milligrams of cadmium per cubic meter of air were found (the majority were 0.04 to 1.44 mgms. per cubic meter) and all of the workmen were exposed to at least twice the maximum allowable concentration. Leading questions elicited universal complaints, but physical examinations yielded no significant results. Definite evidence of absorption of cadmium was shown by analysis of the blood and urine of the workmen. Princi and Geever devised an experiment to simulate as far as possible the environmental conditions of the workers he had studied clinically (196). Twenty dogs were exposed for one year to an average concentration of 4 milligrams of cadmium per cubic meter of air. Ten dogs at a time were exposed to cadmium sulfide in one chamber, 10 were exposed to cadmium oxide in another, and 10 control animals were exposed to air in a third. Thorough laboratory studies and post mortem examinations of the exposed and control animals showed no significant differences except those involving analytical data on the absorption and excretion of cadmium.

McQueen presented a workman as a case of chronic pneumopathy due to cadmium. Increased lung markings interpreted as fibrosis, and electrocardiographic evidence of right axis deviation, were found in a welder who had repeated attacks of pulmonary difficulty after exposure to the fumes of cadmium oxide (166).

After study of the inconsistencies in the reports of occupational disease from exposure to cadmium, it appears advisable to exercise

caution in translating European experience to that in this country, except possibly in a qualitative sense. In order to explain the variance between Friberg's, Hardy's and Princi's findings, one must consider the differences in the material involved, from the aspect of particle size and the physical and chemical states of the compounds in question. Care must be exercised in planning industrial surveys and animal experimentation to appraise these and perhaps other variables.

CHAPTER X.

MAXIMUM ALLOWABLE CONCENTRATION

Prodan stated that no safe limit can be given for the concentration of cadmium in the atmosphere of industrial establishments, and that no extensive study pertinent to this has been made (199). As far as animal experimentation is concerned, the concentration necessary to produce direct toxic action has generally been far in excess of what would be permitted in industry except in the case of an accident. However, from estimations of the probable severity of the exposure to cadmium fumes which has accounted for some of the cases of acute fatal pulmonary involvement, the maximum allowable concentration of cadmium or its compounds in the air has been set at 1 milligram of cadmium per 10 cubic meters of air (1) (4) (5) (53) (200).

After having studied the effects upon dogs of prolonged inhalation of cadmium oxide or cadmium sulfide dusts in a concentration forty times that cited above, Princi has suggested that the tolerable concentration might be raised to ten times its present limit for these specific dusts without risk (196).

Friberg noted that the limit-value at present accepted in relation to acute cadmium pneumonitis ought to provide a satisfactory margin of safety to prevent the occurrence of chronic cadmium poisoning (76).

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