2

III. BIOLOGIC EFFECTS OF EXPOSURE

Metallic or elemental cadmium (Cd), which has atomic number 48 and atomic weight 112.40, has a silver-blue-white appearance. The use of cadmium as a protective coating relies on the resistance of the oxide to further oxidation.[8 (p 8)]

A brown aerosol of cadmium oxide is formed on ignition of cadmium vapor.[9] The metal has a boiling point of 765 C, or 1409 F,[10] and the vapor is readily formed under conditions which allow other metals to be worked. Cadmium will also melt at a low temperature of 321 C, or 610 F,[10] so sufficiently heated cadmium can flow to an area where volatilization can occur. Physical properties of cadmium are summarized in Table XIV-1.

The electrical conductivity of cadmium is less than that of silver or copper, but greater than that of iron. The addition of cadmium to copper, for example, reduces the conductance and the breakage and wear; this yields wire and electrical contacts of improved functional properties. Cadmium is also used in other alloys to produce a material which is more readily machined or melts at a lower temperature.[8 (pp 66-67)]

The principal cadmium ore is greenockite, cadmium sulfide,[9] but it is not a major source of metal production. Cadmium occurs in economically recoverable form only with the sulfide ores of other elements, particularly zinc.[9] Cadmium is obtained commercially as a byproduct in the refining of zinc, lead-zinc, and copper-lead-zinc ores and these are the primary sources of cadmium. Metallic cadmium was formerly prepared by fractional distillation, but this has increasingly been replaced by electrolytic methods.[9]

Estimated US consumption of cadmium (production plus imports) ranged from 4.2 to 6.9 million kilograms in the 1961-1970 period, with the highest consumption in 1969 and the lowest in 1970.[11] The average estimated annual consumption for the period 1961-1970 was 5.3 million kilograms and for the previous decade, 4.4 million kilograms. World production in 1970 was reported to be 35 million pounds, or almost 16 million kilograms.[4]

Electroplating is and has been the leading use for cadmium, consuming from 45 to 60% of the amount produced each year. About one million kilograms/year are used for stabilizers in plastics, and somewhat less than a million kilograms in pigments, with plastics a large consumer of the pigments.[12] One-quarter to one-half million kilograms of cadmium are used annually as an alloying agent in low melting-point brazing alloys, in copper for automobile radiators, in silver-cadmium electrical contacts, and in other metallurgical alloys. These 4 major categories account for 80-90% of the cadmium used, with the rest distributed among minor uses such as nickel-cadmium batteries, fungicides, photography, and television picture tubes.

Cadmium dusts, fumes, and mists are commonly present in some smelting processes involving zinc, copper, and lead as well as in specific processes for extracting cadmium.[13]

NIOSH estimates that 100,000 persons in the work force are potentially exposed to cadmium.

Extent of Exposure

Both the natural occurrence of cadmium and zinc in soil and the application of superphosphate fertilizers[14] result in detectable concentrations of cadmium in vegetables, land animals, and fresh water fish.[15-19] The cadmium content of sea water results in measurable cadmium concentrations in seafood. Cadmium has been reported to accumulate in certain animal tissues and to undergo biologic concentration in oysters.[20]

(a) Community Air

The National Air Sampling Network reported in 1966 and 1967 that 73% of the samples in 136 cities contained less than the minimum detectable concentration of 10 ng/cu m.[21] One study of particle size distribution gave a mass median

aerodynamic diameter (mmad) of 3.1 μm in Cincinnati, Ohio, and an estimated 10 μm in Fairfax, Ohio.[22] These limited data should probably be used with some caution.

(b) Water

Both surface waters[23] and drinking water[24] have been analyzed for cadmium. Analyses of 194 finished water supplies serving 139 municipalities showed a mean cadmium concentration of 0.008 ppm[24]; in 16% of the analyses, the Public Health Service drinking water standard of 0.01 ppm was exceeded. A more recent (1970) review[25] of 969 water systems indicated that 0.2% had concentrations in excess of the PHS drinking water standard of 10 μg/liter. Cadmium concentrations in drinking water can be increased when the water flows through either galvanized or polyvinyl chloride pipe.[15] Water containers soldered with silver-cadmium alloy may also pose a risk of contamination.

(c) Food

Dietary intake of cadmium has been reported by several investigators.[16-19,26-31] Duggan and Corneliussen[31] estimated a daily intake in 1969-70 of 2 μg Cd from dairy products, 3 from meat, fish, and poultry products, 10 from grains and cereals, 8 from potatoes, 3 from leafy vegetables, less than 1 from legumes, 1 from root vegetables, 2 from fruits, 1 from fats and shortening, 1 from sugar and adjuncts, and 5 from beverages. These estimates have not been adjusted for mass or caloric intake and are probably high for the average adult diet.

The UN Food and Agriculture Organization and World Health Organization[32] have estimated from limited results of total diet studies that dietary intake of cadmium varies according to country from 50 or less to 150 μg/day. On the assumption that renal damage may occur when cadmium concentrations in the renal cortex exceed 200 mg/kg wet weight, FAO/WHO proposed a provisional tolerable weekly intake of cadmium of 400-500 μg for each individual.

Another source of cadmium exposure is from tobacco products. Side-stream cigarette smoke was found to contain 0.4-0.7 μg cadmium/cigarette, while the mainstream cigarette smoke contained up to 0.1 μg cadmium/cigarette.[33]

Historical Reports

Bonnell[34] has commented that the occupational toxicity of cadmium was noted as early as 1858 by Sovet,[35] who reported a case of vomiting, cramps, and severe abdominal pain due largely, probably, to ingestion of cadmium carbonate used as a silver polish. Inhalation of the dust and swallowing of the material impacted on the mucosa of the upper respiratory tract may have contributed to the intoxication, which had the characteristics of acute poisoning by oral ingestion of cadmium rather than from inhalation of a cadmium-containing material. According to Christensen and Olson,[36] there were only 64 exposures reported in the literature up to 1945, about 15% of them fatal. However, Fairhall's[37] compilation of cadmium poisoning by ingestion cited 20 cases prior to 1940 and 689 in the period 1941-1946.

Bonnell[34] cited Stephens, in 1920, and Mancioli, in 1940, who described cases of chronic illness due to occupational exposure to cadmium. During World War II, the superimposition of nutritional deficiencies onto cadmium exposure was suggested by Nicaud and coworkers[38] as contributing to bone disease (osteomalacia) in cadmium workers in France. Cadmium is also believed to have been one causal factor in the development of Itai-Itai ("ouch-ouch") episodes in Japan.[1 (pp 137-161),39-41]

Effects on Humans

This section reviews the effects of cadmium on humans, mostly from evidence developed in epidemiologic studies, in terms of types of effects such as organs or organ systems affected. Many of these studies together with additional ones are reviewed, often in more detail, in the section on *Epidemiologic Studies*. In the latter section, there is more emphasis on population studies and on a correlation of human effects with airborne cadmium concentrations.

(a) Pulmonary Effects

(1) Acute Effects

Acute intoxication from exposure to cadmium oxide fumes in concentrations of at least several milligrams/cubic meter has a characteristic clinical picture.[42-45] Initially, there are virtually no symptoms; these usually appear 4-10 hours later, when dyspnea, cough, and not infrequently a feeling of constriction in the chest develop. On occasion, workers may complain of substernal chest pain or

a burning sensation in the chest that is accentuated by coughing. Some may also develop a flu-like syndrome characterized by shaky chills and myalgia localized in the back and limbs. Under this latter circumstance, the illness may be mistaken for metal-fume fever. In any event, acute pulmonary edema may develop within 24 hours. In such cases, physical examination reveals an acutely ill patient with rales heard on auscultation of the chest. Chest X-rays show bilateral pulmonary infiltrates suggestive of pulmonary edema. Pulmonary function testing, when performed, has shown a decreased forced vital capacity (FVC) and forced expiratory volume during the first second (FEV_1). In addition, there is evidence of abnormal gas exchange with a markedly reduced carbon monoxide diffusion capacity. The subsequent clinical course is unpredictable. In most cases, the symptoms resolve over the next week; but in approximately 20% of the people exposed, the dyspnea is progressive and may be associated with wheezing or hemoptysis. In cases that are progressive, death characteristically occurs within the first week after exposure. Chronic sequelae include pulmonary fibrosis and "honeycomb" lung. There are interstitial fibrosis, hypertrophy of circular muscle of the media and formation of longitudinal muscle in the intima of muscular pulmonary arteries, hypertrophy of the media of bronchial arteries, atheromas of the intima of elastic pulmonary arteries, thickening of the elastic lamina and pronounced proliferation of the fibroelastic component of the intima of pulmonary veins, and, occasionally, evidence of recanalized thrombi in both arteries or veins.[42,46] In addition, there has been evidence in two acutely intoxicated men of liver changes.[47,48]

The stages of acute pulmonary edema and acute interstitial pneumonia have been further studied by autopsy on humans exposed to cadmium by inhalation.[42,44,49,50] Townshend[43] in 1968 reported one case of pulmonary edema caused by acute cadmium poisoning which he followed over a period of 4 years. Serial pulmonary function tests showed improvement in lung function during the first 6 months. Four years later, carbon monoxide diffusion capacity was normal, but the forced vital capacity was less than 80% of the predicted value.

There are few data related to the acute dose-response relationship for cadmium in humans. However, estimates of lethal concentrations of 2,500,[51] 2,600,[44] and 2,900[52] mg-min/cu m have been made. These calculations have been based on some estimations or assumptions about the airborne concentrations of cadmium after fatal exposures to cadmium oxide, the pulmonary ventilation, the percentage of cadmium retained, and the concentrations of cadmium within the alveoli of the lungs. While some uncertainties exist, it seems reasonable to conclude that a probably lethal exposure to CdO fume consists of breathing about 5 mg/cu m during an 8-hour period (this is equivalent to 2,400 mg-min/cu m.) This concentration probably should not be considered to be the lowest which can give rise to fatal poisoning, however. A likely interpretation of data obtained through animal experimentation[49] indicates that a concentration of cadmium oxide fumes of about 1 mg/cu m inhaled during an 8-hour period may be dangerous for humans. Sufficient data are not available for making similar estimations for other forms of cadmium.

Blejer et al[47,48] described two cases of cadmium oxide fume poisoning in a silver brazing operation. The first man, exposed at a concentration thought to be above 1 mg Cd/cu m, became acutely ill and died about 3 days later. Post-mortem examination showed he had pulmonary edema, bronchial deepithelialization, extreme hemorrhagic congestion of the lungs, and a "nutmeg" liver. The brazing operation was moved outdoors, whereupon a second worker became ill. He was hospitalized, was administered oxygen under positive pressure, and recovered. Laboratory examinations showed elevated serum glutamic oxaloacetic transaminase (SGOT) and serum bilirubin, suggestive of hepatic damage. Reconstruction of the circumstances of the exposure led to several estimates of the breathing zone concentrations, viz, 10, 20, and 140 μg Cd/cu m. The worker was estimated to have been exposed for about 9⅔ hours, apparently over a period of 3 days.[48] The authors[47] suggested that simultaneous exposure to fumes of cadmium, copper, and zinc (probably as the oxides) and to fluoride gases such as hydrogen fluoride and carbonyl fluoride contributed to the intoxication in both cases.

(2) Chronic Effects

Chronic cadmium inhalation has been reported to cause pulmonary emphysema in man.[53-56] Friberg[57] investigated male workers exposed to cadmium oxide dust in an alkaline storage-battery

factory in Sweden. He found that shortness of breath was a common complaint, and pulmonary function studies revealed increased residual volume in relation to total lung capacity in workers exposed for an average of 20 years. Results from exercise studies were abnormal in many of these individuals. Baader[58] studied a worker who had become ill after being exposed to cadmium oxide dust in a battery factory. From clinical and X-ray evidence, he had "considerable emphysema." He died at the age of 39, apparently from right heart failure. Post-mortem examination showed bullous emphysema, fibroplastic peribronchitis and primary peribronchial interstitial pneumonia of all lobes of the lungs, and purulent bronchitis. From evidence of lesions of various ganglia, Baader suggested nerve tissue lesions as a contributing factor in pathogenesis of the obstructive lung disease. Lane and Campbell[53] described the development of emphysema within 2 years after the first exposure to cadmium. Kazantzis and associates[54] found no evidence of pulmonary abnormalities in workers exposed to cadmium sulfide dust 12-14 years. However, 4 of 6 of those employed for over 25 years had respiratory impairment, including 1 who died of emphysema. Holden[59] found on pulmonary function testing that 8 of 23 men exposed to cadmium 12-39 years had abnormalities suggestive of emphysema. This emphysema may be due to cadmium's inhibition of antitrypsin. Chowdhury and Louria[60] added 5-50 μg/ml Cd(II) to human plasma and found an inhibition of α_1-antitrypsin with a decrease in trypsin inhibitory capacity. Other metals tested, viz, Pb(II), Hg(II), Fe(II), Zn(II), and Ni(II), had little or no effect in concentrations equimolar with that of Cd(II).

Investigations utilizing pulmonary function testing[55] in both cadmium-exposed and control groups have suggested a higher incidence of obstructive lung disease among the exposed workers. There have been several other studies[61-64] in which no pulmonary effects from chronic cadmium intoxication were observed. At least some of these involved exposures at lower concentrations or for shorter exposure times.

(b) Renal Effects

The most common abnormality found in workers exposed to cadmium is proteinuria.[54,55,65] Friberg[55] found proteinuria in 81% of 43 workers exposed to cadmium for an average of 20 years in the alkaline storage battery industry and pointed out that the protein excreted was not the protein conventionally excreted after kidney injury, ie, it was of low molecular weight, about 20,000-30,000. Piscator[66] examined protein in urines of 79 cadmium workers, 55 of whom had been previously studied by Friberg.[55] He found an average excretion of protein of 50 mg/day in 10 healthy, unexposed subjects and 70-2,600 mg/day in cadmium workers. In men excreting more than 150 mg/day, the electrophoretic pattern of urine protein was characterized by a low albumin content and increased contents of α_2-, β-, and γ-globulins. In 75% of the men excreting more than 400 mg/day, there was a distinct β-globulin peak. In a few, he found a post-γ-globulin fraction. Cadmium workers also had a significantly higher concentration of γ-globulin and of protein-bound hexoses in serum than did unexposed workers. Potts[65] studied 70 battery workers and found proteinuria in 34% of those exposed 10-19 years, and 82% of workers exposed for over 30 years. Kazantzis and associates[54] noted that duration of exposure to cadmium was important in the development of proteinuria. They found no proteinuria in those exposed for less than 2 years; proteinuria was found in 3 of the 4 exposed for 12 to 14 years and in all of those exposed for 25 years or more. The proteinuria was characterized by excretion of urinary protein of low molecular weight, between 20,000 and 25,000. The pathogenesis of the proteinuria has not been fully delineated, but Vigliani[67] has suggested that protein may appear in the urine because tubular-bound cadmium interferes with the ability of the normal kidney to catabolize immunoglobulins and other proteins. Others[1 (pp 105-106), 68,69] believe that it results from a decreased reabsorption of normally present protein by the renal tubules. This latter view seems more likely, ie, it is likely that low molecular weight proteins appearing in the urine of persons intoxicated by cadmium would have been reabsorbed by the normal kidney, so that their appearance in urine is an early sign of renal dysfunction. However, as Friberg and associates[1 (p 112)] have suggested, both altered catabolism and altered reabsorption of proteins may exist.

There are few data on acute renal effects. Bilateral renal cortical necrosis has been reported in a fatal case.[44] The concentration of cadmium in the kidney was given as 5.7 ppm wet weight,

which seems not abnormally high in view of the report[70] that the concentrations of cadmium in renal cortices of people 50 years old from several different countries range from 15 to 50 μg/g; even higher concentrations of 60-125 μg/g have been found in kidneys from areas of Japan regarded as not polluted with cadmium.

Other reported evidence of disturbed renal tubular function besides proteinuria includes the finding of glucosuria,[54,61,71-74] amino aciduria,[54,71,75] decreased urine-concentrating ability,[55,71] and abnormalities in renal handling of uric acid, calcium, and phosphorus.[54,71] However, proteinuria can appear alone without the other above-mentioned changes, so that it may often be the earliest sign of renal dysfunction in cadmium intoxication.

A few instances of reduced glomerular filtration rates in cadmium workers have been reported.[55,71,76]

Renal stone formation has been reported in cadmium workers in Sweden.[55,76] Ahlmark and coworkers[76] found that 44% of a group of workers exposed to cadmium dust for more than 15 years had a history of renal stones. When examined, the stones were found to be composed mainly of calcium phosphate.[77] Other investigators have noted a high prevalence of renal stones in nonproteinuric workers.[71,77] Some workers had hypercalcinuria without proteinuria. The high incidence of kidney stones may be the result of disturbed excretion of calcium and phosphorus, as suggested by Axelsson.[77] Information from autopsy and biopsy material of kidneys is limited. Friberg et al[1] (pp 107-108) reviewed findings of several of their published studies and of unpublished studies of autopsy and biopsy material and concluded that the morphologic changes are confined mainly to the proximal tubules, with less evidence of effect in the glomeruli. Kidney cadmium levels were measured and, in general, tended to be lower when morphologic changes were present than when such changes were absent or minor. On this basis, it seems that renal damage following cadmium exposure may result in a decrease in the concentration of cadmium within the kidney. If this is so, a worker with significant renal damage may have a lower concentration of cadmium within his kidneys than one with only slight renal disturbance.[1] (p 107) There is support for this inference from experimental studies in animals, reviewed later.

(c) Olfactory Effects

A potential consequence of cadmium exposure is damage to the olfactory apparatus, which may result in total anosmia. As with lung and kidney damage, duration and concentration of exposure are probably important factors. Potts[65] found olfactory damage in 53-65% of workers exposed 10-29 years and in 91% of those exposed for more than 30 years. Thirty-seven percent of the 43 workers studied by Friberg[55] showed olfactory impairment. Adams and Crabtree[78] reported cases of hyposmia and anosmia among workers exposed to cadmium oxide dust as well as to nickel dust, in an alkaline-battery operation. A group of 106 battery workers were compared with 84 age-matched controls. Olfactory acuity was judged from each subject's evaluation of his own acuity and from a phenol smelling test. Battery workers reported significantly more anosmia (15% vs 0%) and did less well on the phenol smelling test (27% vs 5%). There was a positive correlation between proteinuria and anosmia; 17 workers with proteinuria also were anosmic. Examination of noses showed many cases of local irritation from dust, some submucosal fibrosis in mild cases of deficient olfactory acuity, and cases of ulceration, occasionally with dry crusting, in more advanced cases. Biopsy material from one case showed a mild nonspecific submucosal chronic inflammation with a few small loose focal accumulations of lymphocytes and a few widely scattered eosinophils. The authors attributed the anosmia to exposure to either cadmium or nickel, or to a mixture of the two. The population studied by Friberg[55] was also exposed to nickel. Potts[65] did not report nickel exposures, but the workers made batteries, so there were undoubtedly exposures to nickel dust, as well as to cadmium. However, Tsuji et al[79] reported that several workers exposed to cadmium in a zinc refinery, without evidence of exposure to nickel, had a so-called insensitiveness to smells.

(d) Hematopoietic System

Acute effects on the blood after respiratory exposure at a high concentration of cadmium have been noted both in humans and in animals.[44,80] Elevated hemoglobin in some human subjects may well have been the result of hemoconcentration from pulmonary edema.[44]

Anemia has been described in workers exposed for a long time to cadmium oxide dust and fume.[38,55,81] The anemia was usually moderate. In a group of workers exposed to cadmium 5-30 years,

Piscator, in unpublished studies reviewed by Friberg, Piscator, Nordberg, and Kjellstrom[1 (p 114)] reportedly found a significant correlation between high cadmium and low hemoglobin concentrations in blood. Bone marrow examinations of 19 cadmium-exposed workers revealed no pathologic changes.[55] Peripheral eosinophilia has been reported to occur in some workers.[38,55,62]

(e) Cardiovascular Effects

There are some controversial data on a possible role of cadmium in hypertension. Epidemiologic investigations of the general population have noted a positive correlation between cardiovascular disease and ambient cadmium levels[82]; no distinction was made in these studies between hypertensive and arteriosclerotic diseases. Perry and Schroeder[83] reported that hypertensive patients had increased urinary cadmium and, to a lesser extent, increased urinary manganese levels, as compared with normotensive individuals. In 187 adults studied at autopsy, the 17 suffering from hypertension had either higher concentrations of cadmium or higher cadmium-to-zinc ratios in their kidneys than the normotensive ones.[84] A correlation between cadmium level and mortality from cardiovascular disease in the United States has been reported[82] but cannot be considered to be indicative of a direct cause-effect relationship because the amount of cadmium absorbed from inhaled air during a day in the city of the US with the highest airborne cadmium concentration (Chicago) would be no more than 12% of the total intake. It could be as little as 1% of the total intake, depending on the composition of the diet. Schroeder[85] has commented on the association between hypertensive disease and cadmium and has suggested that the use of galvanized pipes to carry soft water, common many years ago, caused increased cadmium ingestion. On the other hand, workers exposed to cadmium were reported[55] not to have had a higher prevalence of hypertension than other groups.

No definitive relationship between cadmium levels in the kidney and cardiovascular disease has been demonstrated. For example, Morgan[86] determined the cadmium content of liver and kidney tissue from 80 individuals at autopsy and found no significant difference between controls and hypertensives. Also, no significant difference in the Cd/Zn ratio was found. Szadkowski et al[87] measured the excretion of cadmium in the urine and did not find any correlation with hypertension in a large series of individuals. On the other hand, Schroeder[84] reported that the ashed kidneys of a group of hypertensive US patients contained a mean of 4,220 ppm of cadmium whereas a group of ashed kidneys from presumably normotensive US people killed in accidents contained a mean of only 2,940 ppm of cadmium. In a later report,[88] but without additional information, Schroeder reiterated his belief that people dying of cardiovascular diseases have higher concentrations of cadmium in their kidneys than normotensive ones.

(f) Skeletal Effects

(1) Bone

Nicaud and associates[38] described a group of storage-battery workers exposed to cadmium oxide dust who had symptoms of back and extremity pain and difficulty in walking. Isolated cases of bone changes have also been reported in British cadmium workers.[34,71] In some of the workers described by Nicaud et al,[38] pseudofractures were noted on X-ray examination of the scapula, pelvis, femur, and tibia. The causes of these bone changes, similar or identical to those of osteomalacia, are not known. It may be that altered tubular function, with impaired renal tubular regulation of calcium/phosphorus balance, is primarily responsible for bone demineralization, as suggested by Friberg and associates.[1 (p 121)] But other factors, such as decreased gastrointestinal absorption of minerals, changes in Vitamin D activity, or changes in parathyroid activity or other hormonal effects have not been ruled out.

The Itai-Itai ("ouch-ouch") disease which occurred in certain areas of Japan was attributed to pollution of water and crops by industrial, cadmium-containing waste.[1 (pp 137-161),7,40,41,89] The disease is apparently osteomalacia and involves painful joints and bones, especially in the back and legs. Those affected were mostly multiparous, postmenopausal women. A nutritionally deficient (low calcium and protein) diet was perhaps an additional factor. Low estrogen levels may also have had some bearing on the osteoporosis seen in these cases.

(2) Teeth

The development of a yellow ring at the neck of the tooth was reported in early epidemiologic surveys in occupationally exposed persons and was at one time suggested to be a warning sign of chronic cadmium intoxication.[62,90] Whether this is because of surface absorption of cadmium, reaction with

salivary sulfur-containing substances, or through metabolism has not been established.

(g) Liver Effects

Friberg[55] reported abnormal liver function tests in workers exposed to cadmium oxide dust for a mean exposure time of 20 years in addition to kidney changes and emphysema discussed earlier. Other investigators[34,54] have commented that in contrast to the frequent, pronounced changes in renal function, gross changes in liver function are unusual findings in cadmium-exposed workers. It is not known at present to what extent liver abnormalities occur in workers exposed for long periods.

(h) Gonadal Effects

Little attention had been drawn to the effects of cadmium on gonads prior to the mid-1950's when Parizek[91] and Parizek and Zahor[92] described the destructive effects on testicular tissue in animals, since confirmed by others in testicular or ovarian tissues in several species of animals (see later discussion in *Animal Toxicity*). Favino and coworkers,[93] in their studies of fertility of 10 cadmium workers, revealed one case of impotency; abnormally low testosterone blood levels were found only in this man. Smith et al[94] found high levels of cadmium in the testes of men exposed to cadmium fume. They also reported microscopic changes (depression of maturation) in the testes at autopsy, but, because of the relatively small mitotic activity of spermatocytes, they ascribed this depression to terminal illness. Further studies are necessary before any final conclusion can be drawn concerning the possible effects of cadmium on gonadal function in persons exposed to cadmium. It should be noted that the data on gonadal changes developed in animals were all obtained from acute animal experiments, and corresponding doses in man would represent an unusually high, conceivably lethal, exposure.

(i) Teratology

The question of teratogenicity of cadmium has not been thoroughly examined in man but has been investigated experimentally in animals (see discussion on *Animal Toxicity*). Tsvetkova[95] reported that children born of women occupationally exposed to cadmium at high concentrations weighed less than children of a group of women considered to be unexposed controls. There were only 20 controls, and no mention was made of whether consideration was given to other possible determinants of birth weight, such as maternal weight, number of previous pregnancies, socioeconomic conditions, prenatal nutrition, maternal illnesses, and smoking habits. Four of the children born to these cadmium workers had signs of rickets, one had retarded eruption of teeth, and two had undescribed dental troubles. Piscator (written communication, December 1975) has interpreted these changes as the result of fetal zinc deficiency as the consequence of zinc retention by the cadmium-exposed mothers. This point has been discussed in more detail by Friberg and coauthors,[1 (p 129)] who have suggested, in a review of reproductive changes in experimental animals, that teratogenic effects are the consequence of this zinc deficiency in the fetus because of zinc retention by the mother.

(j) Carcinogenesis

Surveys of cadmium workers have indicated that carcinoma of the prostate may be found more frequently in these men than in the general population.[65,96] Prostatic cancer was cited as the cause of 3 of 8 deaths in a survey by Potts[65] of 74 men with more than 10 years exposure in a nickel-cadmium battery factory. Kipling and Waterhouse[96] surveyed a group of 248 workers exposed to cadmium oxide for a minimum of one year. There were 4 deaths from prostate cancer, significantly more than expected. Cancer rates of the bronchus, of the bladder, of the testis, as well as cancer rates at all sites, were not significantly different from the expected rates. According to a communication from Kipling to the International Agency for Research on Cancer (IARC),[4] 3 of these cases of prostate cancer were also 3 of Potts' cases.[65] Kipling and Waterhouse cautioned against drawing conclusions until further studies had been undertaken. They indicated that inquiries of cadmium users had been initiated and that ". . . so far [these] have proved negative . . ." but gave no details.

Adams et al,[71] in a study of the same plant previously described by Potts,[65] reported two cases of prostate cancer among 12 deaths occurring during the 12-year period of study. One prostate cancer death was clearly not in the group reported by Potts, but the other case may also have been one of Potts' cases. Discrepancies in specific details about this plant in the two studies make close comparison of their data impractical.

Lemen et al[97] studied causes of death in 92 workers, from a cohort of 292 in a cadmium smelter,

who had died during the period 1940-1974. Four cases of prostate cancer were found, compared to 1.15 expected on the basis of mortality rates for the US white male population adjusted for age and calendar year. One case was a 64-year old worker who died in 1951; all others were 71 years of age or older. When only those workers who had lived for at least 20 years after their first exposures to cadmium were considered, 0.88 deaths would have been expected vs the 4 observed. The difference between these two figures was said to be significant at the 0.05 level whereas that between the 1.15 deaths expected in the entire cohort and the 4 observed was not significant. These employees were also exposed to arsenic at low concentrations, as is discussed later in *Epidemiologic Studies*.

These studies[65,71,96,97] suggest that occupational exposure to cadmium oxide may increase the risk of prostate cancer in man, but the numbers of men developing prostate cancer were small. In addition, as mentioned above, two, and possibly three, of these studies are not independent ones.

Of the 74 men exposed for 10 or more years at various concentrations of cadmium oxide dust in the production of alkaline batteries reported by Potts[65] in 1965, 8 died. Three of these deaths resulted from carcinoma of the prostate, one from carcinoma of the bronchus, and one from carcinomatosis. Details of the post-mortem examination or the bases for diagnosis of prostate cancer were not given. The age range of these men (65-75) is probably relevant, also.

In 1949, concentrations of cadmium in the air of plate-making and assembly shops ranged from 0.6 to 2.8 mg/cu m, and in the electrode department concentrations as high as 236 mg/cu m were reported. Installation of local exhaust ventilation in 1950 reduced concentrations below 0.5 mg/cu m in most parts of the factory. In 1956, further major improvements reduced levels to 0.1 mg/cu m at most points.

Lemen et al[97] also found a significant excess of malignant tumors of the respiratory tract (12 cases observed compared to 5.11 expected). Eight of these were characterized histologically; one was an undifferentiated small-cell tumor, three were anaplastic, three were squamous-cell carcinomas, and one was an oat-cell carcinoma. While a more local comparison group might have been better, the excess mortality due to lung cancer among the people exposed to cadmium probably would not have been decreased by this procedure. The authors also noted a significant excess in total neoplasms (27 observed vs 17.51 expected).

No excess of any form of cancer was detected in 3 other studies[1 (p 132),98,99] of men occupationally exposed to cadmium, but sample size of each study was small.

A geographical correlation between the frequency of prostate cancer and the amount of suspended particulate air pollution in various communities was reported in 1969 by Winkelstein and Kantor[100] with the suggestion by the authors that cadmium exposure might be involved in the association, but measurements of cadmium in the ambient air were not performed. Smoking histories and socioeconomic factors might also be relevant in evaluating any such association.

In an epidemiologic study of cancer in persons exposed to cadmium, Kolonel[101] compared the incidences of several types of cancer in persons having an inferred occupational history of cadmium work with those in a control population. The basis for inferring a history of occupational exposure to cadmium was indirect, from job classification information revealed in an interview on admission to a cancer research hospital. The test and control populations were all white males, aged 50-79 years, and were all referred to the Roswell Park Memorial Hospital in Buffalo, New York, because of suspected neoplastic disease. One group of controls were those found to have nonneoplastic gastrointestinal disease; a second group of controls were those found to have colon cancer. Kolonel found a significant increase in renal cancer, and a nonsignificant increase in pancreatic cancer among the patients thought to have been exposed to cadmium. He anticipated an increased incidence of prostatic cancer, but found none. He looked for a similar increase in cancer among those exposed to cadmium from dietary intake of cadmium or from smoking, but the association was questionable. In view of the deficiencies in his data on occupational histories, conclusions from this study are uncertain.

In a later publication based on these data, Kolonel[102] commented on evidence of a synergistic relationship between exposure to cadmium and cigarette smoking. In the belief that the greater than additive effect could not be accounted for by the increased cadmium exposure, he suggested that some other component of cigarette smoke

contributed to the synergistic effect. However, in addition to the uncertain evidence commented on above on occupational exposure of the subjects to cadmium, his assumptions about exposure concentrations may have been inaccurate.

In a 1969 letter to the editor of The Lancet, Holden[98] mentioned having studied 42 cadmium workers exposed 2-40 years, 6 of them for more than 10 years, at concentrations of cadmium greater than 4 mg/cu m and the rest exposed at an average concentration of 0.1 mg/cu m. There had been one case of carcinoma of the prostate and one of carcinoma of the bronchus in the group. The point of his letter seemed to be to refute suggestions of hypertension among cadmium workers. Although some of the men had proteinuria and emphysema, none of them had a blood pressure greater than 140/90 mm Hg, including a man of 73 years. He also commented that "none is apparently sterile" and that there was no increased incidence of coronary artery disease. Unfortunately, no details were given in this short communication. It is inferred that he was discussing the same population he previously commented on in a 1965 report[59] of men working in a factory making cadmium-copper alloys for trolley wires.

It has been found by Morgan[103] that the cadmium concentrations in blood and tissues were significantly increased in some patients with bronchogenic carcinoma but, as the author commented, whether this elevated cadmium level was the cause or the consequence of the cancer, or was unrelated thereto, is not known. It is possible that the elevated cadmium concentrations and lung cancer were both related to smoking, cigarette smoke usually containing higher cadmium concentrations than the ambient air.

Malcolm,[104] however, came to the conclusion that cadmium is unlikely to be a cause of prostate carcinoma, even though the data available in 1972 suggested this possibility. Malcolm reviewed some then unpublished experiments on rodents conducted at a British cancer research institute and concluded that cadmium is unlikely to be a cause of prostatic or other internal cancer in man. These animal experiments have subsequently been reported by Levy and associates[105-107] and are reviewed in the section on *Animal Toxicity*.

(k) Other Effects of Cadmium

Acute symptoms have occurred in subjects eating cadmium-contaminated food or beverage, according to a review by Fairhall[37] and a report by Lufkin and Hodges.[108] Gastrointestinal manifestations characteristically occurred ¼ to 5 hours after ingestion and were often marked by increased salivation, nausea and vomiting, abdominal pain, diarrhea, and tenesmus. Cadmium has also caused food poisoning from the use of a cadmium-plated refrigerator shelf as a grill to hold steak over charcoal for broiling.[109] A 2-year old child with encephalopathy originally attributed to lead was found to have a very high cadmium concentration of 710 μg/liter in his urine. It was found that the child was fond of licking freshly polished white shoes (polish solution containing 275 μg Cd/100 ml), occasionally ate silver polish (185 μg/100 ml), and ate red paint (500 mg/100 g) from his crib.[110]

Bui et al[111] analyzed the chromosomes in lymphocytes from Swedish battery-factory workers and Itai-Itai patients from Japan, together with controls from Sweden and Japan, and found no significant differences in chromosomal aberrations between cadmium-exposed people and their respective controls. However, sizes of populations studied were small in each case. Mean frequencies of aberrations ranged from 2.0% in Swedish battery workers to 6.7% in Itai-Itai patients. Shiraishi and coworkers[112,113] cultured cadmium sulfide with human leukocyte cells and examined leukocyte chromosomes from 7 Itai-Itai patients, and in each case found an increased incidence of chromosomal aberrations over controls. The rate of abnormalities in the Itai-Itai patients[112] ranged from 14 to 64% of the 50 cells examined, much higher than the rate found by Bui et al.[111] In view of the possible variety of etiologic factors in Itai-Itai disease and the lack of confirmation of the results of a procedure as methodologically delicate as karyotyping, it is difficult to assess these results until additional studies have been conducted. DeKnudt and Leonard[114] found an increased incidence of aberrations in chromosomes cultured from leucocytes of workers exposed to cadmium, lead, and zinc. These changes consisted of chromatid changes (gaps, breaks, deletions, and exchanges) and chromosome anomalies (gaps, fragments, disturbances of spiralization, translocations, centric rings, and dicentrics), usually with only one structural aberration in each abnormal metaphase. The 35 workers, aged 19-58 years, were divided into two groups according to type

and duration of exposure. The first group, consisting of 23 workers, had been exposed to high concentrations of lead and of cadmium for an average of 12 years; the second group, consisting of 12 workers, worked in a rolling mill for an average of 11 years and were exposed mostly to zinc, but with exposures to lower concentrations of lead and cadmium, also. The two exposed groups had statistically significantly higher incidences of anomalies than controls, but the two exposed groups did not differ significantly from each other. As the authors commented, there are inherent difficulties in interpreting studies of such mixed exposures. They noted that seven of the workers in the first exposed group had previously worked in coal mines and that these workers had a rate of severe aberrations (1.35%) nearly twice that of the other members of the same group (0.71%).

There has been some interest in pancreatic function, since high concentrations of cadmium have been found in the pancreata of autopsied cadmium workers.[94,115] Little investigation, however, has been conducted in this field (see *Animal Toxicity*).

High cadmium levels have also been found in thyroids from autopsy material.[115]

Vorob'yeva[116] studied changes in the chronaxies of cutaneous sensory and optical nerves and skeletal muscle in 160 workers exposed to cadmium oxide and compared the results with what she described as normal values cited in the literature and with standards established from studies of 70 workers in contact with otherwise undescribed toxic substances. There had been complaints of headache, dizziness, irritability, depression, and sleep disturbances. Cadmium concentrations in the workroom air varied from 0.1 to 24 mg/cu m, but sampling and analytical methods were not described. The type of industrial operation or other information on possible contributions to observed reactions by other contaminants was not discussed. There was a prolongation of the chronaxy of cutaneous nerves in many cases as well as in optical chronaxy; the changes were proportional to the years of exposure to cadmium. Motor chronaxy changes in 37 workers were variable; in workers with less than 5 years of work experience, muscle chronaxy was reduced, while in workers with 5 years or more of exposure to cadmium, it was increased. Vorob'yeva concluded that cadmium exposure caused central nervous system changes, but suggested the need for further research to resolve questions about the effect of cadmium oxide on the brain. She commented that the changes in the functional state of the cerebral cortex occurred significantly earlier than other signs of cadmium poisoning, but did not describe what signs of poisoning were being compared and gave no supporting data. She presented no actual evidence of effects on the central nervous system. It is not clear how to assess the significance of these findings to a recommended standard for cadmium.

Cigarette tobacco has been reported[117] to contain considerable cadmium (about 30-40 μg/20 cigarettes), about 30% of which is trapped in the filter or remains in the cigarette residual. Approximately 2-2.4 μg/20 cigarettes is inhaled.[33] Approximately 70% escapes into the smoke.[117] Lewis and colleagues[118] found that, of the cases studied, those who died with a diagnosis of bronchitis or emphysema or both had elevated liver cadmium concentrations. Unfortunately, data were not available in this study on occupation or history of cigarette smoking. Another study[103] has reported increased cadmium levels in serum, liver, and kidneys of patients dying with bronchogenic carcinoma.

In a study[119] of 5 people, it was possible to establish that the urinary route of excretion predominates markedly over the gastrointestinal route. Five people were given oral doses of ^{115}Cd-labeled cadmium nitrate, and the radioactivity in urine and feces was followed for 47 days. Urinary excretion of cadmium has been reported in a number of studies.[87,120,121] These studies indicate that the daily urinary excretion in the general adult population is approximately 1-2 μg. Even if fecal excretion also were 1-2 μg, total daily excretion would probably be somewhat less than daily assimilation from food, water, air, and cigarettes, in the case of smokers. This is consistent with the indications from autopsy data that for most of their lives people are not in cadmium balance.[1 (pp 59-65)]

The urinary excretion of cadmium increases markedly with the onset of proteinuria in high cadmium exposure.[71] This is consistent with animal data.[122,123] In man, the magnitude of increased excretion of cadmium in association with proteinuria is quite variable, but may be more than 100 times normal.[71,124] This probably represents an actual mobilization of cadmium stores in the kidney

(and possibly elsewhere in the body), since the kidney cadmium concentration of exposed workers with renal damage is appreciably lower than the concentration in exposed workers who do not have renal damage.[1 (pp 107-08), 34,94]

Epidemiologic Studies

One of the earliest attempts in the United States to study the effects of continued exposure to cadmium in industrial workers was made by Hardy and Skinner[81] in 1947. They reported the clinical histories of five men (ages 28-53) engaged 4-8 years in the manufacture of cadmium-faced bearings. Atmospheric cadmium fume concentrations in the workplace ranged from 0.06 to 0.68 mg/cu m. Cadmium concentrations in urines studied on one occasion were less than 50 μg/liter in all cases. Symptoms reported by these men were varying degrees of fatigue, gastrointestinal upset, and respiratory problems, eg, coughing, sternal pain, and throat irritation, especially on damp days. Four of the five men who claimed to have had good teeth prior to employment had developed dental caries. Two cases had reduced concentrations of blood hemoglobin (70% on Sahli scale). In all five men routine X-ray and urinalysis were normal. The authors suggested that the reported symptoms were due to prolonged cadmium exposure.

Princi[62] studied 20 cadmium smelter workers exposed at atmospheric concentrations of cadmium fumes varying from 0.2 to 6.6 mg/cu m and cadmium dusts (mainly CdS) ranging from 0.04 to 19.0 mg/cu m, in one case as high as 31.3 mg/cu m for 2-3 hours/day. Exposure times varied from 6 months to 22 years (median 4.5 years). Princi noted that personal protective measures were not adhered to. The workers were examined at monthly intervals for three months. The most characteristic finding was a yellow ring at the base of the teeth in 9 of 15 men with natural teeth. From the data presented, degree and extent of coloration did not seem to be related to exposure time, except that the yellow ring did occur more frequently in workers exposed for more than two years. Hematologic tests revealed no significant changes, although the author stated that the hemoglobin and red blood cell counts were slightly lower than expected for that altitude (Colorado, about 5,300 feet). Princi found no evidence of a significant increase above normal of chest complaints; X-ray examinations disclosed no pneumonitis, pulmonary fibrosis, or skeletal changes in long bones. Absorption of cadmium was demonstrated in most cases by levels of blood cadmium (10-40 μg/100 g) and urinary cadmium (25-125 μg/liter). No correlation could be found between blood and urinary values or time of exposure. Renal studies were not reported, although the author mentioned that there were no complaints of genitourinary dysfunction. He found no proteinuria, but his method of detecting protein (boiling test), according to a later communication discussed by Friberg et al,[1 (p 103)] probably would not have detected cadmium-induced proteinuria.

Lemen et al[97] studied the mortality experience between 1940 and 1974 in the same plant studied by Princi.[62] In this later report, the plant was described as producing cadmium metal of high purity by electrolysis followed by melting and distillation in the absence of oxygen. Cadmium oxide was produced by melting the metal in the presence of oxygen and capturing the fume. Cadmium sulfide was produced intermittently by dissolving the metal in sulfuric acid and passing hydrogen sulfide through the filtrate. Princi[62] had previously found environmental concentrations of cadmium fume of from 0.04 to 6.6 mg/cu m and of cadmium dust of 17.23 mg/cu m, with one man being exposed for several hours/day at a concentration of 31.3 mg/cu m. An industrial hygiene survey in 1973 reported by Lemen et al[97] found that most air samples contained less than 1 mg/cu m of cadmium, but some samples ranged up to 24 mg/cu m. Two samples in one department contained 74.8-90.3 μg/cu m of cadmium and 0.3-1.1 μg/cu m of arsenic. A sample taken in another department showed 1.1 mg/cu m of cadmium and 1.4 μg/cu m of arsenic. Prior to initial roasting, bulk samples of preprocessed ore contained 70% cadmium, 6% zinc, 4.3% lead, and 0.3% arsenic; after initial roasting the calcined ore contained 42.2% cadmium, 3.53% zinc, 0% lead, and 0.02% arsenic. Further refining steps reduced impurities further, so that exposure to metals other than cadmium was "considered insignificant." Since a respirator program was in effect, worker exposures were probably less than would be expected from the environmental levels reported. The authors reviewed the mortality experience of a group of 292 white male workers, comparing it with corresponding age-calendar year

statistics for the US white male population. As was discussed in *Effects on Humans*, there was an excess of total malignant neoplasms (27 observed vs 17.51 expected), respiratory system tumors (12 vs 5.11), and prostate tumors (4 vs 1.15 for the entire cohort and 4 vs 0.88 for those who had lived for at least 20 years after their first exposure to cadmium). In addition, there was a nonsignificant excess of deaths from nonmalignant respiratory disease (8 vs 5.04) but a significant decrease in deaths from heart disease (24 vs 43.52), not accounted for by the excess in neoplasms. Total deaths (92) were slightly less than expected (99.32).

In 1950, Friberg[55] reported a comprehensive investigation of 58 workers in a Swedish nickel-cadmium battery factory. The workers were divided into two groups based on their periods of employment. He compared 43 workers (Group I) employed for an average of 20 years, ranging from 9 to 34 years, with 15 workers (Group II) who had worked an average of 2 years, varying from 1 to 4 years. Mean age of workers in Group I was 44 (30-74) as compared to 35 (25-57) in Group II. For controls, Friberg studied age-matched groups of sawmill workers, ie, workers not exposed to cadmium. In the battery factory, the workers were exposed to cadmium (Cd0), iron, nickel, and graphite dusts. Air analysis performed at the start of the investigation in 1946 (prior to technical improvements) was considered representative of the workers' exposure in prior years. The amount of cadmium in the dust ranged from 3 to 15 mg/cu m, and 95% of the cadmium-iron dust consisted of particles of less than 5 μm. After protective measures had been installed, factory air analyses (1947, 1948) showed decreased cadmium concentrations (0.2-1.9 mg/cu m) in various plant areas.

The men in Group I complained of more fatigue, shortness of breath, coughing, impaired sense of smell, and sensations of dryness in the mouth than did those in Group II. On examination, 16 of the 43 workers (37%) in Group I had impaired olfactory sense (14 had total anosmia) vs 1 of 15 (6%) in Group II. No correlation of anosmia with atrophic changes in the nasal mucous membranes was found. Atrophic changes were observed in 10 out of 19 cases examined. Of these 10 cases, 6 had anosmia while 4 had normal olfactory sense. Mean values for respiratory function tests (ie, spirometric examination of various lung volume fractions and ventilation ratios) for both Groups I and II were not significantly different from the means of the control groups except for, in Group I, a significant increase in residual capacity and residual quotient and a possibly significant decrease in vital capacity. Considering individual differences, Friberg observed a significant increase in the residual quotients (residual capacity/total capacity) of 12 out of 42 workers (29%) in Group I when compared to matched controls. He considered the increased residual quotient in these cases to be "chiefly caused by a pulmonary emphysema, in the absence of other conceivable causes." In discussing etiologic aspects, he pointed out the possibility that exposure of the battery workers to the other substances found in factory air analyses, particularly nickel, may have contributed to the pulmonary emphysema. His experiments on rabbits demonstrated to him that both cadmium-iron dust and nickel-graphite dust may give rise to emphysematous lung changes, although more pronounced with much smaller concentrations of cadmium in comparison with nickel.

Examination of men in Groups I and II for cardiovascular function based on blood pressure, heart X-ray, and electrocardiogram demonstrated no significant differences from their age-matched controls. Renal function tests carried out in 18 workers of Group I showed a reduction in average urine concentrating capacity (in 9 cases urine specific gravity was 1.019 or less) and a decrease in average inulin clearance (90.3 $\pm$ 5.6 ml/min) as compared to normal values (124.1 $\pm$ 2.2 ml/min) in Swedish males. Precipitation tests with trichloroacetic acid for urinary protein gave positive results in 35 of the 43 workers (81%) in Group I vs 0% in Group II. Further examination of the urinary protein by electrophoretic mobility (9 cases) and ultracentrifugal analysis (2 cases) demonstrated a protein component with lower mobility and molecular weight (20,000-30,000) than ordinary urinary proteins. In this study, proteinuria was found only in the group of workers employed for longer than 9 years (average 20 years). There was a tendency for the renal function tests to correlate with proteinuria. In 12 cases (23%) with relatively persistent proteinuria, the inulin clearance and urine concentration tests showed the lowest mean values. Friberg,[55] however, was not then of the opinion that proteinuria is a result of kidney injury, but rather suggested the possibili-

ty that the kidney injury was secondary to the excretion of the protein component. On examination of the workers' medical records since their time of employment, Friberg found that 8 of the 43 workers in Group I had a history of proteinuria and 5 others were treated for kidney stones. In contrast, none of the workers in Group II had a history of proteinuria and only one had occasionally had pains described as resembling those from kidney stones.

Hematologic tests revealed slightly lower mean values for hemoglobin (86 vs 92) and red cell counts (4.6 vs 5.0) for Group I compared to Group II. However, this could be due to the difference in mean age between the groups (44 vs 35). The average erythrocyte sedimentation rate was moderately increased in both groups, being more marked in Group I (23.5 mm/hour) than in Group II (14.3 mm/hour). Dental changes consisting of a yellow coloring at the base of the teeth, similar to those found by Princi[62] and Barthelemy and Moline, [90] were observed in 12 of 37 workers with natural teeth in both groups and could not be correlated with the use of nicotine. Consistent with Princi's findings, [62] no skeletal changes of the type described by Nicaud et al[38] were found on X-ray examination. Bicycle ergometer testing showed lower working capacity in both Group I and Group II, compared with age-matched controls, but Friberg considered the differences in Group II to be insignificant, whereas Group I results seemed to correlate with higher residual quotients found in pulmonary tests, and on this basis were consistent with "lung changes in the form of an emphysema."

This important study demonstrated the ability of cadmium to cause renal damage and emphysema. It also pointed the way to subsequent proof of the importance of low molecular weight proteins in the urine in detecting effects of cadmium in humans.

Baader[125] reported that 8 of 11 battery workers exposed to cadmium had partial or complete loss of sense of smell. Six of the eight had low molecular weight protein in their urines. Ten of the 11 workers had emphysema. Two had warts, one in the nostril, the other in the epiglottis. Baader[58] commented that women workers were more sensitive to cadmium exposure than male workers, and that blond women were especially sensitive. He gave no details or supporting data, other than to comment that blond women were susceptible to vomiting and fainting, from which one might question whether inhalation of cadmium compounds was the cause.

Bonnell[34] examined 100 workers exposed to cadmium oxide fumes and 104 controls with similar age distribution in 2 British copper-cadmium alloy factories. Nineteen of the 100 exposed workers had emphysema, proteinuria, or both, while 3 of the control group had either emphysema or proteinuria. All 19 men with signs and symptoms had been exposed to cadmium for more than 5 years and 13 of them for more than 15 years. Four additional workers required hospitalization because of shortness of breath. Significant differences in results from certain respiratory function tests were found by Kazantzis[126] between the exposed and the control groups in these same factories, particularly in the time constant of the expiratory forced vital capacity curve. In the group of these workers exposed to cadmium for more than 10 years, Buxton[127] found that the volume of residual air and the residual quotient (ie, residual air as expressed as a percentage of the total lung volume) were both significantly increased. This finding is consistent with Friberg's.[55] The same two factories were reexamined 4 years later in 1957,[72] and 83 of the original 100 men were still working. An additional 24 workers with emphysema or proteinuria, or both, were found, making a total of 43 (43%).

King[128] conducted environmental surveys of these same two plants. Area samples were filtered on dextrose pads and analyzed polarographically after treatment by hydrochloric acid to separate cadmium from copper. Particle sizes in all samples tested were mostly less than 0.5 μm by weight analysis. Air cadmium concentrations in one factory 8 feet from the furnaces varied from 13 to 89 μg/cu m, and in the other 18 feet from the furnaces they were 4-132 μg/cu m in one shop and 1-270 μg/cu m in another shop.

In addition, there were undoubtedly exposures at much higher concentrations, based on the occasional presence of visible emissions of brown (CdO) fumes. King felt that because of variations in concentrations observed and because of significant improvements in ventilation introduced before his survey it was not possible to draw a valid relationship between concentration and disease incidence.

Smith and coworkers[129] in 1955, Potts[65] in 1965, Adams and Crabtree[78] in 1961, and Adams and associates[71] in 1969 have reported successive studies in one factory (originally two factories) where nickel-cadmium storage batteries had been manufactured under the same medical supervision since 1934. In the present factory, annual medical and regular environmental evaluations have been carried on since 1957. Smith et al[129] developed a method for the quantitative measurement of cadmium in urine in order to study the relationship between cadmium excretion and proteinuria in these factory workers. A total of 120 employees exposed to cadmium oxide dust were compared to a control group of 100 workers of similar age without any known cadmium exposure. Proteinuria was observed in 20% of the exposed workers as compared with 5% of the control group. The normal range of urinary cadmium was found to be 0-20 μg/liter, while the range in workers exposed to cadmium was 10-580 μg/liter. Proteinuria did not appear to be related to urinary cadmium. Potts[65] reported 44% of 70 men (aged 37-73) with over 10 years (maximum 40 years) of cadmium exposure to have proteinuria, and 64% to have some degree of anosmia. Apart from proteinuria, there was no evidence of renal damage by clinical examination of two workers or post-mortem examination of two men who had proteinuria for many years. He investigated deaths of past workers and found 8 deaths out of 74 men with at least 10 years' exposure. Five of these deaths were from cancer, of which three were prostatic (discussed earlier in *Effects on Humans*). However, the source of information as to the cause of death was not stated (ie, whether from a post-mortem examination or the death certificate). Adams et al[71] found that 14 of 100 men then working had proteinuria, and 14 of 100 had anosmia (five with proteinuria). Although the average FEV_1 for the group was significantly reduced (p less than 0.001) from normal, 22 of 27 men examined were within normal range. In a previous study by Adams and Crabtree[78] in 1961, the incidence of proteinuria was 17 of 106 exposed workers, indicating minor change over the years. Air samples taken at regular intervals and analyzed for cadmium in the years 1957-1967 showed concentrations that ranged from 0.05 to 0.5 mg/cu m in assembly areas, 0.05 to 1.0 mg/cu m in platemaking areas, and 0.2 to over 5.0 mg/cu m in the negative electrode material department. Marked decreases in airborne cadmium were noted in 1950 and 1956, after which concentrations were fairly stable until 1967, when new facilities for platemaking reduced the airborne cadmium levels in that operation to less than 0.1 mg/cu m.[65] Dust measurements showed approximately 20% to be in the respirable size range.[71]

Kazantzis and colleagues[54] reported on a group of 12 workers employed in making cadmium sulfide pigments (cadmium zinc sulfide or cadmium selenosulfide) and cadmium oxide. Of the 12 workers, 6 had worked 25-31 years with cadmium. Of these 6, all had proteinuria, 3 had mild respiratory symptoms such as breathlessness on exertion, and one had recently died from emphysema. There was some impairment in respiratory function tests, but no abnormal physical signs were detected. The 4 men with 12-14 years' exposure without clinical proteinuria still were excreting protein, electrophoretically similar to that excreted by the men with clinical proteinuria. The urinary protein had a higher than normal amount of globulin components, which was suggestive to the author of nonspecific tubular malfunction, but he also observed some glomerular fibrosis in two kidney biopsies and in one autopsy. Only 3 workers who had been exposed less than 2 years showed no abnormalities. In 4 of the 12 workers, there was increased urinary excretion of calcium and, in 3 of 8 men with proteinuria, there were glycosuria, aminoaciduria, and decreased water reabsorption. The authors found no yellow discoloration of teeth. They found no definite evidence of sterility based on fertility histories. One worker had progressive loss of ability to smell and another had a perforated and ulcerated nasal septum, thought by the authors[54] to be possibly unrelated to cadmium exposures. No environmental measurements were reported.

Ahlmark and associates[76] reported on 110 cadmium-exposed workers and 22 controls. Several test measurements showed that kidney functions were reduced with long exposure. Urinary protein excretion increased regularly with length of exposure from 100 mg/24 hours (ranging from 50 to 170) at less than 5 years to 955 (ranging from 370 to 1800) mg/24 hours at 31 years and over. The incidence of kidney stones increased from 9.1% in the controls to 12.3% in the 6- to 10-year exposed group and to 43.6% in the greater than 15-year ex-

posure group. No environmental measurements were reported from this nickel-cadmium storage battery plant, whose workers had been previously studied by Friberg.[55]

Suzuki and coworkers[61] reported on a polyvinyl chloride-film plant in which lead and cadmium stearates were used as stabilizers. In 1963, 27 exposed and 7 nonexposed workers were examined. The risk due to lead was presumed by the authors to be negligible. Examination of their data largely supports this presumption; urinary coproporphyrin levels were not increased in exposed workers compared with that of controls, and most of the urinary lead levels were below 200 μg/liter. Although airborne lead concentrations were higher than those of cadmium, particle sizes of lead compounds were larger than those of the cadmium stearate. Eight of 17 workers reexamined in 1964 had increases in degree of urinary protein excretion by the trichloracetic acid (TCA) test. The numbers that were positive were significantly greater in the exposed workers than in the controls in the 1964 tests. Statistically, this might possibly have been due in part to the larger number of controls and therefore to a more normal distribution curve which is apparent in the 1964 data (24 controls vs 7 controls in 1963). These increases were demonstrated by all three methods of testing for urinary protein, namely 25% TCA test, sulfosalicylic acid test, and boiling test, with TCA being the most, and boiling the least, sensitive. No significant differences in respiratory function were found between exposed and control groups. No significant differences in mean urinary cadmium levels were demonstrated, though there were a few slightly higher urinary cadmium levels in the exposed group. No differences in olfactory acuity between the two groups were shown. Yellow discoloration of the teeth of exposed workers was looked for but not found. Liver function, as evidenced by the results of thymol turbidity and serum cholesterol tests, was not significantly different in exposed and control groups. Similarly, there were no significant differences in hemoglobin, urine specific gravity, or urine occult blood, but there was a slight increase in urine sugar (by test tape) in exposed workers as opposed to controls. Both groups had less than 0.05% of cells with basophilic stippling. However, the average age of the workers in this study was lower and work experience was less than that of work populations described in US, UK, and European studies. Workroom air was sampled by impingement in 10% nitric acid at a sampling rate of 20 liters/minute. Lead and cadmium in the samples were analyzed by appropriate modifications of dithizone colorimetry. Each work operation, involving exposure to lead stearate and cadmium stearate as well as to organic plasticizers, took 20 minutes to complete and these processes were repeated 3 or 4 times in each 8-hour work shift. Environmental measurements showed 0.03-0.7 mg/cu m cadmium in 1963 and 0.02-0.2 mg/cu m in 1964, but the operations covered only about 1 hour/day. Particle size distributions were studied in several operations, including casting of both lead and cadmium stearates (mixed casting) and of cadmium stearate alone (cadmium casting). These distributions were: 25% in mixed casting and none in cadmium casting in the 6-20 μm range; 17% in mixed and none in cadmium in the 0.7-2 μm range; and 42% in the mixed and 83% in the cadmium casting in the 0.4-0.7 μm range.

Tsuchiya[63] reported on 13 workers (aged 19-32 years) exposed to cadmium fume (probably CdO fume) in a silver and cadmium alloy smelting operation, compared with 13 age-matched nonexposed factory workers. The periods of exposure ranged from 9 months to 12 years. Samples were collected by an electric dust sampler and were analyzed polarographically. One day of air sampling continuously at nose level on each of 5 workers selected for a time study gave TWA's of 68-250 μg/cu m of cadmium, with an overall weighted average exposure for the 5 workers of 125 μg/cu m. While most workers were not exposed for 8 hours/day (about 6 hours/day was common), workweeks were 5-6 days. Both the specific gravity and the concentration of hemoglobin in blood were significantly lower in all cadmium workers than in controls, while urine coproporphyrin levels were higher. Urinary protein levels by quantitative microdetermination were considerably increased in exposed workers except for 3 workers who had only 9 months of exposure. Workers with more than 5 years' exposure had the highest urine protein levels. The cadmium workers excreted 114-667 μg/ml, and the control group 29-82. Similarly, urinary cadmium levels were elevated in exposed workers (35-140 μg/liter) except in the same 3 workers and in 9 controls, whose urinary cadmium levels were all lower than

15 μg/liter. Other than proteinuria and anemia, no abnormalities were noted. These findings are consistent with the impression from reviewing other reports on cadmium toxicity that serious renal effects of cadmium, as presaged by high proteinuria and as evidenced by increased cadmium excretion, develop slowly and with early warning of serious changes.

Tsuchiya[63] concluded that his data argued against the TLV of 0.1 mg/cu m and suggested that a value of about 0.05 mg/cu m would be preferable, at least for Japanese workers.

In 1976, Tsuchiya[130] reported on the same plant he had studied 10 years earlier.[63] Five of the original 13 workers were still employed there; others had left the company and new workers had been employed, with a total of 16 workers being involved in the later study. The working environment had been improved in the interim, except for a period in 1970 when engineering controls did not function properly, and workers had started wearing respirators at least part of the time. Some workers with significant proteinuria in the previous study had been transferred to other operations. Except for two of the original five workers, none had proteinuria by sulfosalicylic or TCA test. Two of these who were not proteinuric by these tests had increased concentrations of β_2-microglobulin in the urine, one slightly and the other moderately increased. One worker who had a severe proteinuria from 1965 to 1970 had been hospitalized in 1970. After discharge from the hospital, he changed jobs and was lost to further examination. A renal biopsy taken in the hospital showed slight microscopic changes in the tubules, with a very slight thickening of Bowman's capsule in the glomeruli; there was no clinically apparent impairment of renal function.

In 1965, environmental concentrations had averaged 125 μg/cu m of cadmium, then had decreased, rising in 1970 to 282 (11-1,116) the first half of the year and 114 (7-586) the second half. Subsequently, environmental concentrations decreased; in 1971 they were 28 (2-118) μg/cu m the first half of the year and 25 (4-65) the second half; in 1972 they were 29 (11-57) the second half (first half-year not being given); and in 1973 they were 16 (7-29) the first half and 16 (9-20) the second half. The improvement during and after 1970 was attributed in part to replacement of the gas furnace with an electric furnace.

The original 5 workers improved during the 10-year period in terms of clinical test results. New workers had not developed proteinuria. Glucosuria was not observed, but the author[130] commented that the paper test method used might have been less sensitive than quantitative methods used by some investigators. All workers in the later study were normal with respect to blood specific gravity, erythrocyte counts, hemoglobin, and hematocrit; this represented an improvement in the case of the older-service workers, suggested to be due in part to improved nutrition and in part to decreased exposure to cadmium. A positive correlation between blood and urine cadmium was not found. Tsuchiya concluded that cadmium-induced proteinuria is reversible in some workers (probably those with proteinuria of short duration).

Tsuji et al[79] studied a number of workers exposed to cadmium in a zinc refinery. About 90% of the workers reported on were male, the rest female. Proteinuria detected by sulfosalicylic acid occurred in 14.7% of the men and 15.5% of the women. Analysis of sugar in urine by a test tape showed positive results in 7.8% of the men and 1.4% of the women. There were some complaints of respiratory tract symptoms, nasal symptoms including anosmia, weight loss, and nocturnal pollakiuria. Many examinees had a history of stomach or duodenal ulcers. Yellow rings on the teeth were looked for but not found, but the authors commented that stained teeth, poor dental repair, and ill-fitting dentures made the examination of questionable significance. Environmental data were not reported. If men and women were similarly distributed between the various types of exposure, an inference that the sexes were not different in their sensitivity to cadmium would be reasonable; however, it is not clear whether men and women were so distributed.

Tsvetkova[95] investigated whether cadmium affects reproduction. She examined 106 women, aged 18-48, who had spent 2-16 years in work involving cadmium exposure. Some of these workers were exposed to cadmium oxide at concentrations stated to be 0.1-25 mg/cu m, some in a chemical factory involving exposure to soluble cadmium salts at 0.16-35 mg/cu m, and some in a zinc-casting factory where cadmium sulfate, cadmium sulfide, and metallic cadmium were present in a concentration of 0.02-25 mg/cu m. Sampling and analytical procedures were not described. Tsvet-

kova was unable to show changes in the menstrual cycles of women exposed to cadmium as compared to unexposed women serving as controls. There were isolated menstrual changes but these were attributed to endocrinal-gynecologic illness which, however, the author[95] attributed to working with cadmium. Courses and times of pregnancies were normal. However, children born to these cadmium-exposed women weighed less than children of control workers. Four of the children born to cadmium-exposed women had signs of rickets, one had retarded eruption of teeth, and two had dental disease otherwise undescribed. These changes were not present in children of control workers. Details of findings and bases for conclusions were not presented. Most of the paper was concerned with the effects of cadmium on reproduction in rats, described later under *Animal Toxicity*. At the concentrations to which these women were exposed, renal changes might be expected as well as renal complications of pregnancies, but Tsvetkova did not comment on these points.

Piscator et al[131] studied 53 women, aged 18-71, all but four of whom worked in a cadmium-nickel battery factory previously studied by Friberg,[55] who had found renal and lung damage in male workers approximately 25 years previously; two of the women then worked in another factory, and two were retired. The control group consisted of 34 women, aged 18-60, who worked in a candle factory in the same city as the battery factory; these women had no known exposure to metals. The exposed and control groups were fairly well age-matched except that there were no controls over 60 years of age; 5 of the exposed group were 60-71 years old. Air concentrations, said to be below 100 but mostly about 40 μg Cd/cu m, based on personal sampling, were considerably less than the concentrations at which the previously studied men had been exposed (M Piscator, written communication, October 1975). Sedimentation rates, blood hemoglobin, 26 serum constituents, and various urine components including total protein and β_2-microglobulin were studied in these workers. In the age group 50-59, there was a statistically insignificant increase in hypertension in exposed women. There was a significant increase in average haptoglobin and sedimentation rate in the 40-49 age group and a nonsignificant increase in the 18-29 year age group. Serum iron was lower in the 50-59 year group. There were no significant differences in urinary findings. Among the controls there was one case with a very high excretion of β_2-microglobulin; the pattern obtained by electrophoresis of urine suggested an effect on tubular function but there was no glucose in the urine, and a bacterial infection involving the tubules was suggested as the explanation. There was a slight tubular dysfunction in a 71-year-old exposed woman, but without increased β_2-microglobulin excretion. She had been classified as a suspect case in 1969.

Piscator et al[131] also observed significant differences in blood and urine cadmium, and found that urine cadmium, but not blood cadmium, increased with age. They also noted a slight decrease in urine zinc with exposure time, except that urine zinc was increased by use of drugs for treatment of hypertension. Smokers had significantly higher blood cadmium levels than nonsmokers; differences between cadmium-exposed smokers and nonsmokers were not found in urinary excretion of cadmium but control smokers excreted more cadmium than control nonsmokers. It was believed that cadmium might have been deposited on cigarettes during work, then vaporized during smoking and inhaled. They found a significant correlation between blood and urine cadmium in nonsmokers exposed less than 10 years but not in smokers.

Kjellstrom and associates[132] studied the excretion of β_2-microglobulin in male and female workers in the battery factory originally studied by Friberg.[55] There were 240 male and female workers exposed to cadmium oxide dust and to nickel hydroxide dust in the study group, and there were 87 unexposed male controls. The exposed workers were employed in the department where materials for battery electrodes were made (material plant) or where the electrodes and batteries were assembled (assembly plant). Stationary and personal samples were collected on millipore filters except in 1959 and prior years and analyzed by atomic absorption spectrophotometry. Particle size analysis in 1972 showed that 95% of the particles were smaller than 5 μm. Environmental concentrations had been occasionally measured in the factory from 1946 on, but systematic measurements based on personal sampling had not been performed. Individual samples in the assembly plant in 1946, based on stationary samplers, averaged 6.8 mg Cd/cu m (range 3-15), were reduced in 1947 to an average of 760 μg/cu m (range 400-1,000),

becoming further reduced gradually to 340 μg/cu m (range 3-2,150) in 1961. Between 1967 and 1972, sample averages ranged from 22 to 91 μg/cu m and individual samples ranged from 6 to 802 μg/cu m. Concentrations of nickel hydroxide were reported to be 2-10 times the cadmium concentrations. In 1968, stationary samplers in the material plant were analyzed and found to contain cadmium equivalent to 7 and 31 μg/cu m; however, personal samples showed airborne concentrations of 10-4,800 μg/cu m (median of 290). In 1972, stationary samplers showed levels of 8-170 μg/cu m and personal samplers showed 280-690 μg/cu m. Exposure concentrations at the time of the study, apparently referring to both plants, were described as about 50 μg/cu m. Protective masks were occasionally but not consistently used by the workers.

Diagnosis of proteinuria was made in those whose microglobulin excretion was greater than the upper 95% confidence limit of the normal concentration in the urine; the authors cautioned that this was not considered necessarily to be a clinically significant proteinuria. There was an increased incidence of microglobulinuria in the exposed group. In the unexposed controls, 3.4% had microglobulinuria. In the assembly plant, women had a 2.3% incidence of this type of proteinuria and men had a 25% incidence. The men who worked in the material plant had a 52% incidence of microglobulinuria. These incidences in male workers were significantly different from control incidences at p less than 0.001; differences in incidences between female workers and controls were not significant. The 2.3% incidence among working women represents one case of microglobulinuria among 41 women. Yet 15 of the women had been exposed for more than 5 years. The authors speculated that the lower rate of microglobulinuria among women might in part reflect a lower smoking rate; of the 13 women whose smoking habits were known, 5 were smokers. Nonsmoking cadmium-exposed workers had a lower prevalence of the defined proteinuria than smoking cadmium-exposed workers. Nine of the workers were separately treated in the study because they were from Yugoslavia, where tubular proteinuria is endemic (Balkan nephropathy); two of them were found to excrete increased amounts of microglobulin. In the 185 employees that worked continuously with cadmium, the prevalence of microglobulinuria increased with exposure time.

Lauwerys and coworkers[133] studied Belgian cadmium workers exposed for periods up to 40 years. They took breathing zone samples of total cadmium particulate and, in the most polluted sites, of respirable cadmium particulate, ie, aerodynamic diameter of less than 5 μm. Samples were analyzed by atomic absorption spectrophotometry. The workers were drawn from 3 different factories, an electronic workshop, a nickel-cadmium storage battery factory, and a plant producing cadmium. Each factory had a control group selected to match the exposed group in sex, age, weight, height, smoking habits, and socioeconomic status. Since no important modifications had occurred in the different industrial processes since their institution, the authors believed that levels of airborne cadmium found in the 3 plants were quite representative of past exposure. A description of the exposed groups and the workroom cadmium levels found are given in Table III-1.

Control groups were described as C1, C2, and C3, corresponding to the three exposed groups. Exposed groups were exposed to dust of cadmium or its compounds; four workers in Group E3 were also intermittently exposed to fume.

In group E1, the only change was a slight increase in urine cadmium; there were no significant differences in pulmonary function indices, but it was noted that an effect of cigarette smoking on pulmonary function was evident.

In group E2, in both smokers and nonsmokers, all pulmonary indices were on the average lower than the corresponding control group, but these differences were not statistically significant. Blood and urine cadmium concentrations were higher than control levels. Electrophoresis showed evidence of glomerular proteins in four workers. One worker known to have glomerulonephritis had what was described as excessive proteinuria.

In group E3, pulmonary indices (FVC, FEV_1, and peak expiratory flow rate) were significantly lowered. Cough but not expectoration was more common in E3 than in C3 workers. There were slight but statistically significant changes in some of the blood enzymes, viz, an increased β-galactosidase, an increased lactic dehydrogenase, and a decreased RBC acetylcholinesterase; hematocrit was also lower in E3 than C3. However, these changes were not sufficient to suggest adverse health effects. There was an abnormal electrophoretic pattern of urinary proteins found in 15

workers in E3. Urinary cadmium was elevated, markedly so in those whose proteinuria was believed to be pathologic. There were slight increases in blood cadmium, also. Of the 15 workers whose urinary proteins showed abnormal electrophoretic patterns, selective glomerular proteinuria was diagnosed, on the basis of electrophoretic pattern, in 7; in the other 8, there was a mixed proteinuria, ie, of the glomerular-tubular type, and this was confirmed by immunoelectrophoresis.

It is interesting that E3 workers, consisting of 22 men exposed 21-40 years, were more markedly affected by exposure at 66 μg/cu m than the E2 workers, consisting of 27 men exposed for less than 20 years at more than twice that concentration (134 μg/cu m), and this suggests the importance of length of exposure, compared to exposure concentration, in the development of chronic toxicity from cadmium. However, some of the E3 workers were also exposed to cadmium fumes, apparently at higher concentrations.

The authors[133] suggested that their data supported a reduction of the environmental limit of cadmium dust to 50 μg/cu m. They also recommended that urine cadmium determinations be performed, and that urinary cadmium should be kept below 15 μg/g of creatinine.

Lauwerys and coworkers[134] also studied a group of 90 workers exposed to cadmium oxide dusts for less than 20 years (average of 7.5 years) and another group of 25 workers exposed for over 20 years (average of 27.5 years). Concentrations at the time of the study were usually below 90 μg/cu m total cadmium dust and below 30 μg/cu m respirable dust. Both groups had slight but significant reductions in pulmonary function, a marked increase in blood and urine cadmium, and kidney lesions diagnosed from electrophoresis of urine protein. The incidence of kidney lesions was 9% in the group with the shorter work experience and 64% in the group with the longer exposure. Exposure caused a higher increase in urine cadmium than in blood cadmium. Their data on blood cadmium suggested that it did not increase with duration of exposure, that it does not reflect body burden of cadmium, but that it may reflect current exposures. They suggested that at low cadmium exposure concentrations urine cadmium might at least partially reflect body burden. They did not find a correlation between cadmium in the urine and duration of exposure with or without kidney lesions.

Further details of these studies[133,134] as well as of those on other workers exposed to cadmium have been published in a comprehensive report, also from the Catholic University of Louvain, Belgium, by Materne et al.[135] Some of these worker groups were also exposed to lead, which may make some of the observations less clearly attributable to cadmium. However, the authors concluded that lead absorption had little or no role in the kidney changes, and that the effects in the kidneys were from cadmium absorption by these workers. In Factory I, involving electronic manufacture, 26 exposed women and 26 control women were studied. There was no lead exposure in this group. In Factory II, where nickel-cadmium batteries were made, 21 exposed male and 6 exposed female workers were studied, with 19 control males and 4 control females. In Factory III, involving cadmium production, 25 exposed and 25 control males were studied. In Factory IV, also involving cadmium production, 66 exposed and 65 control men were studied. Controls were matched with cadmium-exposed workers in age and in smoking habits. Airborne cadmium concentrations were variable, ranging between 7 and 19 μg/cu m in Factory I, 6-94 in Factory II, 1.2-97 in Factory III, and up to several mg/cu m in Factory IV, after omitting several values (eg, 27 mg/cu m) that were believed due to gross contamination of samples. The concentration ranges mentioned were smaller in specific work sites within a factory.

Differences between exposed and control groups were often less remarkable than differences between smokers and nonsmokers. In Factories II and III there were decreases in hematocrit; while this might be attributed to lead, airborne lead concentrations were in the range of 40-50 μg/cu m, which seems unlikely to be high enough to cause anemia, so possibly the reduction in hematocrit was due to cadmium alone or to cadmium and lead.

Another group consisting of 108 exposed and 110 control workers were exposed at 74-210 μg/cu m total (20-30 μg/cu m respirable) cadmium dust, of whom 18 exposed workers had what was described as pathologic urine proteins on electrophoresis. Proteinuria was also seen in some workers in Factories III and IV, together with pulmonary function decreases. The authors concluded that, in order to prevent any renal impairment, airborne cadmium, whether dust or fume, should not exceed 50 μg/cu m.

Animal Toxicity

In the ensuing discussion of animal toxicity, emphasis is given to those investigations which significantly add to information from human studies, eg, reproductive effects and experimental carcinogenesis, with a resultant lack of emphasis on those effects more extensively studied in humans, such as renal and pulmonary effects. In addition, in such areas as testicular effects and biochemical studies, where there are many published studies, the more representative or important studies have been selected for discussion.

(a) Skin

Little is known about the absorption of cadmium through the skin. The only cadmium salt which has been studied in this regard is the chloride, and the only species of animals studied has been the guinea pig.[136,137] An absorption of 1.8%/5 hours was observed when the concentration of aqueous solution applied was 0.239 M. At lower concentrations, the absorption was less than 1%/5 hours. From these data, significant absorption of cadmium through the skin does not seem likely, but more definitive studies are needed.

(b) Blood Effects

Decker et al[138] studied the effects of long-term ingestion of low levels of cadmium in young rats (34 days old). Six groups of rats were given water containing from 0.1 to 50 ppm cadmium chloride; controls received distilled water only. The animals were killed at various intervals up to one year, and blood and tissue samples were then analyzed. A 50% reduction in hemoglobin was found in rats ingesting 50 ppm cadmium for three months. Rats given from 0.1 to 10 ppm cadmium for one year showed no differences from control groups.

Fitzhugh and Meiller,[139] in a study published only as an abstract, reported giving Cd(II) as cadmium chloride (15-135 ppm) to 3-week old rats in their diets for up to six months. There was evidence of toxicity at concentrations of 45, 75, and 135 ppm. At 135 ppm, dietary cadmium caused a marked anemia with hemoglobin values as low as 4 g, and erythrocyte counts of two million in some cases were observed. A reduction in growth weight occurred, and in some instances early death. Some animals on 45 ppm had no blood changes after one year, and only one animal on 15 ppm had marked anemia. Bleaching of the incisor teeth was observed in all animals except in some animals receiving 15 ppm Cd(II).

Oral administration of large doses of an unstated form of cadmium (75 mg/kg) to Japanese quail [140] for four weeks produced severe anemia (hematocrit value reduced about 50%) and growth retardation. Low concentrations of iron with high concentrations of cadmium in the liver were observed. The authors suggested from their data that a primary effect of cadmium under these conditions and in this species was the production of an iron-deficiency anemia, which could be prevented by adequate dietary ascorbic acid. Friberg[55,141] has also suggested that the type of anemia induced by cadmium is mainly hypochromic and microcytic. He studied the effect of iron in male rabbits injected sc with 0.65 mg/kg of Cd(II) daily for 70 days.[141] One group received iron, and another group was given liver three times a week. In animals given iron, the hemoblogin values were significantly higher than the other groups; however, even large amounts of iron did not completely prevent the development of anemia. This observation indicates that the anemia was due in part to an alteration in iron utilization. In this connection, Kench and Gubb[142] reported a study in which chick embryos were injected seven days before hatching with 12-15 μg Cd(II). The livers of the newly hatched chicks were found to have impaired biosynthesis in vivo of catalase, a heme-containing enzyme.

Dalhamn and Friberg[143] administered cadmium sulfate sc to 3 groups of rabbits, 6/group, 6 days/week, for 10 weeks, at 650 μg Cd/kg. Two of the groups were injected thrice daily with dimercaprol, one at 4 and the other at 12 mg/injection; the third group received only cadmium sulfate. Four of the animals on the high dose of dimercaprol and 3 receiving only cadmium sulfate died during the experiment. There was a progressive weight loss in all groups, greatest in high-dose dimercaprol animals. Proteinuria developed in all but two rabbits, earlier in most of the animals receiving the higher dose of dimercaprol. There was a significant and progressive decrease in hemoglobin concentrations in the blood, but a significant decrease in erythrocyte count occurred only in the high dose dimercaprol animals. Postmortem examination showed that all animals had hepatic cirrhosis, nephrosis, and splenic fibrosis. Cadmium concentrations of organs studied did not differ from group to group; they were 60, 30, and 24 mg/100 g wet tissue in liver, kidneys, and

spleens, respectively. It was concluded that dimercaprol had no prophylactic action on cadmium poisoning and probably enhanced the poisoning.

The evidence of renal damage with proteinuria in humans intoxicated by cadmium can be interpreted to indicate that protein metabolism is affected by cadmium. Lawford[144] observed two abnormalities in the protein pattern (a decrease in one component and a concomitant increase in two other components) in the serum of rats given 50 ppm Cd(II) as cadmium chloride in their drinking water for four weeks. Positive identification of one component band was not made. However, it was possible to bind radioactive iron to the increased components, which suggested that these bands were serum transferrin. In a study by Jacobs et al,[145] Japanese quail were fed a protein diet which contained 75 mg/kg of zinc and to which 75 mg/kg of cadmium chloride was added. Controls received the usual diet containing 75 mg/kg of zinc, since young quail are sensitive to zinc deficiency. After 4 weeks, 80% of the cadmium-fed birds developed severe anemia associated with an increased concentration of transferrin (15% in controls vs 23% in the cadmium group) and moderate decreases in the serum albumin (31% vs 27%) and lipoprotein fractions of the plasma. This resulted in a significant increase in the transferrin-albumin ratio (controls 0.49 vs cadmium group 0.86). The plasma protein electrophoretic pattern of cadmium-treated birds did not show the abnormal serum pattern described by Lawford[144]. The authors postulated that the effect of cadmium in elevating transferrin might be explained by the iron-deficiency anemia. Since transferrin functions as the iron donor and it is bound in this process, a lack of iron would allow the transferrin to be released into the blood and thus result in hypertransferremia. In a prolonged exposure study by Axelsson and Piscator[123], rabbits (Belgian Giant) were given daily sc injections of 0.25 mg/kg Cd(II) five days/week for 11-29 weeks. There was an initial reduction in serum albumin and an increase in α- and β-globulins. This appeared to be an acute reaction since prolonged treatment resulted in a decrease of the α_2-globulins. Haptoglobin determinations showed the development of ahaptoglobinemia after 11 weeks, indicating hemolytic anemia.

(c) Vascular Effects

Schroeder[88] attempted to duplicate the human condition of chronic hypertensive disease in small laboratory animals. Rats and mice were given trace amounts of cadmium (5 μg/ml) in their drinking water from the time of weaning. Cadmium produced hypertension in rats after approximately one year and this effect increased with age. The incidence in females was higher than in males. However, the mortality was greater in males with hypertension, and median life spans of both sexes were shortened compared to controls (156 vs 140 days, p less than 0.005). Schroeder[88] also reported results of another experiment in which 80% of rats receiving soft water were hypertensive by 500 days of age vs 17.7% of those rats receiving hard (calcium-containing) water. Another part of the study demonstrated that following the ip injection of cadmium acetate (1.5, 2 or 3 mg/kg) mean blood pressures (apparently systolic) were increased an average of 47 mm Hg. When cadmium-hypertensive rats were given a zinc chelate (2-diaminocyclohexane disodium zinc tetraacetate), they became normotensive within a week. Analyses for cadmium and zinc in the kidneys and liver of 90 hypertensive and normotensive rats suggested a reasonable correlation between the renal ratio of Cd/Zn with the level of blood pressure; hepatic ratios were not significant. A renal Cd/Zn ratio of more than 0.80 indicated hypertension. The author[88] suggested on the basis of his animal data that cadmium might be a factor in hypertension of unknown origin in humans.

Others[146-151] have also found hypertensive effects of Cd(II) in animals.

Porter et al[152] found no elevation of blood pressure in Cd(II) intoxication. They administered cadmium acetate ip at 2 mg Cd/kg to female Sprague-Dawley-derived rats, then a second ip dose of 1 mg Cd/kg 3 weeks later. From days 14 to 27 after the second administration, various autonomic drugs were administered in sequence by vein, and systolic blood pressures were recorded. With norepinephrine but not epinephrine, drugs causing elevated blood pressure in control rats, there was a lesser elevation in cadmium-treated rats; with acetylcholine, isoproterenol, and atropine, but not propranolol, drugs causing decreased blood pressure in control rats, there was a lesser decrease in cadmium-treated rats. Aortic strips from cadmium-treated rats had a diminished reactivity to angiotensin, epinephrine, barium, and tyramine. The authors concluded that cadmium desensitizes rat vasculature to vasoconstrictors and dilators independently of any ability to cause hypertension.

Fowler and coworkers[153] gave drinking water containing 0, 0.2, 2, 20, and 200 ppm Cd(II) as cadmium chloride to male rats for 6 or 12 weeks. Rats were also given a diet with normal (0.7%) or low (0.1%) calcium. The animals' feed also incidentally contained 0.4 ppm cadmium, so even controls were ingesting some Cd(II). (Similarly, animals in other experiments probably also ingested small amounts of cadmium normally present in feed.) Kidneys of animals on a low calcium diet had a higher cadmium concentration than those on a normal diet. The cadmium feeding caused constriction of smaller and dilation of larger renal arteries and a fibrosis of peritubular capillaries. There was an increased BUN but little tubule cell damage. The authors suggested that cadmium-induced vascular damage has a role in cadmium nephropathy. While dietary calcium did not influence the vascular effects of cadmium, the authors briefly referred to their unpublished observations that dietary calcium did affect blood chemistry and parathyroid glands in the same animals.

Singhal et al[154] have suggested that hyperglycemia and arterial hypertension from Cd(II) intoxication might be related to increased synthesis of epinephrine in adrenal glands. They injected cadmium chloride, 1 mg/kg ip, in rats daily for 45 days. Adrenal weights were increased, as were levels of adrenal norepinephrine and epinephrine and activity of adrenal tyrosine hydroxylase. Tyrosine hydroxylase activity and norepinephrine and epinephrine levels had returned to normal 28 days after the last Cd(II) injection, but the adrenals had only partially recovered their original weights.

(d) Reproductive Effects

Little attention had been drawn to the effects of cadmium on gonads prior to the mid-1950's when Parizek[91] and Parizek and Zahor[92] described the necrotic effects on testicular tissue in rats, which has since been confirmed by many others in several animal species. Parizek and Zahor[92] injected 80 male rats sc with 1 ml of 0.03 M solution of cadmium chloride. The rats were killed at various intervals from 2 to 48 hours after the injection. Microscopic changes in the testes were observed as early as 2-4 hours after injection, as evidenced by edema and capillary stasis. Testicular tissue damage progressively increased with time. After 48 hours, complete testicular necrosis was found in all 80 animals. Similar data were developed by Mason et al[155] at various doses of cadmium chloride (0.57-6.8 mg Cd/kg) given sc to rats. Again, edema preceded an ischemic necrosis which was associated with increased intratesticular pressure, hemorrhaging, and ultimate interference with testicular blood supply. In this study, a dose-response relation was found at the lower dose levels, 0.57-1.4 mg/kg. At the lowest dose, no effect was observed, at 0.85 mg/kg ischemic necrosis of seminiferous tubules occurred in 32% of the rats, at 1.1 mg/kg there was a 90% incidence, and at 1.4 mg/kg 100% of the rats had these injuries. It was suggested that the unusual sensitivity of the testes to cadmium was related to the unique vasculature, ie, pulseless, semistagnant flow, which might have facilitated alteration of capillary endothelial permeability by cadmium.

Sangalang and O'Halloran[156] studied testicular injury and changes in androgen synthesis in brook trout exposed to Cd(II) for 24 hours at 1, 2, or 25 ppm. Testes of the fish treated at 25 ppm showed extensive hemorrhagic damage. Formation of 11-ketotestosterone, 11-β-hydroxytestosterone, and testosterone from ^{14}C-pregnenolone in vitro was used to study the effects of Cd(II) exposure on androgen synthesis by the testes. The results showed that cadmium inhibited the formation of the steroids in vitro; whether this reflects the situation in vivo is not known. However, the study suggests that cadmium-induced testicular damage is not confined to species with scrotal testes.

In order to investigate the testicular damage from cadmium in more detail, Parizek[91] injected rats and mice with cadmium chloride (2.2-4.5 mg Cd/kg) into the interscapular region sc. Some of the rats were treated with testosterone (1 mg/ml in olive oil) or zinc acetate (0.2 moles). Microscopic changes (hyperemia and interstitial edema) in the testes of cadmium-treated animals occurred within a few hours after injection. Forty-eight hours later, there was destruction of tubular epithelium, and interstitial tissue was hemorrhagic. After 10 days, there was replacement of testicular tissue by eosinophilic material. There was also a decrease in weight of the accessory sex organs, seminal vesicles, and prostate glands. However, when testosterone was given 10 days after the cadmium, the weights of these glands increased again, suggesting that the weight loss was the consequence of a hormone deficiency. Doses of zinc acetate 80,

100, and 200 times that of Cd(II) (3.33-4.8 mmole zinc acetate/kg) administered before, during, and after the Cd(II) prevented the testicular damage. The protective effect of Zn(II) against cadmium-induced testicular damage was confirmed by Webb,[157] who suggested that prior injection of zinc induced hepatic synthesis of a specific binding protein that immobilized cadmium. Protective effects by Zn(II) or Se(IV) against injury by Cd(II) to rat testes were also found by Kar et al[158] and by Mason and coworkers.[159,160]

Since the injury to rats' testes does not occur before the age of 7-16 days, the possibility that a hormonal balance in immature animals prevents testicular vascular damage from cadmium was investigated by Gunn et al.[161] Four groups of mature male mice were injected sc with 0.03 mmole/kg cadmium chloride (3.4 mg Cd/kg). Each group received 0.1 ml of either saline solution, sesame oil, testosterone (100 μg), or estradiol (100 μg) 3 times/week for 7 weeks. The cadmium treatment consistently produced vascular damage to the testes, characterized by marked edema, capillary hemorrhage, and tubular necrosis. Treatment with testosterone did not alter this response; however, estradiol protected the testes from vascular damage. This protective action of estradiol was reversible, since the testes were again susceptible to vascular damage by Cd(II) when the estradiol treatment was stopped.

Nordberg[162] gave CBA mice single sc injections of cadmium chloride at 1 mg Cd/kg, causing complete testicular necrosis. Single doses of 0.25-0.5 mg/kg caused little or no testicular damage. When these lower doses were administered 5 days/week for 6 months, testicular changes were slight at 0.5 mg/kg and within control limits at 0.25 mg/kg, though testicular cadmium levels were 6-7 ppm, compared with 0.3 ppm after single injection at 1 mg/kg. Repeated administration of 0.25 mg/kg, to induce metallothionein synthesis, protected the mouse testes from the necrotizing effect of a subsequent injection of cadmium chloride at 1 mg Cd/kg. When cadmium partially bound to metallothionein was injected at 1.1 mg/kg, no testicular necrosis developed. When CBA mice were given sc injections at 0.25-0.5 mg/kg 5 days/week for about 6 months[163] kidney damage occurred, as evidenced by proteinuria, altered composition of urine protein on electrophoretic examination, and a marked increase in urine cadmium concentrations at the time of development of electrophoretic patterns of urine protein judged to be pathologic. Similarly, rabbits administered cadmium chloride sc 5 days/week for 24 weeks at 0.5 mg Cd/kg did not develop macroscopically or microscopically evident testicular changes, though marked kidney damage developed.[164] This suggests that repeated administration of cadmium compounds at doses that cause slight or no kidney malfunction will not cause testicular damage.

Madlafousek et al[165] found that the copulatory activity of most male rats tested was lost within 3 weeks of injection with cadmium chloride at a dose previously found in that laboratory[91] to cause complete testicular necrosis and permanent sterility. The effect could be prevented by administration of androgens. Two months after Cd(II) administration, there was only slight impairment of sexual behavior; normal copulatory activity and ejaculatory behavior accompanied by the production of plugs had resumed in these animals. Spontaneous restitution of normal sexual activity did not occur in surgically castrated males.

Friberg et al[1] (pp 124-27) have reviewed results from investigations of testicular necrosis from Cd(II) and have persuasively argued that damage to the germinal epithelium is probably secondary to cadmium-induced vascular damage.

Studies of the marked effect of cadmium on male gonads stimulated several studies of possible effects on ovaries. Experiments have shown that sc injection of Cd(II) has a sterilizing effect on the ovaries of rats and gerbils.[166-169] Kar et al[166] reported acute changes in ovaries of prepubertal rats (6-8 weeks old) following administration of cadmium chloride sc at 10 mg/kg. Cadmium treatment had an insignificant effect on ovarian and uterine weights, but the rate of follicular atresia was markedly changed. Initially, the large- and medium-sized follicles were damaged; granulosa cells and ova showed signs of atrophy. At 48 hours after injection, all follicles were destroyed. Response of the ovaries to exogenous gonadotropin was inhibited. The authors suggested that the observed atresia might be due to interference with pituitary factors. Parizek et al[167] injected 5-day old female rats with either testosterone or 19-nortestosterone. After 3-6 months, the rats had a persistent estrus, after which they were injected sc with cadmium chloride or acetate at 0.02-0.04 mmole/kg. All ovaries examined had massive hemorrhages ac-

companied by necrosis. Kaul and Ramaswami[168] compared the effect of a single sc injection of Cd(II) on the ovaries of either mature or immature female gerbils. Mature animals were given 0.45 and immature animals 0.22 mg/kg. There were no significant changes in ovarian weights of immature gerbils, but there was a gradual reduction in ovarian weights of adult females. There were extensive hemorrhages and widespread atresia in both mature and immature female gerbils.

Whether the follicular atresia is from a direct effect of cadmium on germ cells or a secondary effect from alterations in blood, especially capillary, supply, is not known. The latter effect was suggested by the development of placental necrosis in pregnant rats.[169]

Kar et al[158] found that simultaneous injection of zinc acetate or selenium(IV) oxide and cadmium chloride into rats did not result in the ovarian damage produced by cadmium chloride alone.

Tsvetkova[95] exposed groups of female rats to cadmium sulfate for up to 7 months at 2.8 mg/cu m. At 2 months 50% and at 4 months 75% of the animals had a prolongation of the estrous cycle. Litter sizes were the same in exposed and control rats, but neonates from exposed dams were smaller and weighed less than those from controls. Fetuses taken from exposed dams on the 22nd day of pregnancy had a higher cadmium level in the liver than fetuses taken from control rats.

Parizek et al[170] found that injection of cadmium acetate in the range of 30-40 μmole/kg in several groups of pregnant rats caused 40% of the pregnant rats to die within the first 24 hours after cadmium administration. The rats were injected on the 21st day of pregnancy. In 80% of these pregnant rats, bilateral hemorrhagic renal necrosis was observed.

Chernoff[171] administered 4-12 mg/kg cadmium chloride to CD-strain rats sc on 4 consecutive days beginning on day 13, 14, 15, or 16 of gestation. There was a dose-related increase in fetal deaths, decrease in fetal weight, and increase in rate of anomalies, which included micrognathia, cleft palate, clubfoot, and small lungs. He concluded that the decrease in lung size, observed in fetuses from animals injected at 8 mg/kg on days 14-17 of gestation, was a specific retardation rather than the result of overall growth retardation. He did not find a basis for concluding whether the fetal anomalies were the result of a direct action on the fetus, placental effects, maternal effects, or a combination of these factors. Data on deaths of dams were not reported, from which it is inferred that none occurred.

Barr[172] found that cadmium chloride (16 μmole Cd/kg) was not teratogenic when administered sc to 2 different stocks of Wistar rats on day 9, 10, or 11 of gestation, but was when administered ip. There was uniformly a weight loss in dams after ip Cd(II) for 1 or 2 days, but in 2-4 days more their weights returned to preinjection values or more; by 21 days, injected rats did not differ significantly in weight from control rats. Rats given Cd(II) sc had little or no weight loss. Doses greater than 22 μmole Cd/kg often killed pregnant rats. Anophthalmia or microphthalmia was found in the greatest number from Cd(II) administration on day 9 and was seldom found when cadmium was given after day 9. Dysplastic or absent ears were found only after administration of cadmium on day 9. Few facial malformations were seen, in contrast to the findings of Mulvihill et al[173] in hamsters. Hydrocephaly was often observed after administration of cadmium on day 9 or 11, but not when cadmium was given on day 10. There were a few cases of encephalocele and exencephaly in day-9 and day-11 groups. A thin abdominal wall (less than 0.5 mm) was seen, especially in day-9 rats, and correlated highly with a left-sided umbilical artery, ear dysplasia, undescended testes, and renal agenesis in one stock of Wistar rats but not in the other stock. Other changes seen in some groups of at least one strain were diaphragm hernia, anal atresia without gross abnormalities of the gut, dysplastic or absent tail, hydronephrosis, and a small rate of appearance of dysplastic forelimbs. The authors suggested that cadmium-induced interference with zinc metabolism might explain some of the changes seen, at least the limb defects.

Ishizu et al[174] administered cadmium chloride sc to pregnant mice on the 7th day of gestation at doses of 0.33-5 mg/kg. An increased rate of malformations was not seen at 0.33 mg/kg, but there was a dose-related increase at higher doses (0.63, 2.5, and 5). Exencephaly was the most common change in these fetuses, taken from the dams on the 18th day of gestation, and many of the exencephalic animals had their eyes open. There were also spina bifida, absence of tail, and vaginal atresia. There were malformations in the ribs as well as in the skull and vertebrae. Some dams in all

cadmium-injected groups aborted; in addition, dams did not have weight increases expected during pregnancy. Amniotic fluids observed during removal of fetuses were hemorrhagic. Total fetal cadmium concentrations were not significantly increased, but placental concentrations were.

Investigators in Ferm's laboratory[173,175,176] performed several studies, all involving injection of cadmium sulfate by vein into pregnant hamsters, at a dose of 0.88 mg Cd/kg. Gale and Ferm[175] administered the cadmium sulfate on the 8th or 9th day of gestation, and fetuses were removed from dams on the 15th day. The most frequently observed malformations were in the brain (exencephaly and encephalocele), eye (anophthalmia, microphthalmia, and exophthalmos), jaw (cleft lip and micrognathia), tail, and forelimbs and hindlimbs (amelia, micromelia, and ectrodactyly). Malformations of the head were seen more frequently in animals injected on the morning of the 8th day, while the limbs were more likely to be malformed in animals given cadmium on the evening of the 8th day or the morning of the 9th day. The authors suggested that some of the malformations might be the result of an effect of Cd(II) on the permeability of the mesenchymal cell membranes. Ferm[176] also administered the cadmium salt on the 8th or 9th day of gestation, and again the dams were killed on the 15th day and fetuses removed for examination. Facial malformations and exencephaly were more frequently found in fetuses from animals given cadmium on the morning of the 8th day than in those from animals injected on the evening of that day, while injections at the latter time caused more rib and forelimb malformations. Fetuses from animals injected on the 9th day had mostly rib and limb defects. Mulvihill et al[173] injected the cadmium salt on the 8th day of gestation and removed the fetuses on the 12th, 13th, or 14th day. Heads of fetuses were fixed and processed for palatal examination. Cadmium-induced changes in facial development included unilateral and bilateral cleft lips and palates, in addition to abnormalities in cartilage formation and delayed ossification. The authors suggested that these effects were the result of mesodermal deficiency rather than of a delay in transposition of the palatine shelves, but could not determine whether this was from a specific action on maternal metabolism with secondary effects on differentiating embryonic tissues or an interference with placental transfer of an essential metabolite. They did not comment on whether a cadmium-induced zinc deficiency might be the proximal cause of either of these mechanisms.

In other studies of the teratogenic effects of cadmium, Ferm and Carpenter[177,178] showed that Zn(II) inhibited the teratogenic effect of Cd(II). Administration of cadmium sulfate to hamsters by vein at 0.88 mg Cd/kg caused abnormalities similar to those seen in other studies (cleft lips and palates, microphthalmia and anophthalmia, and encephalocele and exencephaly).[177] Simultaneous administration of zinc sulfate at 0.45 mg Zn/kg reduced embryonic resorption and malformation rate to control levels. If the injection of Zn(II) was gradually delayed after Cd(II) injection, the protective effect lessened, and no protective effect was evident after a delay of 12 hours or more. Cobaltous acetate did not have a similar protective effect on Cd(II)-induced terata. Pathologic changes were not seen in dams injected with both Zn(II) and Cd(II).[178]

These studies of teratogenicity usually analyzed data by considering the individual fetus as the treatment unit. While the litter rather than the individual animal or fetus might be better as the unit for comparison, it is doubtful that different conclusions on cadmium teratogenicity would have been reached thereby.

Wills et al[179] studied the effects of Cd(II) on reproduction and on blood pressure in rats and monkeys. Male and female rats were given feed containing cadmium chloride at 33 or 73 ppb. Monogamous matings were performed and continued until 4 litters/couple had been delivered. Offspring and subsequent generations were similarly fed and paired except for a few from the first and fourth litters and all animals from the second and third litters of each generation. These animals and animals dying during the experiment or killed at its end were examined macroscopically, and, in the case of abnormal tissues and organs, microscopically. Reproduction was continued for a total of 4 generations. The lower concentration (33 ppb) had little effect. At the higher dose level (73 ppb), there was a slight increase in fertility, especially in the last two litters in each generation. There was a slight increase in longevity of animals fed at 33 ppb and a slight decrease at 73 ppb. There was a deficit in weight gain, greater at 73 than at 33 ppb. There were initial increases

in systolic blood pressures, but these were within the range of control values, and they later subsided, suggesting to the authors that Cd(II) increased neurogenic hypertensive activity which disappeared as the rats became accustomed to the pressure-measuring procedure.

There were no significant macroscopic or microscopic changes in the 276 rats examined. Changes seen were usually of a minor nature and were attributed to spontaneous disease. Tumors were of various types and not significantly different in controls and test animals. A noteworthy finding was the absence of kidney or important vascular lesions. In fact, the authors[179] concluded that feeding of Cd(II) at the lower of these two doses may have been beneficial.

They also fed four female monkeys cadmium chloride in a sweetened beverage at 1.5 and 3.0 μg/kg/day, with 2 monkeys at each dose level and a fifth as a control. The control monkey and one at 1.5 μg/kg/day died after about 6 months, apparently from disease unrelated to Cd(II) ingestion. The three remaining animals survived the 18 months of treatment. They were mated with normal males, following which two, one at each dose level, became pregnant. Both delivered one infant, the one at the lower dose prematurely. Both infants nursed and developed normally, and neither appeared to have any abnormalities. Systolic blood pressures of the dams were not significantly affected by Cd(II) ingestion; however, the number of animals was too small for statistical validation.

Epstein et al[180] studied 174 compounds, including cadmium chloride, for their ability to cause mutations in mice by a modified dominant lethal assay. Cadmium chloride was administered to male mice ip at 1.35-7.0 mg/kg. Detailed data on those substances not causing significant evidence of mutagenic activity, including cadmium chloride, were not presented; however, according to a footnote, early fetal deaths and preimplantation losses from cadmium chloride were within control limits, but there was a reduced rate of pregnancy. This suggests that Cd(II) may have caused testicular dysfunction in the treated males prior to mating, which might have made the dominant lethal assay less sensitive for this compound. Gilliavod and Leonard[181] also found no increase in dominant lethal mutations from administration of cadmium chloride to male BALB/c mice. They injected cadmium chloride ip at 0.5, 1.75, or 3.0 mg/kg and injected controls with saline solution. Mice administered 1.75 mg/kg were mated, after which pregnant females were examined for corpora lutea, implantations, and live and dead embryos. Pregnancy rates were 45-68% in test animals and 57-68% in controls. There was no increased incidence of dominant lethal mutations in test animals over that in controls. All sires were killed 3 months later and dividing spermatocytes were found not to have chromosomal rearrangements such as reciprocal translocations. Similarly, male offspring of mice injected at 1.75 mg/kg were found not to have translocations.

NIOSH has indicated its interest in possible teratogenic or mutagenic effects of some chemical agents, including cadmium, in the *Federal Register* 41:12731-32, March 26, 1976. This statement of concern was based on unevaluated information in the 1976 edition, being prepared for publication, of NIOSH's *Registry of Toxic Effects of Chemical Substances*, which refers to several reports of experimental teratogenicity[171,172,178] and to a separately published abstract of one of these reports.[171] These studies, together with additional investigations of experimental teratogenicity, have been reviewed in the discussion above.

(e) Carcinogenesis

In 1967, Gunn and associates[182] reported that 4 sc doses of 0.17 mg of cadmium chloride produced pleomorphic sarcomas at the site of injection 12-16 months later in 3 out of 30 male Wistar rats. Others[183-187] have also induced injection-site sarcomas in rats by suspensions of CdO, CdS, $CdSO_4$, or Cd metal powder. Injection of cadmium chloride sc at 30 μmole/kg also caused, in addition to injection-site sarcomas, interstitial cell tumors of testes.[188,189] However, injection of zinc acetate (3 mmole/kg) inhibited the development of both types of tumors resulting from Cd(II) injection.[188,189] Cadmium sulfate or cadmium-precipitated ferritin injected sc or po in rats and mice also caused testicular atrophy, often followed by hyperplasia of Leydig cells which in rats tended to progress to neoplasia.[190]

In a series of experiments reported by Schroeder and coworkers[191] and by Kanisawa and Schroeder,[192] Long Evans rats were given water containing cadmium acetate at 5 ppm from weaning to death (up to 4 years). In some experiments, other metals were included in the drinking water.

Longevity of male rats fed Cd(II) exceeded that of controls, but that of female rats was less than controls. Cd(II)-fed rats did not have a significant increase in tumors above the incidence in controls.

Levy and coworkers[105-107] investigated in rodents the ability of Cd (II) to cause prostate cancer. They injected cadmium sulfate sc once a week into the flanks of specific pathogen free (SPF) CB-strain hooded rats for two years at dose levels of 87, 44, 22, or 0 μg Cd/kg,[105] and 3 times/week introduced cadmium sulfate through an intragastric catheter into the stomachs of SPF CB rats for 2 years at 350, 180, 87, or 0 μg Cd/kg[106] and of Swiss mice once a week for 18 months at 1.75, 0.88, 0.44, or 0 mg Cd/kg.[107] Rats injected sc at 87 mg/kg had a significant decrease in weight gain but not rats injected at lower doses. No other changes in experimental animals attributable to cadmium were found except for a low incidence of injection-site sarcomas and for cadmium accumulations in spleens, livers, kidneys, and testes in sc-injected rats, with the most marked accumulations in the kidneys. There was no evidence of an elevated incidence of proteinuria in rats, above that high incidence common to older rats of the CB strain. There was a high incidence of testicular changes and Leydig-cell tumors common to both treated and control rats. There were no prostate neoplasms or pre-neoplastic changes in the prostate glands of either rodent species. However, the near absence of toxic changes from Cd(II) in these experiments raises a question whether the doses administered were high enough to produce prostate neoplasms, assuming such a capability by cadmium.

In a screening study[193] of possible carcinogenicity by a large number of compounds, ethyl cadmate (cadmium diethyl dithiocarbamate) caused an increased incidence of tumors in mice treated sc or po. However, several other dithiocarbamates also caused an increased incidence of tumors in mice in this study, so it is likely that this tumorigenesis resulted from the dithiocarbamate rather than from the cadmium.

NIOSH stated its concern about possible tumorigenicity of a number of chemicals including cadmium in an announcement in the *Federal Register* 40:26390-496, June 23, 1975. This concern was based on then-unevaluated reports of neoplastic effects listed in the *Registry of Toxic Effects of Chemical Substances*. In the 1976 edition of this NIOSH registry being prepared for publication, there are several references on possible tumorigenicity of cadmium compounds which have been cited in the discussion above. [182-185,187-189,193] One additional reference in the registry not discussed above is to the IARC review of cadmium.[4] This review summarized results of several experimental and epidemiologic studies giving information relevant to carcinogenicity of cadmium compounds, and suggested that the data were insufficient to permit conclusions on whether or not cadmium is carcinogenic.

(f) Biochemical Studies

A significant factor in the absorption, distribution, and retention of low and moderate levels of oral or parenteral Cd(II) is the presence and possibly the induced synthesis of the low-molecular weight protein thionein, which binds certain heavy metals to form metallothioneins.

Metallothionein was first isolated by Margoshes and Vallee[194] from horse kidney cortex and was shown to contain a high concentration of cadmium with a lesser amount of zinc. Subsequently, Kagi and Vallee[195,196] purified this material, showing that it was a homogeneous, low molecular weight protein (10,000 mol wt) containing 5.9% cadmium, 2.2% zinc, and 8.5% sulfur, and having very low spectral absorptivity at 280 nm, indicating a lack of aromatic amino acids in its composition but with a specific absorptivity at 250 nm due to cadmium-sulfur groupings. These investigators suggested that the metal-free protein be called thionein, and that the cadmium protein be called cadmium-thionein. Ninety-five percent of all sulfur in the metal-free thionein molecule was present as the sulfhydryl group of cysteine. Moreover, cysteine accounted for 1 of every 3 to 4 amino acids, ie, 25-30% of the amino acids of this protein are cysteine molecules. Pulido et al [197] showed that a similar protein could be isolated from human renal cortex. This purified metallothionein had a molecular weight of 10,500 and contained 4.2% cadmium, 2.6% zinc, 0.5% mercury, and 0.3% copper. As with the equine protein, the sulfur content was high, namely 8.1%, and the characteristic ultraviolet absorption band at 250 nm was present.

Following these early reports from the Harvard group,[194-197] one group of workers at the Karolinska Institute in Sweden[198] and another at Dalhousie University in Nova Scotia[199-201] have found that there are two cadmium-binding proteins, both

of which are of low molecular weight (10,000-12,000) with high sulfur content, in rabbit and rat liver. Two forms of cadmium-thionein found by Nordberg and coworkers[198] differed slightly in amino acid content other than cysteine and had isoelectric points (pI) of 3.9 and 4.5. The protein with pI 4.5 contained zinc as well as a lower amount of proline and a higher amount of glutamate than did the form with pI 3.9. The molecular weights of both the fractions were estimated to be about 6,000; possibly, but not likely, the molecular weights were an integral multiple of 6,000. There is no evidence of the existence of isomorphic forms of thionein, but it seems possible that thionein represents a family of low molecular weight proteins containing large amounts of sulfur and which bind heavy metals in general.

The capacity of thionein to bind heavy metals suggests a possible role in heavy metal metabolism or as a detoxifying mechanism. Thionein in its various metal forms has now been found in liver, kidney, testis, spleen, pancreas, and intestines of mice, rats, monkeys, and man, indicating by its wide distribution a probable role in cadmium metabolism and toxicology.[194-198] This is best illustrated at present by the induction of thionein biosynthesis by administration of low initial levels of Cd(II).[202,203]

In his studies, Webb[204] showed that thionein is induced by Zn(II), Cd(II), and Hg(II), but not by Cu(II), Ni(II), or Pb(II). Its synthesis was inhibited by cycloheximide but not by actinomycin D, which suggests that induction of thionein is controlled at the translational level and not at the transcriptional one. From these and other facts, Webb suggested that thionein is a part of a mechanism that has a relatively specific affinity for Group IIB elements and not for heavy metals in general.

Grasso,[205] in a review of morphologic and biochemical studies of the effect of cadmium on renal function, has suggested that any protection against renal damage afforded by thionein is probably limited, in view of the rather small amounts of cadmium that can cause morphologic and functional changes in the kidney. Nordberg et al[206] found that cadmium-thionein caused a greater degree of damage to renal tubules and was lethal at lower doses than cadmium chloride in CBA mice administered these forms of Cd(II) iv or sc. As was reviewed earlier, metallothionein can protect mouse testes from cadmium-induced injury.[162,164]

Phosphorylation coupled to aerobic oxidation of succinate or reduced diphosphopyridine nucleotide is uncoupled at low concentrations of Cd(II).[207,208] In rat liver mitochondria, [207,208] addition of Cd(II) in vitro uncoupled phosphorylation, at a low concentration (5 μM). This was observed with the oxidation of both succinate and citrate. The uncoupling effect of cadmium was completely reversed by the chelating agent ethylene diamine tetraacetic acid. In a more recent study by Mustafa and Cross[209] using pulmonary alveolar macrophages, the inhibition of oxidation by Cd(II) in the cells and mitochondria of this preparation was demonstrated. Both phosphorylation and respiration were abolished with 5-10 μM Cd(II). The uncoupling action appears to involve the binding of cadmium to dithiol groups of the enzymes. Many heavy metals combine with -SH groups and a large number of enzymes contain -SH groups which are required for their activity. If heavy metals combine with these -SH groups, the enzymes would likely be inhibited. Using succinoxidase, a sulfhydryl enzyme, Barron and Kalnitsky[210] studied the effects of a number of heavy metals on this enzyme-metal complex. Cadmium, bismuth, and mercury had the greatest inhibitory effects, producing 50% inhibition at concentrations of 7,12, and 12.5 μM, respectively. Webb[204] found that in addition to the inhibition of α-oxoglutarate dehydrogenase by heavy metals at the -SH groups, other metal-sensitive sites were involved. These sites were sensitive to inhibition by cadmium, zinc and copper.

Glucose is metabolized by a number of phosphorylating enzymes to yield high energy phosphate compounds. The effect of Cd(II) on glucose metabolism has been studied both in vivo and in vitro. Harkonen and Kormano[211] injected rats with Cd(II) and determined the major energy metabolites in the testes. Following the sc injection of 0.04 mmole/kg of Cd(II), rats were killed at 0.5, 1,2 and 4 hours and the testes removed. Glucose concentrations increased significantly at 30 minutes and again at 2 hours. There was a marked decrease in glucose-6-phosphate and adenosine triphosphate at 2 hours. Glycogen and total high energy phosphate were considerably lowered at 4 hours, at which time lactate concentration was increased. It was suggested that the decrease in high energy metabolites might be related to the ischemic or anoxic state of the rat testes. In a

recent report from Canada,[212] the effect of cadmium on the glucose synthesizing enzymes (gluconeogenesis) in the liver and kidney was studied in vivo. Rats received daily ip injections of cadmium chloride (1 mg/kg) for 45 days; controls were given saline. To determine the effect of cadmium withdrawal, other rats which had received the same treatment were maintained without further cadmium administration for another 28 days. Cadmium enhanced gluconeogenesis, as was evidenced by increased activities of four glucose-synthesizing enzymes in both the liver and kidney. This was correlated with an increase in blood glucose levels and a concomitant decrease in liver glycogen. Discontinuation of the daily injections of cadmium for 28 days failed to reverse the increases in glucose synthesis found in the liver and renal cortex. The data suggested a possible biochemical basis for some of the toxic effects exerted by cadmium. These observations were in direct contrast with an earlier study of Rutman et al [213] on the effect of metal ions in vitro on gluconeogenesis by rat kidney cortex. Of a number of metal ions whose effects on glucose formation were examined, Cd(II) exerted the greatest inhibition.

Cyclic adenosine monophosphate (AMP) metabolism was examined to determine whether the testicular damage following exposure to cadmium was related to changes in this mediator.[214] Rats were injected ip with 1 mg/kg cadmium chloride daily for 45 days. Testicular and prostatic as well as body weights were decreased in the cadmium-treated rats compared to controls. Cyclic AMP levels in testes were unchanged because, though adenyl cyclase was significantly increased, the increase was offset by a concomitant increase in phosphodiesterase activity. Cyclic AMP-dependent and AMP-independent forms of testicular protein kinase were decreased in activity, but the binding of cyclic AMP to protein kinase was not affected. The results were opposite in the prostate gland, ie, there was a decrease in cyclic AMP, attributed to a decrease in activity of adenyl cyclase; cyclic AMP binding to prostatic protein kinase was increased, together with an increased activity of cyclic AMP-dependent protein kinase.

Kench and Gubb[142] found cadmium intoxication in the chick to result in inhibition of lipoamide dehydrogenase, δ-aminolevulinate synthetase, and xanthine dehydrogenase. They also found an impairment in the in vivo biosynthesis of catalase, a heme-containing enzyme.

Ribas-Ozonas and coworkers[215] found Cd(II) to cause a significant decrease in the activity of alkaline phosphatase (a zinc-containing enzyme) in both kidney and prostate gland in guineas pigs. They did not find any effects on acid phosphatase and esterase activities. Vigliani[67] found a severe reduction in kidney leucineaminopeptidase activity in mice after Cd(II) administration at 50 μg/day for 5 days.

(g) Interaction with Zinc and Other Metals

The fact that cadmium is in the same group of the Periodic Table as zinc, ie, IIB, has led to research on the question of whether cadmium interferes with the metabolism of the essential element, zinc. Similarly, since cadmium occurs in solution in only one valence state—Cd(II)—and binds to -SH groups, as do other heavy metals including copper, there have been several investigations of whether the metabolism of any of the common essential divalent minerals could be affected by the presence of Cd(II).

Supplee,[216] in a study of poultry growth, and Cotzias et al,[217] in a study with rabbits, developed evidence of an antagonistic effect of zinc and cadmium, with a suggestion[218] that cadmium might in part act as an antimetabolite for zinc.

Hill et al[219] reported evidence that Cd(II) interfered with the metabolism of copper and iron, as well as zinc, in a study on chicks; additional amounts of these essential metals reversed some or all of the adverse effects of cadmium. Bunn and Matrone[220] showed similar interactions in rodents. Lease[221] reported evidence that Cd(II) given orally to chicks decreased the intestinal tract absorption of zinc and postulated that cadmium interferes with zinc absorption by occupying the same transport binding sites.

Parizek and colleagues[222] found that the lethality of injected cadmium chloride in rats could be greatly reduced if zinc chloride or zinc acetate were injected 5 hours prior to the cadmium dose. Cupric chloride did not have this protective effect. These results, together with those previously cited, suggest that zinc could alter the acute and chronic toxic action of orally or parenterally administered Cd(II) by competing for receptor sites of cadmium.

Petering and coworkers[223] showed that Cd(II) administered in the drinking water at a concentra-

tion of 3.4 μg/ml caused definite alteration of both zinc and copper metabolism when dietary zinc was suboptimal and the Zn/Cd ratio was 1, but that these effects could be prevented by raising the level of dietary zinc to a Zn/Cd ratio of 4/1. The increased amount of dietary zinc did not affect the elevated level of cadmium in blood or kidney, but it did inhibit the increase in the liver concentration of cadmium. Under these conditions of low intake of cadmium, there was no evidence of testicular effect or accumulation of cadmium in the testes. When the Zn/Cd ratio was 1, testicular zinc levels were significantly lower than normal, but at a 4/1 ratio, testicular zinc concentrations were normal. This suggests an indirect effect of cadmium on zinc metabolism in testes.

Webb,[157] using high doses of injected Cd(II), found that prior injection of Zn(II) in rats protected testes from the adverse effects of cadmium and caused the synthesis of the cadmium-binding protein thionein in the livers of rats.

Starcher[224] and Evans and coworkers[225] have reported that copper and zinc absorption in the gut involves a thionein-like protein, the sites of which are blocked by cadmium. Following the oral administration of ^{64}Cu (1-30 μg as the nitrate salt) to chickens,[224] absorption was greatest in the duodenum. The radioactive copper was bound to a protein of low molecular weight (10,000). Both zinc and cadmium antagonized the binding of copper to its protein complex.

As was discussed earlier in this Section, Zn(II) can also prevent various experimental effects of Cd(II), such as hypertension,[88] fetal abnormalities,[177,178] ovarian damage,[158] or testicular injury.[91,157-160,223] It also prevented the development of tumors at the site of sc Cd(II) injection as well as those remote from the injection-site, ie, in the testes.[188]

In addition to the protective action of dietary zinc and copper and of the induction of thionein synthesis in response to administration of cadmium, other physiologic and nutritional factors have been ascribed a protective role against cadmium toxicity. Gunn and coworkers[226] have shown that estrogens reduce the damage to the testicular vasculature of rats caused by cadmium chloride at sc doses of 3.36 mg/kg. Gunn and coworkers[161,227] have also reported that cysteine and other thiols protect against some of the testicular damage due to parenteral cadmium.

Selenium also can antagonize cadmium toxicity.[158-160,228] Simultaneous sc administration of cadmium chloride and sodium selenite resulted in the appearance of a peak blood concentration of cadmium about 13 times that caused by injection of the same amount of cadmium alone.[228] The decrease in toxicity of cadmium by the combined administration, as well as the elevated concentration of cadmium in the blood, was attributed to blockage by selenium of uptake of cadmium into tissues. This results, then, in both retention of cadmium within the blood and, presumably, its increased excretion from the body in correspondence with its markedly elevated concentration in the blood. Holmberg and Ferm[229] found that selenium as sodium selenite protected hamsters from the teratogenic effects of cadmium administered by vein to the dams. As discussed earlier, selenium can also prevent cadmium-induced ovarian[158] or testicular injury[158-160] in rats. The effect of selenium may be related to a chemical similarity to sulfur and to the ability of sulfur to complex or otherwise detoxify various metal salts.

(h) Other Effects

Several investigators have studied the possibility that hyperglycemia and glucosuria in cadmium intoxication might be due to pancreatic effects. Ithakissios et al[230] injected rats every other day for a total of 70 days with cadmium acetate solution at 0.25-0.50 mg Cd/kg ip. One group of rats had their pancreata perfused with buffered glucose solution, while other treated rats were studied for changes in plasma glucose, immunoreactive insulin (IRI), and urine glucose, following which $^{14}CO_2$ radiorespiration was studied. Pancreata from animals given 0.5 mg/kg secreted less insulin, but there were no significant changes in plasma glucose or insulinogenic index (ratio of plasma insulin to glucose). Treated animals excreted less radioactive carbon dioxide from the lungs than controls, and excreted more radioactive carbon and more glucose in the urine. IRI released during perfusion was decreased.

Ghafghazi and Mennear[231] came to a similar conclusion that cadmium affected pancreatic function based on their perfusion of isolated rat pancreata with 0.5-1 mM Cd(II) and finding inhibitions of the secretion of insulin in response to glucose, tolbutamide, and potassium.

Nomiyama et al[232] found evidence that aminoaciduria and enzymuria are earlier indices of

renal changes than proteinuria or glycosuria. They administered cadmium chloride to rabbits in the diet at 300 ppm Cd for up to 54 weeks. Aminoaciduria and enzymuria were detected after 14-16 weeks. Anemia was observed after 27 weeks; later, proteinuria and glycosuria appeared. There was loss of body weight and appetite after 42 weeks. There was no evidence of osteomalacia. They concluded that excretion of amino acids and enzymes in the urine can be used to detect early cadmium intoxication, whereas tests of tubular function should be useful to detect later cadmium nephropathy. However, their method for detecting urinary protein (a semiquantitative application of the biuret reaction) may not have been sufficiently sensitive to allow reliable estimation of small concentrations of urine protein. Axelsson and Piscator[233] found significant increases in amino acid excretion in the urine of cadmium-intoxicated rabbits only after development of proteinuria, as detected by more sensitive methods for protein determination. They administered cadmium chloride sc at 250 μg/kg to groups of Belgian Giant rabbits 5 days/week for 11, 17, 23, or 29 weeks; another group was similarly administered cadmium chloride for 24 weeks and observed an additional 25 weeks. Renal tubular changes were judged from microscopic examination of tissues, by a glucose reabsorption test, by alkaline phosphatase activity changes in the renal cortex, and from electrophoretic examination of urine protein; glomerular filtration was judged from a creatinine clearance test with extrinsic creatinine. Renal tubular damage was localized to the proximal segment. In rabbits exposed for a longer period, there were some microscopic changes in the glomeruli without definite impairment of the filtration rate. Cadmium was deposited mainly in the renal cortex, largely in the proximal segment of the tubules but also, to a lesser degree, in the distal tubules but not in the collecting tubules, glomeruli, or stroma. Excretion of cadmium in the urine increased greatly after renal damage occurred, correlating with proximal tubule function; eventually, after renal damage had occurred, cadmium was excreted in the urine in greater daily amounts than were being administered daily. Most of the cadmium in the urine was bound to colloids or cells.

In cats, fatty infiltration of the liver has been described[80] following exposure at high concentrations of cadmium oxide fume or dust, but not cadmium sulfide, for short periods of time. Liver enzyme changes were noted in animals given 1 ppm Cd(II) in drinking water (as cadmium chloride) for 11 months.[234] There was evidence of alterations in hepatic carbohydrate metabolism, ie, there was an increase in phosphatase and a decrease in aldolase activity. When larger amounts (10 ppm) were given for short periods, 60 days, oxidative phosphorylation activity in hepatic mitochondria was altered, ie, there was an uncoupling action by Cd(II). Cd(II) did not affect mitochondrial oxidative phosphorylation when fed at 1 ppm in water for a long period, 335 days.

The possible relationship of cadmium administration to dental caries has been investigated. Ginn and Volker[235] administered 50 ppm Cd(II) (as cadmium chloride) in food or in water to rats for 150 days; other rats were administered fluoride. Unlike fluoride, cadmium did not inhibit development of caries, and it may have increased caries susceptibility. Cd(II) decreased the degree of pigmentation of incisor enamel in these rats, and there was a reduction in blood hemoglobin. The authors suggested that the effects on enamel and blood were the results of interaction of cadmium with iron-containing proteins. In another experiment with rats given 40 ppm cadmium chloride in drinking water during the period of calcification of molars,[236] there was no increase in numbers of carious lesions, but there was an increase in their rate of progression, attributed to Cd(II) intake.

Correlation of Exposure and Effect

Cadmium compounds affect many organs and body systems. There is evidence from man or lower animals of effects on the respiratory tract, on the nervous system, on the liver, on formed elements of the blood, on vascular function, on male and female gonads, on thyroids, on pancreata, on bones, and, probably most importantly, on kidney function. In addition, there is evidence that cadmium may cause cancer and birth deformities.

(a) Respiratory Tract Effects

In the respiratory tract, irritation of the nasal mucosa with partial or total loss of the sense of smell has been observed in association with cadmium and nickel exposure[55,65,78] but, at least in one case,[79] there was a loss of sense of smell without evidence of exposure to airborne nickel in a zinc

refinery. Thus, it seems appropriate to conclude that exposure to cadmium compounds, albeit at high concentrations, can cause partial or total loss of the sense of smell. Whether this is due to olfactory nerve damage or to a more local effect is not clear. However, as was mentioned previously, Vorob'yeva[116] found increased chronaxy of the sensory nerves of the skin and the optic nerve in workers exposed to dusts of cadmium oxide.

Exposure at high concentrations has caused acute, fatal, pulmonary edema.[42-50] Lethal exposure levels have been estimated at 2,500-2,900 mg-min/cu m.[44,51,52] This is equivalent to 5-6 mg/cu m for an 8-hour day. Several epidemiologic studies[55,62,116] have reported workplace environmental concentrations well in excess of this concentration, without deaths. It may be that workers were not exposed to cadmium at such high concentrations for more than brief periods, and, since many of the measurements were based on area samples, that workers may not have been exposed at these concentrations at all. Or the discrepancy may in part be explained by different acute toxicities of fumes and dusts, since the latter studies[55,62,116] involved dust exposure. It is concluded that exposure at Ct's (product of concentration and exposure time) of around 2,500 mg-min/cu m may cause acute effects and should be prevented. The main relevance of this conclusion to an occupational standard for cadmium is to the development of a ceiling concentration and to work practices for operations generating large quantitites of cadmium oxide fume, such as brazing with cadmium-containing alloys.

There is considerable evidence of chronic obstructive pulmonary disease (emphysema) from prolonged exposure of workers to cadmium compounds.[34,53-56,58,59,126,127] In Friberg's comprehensive study of nickel-cadmium battery workers, published in 1950,[55] mean values from spirometric tests and spirometric measures in individual workers showed changes attributed to emphysema. While these effects could have been attributed to either nickel or cadmium, Friberg concluded, in part from his animal tests, that, although either nickel or cadmium was capable of causing emphysematous changes, cadmium was more potent in this respect than nickel. Baader[58] confirmed many of Friberg's findings in a German nickel-cadmium plant, but reported his findings in less detail. Bonnell[34] found some workers with sufficient obstructive lung disease to require hospitalization for shortness of breath; these workers were exposed to cadmium oxide fumes. Kazantzis[126] confirmed by spirometry that many of the workers in this plant had reduced pulmonary function, primarily in the time constant of the vital capacity curve. In those workers in this plant exposed for more than 10 years, Buxton [127] found significantly increased residual air volume and residual quotient, consistent with Friberg's observation[55] of a significant increase in residual quotient. Other epidemiologic studies, including recent ones from Belgium,[133-135] continue to confirm the ability of cadmium to cause functional changes consistent with emphysema. This cadmium-induced emphysema may be related to cadmium's ability to inhibit antitrypsin activity.[60]

(b) Blood Effects

Anemia associated with cadmium exposure has been reported in several groups of workers.[38,55,81] A few cases of elevated hemoglobin[44] probably indicate hemoconcentration from acute pulmonary edema. Anemia in experimental animals as the consequence of high doses of cadmium has also been reported,[138-140,143] and appears to be the result of iron deficiency. Elsewhere, cadmium's ability to cause zinc deficiency has been discussed (see Animal Toxicity), but there is only sparse evidence of cadmium's ability to cause iron deficiency, though other mechanisms for production of an iron-deficiency anemia could exist. However, bone marrow changes were not found in 19 workers studied by Friberg.[55] An apparent iron-deficiency anemia could be caused by a deficiency of copper, which is probably carried by the same transport mechanism (thionein) as cadmium. A deficiency of copper would not usually result in a marked alteration of bone marrow but would be evidenced by a normocytic anemia.

(c) Vascular Effects

Perry and Schroeder[83] have presented evidence of increased excretion of cadmium in the urine of hypertensive people, which may suggest that cadmium absorption can cause hypertension, and some experimental evidence from animal studies has supported this suggestion.[88,146-151] This hypertension may be due to cadmium's ability to inhibit utilization of zinc.[88] However, cadmium-induced hypertension has not been confirmed in workers studied[55] or in some experimental animals.[152] The facts implicating cadmium and those absolving it

as a factor in hypertension are impressive. Evidently, more research is needed to clarify the role, if any, played by cadmium in the genesis of hypertension. That one group of workers studied did not have elevated blood pressure[55] when other marked effects (anemia, proteinuria, emphysema, and anosmia) were present suggests that either high doses of cadmium or the presence of cofactors are required, but evidence for this argument is not adequately reassuring.

(d) Pancreatic, Thyroid, and Adrenal Effects

High cadmium levels in pancreata[94,115] and in thyroids[115] from human autopsy material suggest adverse effects of cadmium on these glands. There is limited confirmation of decreases in pancreatic function from animal studies.[230,231] There is also evidence from animal studies [154] that cadmium may increase adrenal activity.

(e) Nervous System Effects

Evidence of an adverse effect of cadmium on the nervous system is sparse. Vorob'yeva[116] found changes in the chronaxies of cutaneous sensory and optical nerves of workers exposed at high concentrations of cadmium. Other reports of fatigue[81] and duodenal or stomach ulcers[79] may conceivably reflect nervous system effects of cadmium, but such an attribution is very uncertain from the data presented. It does not now seem appropriate to conclude that cadmium exposure in the workplace will cause effects on the nervous system, but additional research to clarify this point is needed.

(f) Effects on Bones and Teeth

Bone changes from cadmium absorption have been especially marked in the Itai-Itai episode in Japan.[40,41,89] However, possible contributions by nutritional deficiencies, hormonal imbalance, or other factors seem likely. A group of workers in France also developed osteomalacia after exposure at high concentrations of cadmium,[38] but nutritional deficiencies were probably a contributing factor in these cases, also. There seems little reason to doubt that cadmium absorption was a significant factor, though not necessarily the only factor, in the etiology of osteomalacia in cadmium workers and in people absorbing high amounts of cadmium from pollution of water and resultant pollution of food (the Itai-Itai incidents). However, very high amounts of absorbed cadmium were required to produce the disease, so it is not a probable consequence of exposure to cadmium at concentrations relevant to development of an occupational health standard. Some evidence of carious teeth in association with cadmium exposure was presented by Hardy and Skinner,[81] and there is limited support for this in animal studies.[235] A yellow fringe on the teeth of workers has been observed by several investigators.[62,90] Its cause is not known, but it may reflect deposition of pigment formed from reaction of cadmium with sulfide from decomposition of proteins in the mouth, particularly at the rims of the dental alveoli.

(g) Hepatic Effects

There are a few reports of changes in liver function in cadmium workers.[55,61] Other studies have failed to confirm these findings.[34,54] Fatty infiltration of livers of cats,[80] liver damage in rabbits terminating in cirrhosis,[55] and changes in activities of liver enzymes in rats[234] have been reported as a consequence of cadmium administration to these animal species. Inadequate investigations of hepatic effects in workers exposed at high concentrations and lack of specific hepatic effects at the lower exposure levels, which caused only renal effects or renal and pulmonary effects in more recent studies, are suggested as the explanation for these apparent contradictions, but additional investigations are needed to confirm this suggestion.

(h) Gonadal Effects

Gonadal effects have been repeatedly demonstrated in lower mammals administered cadmium salts.[1 (pp 124-127),91,92,155,166-168] Testicular damage has also been noted in animals (trout) without scrotal testes.[156] Marked necrosis of testes and follicular atresia in ovaries have been consistently found. Repeated administration of cadmium at doses causing significant kidney dysfunction in mice and rabbits[162-164] did not cause testicular effects, indicating that absorption of cadmium in amounts not causing renal effects will not cause testicular changes or, probably, ovarian changes. Ovarian or testicular effects in humans have not been found, but they have not been investigated to a significant extent, probably because of the greater difficulties posed by studies of gonadal function in humans. One investigation[93] of fertility in cadmium workers found one case of impotency with low blood testosterone levels. Kazantzis et al[54] interviewed cadmium workers and took fertility histories, finding no definite evidence of sterility (this point was not further elaborated upon). Smith et al[94] noted high cadmium concentrations in testes of men exposed to cadmium fume. It is concluded that

gonadal malfunction may occur in workers exposed only rarely at sufficiently high concentrations, but it is unlikely that it would occur in concentrations relevant to establishment of an environmental limit, ie, at 100 μg/cu m or below. Methodologic difficulties in studying gonadal function in workers will make needed research in this area difficult. Subjective impressions of workers may add useful information.

(i) Renal Effects

There is a great amount of evidence of the ability of cadmium compounds to cause renal changes. In most cases, this evidence consists of reports of urinary excretion of protein, usually noted as being a low molecular weight protein.[34,54,55,57,61,63-65,76,133,143] In some cases, glucosuria[54,61,71-73] or aminoaciduria[54,71,75] were observed. (The glucosuria may have been the consequence of alterations in pancreatic function,[230,231] though renal dysfunction seems a more likely cause.) More overt evidence of renal dysfunction has also been observed, eg, reduced inulin clearance,[55] reduced urine-concentrating ability,[55,71] changes in the processing of uric acid, calcium, and phosphorus by the kidney,[54,71] and several cases of formation of renal stones.[55,76,77]

Renal dysfunction may be the cause of osteomalacia, though nutritional, hormonal, or thyroid-parathyroid influences may be involved in addition to, or in place of, such changes in kidney function as the adult Fanconi syndrome. Support for the theory that osteomalacia is the consequence of kidney changes comes from a case reported by Adams et al[71] of osteomalacia in a man with a severe defect in tubular reabsorption.

Data on which to develop the mechanism for cadmium-induced renal injury and on the detailed nature of the renal injury have not been presented in this Chapter. It seems evident that the primary effect is a decrease in tubular reabsorption of low molecular weight proteins, with a lesser effect on glomerular filtration, perhaps as a sequel to tubular malfunction. Friberg and coauthors have presented a detailed review of this[1 (pp 105-113)] and their hypothesis is recommended as the most useful explanation based on evidence so far available: ". . . cadmium is probably transported to the tubules bound to the low molecular weight protein, metallothionein. During normal conditions this protein will be reabsorbed in the tubules just as other proteins, and cadmium will accumulate in the renal tissue. Cadmium excretion in 'normal' people and in workers with short periods of exposure to low air concentrations of cadmium thus is low because proteins are almost completely reabsorbed. With increasing exposure more cadmium than can be bound by metallothionein will eventually be accumulated in the kidneys. Cadmium will then exchange with zinc in enzymes necessary for reabsorption and catabolism of proteins. . . As a result of these anti-enzymatic actions less protein will be catabolized or reabsorbed, causing tubular proteinuria. Cadmium excretion will increase also as less metallothionein will be reabsorbed. At this stage the accumulation rate of cadmium will become slower, but cadmium will still be reabsorbed and cadmium levels in the tissue may get still higher. The reabsorption defect will be greater and eventually renal cadmium will cease to increase. Tubular cells will be damaged by cadmium, and it is conceivable that cadmium will be excreted together with desquamated tubular cells, resulting in a decrease in renal levels of cadmium. If glomerular function is impaired, there will also be less filtration of metallothionein."

It is apparent that urinary excretion of low molecular weight proteins and perhaps also urinary excretion of glucose or amino acids constitute early evidence of altered tubular function. This evidence does not usually appear until some time after exposure at sufficiently high cadmium concentrations has started. Tsuchiya[63] found no proteinuria in men exposed at an average of 125 μg/cu m for less than 9 months, and workers with more than 5 years' experience had the highest urine protein levels. Kazantzis et al[54] noted that duration of exposure was important in the development of proteinuria; there were no workers with proteinuria in the group with less than 2 years' exposure, there were 3 workers with proteinuria in the group of 4 exposed 12-14 years, and all workers exposed more than 25 years had proteinuria. Friberg[55] found proteinuria only in those workers with more than 9 years of exposure; had more sensitive methods been used, he might have been able to demonstrate protein in urine after shorter periods of exposure. Tsuchiya[130] concluded, on the basis of a reexamination of workers previously studied[63] and found to have proteinuria, that proteinuria is reversible in some workers (probably those with proteinuria of shorter duration). Thus, testing of workers' urine at frequent

intervals should enable early detection of absorption of toxic levels of cadmium in time to take preventive measures that will prevent the development of serious kidney damage and, if the tubular changes can be reversed, that will enable the organism to correct the early malfunction in the tubules.

Monitoring of blood and urine cadmium do not, on the basis of available evidence, give sufficiently advanced warning of kidney dysfunction. It appears that urine cadmium may rise gradually as undue cadmium absorption continues, but does not rise markedly until more severe, probably irreversible, kidney injury has occurred. After marked kidney injury and marked increase in cadmium excretion has occurred, kidney cadmium levels may decrease significantly. This is taken into account in the hypothesis of Friberg et al quoted above and is exemplified by the finding of Lauwerys et al[133] that workers with severe proteinuria had high cadmium levels in their urine. A more detailed review of the possible significance of cadmium in blood and urine has been presented by Friberg and coauthors.[1] (pp 55-59, 65-72)

(j) Cancer

There has been much interest in the possibility that cadmium exposure may cause cancer, but the issue remains in doubt. Cadmium can clearly cause injection-site sarcomas in rodents[182-187] as well as testicular tumors from sc injection in another area.[188] Development of injection-site and testicular tumors could be prevented by injection of zinc salts.[188] However, injection-site sarcomas in rodents are not indicative of risk of cancer in man (except, perhaps, by injection). The testicular tumors are probably the consequence of hyperplasia and metaplasia from tissue regeneration following extensive tissue damage in the testes from absorption of cadmium. Experimental studies in rodents administered cadmium by long-term feeding[192] did not develop a significantly increased incidence of cancer, but feeding levels may have been too low to allow detection of an increased incidence of neoplasms. Similarly, the investigations of prostate cancer in rats and mice, [105-107] although negative, used dose levels that did not produce other significant evidence of cadmium toxicity and, hence, are not conclusive.

There have been several suggestions of an increased incidence in prostate cancer in cadmium workers.[65,71,96,97]. The replication, at least partial, of the population studied (British battery workers) in three of these reports[65,71,96] should be noted. Credence to only one of them, however, at least raises suspicions of a role by cadmium in the pathogenesis of some cases of prostate cancer. In addition, Lemen et al[97] found 4 cases of prostate cancer among 92 deaths in a study of mortality among 292 workers at a US smelter. The small number of cases in this report as well as the advanced ages of most of the men in all of the mentioned reports makes the argument that cadmium causes prostate cancer less persuasive than is desirable for firm conclusions. The high incidence of prostate cancer, at least histologically demonstrable prostate cancer whether in situ or invasive, in older men complicates the problem of settling etiologic relationships. Moreover, the men developing prostate cancer in British battery factories[65,71,96] were also exposed to nickel.

Lemen et al[97] also found an excess in total neoplasms, mainly in lung cancer, in this same population of workers at a smelter. NIOSH has previously concluded that inorganic arsenic causes a significant excess of cancer, especially lung cancer, based on a review[237] of epidemiologic studies of various populations including smelter workers. Whether exposure to arsenic at concentrations as low as 1 μg/cu m would cause lung cancer is not known; but it also isn't known whether past exposure concentrations had been low. Thus, the role of cadmium in the production of lung and other cancers in the population studied by Lemen et al is not clear. Kipling and Waterhouse[96] surveyed 248 cadmium oxide workers, and found no excess of bronchial carcinoma in this group. The number of the original group still alive was not stated except that it was mentioned that 30 of the 248 were still working.

A summary of the data of Kipling and Waterhouse and of Lemen and associates is presented in Table III-2.

(k) Reproductive Effects

Birth deformities in children of cadmium workers have not been studied, except in a study from the USSR where several children of female cadmium workers were found to have rickets or dental troubles. The number of such deformities was small and details important to an evaluation of the report are lacking, but the implication of the study, ie, that cadmium may be a teratogen, is supported by experimental investigations in

rodents.[95,170-178] Most of the abnormalities in rodents could be classified as delayed or erroneous ossification, such as spina bifida, facial and skull abnormalities, tail abnormalities, and defects in or absence of limbs. Development of cadmium-induced fetal aberrations could be completely prevented by injection of Zn(II) at the time of, or soon after, injection of Cd(II).[177,178] Thus, it is likely that cadmium's ability to inhibit zinc utilization is the cause of most or all of the teratologic effects observed, and that, if cadmium absorption were reduced sufficiently so that zinc utilization were not interfered with, cadmium would not be teratogenic. It should be noted, also, that in a reproduction study[179] involving several generations of rats teratogenic effects were not found.

Studies of whether cadmium is mutagenic are inadequate. Indications that Itai-Itai patients had an excess of chromosomal aberrations[112] were not confirmed in another study of Itai-Itai subjects,[111] involving a small population, however. In the same study,[111] Swedish battery workers exposed to cadmium were found to have a lower incidence of chromosomal changes than controls, but again the population studied was small. The significant difference between the chromosomal aberration rates in Swedish and Japanese persons in this study[111] is a curious but unexplained point. Another study[114] also found chromosomal anomalies in workers exposed to cadmium, but these workers were also exposed to lead and some to zinc in addition to cadmium and lead. Studies of dominant lethal mutations in mice[180,181] indicated that cadmium was not mutagenic by this test. In addition, male mice and their male first-generation offspring did not have aberrations in spermatocytic chromosomes.[181]

(l) Effects on Smokers

Several studies of the effects of cadmium on smokers as compared with nonsmokers have been conducted.[131-135] As would be expected, pulmonary function is poorer in smokers than in nonsmokers exposed to cadmium.[135] An additive rather than a potentiating effect seems more likely from the limited data. Smokers also had a higher incidence of proteinuria than did nonsmokers in a cadmium-exposed population in a Swedish battery factory.[132]

In addition, blood cadmium levels were higher in smokers than in nonsmokers exposed to cadmium in the workers studied by Piscator et al.[131]

(m) Sex Differences

Several workplaces have partially or completely replaced their male work force with women, so that comparative studies of the two groups of work populations might reveal something about differences in sensitivity to cadmium due to sex. However, with the replacement of male workers with women, control measures to improve workroom hygiene have also been instituted. Thus, the apparently greater resistance of women to cadmium, evidenced by fewer effects in women than in men previously employed in the same workplace, is probably due to the lower concentrations of cadmium aerosols to which women were exposed. For example, Piscator et al[131] studied women workers, most of whom worked in the plant previously populated by the men studied by Friberg,[55] and found significantly fewer effects than in the men studied previously; in fact, it is doubtful that his population was adversely affected at all. However, concentrations to which the women were exposed were significantly less (under 100 μg/cu m) than those of the male workers (3-15 mg/cu m), who developed many toxic effects, including emphysema and renal dysfunction. Tsvetkova[95] studied female workers in a plant where concentrations of cadmium were reportedly 0.1-25 mg/cu m; she found no effects in the workers (although she observed rickets and dental troubles in offspring), but it is not evident that she investigated such effects as those on the pulmonary and renal apparatus. Lauwerys et al[133] found no adverse effects in female workers but did observe evidence of altered pulmonary and renal function in male workers. However, the female workers were exposed at 31 μg/cu m whereas male workers were exposed at higher concentrations (66 μg/cu m and higher).

Tsuji et al[79] did not present environmental exposure data, so it is not clear whether their male and female workers were exposed at the same concentrations. If they were, a conclusion that the male and female workers did not differ significantly in sensitivity would be warranted. There was a 14.7% incidence of proteinuria in their male workers and 15.5% in female workers; there was a 7.8% incidence of glucosuria in male workers and a 1.4% incidence in women, based on measurement by test tape, which may be an inadequately sensitive method.

(n) Quantitative Relationships

Table XIV-2 shows toxic effects noted at various exposure concentrations in some epidemiologic studies. The concentration levels shown in the table are frequently oversimplifications of what was found in the environmental surveys, especially at the higher concentration values, and the discussion of the individual papers in *Epidemiologic Studies* should be consulted for a more thorough discussion of environmental concentrations found. It is nevertheless evident that environmental exposure levels of several tenths of a milligram of cadmium/cubic meter have usually resulted in emphysema and proteinuria and, often, in other effects such as anemia, anosmia, and a yellow fringe on the teeth. Changes in the respiratory system have not been reported at exposure concentrations less than 100 μg/cu m, except in groups studied by Lauwerys et al.[133,134] One of these groups[133] of workers, exposed at 66 μg/cu m, had a mean reduction in pulmonary function; however, some of these workers were reported to have been intermittently exposed to cadmium fume at unstated concentrations. It may be that they were exposed to fume at higher levels and that their pulmonary function results heavily weighted the average values. Fifteen of the workers in this group had proteinuria, so that only a few of these cases of proteinuria could be attributed to the additional fume exposure. The fact that all the workers in this group had been exposed to cadmium for from 21 to 40 years is probably significant, in that length of exposure is probably an important factor in development of cadmium toxicity. Taking these and other data into account, Lauwerys and coworkers recommended a workplace environmental limit of 50 μg/cu m, the same as the previous recommendation of Tsuchiya.[63]

There is some evidence of proteinuria in workers exposed to cadmium at concentrations less than 100 μg/cu m. As mentioned above, Lauwerys et al[133] found proteinuria in workers exposed 21 years or more at 66 μg/cu m. In another study by Lauwerys et al,[134] both proteinuria and slight but significant reductions in pulmonary function occurred in workers exposed at concentrations stated to be below 90 μg/cu m. The incidence of renal effects in this group was 9% in the group exposed for less than 20 years and 64% in the group exposed for more than 20 years.

In the population described by Piscator et al[131] there were no significant findings except an increase in haptoglobin in two groups classified by age. One elderly woman who had been classified as a suspect case in 1969 had proteinuria when airborne cadmium concentrations may have been higher. One control also had proteinuria, attributed to a bacterial infection of the tubules.

A striking demonstration of the effect of the concentration of airborne cadmium on renal disease is given by the two reports of Tsuchiya[63,130] describing workers in one plant, studied 10 years apart. In the earlier report,[63] environmental concentrations were around 125 μg/cu m and anemia (attributed in part to inadequate nutrition[130]) and proteinuria occurred in these workers. In his second survey,[130] Tsuchiya found some improvement in the condition of workers who had been examined in the previous study, and found no effects in workers who replaced those leaving employment after the first study. Environmental levels in the later report were reported to be 16-29 μg/cu m with higher concentrations for part of the time.

Thus, an environmental limit that will protect against the development of chronic obstructive pulmonary disease and against renal lesions as evidenced by low molecular weight proteinuria should be sufficient to protect against all toxic effects of cadmium with the possible exception of development of deformed offspring or neoplasms, if these are consequences of cadmium exposure.

Friberg and coauthors[1] (*pp* 79-80, 197-201) have discussed mathematical models for accumulation of cadmium in the renal cortex. Based on an accumulation model involving a simple logarithmic curve, they calculated the following exposures that would result in reaching the threshold of renal cadmium for renal injury: for occupational exposure, 30 μg/cu m in 10 years; for food intake, 0.4-0.6 μg/g wet weight; for community air (ie, continuous) exposure, 1-2 μg/cu m in 50 years; and from smoking alone, more than ten packs of cigarettes/day. However, various assumptions of uncertain validity are required for these calculations, and different assumptions could lead to different conclusions. Among these assumptions are pulmonary absorption, excretion rate, biologic half-time in the renal cortex, and kidney weight. The critical assumption is that the threshold cadmium concentration in the kidney cortex is 200 μg/g wet weight, and, while there are insufficient data on which to validate this assumption, it seems that this threshold concentration probably lies between 100 and 300 μg/g.

TABLE III-1

DESCRIPTION OF POPULATION EXPOSED TO CADMIUM

Group	Airborne Cd, μg/cu m		Population	Length of Exposure, years	
	Total	Respirable		Range	Average
E1	31	1.4	31 Women	1-12	4.1
E2	134	88	27 Men	0.6-19.7	8.6
E3	66	21	22 Men*	21-40	27.8

*Four of these men were also exposed intermittently to cadmium fumes.

TABLE III-2

SUMMARY OF CANCER MORTALITY DATA OF KIPLING AND WATERHOUSE[96] AND OF LEMEN ET AL[97]

Cancer Site	Number of Cases		Probability of Chance Occurrence
	Expected	Observed	
Kipling and Waterhouse*			
All sites	13.13	12	Nonsignificant
Bronchus	4.40	5	"
Bladder	0.51	1	"
Prostate†	0.58	4	0.003
Testis	0.11	0	Nonsignificant
Lemen et al*			
All sites	17.51	27	0.05
Respiratory system	5.11	12	0.05
Digestive system	5.78	6	Nonsignificant
Prostate§	1.15¶	4	"
Other unspecified	6.62	9	"

*Environmental data were not presented by Kipling and Waterhouse. In a 1973 industrial hygiene survey of the smelter studied by Lemen et al, most concentrations of cadmium were below 1 mg/cu m, but they ranged up to 24 mg/cu m; there were also low concentrations of arsenic found (about 1 μg/cu m).

†The ages at death of 3 of these 4 men were given by Potts[65] as 65, 65, and 75.

§The ages at death of these 4 men were 64, 71, 77, and 79.

¶If the comparison between observed and expected cases of prostate cancer deaths is limited to those who lived at least 20 years since their first exposure, the expected number is 0.88, which is significantly different from the 4 observed cases at $p<0.05$.