II. HEALTH EFFECTS

Background

Cobalt occurs naturally and constitutes about 0.001% of the earth's crust [1]. It is an integral part of the cyanocobalamin molecule (vitamin B12), which is essential in the human diet to prevent the development of pernicious anemia [2,3]. The average daily intake of cobalt from food for adults in the United States has been estimated to be about 300 μg, with an additional 6 μg obtained from water and less than 0.1 μg from community air [4].

Even though cobalt salts had been used for centuries to color pottery and jewelry [1,5], the first major industrial application of cobalt metal did not occur until 1927 [6]. At that time it was discovered that tungsten carbide, often in combination with titanium carbide and other metals, could be heated in the presence of cobalt used as a binder. This process resulted in a new substance referred to as cemented tungsten carbide or hard metal.

The current OSHA standard for occupational exposure to cobalt is based on the Threshold Limit Value (TLV) of the American Conference for Governmental Industrial Hygienists (ACGIH) in effect in 1968 [7]. In 1975, the ACGIH Committee on Threshold Limit Values proposed lowering the TLV for cobalt metal fume and dust to 0.01 mg cobalt/cu m [8]. This proposed value was subsequently amended to 0.05 mg cobalt/cu m in 1976 [9], and it remained as an intended change in 1980 [10].

Data projected for the first quarter of 1980 from the National Occupational Hazard Survey, conducted by NIOSH in 1972-74, indicate widespread potential for exposure to cobalt. About 867,000 workers were estimated to be exposed to cobalt oxides, and 235,000 to cobalt metal. At least 300,000 were estimated to be exposed to what was identified only as cobalt drier, and 79,000 possibly exposed to one drier, cobalt naphthenate. Exposure estimates for various cobalt salts are much lower, ranging from 1,700 to 21,000 workers, but are still substantial. (Exact figures are given in Table IX-1.)

Much of the information on cobalt's effects on humans is not from the occupational setting. For example, at one time it was common to prescribe mixtures of cobalt and iron to anemic patients in order to stimulate red blood cell production. This practice led to the discovery that cobalt, in addition to producing polycythemia, could adversely affect the thyroid. Another example is the considerable research conducted on the heart effects of cobalt after an outbreak of acute cardiomyopathy in beer drinkers who had consumed cobalt as an additive in beer.

Almost all information on adverse effects in workers exposed to cobalt is from the hard metal industry. Pulmonary fibrosis was first described in hard metal workers in a 1940 report in Germany [11], which was soon followed by others. Such reports persist even though the current Federal standard (29 CFR

1910.1000) for cobalt of 0.1 mg/cu m was based, to a great extent, on prevention of hard metal disease.

Respiratory Effects

Exposure to a single substance in the occupational environment rarely occurs. For cobalt, almost all reported cases of respiratory effects in workers concerned mixed exposures in the cemented tungsten carbide industry. Other substances present were tungsten carbide, and sometimes other metal carbides or material from grinding wheels. Workers who manufacture alloys containing cobalt are potentially exposed to many other metals including nickel, chromium, iron, vanadium, and molybdenum. The effects of concomitant exposure to these materials is unknown.

(a) Hard Metal Disease

Numerous case reports [12-22], medical examinations [11,23-32], and industry-wide studies [33-38] demonstrate the presence of hard metal disease in the occupational environment (Table IX-2). Although this is by no means a recent discovery, pulmonary fibrosis remains a problem in the cemented carbide industry. A common pattern of the illness is described in these reports. First, the worker develops a cough, followed by labored breathing on exertion. The person may lose a substantial amount of weight and develop a progressive interstitial pulmonary fibrosis; in the final stages leading to death, cor pulmonale and cardiorespiratory collapse are usually experienced. Chest radiographs reveal increased linear striations and diffuse nodular opacities in the middle and lower zones of the lung [39]. The degree of abnormality evident in the radiographs becomes greater as the stage of the disease becomes more severe. In some cases, the disease has been reversible or has not progressed [13,23-28] if it was detected at an early stage and the worker received no further exposure to cobalt.

While chest radiographs can detect fibrotic lesions, diagnostic tools capable of measuring adverse effects at an earlier stage are clearly needed. Spirometric examination to detect restrictive ventilatory impairment is one possibility, but the results do not agree totally on the sensitivity of this test. Perhaps much of the conflicting evidence is the result of the less sophisticated equipment available to the earlier investigators. Miller et al [23], in 1953, observed that three tool grinders had reduced vital capacity, but all three also had reticulations clearly evident in chest radiographs. Barborik [33], in 1966, observed disturbances of pulmonary ventilation in 25 of 116 cemented carbide workers, but he also observed changes in the chest radiographs of 31 of 193 (not all received spirometric examinations). Turos et al [29], in 1969, actually found a greater number of abnormal radiographs than changes in vital capacity in a group of 62 cemented carbide workers. In contrast, a more recent study of 22 tool grinders by Lichtenstein et al [40] found no radiographic evidence of fibrotic lesions even though several workers had slight reductions in forced vital capacity.

A series of reports [41-43] described the results of lung function tests in 155 Swedish cemented carbide workers and 74 controls matched for sex, age, and smoking history. Tests conducted included spirometry and single breath nitrogen washout. Persons exposed at cobalt concentrations of 0.005-0.01 mg/cu m, persons dry polishing sintered material (average exposure of 0.01 mg/cu m), and persons wet polishing sintered material (average exposure of 0.008 mg/cu m) showed some changes in pulmonary function during the working week, but recovered over the weekend. Inspectors (average exposure of 0.002 mg/cu m) showed no changes. Persons who were heavily exposed (average cobalt concentration of 0.06 mg/cu m) showed changes throughout the week, which did not regress over the weekend or even over 1-month vacations. Smokers were more affected than nonsmokers. The authors interpreted the changes in pulmonary function tests as evidence of airway obstruction. They noted that they could not exclude the possibility of chronic reduction of lung function in the most exposed group.

Although diffuse interstitial lung disease has clearly been demonstrated as an occupational disease related to exposure in the hard metal industry, the dust concentrations that cause an effect and the role of cobalt must be considered. Exposure estimates were given in some cases, but the duration of exposure was unclear for persons who developed fibrosis. In some instances, fibrosis was reported after only a few years of exposure [11,13,29]; in others, some persons had been exposed more than 20 years [26,30,34]. Recent investigations [30,40] have shown localized clouds of dust in the breathing zones of grinding machine operators, a factor that may have been missed in earlier reports. All of these factors could account for discrepancies in the observed levels of airborne cobalt at which fibrosis has occurred. Nevertheless, some correlation between cobalt exposure and adverse effects in hard metal workers can be made. Because mixed exposures to cobalt and other substances occurred, the role of cobalt in producing the effects can be established only when supporting evidence in experimental animals becomes available. Such information exists now only for cobalt metal [44] and cobaltous oxide [45].

Exposures in the hard metal industry where the cobalt concentration in the air averaged several milligrams were clearly intolerable to workers. For example, Kaplun's study [35], reported in 1957, described pulmonary changes in 8 of 247 workers; exposure levels measured in the plant were 0.8-12 mg of cobalt/cu m of air. The workers complained of nausea, abdominal pains, loss of appetite, cough, and a deterioration of the sense of smell. Some also had decreased hemoglobin (Hb) levels and red blood cell (RBC) counts, liver and spleen enlargement, and dermatitis. After dust control measures were implemented, the levels of airborne cobalt decreased to 0.4-3.3 mg/cu m. Later, 117 workers were examined, and 35 (30%) had chronic bronchitis, 33 (29%) had early fibrotic changes evident in chest radiographs, and 52 (44%) had decreased blood pressure. Reasons for the increased incidence of pulmonary changes at the lower exposure level were not given. Any number of factors could have been involved, including the slowly progressive nature of fibrosis in an aging workforce.

Barborik [33] described an investigation of 193 hard metal workers (104 men and 89 women) who had been employed for 1-13 years. Dust concentrations in the plant were 13-100 mg/cu m, and the dust contained 5-25% metallic cobalt. Of the 193 workers, 47% suffered from cough; numerous workers in the preparatory area and the forming area also complained of labored breathing, a burning sensation in the throat, and loss of the sense of smell. In 31 workers, distinct changes were observed in radiographic films of the lungs, and 25 of the 116 workers examined showed moderately severe to severe disturbances of pulmonary ventilation.

Salikhodzhayev and Vengerskaya [36] reported that 73 of 178 hard metal workers (41%) had chronic rhinitis and rhinopharyngitis. Cobalt concentrations in the air ranged from 0.4 mg/cu m where the distillers were unloaded to 2.9 mg/cu m at the sifting site. In a subsequent report [46] that appears to be on the same workers, 50% of those examined reported toxic signs or symptoms. The most frequent worker complaints included labored breathing, coughing, pounding of the heart, headache, dizziness, nausea, loss of appetite, and olefactory disorders. Medical tests revealed evidence of altered kidney and liver function.

In several studies, airborne dust measurements were made, but the information is inadequate to provide a meaningful relationship between cobalt exposure and fibrosis. For example, Moschinski et al [34] examined 282 male and 23 female workers at four plants, 56 of whom had radiographic evidence of fibrosis, but found no relationship between duration of exposure and onset of symptoms. A similar difficulty exists in analysis of the report of Reber and Burckhardt [13]. Nine workers showed signs of pneumoconiosis, but one of two exposure estimates varied from 0.06 to 0.3 mg cobalt/cu m. Tolot et al [24] and Dorsit et al [25] observed 3 cases of fibrosis and 26 cases of lesser pulmonary involvement in workers employed in a plant that manufactured alloys of sintered metals. Since dust concentrations were 2.3-10.6 mg/cu m and contained 0.01-0.3% cobalt, this might demonstrate a fibrotic response at very low concentrations of cobalt. However, the major components of the dust were not identified. Jirkova [30], in 1971, described an examination of 61 grinders employed in the production of sintered carbides. Concentrations of airborne cobalt near grinding machines with cooling or dust-collecting equipment averaged 0.043 mg/cu m (range, 0.006-0.09). Near grinding machines without safeguards, the concentration was 1.2 mg/cu m (range, 0.84-1.3). Unfortunately, the report did not state whether all 6 workers with fibrosis or the 23 with lesser signs were exposed at the higher dust levels and whether all of the workers used both types of equipment.

Few reports described toxic effects in hard metal workers at relatively low and constant concentrations of cobalt. Fairhall et al [37] found little evidence of fibrosis in a group of 1,802 workers, some of whom were probably exposed to cobalt at measured levels of 0.05-0.14 mg/cu m. Because this cross-sectional industry survey was reported only 20 years after the process was first developed, many persons in the group had probably been exposed to cobalt for only a short time. Miller et al [23], also in an older study, described three cases of fibrosis in tool grinders. The concentrations of cobalt in the breathing zone of grinding machine operators were 0.1-0.2

mg/cu m; tungsten was not found in general air samples. These three workers had been exposed for 6-8.5 years, and had used silicon carbide and aluminum oxide wheels, although a diamond wheel was used for most grinding. In 1975, Lichtenstein et al [40] found some cases of early signs of restrictive ventilatory impairment, but no radiographic evidence of fibrosis, in 22 grinding machine operators using diamond wheels and exposed to cemented carbide dust for 1-30 years. The mean TWA concentration of cobalt in the breathing zones of seven individuals was 0.18 mg/cu m (range, 0.03-0.43); four concentrations exceeded 0.1 mg/cu m. The latter two studies [23,40] support a tentative conclusion that hard metal workers can develop fibrosis or prefibrotic changes when exposure to cobalt is in the range of 0.1-0.2 mg/cu m. The Swedish studies [41-43] suggest possible chronic lung obstruction at average concentrations of 0.06 mg/cu m.

(b) Other Respiratory Diseases in Hard Metal Workers

Several reports have also described evidence of bronchitis [11,13,29,34], emphysema [13,14,16,30], or asthma [13,14,24-26,47] in workers exposed to cobalt in the hard metal industry. Bronchitis was said to be more prevalent in workers exposed to what were described only as large dust particles; pneumoconiosis was said to have occurred more often after exposure to dusts of smaller size [11].

The asthmatic responses seem to represent a true sensitization to cobalt. These persons developed a hacking [26] or wheezy [14,26] cough within 1 month [26] to 1.7 years [24,25] of initial exposure to cobalt. One person also had eczema [13]. Recovery occurred when the workers left the work environment [13,14,24-26,47]. One worker remained on his job as a tool grinder, and he developed nodules visible on chest radiographs 2.5 years later [26]. The others had no signs of fibrosis.

A recent study at a Swedish hard metal plant attributed four cases of allergic alveolitis to exposure to soluble cobalt dissolved in the coolant used for wet grinding [48]. One worker showed only signs and symptoms of asthma, but the other three showed evidence of mild pulmonary fibrosis as well. All four had contact eczema and were sensitive to cobalt. Even though they ceased all exposure to cobalt, the four persons have continued to show abnormalities on their chest radiographs.

(c) Other Reports of Respiratory Disease in Workers Exposed to Cobalt

Studies of the effects of cobalt exposure on workers not employed in the manufacture or use of hard metal are rare, but some indicate pulmonary disease in these workers. At a Finnish metal refinery, one or two new cases of bronchial asthma had been diagnosed annually in a group of 230-240 cobalt workers [49]. A cross-sectional study demonstrated a highly significant correlation between exposure to cobalt sulfate and asthma. In contrast, nonasthmatic cobalt workers at the same plant had no evidence of any excess of chronic bronchitis. Kochetkova [50] described the death of a woman with a history of 7 years of exposure to metallic cobalt dust. The cause of death was cardiopulmonary insufficiency resulting from massive fibrosis. Levels of

cobalt in the lung, liver, heart, and kidney tissue were described as markedly elevated. Her heart was enlarged, the liver and spleen were congested, and the cortical layer of the kidneys was swollen. In contrast, Cau et al [51] did not find radiographic evidence of fibrotic damage to the lungs of seven workers employed as sifters of cobalt powder. The workers had been exposed from 2 to 5 years, and they complained of cough, exertional dyspnea, nasopharyngeal irritation, and digestive disorders; two subjects had polycythemia. The authors concluded that exposure to finely divided cobalt metal dust did not induce pulmonary damage. In light of the toxic signs described by the workers and the short duration of exposure, this conclusion seems inappropriate.

An extensive study of workers exposed to cobalt was reported by Verhamme [52] in 1973. Medical examinations had been given to workers at a plant where cobalt oxides, powders, and salts were produced. Measurements of airborne cobalt were not reported, but the author believed that workers in the hydrometallurgic area had little or no dust exposure and that workers in the salts, oxides, and finished powders production areas were the most exposed groups. The finished powders had an average diameter of less than 1.4 μm, and oxides averaged 3 μm in diameter. Radiographic examination of 120 workers revealed no changes in 112 persons, accentuated pulmonary reticulations in 1 worker, fibrotic changes in 4 individuals known to have had tuberculosis, and evidence of pneumoconiosis in 3 workers with extensive coal mining experience. Several workers employed 15-20 years in the production of cobalt oxides showed symptoms of chronic bronchitis that improved or disappeared with job transfer. The plant had assigned workers to areas on the basis of their medical histories.

(d) Evidence in Animals

Several investigative groups have administered cobalt intratracheally in animals and reported adverse effects on the lung. Harding [53] found marked edema and hemorrhages in the lungs of rats shortly after they were administered large doses of cobalt metal. Guinea pigs given 10 or 25 mg of cobalt metal developed acute pneumonitis [54]. The lungs of guinea pigs that survived a 50-mg injection of cobalt metal had perivascular diffuse cellular infiltration and many eosinophils within the alveoli [55]. Regional obliterative bronchiolitis, with peribronchiolar fibrosis and arteriolar spasm, was also present. After 12 months, there was fibrocellular infiltration and there were regions of adenomatosis where cobalt metal was deposited. Those that survived a 25-mg dose had similar but less intense evidence of damage to the lungs, and a 10-mg dose produced no long-term tissue damage. The effects in guinea pigs [55] were consistent with those described by Schiller [56], who observed that as little as 1 mg of cobalt produced intra-alveolar pulmonary edema and inflammation of the bronchioles of rats after 6 hours; no tissue damage was observed 3 months later. These studies clearly demonstrate adverse reactions of both a short- and long-term nature.

Although tungsten carbide was nontoxic when administered intratracheally to animals, different results occurred when this substance was mixed with cobalt. Delahant [54] noted that tungsten metal dust, tungsten carbide, and a

91:9 mixture of tungsten carbide and cobalt administered in 150-mg doses produced no deaths in guinea pigs. Elaborating on this study, Schepers [57] reported that the lungs of guinea pigs administered the 91:9 mixture contained focal accumulation of massed particles in the alveolar spaces surrounded by fibrous tissue. This study [57] supports the previous one [55] suggesting a fibrogenic potential for cobalt, but it does not clarify whether the reaction is intensified by the presence of tungsten carbide.

Studies that have examined subchronic or chronic effects of inhalation of cobalt compounds are limited. In one such experiment, Kerfoot et al [44] exposed miniature swine to aerosols of cobalt metal. Two experimental groups, exposed to cobalt at 0.1 mg/cu m or 1 mg/cu m, and one control group of five animals were used. To investigate the suggestion of Bruckner [58] that pulmonary reactions to cobalt may be mediated through a hypersensitivity mechanism, Kerfoot et al first exposed the experimental animals 6 hours a day for 5 days. After a 10-day lapse, the animals were reexposed 6 hours daily, 5 days a week for 3 months. All animals appeared normal until the 4th week of exposure, after which time the animals from both cobalt groups became lethargic. Some animals appeared to be wheezing during exposure; this was confirmed by auscultation.

Postexposure pulmonary function tests showed a significant reduction in mean tidal volume, mean total compliance, and mean specific compliance in both cobalt-exposed groups [44]. The authors interpreted change in compliance as demonstrating functional lung impairment. This change was reversed in animals examined 2 months after the cobalt exposure ended.

Serial radiographs conducted on all animals showed no evidence of diffuse pulmonary disease [44]. The animals were examined grossly and by light microscopy at necropsy, and the lungs, heart, liver, and kidneys did not show any persistent or significant abnormalities. There was no evidence of cobalt in any lung tissue examined. Electron microscopic examination of lung biopsy tissue taken at the end of exposure revealed masses of collagen, elastic tissue, and fibroblasts in some of the tissues. However, no quantitative analysis was presented, nor was there mention of the methodology used in selecting tissue sites for examinations. The greatest changes were observed in the high-concentration cobalt exposure group, with the fewest changes being observed in controls.

In a Soviet study, male albino rats received exposures to aerosols of metallic cobalt continuously (24 hours a day, 7 days a week) for 3 months [59,60]. There apparently was a concurrent control group, but the reports did not contain important details such as the number of animals exposed or tables of results presenting actual data. Chronic inhalation of cobalt at 0.5 mg/cu m was said to be irritating to the lungs [59]. The animals exposed to cobalt at 0.05 and 0.005 mg/cu m were described as having changes similar to, but less pronounced than, the changes in animals exposed at 0.5 mg/cu m. The lowest concentration (0.001 mg/cu m) produced what was described only as a weak general toxic effect.

Microscopic examination of lung tissue from animals exposed at the highest concentration of 0.5 mg/cu m revealed accumulations of macrophages in the alveoli [60]. Interalveolar septa were consolidated in several areas of the lung. The severity of these changes reportedly was related to the exposure concentration. The lungs of animals exposed at 0.001 mg/cu m were described as similar to those of controls. While information in this report is not completely satisfactory, effects such as consolidation of the alveolar septa are indicative of a prefibrotic condition.

Wehner et al [45] exposed 2-month-old Syrian golden hamsters to cobaltous oxide aerosols at 10 mg/cu m for their lifespans. The animals were exposed for 7 hours daily for 5 days a week to aerosols with a median diameter of 0.45 μm. Particulate material accumulated in alveolar macrophages and became denser as exposure continued. Emphysema became apparent. The extent of the changes became more severe as exposure time increased, and hyperplasia and hypertrophy of alveolar lining cells also appeared. Macrophages, frequently containing particulate matter, increased in number throughout the lung, and numerous focal accumulations of these cells could be found. Proliferative changes involving the epithelial components of bronchi and bronchioles became detectable early during exposure and increased in severity with exposure time. Laryngeal lesions occurred in five animals (10%) during the study. The lifetime exposure of hamsters to cobaltous oxide clearly resulted in pneumoconiosis, but it did not significantly shorten their lives.

From the experimental studies in animals, the ability of some cobalt compounds to cause pulmonary fibrosis is evident. However, the information is insufficient to determine what effect, if any, exposure to other substances often present in cemented tungsten carbide may have on the development of hard metal disease. Thus, the possibility must be considered that adverse effects in workers exposed to cobalt at the 0.06-0.2 mg/cu m range were aggravated by exposure to mixtures. However, the degree of worker exposure to cobalt is clearly related to the number of signs and symptoms observed in workers. Thus, decreasing exposure to cobalt should reduce the risk of adverse health effects. For cobalt metal, results in animals indicate that worker exposure should be limited as much as possible, and that in no case should the present Federal limit be exceeded. Similar information is not available for any other cobalt compound, including those in commercial use.

Effects on the Skin

The incidence of sensitivity to cobalt in the general population appears to be low; in a small group (41 persons), none showed a positive response [61], whereas 0.8% and 1.8% did in two larger studies [62,63]. In persons with dermatosis, the observed incidence of sensitivity to cobalt, although somewhat dependent on experimental design, has been about 5-10% [62,64-66]. Intradermal testing results were more easily correlated to occupation than the results from patch tests [67]. Some cobalt-sensitive persons react to extremely low concentrations; in one study, 14 of 60 responded to topical application of 0.16% cobaltous chloride [68]. In another group, several of the 18 cobalt-sensitive individuals tested responded to 0.000001% cobaltous

chloride given intradermally [69]. Of 379 persons with hand dermatitis, 17 who had not been cobalt-sensitive responded to cobaltous chloride when given a second patch test 6-21 months later [65]. These results suggest that the patch test itself induced sensitivity to cobalt in some cases. A single report [70] demonstrated that most persons who are sensitive to cobalt sulfate respond to cobaltic trisethylenediamine chloride, chloropentamine cobaltic chloride, and sodium cobaltinitrite as well. Thus, sensitization to cobalt, regardless of the compound involved, seems probable.

A number of studies [67,70-80] have considered sensitivity to nickel and chromium as well as to cobalt in persons with dermatitis or eczema. The populations studied ranged from 9 [74] to 5,416 persons [75]. The percentage showing a positive response to cobalt ranged from 1.6 [67] to 100 [76]. Cobalt-sensitive individuals showed an incidence of positive responses to nickel, or chromium, or both substances that ranged from 18.2% [77] to 100% [74,76,78-80]. When all available data are combined, approximately 5% of the persons studied were cobalt-sensitive; 82% of these had combined metal sensitivities. All three metals are prevalent in the general environment, which suggests that individuals with cobalt sensitivity also have had contact with nickel and chromium. Their responses thus could represent independent sensitization reactions, so that cross-sensitivity is not necessarily implied.

Very few reports on skin diseases in workers who have contacted cobalt have been published. Skog [81] evaluated the reaction of 14 hard metal workers with eczema to patch tests with a 2% cobaltous chloride solution. Only three were sensitive to cobalt. In the other cases, eczema was believed to be due to the irritant effect of hard metal dust. In another study [29], 6 of 68 hard metal workers had dermatitis or eczema at the time of a medical examination. Four persons, including one with no skin disorders, responded to topical applications of 2% cobaltous chloride. Two remained sensitive to cobalt when tested 3 years later even though they had transferred to work environments free of hard metal dust. Among 436 pottery workers, 12 responded to the topical application of a 5% solution of cobaltous nitrate [82]. In workers with dermatitis, only 1 of 18 (5.6%) who had this condition for a month or less was sensitive to cobalt, compared with 9 of 28 (32.1%) workers with dermatitis for more than a month. In a survey of 1,004 persons with eczema from occupational and nonoccupational causes, 41 of 246 (16.7%) building trades workers with cement eczema were sensitive to a 5% solution of cobaltous chloride [83]. Twenty-six of 293 (8.9%) other individuals with occupationally-related eczema were sensitive to cobalt, as opposed to 77 of 296 (26%) with nonoccupational dermatoses. Considerably more information is needed before a realistic estimate can be made of the extent to which cobalt-induced dermatosis affects the workforce. Nevertheless, sensitization to cobalt does occur, and persons once sensitized would have difficulty continuing to work with cobalt. It is probable that many of these persons are transferred to other jobs.

The mechanism of the allergic response to cobalt after dermal contact is unknown. Haxthausen [84] contended that about 90% of the cobalt is absorbed from the skin following intradermal administration before any allergic reaction becomes visible. Norgaard [85], however, reported that cobalt is not

absorbed through intact skin when applied to the forearm as a 0.3% or 5% solution. This same study reported systemic absorption of cobalt in solutions applied to the depilated skin of rabbits and guinea pigs [85]. Another investigative group also observed systemic absorption when solutions of cobaltous chloride were placed on the clipped backs of guinea pigs [86]. From this information, NIOSH concludes that the risk of systemic poisoning from dermal absorption of soluble salts of cobalt is minimal for skin contact under normal working conditions. Abraded skin should be adequately protected to prevent contamination with cobalt compounds so that systemic absorption will not occur.

No information is available to judge the effects of many cobalt compounds. Some organocobalt complexes are uncharged and relatively apolar, which would indicate that they probably can be absorbed dermally at least as effectively as the inorganic salts. At least some of these complexes may be stable compounds in body fluids, so that their toxic effects could differ from the simple salts.

Cardiac Effects

Some cobaltous salts have been implicated as a causative agent in certain forms of cardiac disease. Cobalt, in the form of cobaltous sulfate or cobaltous chloride, was used as a foam stabilizer in beer during the mid-1960's in various countries, including the United States. Between 1964 and 1966, American breweries reportedly added 1-1.5 ppm of cobaltous chloride to 20-25% of all beer sold in the United States [87]. At the same time, several epidemics of a peculiar form of cardiomyopathy occurred among heavy beer drinkers in Quebec, Belgium, Omaha, Minneapolis, and New York [87-92]. All patients were heavy beer drinkers. For example, the Quebec group consumed daily from 2 to more than 6 liters of beer containing 0.8 to more than 1.6 mg cobalt/liter [93-95]. The signs and symptoms of illness in the beer-drinking patients included gastrointestinal problems, labored breathing, abdominal pain, cyanosis, lowered blood pressure, heart enlargement, pericardial effusion, rapid heart rate, and electrocardiographic (ECG) abnormalities. In one group, azotemia or oliguria, or both, were frequently noted, especially in fatal cases [90]. Sullivan et al [96] found cobalt concentrations 10 times normal in heart tissue of several persons who had died from beer drinkers' cardiomyopathy. In 20 who survived, 11 had ECG abnormalities persisting for up to 24 months [97].

The extensive literature on beer drinkers' cardiomyopathy suggests that factors in addition to cobalt may have contributed to the effects seen. Several authors suggested that cobalt may have increased existing cardiac impairment induced by thiamine deficiency [90,93] or excessive ethanol consumption [87,90]. Nutritional deficiencies other than lack of thiamine also may have contributed to the cardiomyopathy. The diet of a group of Belgian beer drinking patients was nutritionally inadequate, especially in regard to protein [91]. In contrast, chronic beer drinkers who did not develop marked cardiac abnormalities had nutritionally adequate diets. They

were brewery workers who had consumed a daily average of 16 glasses of beer containing 1.2 ppm cobalt.

The effects of cobalt on cardiac function have been examined in controlled experiments in humans. Garello et al [98] hypothesized that cobalt exerts a direct effect on the biochemical phenomena responsible for cardiac contraction. This hypothesis was based on the observation that a daily intramuscular (im) injection of 20 mg cobalt benzenesulfonate (equivalent to 3.2 mg cobalt) for 5 consecutive days resulted in slight increases in heart rate, atrioventricular conduction time, and duration of systole. Similar ECG changes had been reported [99] after im injection of mixtures containing 20 mg cobaltous chloride and 10 mg cobaltous benzenesulfonate. These experiments, of short duration, in humans do not account for the severe effects observed in the beer drinkers.

Animal experiments, often conducted for longer periods, present a different picture. In 20 male guinea pigs fed cobaltous sulfate for 5 weeks at high levels (stated to be 20 mg cobalt/kg daily), heart weights and ratios of heart weight to body weight were increased, and pericardial effusion was observed in 9 (45%) animals; myocardial degenerative changes were present in 15 (75%) [100]. Swigart [101] also found a significant increase in mean heart weights as well as right ventricular hypertrophy in rats administered 2.5 mg cobalt/kg (as cobaltous chloride) intraperitoneally (ip) for 63 days. Although microscopic changes were not reported in Swigart's experiment, Lin and Duffy [102] found cardiac lesions in rats following ip injection of 5 mg/kg cobalt (as cobaltous nitrate) daily for up to 7 days. The lesions resembled those observed in cardiomyopathy due to alcoholism, thiamine deficiency, and chemical toxins, and similar observations in rats [103] and in rabbits [104] were made by other investigators.

Kucharin and Sinitsin [105], in 1976, reported on a condition characterized as allergic myocarditis in five workers employed in the cobalt shop of a foundry for 2-19 years. Cardiac enlargement was the principal clinical finding. All five persons had abnormalities in ECG patterns that improved or disappeared in 1-2 years. At the height of their illness, heart volume was increased 51-110%. Blood counts reported for one subject indicated elevated Hb and RBC levels. The authors considered the disease to be of occupational origin and attributable to cobalt. However, data to support this conclusion were not provided in the report.

Alexandersson and Atterhog [106] examined dry and wet grinders exposed to cobalt at 0.01 mg/cu m and powder handlers exposed at 0.06 mg/cu m. No ECG changes were observed in dry grinders or powder handlers, even though the powder handlers showed evidence of impaired pulmonary function. The ECG's of wet grinders were abnormal and showed a high incidence of ectopic (premature) heartbeats. However, the authors believed that the ECG changes were related to exposure to cutting oils rather than cobalt.

Only one study in animals has examined the effects on the heart of cobalt exposure similar to that encountered in the workplace. In the study on miniature swine exposed to cobalt metal dust at 0.1 or 1 mg/cu m, Kerfoot and

coworkers [44] observed abnormalities in ECG's taken at the end of the 3-month exposure period. These alterations were interpreted by the authors to indicate a decrease in the strength of ventricular contraction and repolarization abnormalities.

Sufficient evidence exists to suggest that both cobalt metal and cobalt salts can produce cardiac changes, but apparently only at high doses. It should be noted that the amount of cobalt ingested daily by persons who consumed 6 liters a day of beer was about 5-10 mg, much higher than the amount inhaled by a worker breathing 10-15 cu m of air in a day at the current Federal limit of 0.1 mg/cu m. The question of whether changes such as those seen in the miniature swine could result in significant problems over a long period of exposure in especially susceptible individuals, such as those with existing heart disease and, possibly, persons who consume alcohol on a regular basis, needs to be examined.

Effects on Blood

Cobalt-induced polycythemia is a well known effect. This property of cobalt has been exploited therapeutically in the treatment of refractory anemia [107-115]. The information collected for this review, however, revealed that other lesser known effects may occur at concentrations below those needed to produce polycythemia. The information available, although often incomplete, is presented below.

The polycythemic effects of cobalt have been observed not only in patients but also in controlled experiments in persons with normal blood counts and in animals. Volunteers receiving oral doses of cobaltous chloride ranging from 100 to 1,200 mg daily for 1-12 weeks [107] or 120-150 mg daily for 1-3 weeks [116] experienced an increase in RBC and Hb levels. Numerous studies [117-125] in animals administered cobaltous chloride at high dosage levels for as long as 16 weeks either orally, or by subcutaneous (sc) or ip injection, also reported slight to substantial increases in RBC or Hb. One study in mice demonstrated an increase in RBC's subsequent to ip injection of cobaltous nitrate [126]. However, inhalation studies in animals exposed to cobalt metal [44,59] provide little evidence to support the contention that polycythemia would be expected in workers exposed to cobalt at low concentrations. Similar studies on cobalt salts have not been conducted. Since the effects of cobalt on the blood would be expected to depend on its ability to concentrate at certain critical sites, cobalt salts might demonstrate effects at levels differing from cobalt metal. However, the mechanisms responsible for the changes in blood that are induced by cobalt are not known.

While a polycythemic effect is clearly demonstrated in the reports described above, cobalt may also interfere with iron absorption from the gastrointestinal tract, indirectly affecting Hb formation. Rats administered 0.3-3 mg of iron by stomach tube had a significant decrease in iron absorption with the addition of 3 mg cobalt as the chloride salt [127,128]; this finding was confirmed in a subsequent study [129].

Several surveys have examined the possibility that polycythemia might result from industrial exposure to cobalt. Fairhall and coworkers [37] found no evidence of polycythemia in a survey of 1,802 cemented carbide workers. Cobalt exposures ranged from 0.05 to 0.14 mg/cu m. Verhamme [52] also found no evidence of polycythemia in 83 workers at a plant producing cobalt oxides, powder, and salts. However, Barborik [130] and Kaplun [35] independently found evidence of polycythemia in hard metal workers. Kaplun reported that RBC's were increased in workers described as having many years of service; the levels of airborne cobalt were 0.4-3.3 mg/cu m. Barborik found a higher mean Hb level in 88 male and 70 female workers than in a control group of 149 men and 70 women. RBC's, measured in 41 men and 34 women, were also elevated. Sixteen workers had Hb levels at least 19% above those found in controls, and seven had RBC increases in excess of 12.5%. All but two workers remained at their jobs, and a subsequent survey failed to duplicate these results. In contrast to the well known polycythemic effect, Sozieva [131] found a reduced Hb level in 22.8% of a group of hard metal workers exposed to cobalt. Hypotension was also said to be present in most of the exposed workers. Dust levels ranged from less than 10.6 to 62.6 mg/cu m, but the cobalt content was not reported. Kaplun [35] also found decreased Hb levels and RBC's in 247 hard metal workers exposed to cobalt at 0.8 to 12 mg/cu m. Although limited, this information suggests complex and possibly conflicting mechanisms of action of cobalt on blood components.

Even though experiments in animals suggest the possibility that cobalt could affect the white blood cell (WBC) count, this effect has apparently not been examined in workers. Miniature swine exposed to cobalt metal dust showed an increase in WBC's during the 3rd week of exposure [44]. Other investigators have examined the effect of cobaltous chloride [122,132-136] or cobaltous nitrate [126] on the WBC's of animals. Some reported a slight to significant increase [122,133-136], one reported a decrease [132], and one reported no significant change [126]. Since WBC's would be affected by infection, NIOSH concludes that this limited information is insufficient to demonstrate a causal relationship with exposure to cobalt.

Effects on blood components other than the cells may occur at exposure levels not producing polycythemia. A number of animal studies demonstrated certain nonspecific changes in blood protein levels. Significant increases in total protein and globulin levels were found in rabbits receiving im injections of cobaltous chloride [135]. Similar changes in serum globulin levels, but not in total protein, were found in a second study [137]. Cobaltous chloride administered to dogs by sc injection and to rabbits by ip injection resulted in significant increases in alpha-globulin levels even though RBC and Hb levels were unaffected [138]. Similar results were obtained when rabbits were exposed to aerosols of cobalt metal. Miniature swine exposed to cobalt metal dust at 0.1 or 1 mg/cu m had slight increases in alpha-globulin levels [44]. In humans, the mean erythropoietin level was 58% above that of controls in 21 persons employed in the hydrometallurgical production of cobalt even though no changes in RBC, hematocrit, or Hb levels were found [139]. Concentrations of airborne cobalt ranged from 0.43 to 1.6 mg/cu m. Increased serum globulin levels cannot be related readily to any specific disease state, but the increases in erythropoietin, a substance that

migrates electrophoretically with the alpha-globulins, may be highly relevant to the polycythemic effects of cobalt. Erythropoietin is involved in the regulation of erythrocyte production.

A second effect that could be relevant to persons exposed to cobalt in the occupational environment is the apparent ability of cobalt to prolong the time needed for blood clot formation. Ternovi and Mosketi [140] reported significant changes in blood clotting time (35% increase), thromboplastic activity (28% decrease), and clot retraction time (20% increase) in 15 persons administered cobalt orally as a solution of cobaltous chloride at 1 mg a day for 3 days. These findings seem to be supported by results of animal studies [133,136,141-143] and from patients administered cobaltous chloride for treatment of anemia. In the patients, infants receiving 120-200 mg cobaltous chloride for up to 100 days had increased leukocyte and thrombocyte counts [112], but these findings were not confirmed in those that received cobalt for 1-3 weeks [116].

The information available suggests to NIOSH that the effects of cobalt on the blood are multiple and poorly understood. Polycythemia is clearly one manifestation of exposure to cobalt metal or cobalt salts, and increases in erythropoietin could be a factor in producing this effect. The airborne concentrations of cobalt at which this polycythemic effect would be significant are poorly documented, but they appear to be well above the Federal standard for cobalt metal. Information is not adequate to judge whether this airborne concentration, 0.1 mg/cu m, would be adequate to prevent polycythemia from other cobalt compounds. Because RBC's have been found to decrease in exposed workers only at very high airborne concentrations of cobalt, this effect is judged insignificant if exposure is through inhalation. The role of cobalt in retarding blood clot formation is not well documented, but preliminary evidence suggests that it could be highly significant.

Effects on the Thyroid

The goitrogenic effects of cobaltous chloride were first noted in 1954 in individuals being treated for sickle cell anemia [144]. More detailed descriptions later reported that two children given approximately 3 mg/kg daily of cobalt preparation developed visible goiters [145,146]. One child also had signs of hypothyroidism. A third patient who developed a goiter also had a significant reduction in radioiodine uptake. Placebo tablets were substituted for the cobalt preparation, and thyroid function returned to normal by 12 weeks. Numerous additional reports that followed now show that 2-10 mg cobalt (as chloride)/kg given orally each day for 2-4 months will induce goiter formation in a small percentage of persons [147-154]. In all cases, the thyroid hyperplasia has been reduced or reversed after cobalt administration was stopped.

Controlled clinical studies have also examined the effects of cobalt on the thyroid gland. In one study, 12 adults with normal thyroids were given 50 mg of cobaltous chloride orally three times a day for 2 weeks [155]. Radioactive iodine uptake was reduced in all but one person after the 1st

week; by 2 weeks all uptake levels were near zero. The effect was reversible after cobalt administration ceased. In a separate study, the majority of individuals given cobaltous chloride either orally or by iv infusion also had decreased iodine uptake in the thyroid [156]. In fact, cobaltous chloride has been tested as a treatment for hyperthyroidism. Pimentel-Malaussena et al [157] observed that four of eight patients receiving 150-600 mg a day for up to 117 days responded with clinical improvement as manifested by reductions in tachycardia, metabolic rate, and uptake of radioactive iodine. Three of four, however, had thyroids of increased size, and the authors concluded that the action of cobalt was unpredictable.

The results of studies in guinea pigs [158] and rats [159,160] support the evidence in humans that cobaltous chloride can affect thyroid function and cause microscopically observable changes. In addition, a moderate reduction of iodine uptake was demonstrated in rats that received 20 mg/kg of cobaltous oxide or cobaltic oxide sc daily for 45 days [161]. These studies, like those in humans, were all conducted at high doses and by routes of administration not typically found in the workplace.

The most conclusive evidence that cobalt can affect the thyroid at low doses is the study of Popov et al [60]. In this experiment, rats exposed continuously to aerosols of cobalt metal were killed for examination after 1.5 or 3 months of exposure or after 3 months of recovery. The thyroid glands of animals exposed at the highest concentration, 0.5 mg/cu m, showed microscopic evidence of follicles containing foci of epithelial hyperplasia. Changes in thyroid function were noted in animals exposed at 0.05 mg/cu m but not at 0.005 and 0.001 mg/cu m. This continuous exposure at 0.05 mg/cu m would correspond to an 8-hour exposure of about 0.2 mg/cu m.

Cobalt metal, cobalt oxides, and cobalt salts have caused alterations of the thyroid glands of humans or animals. These effects represent both functional and morphologic alteration of the gland. The only experiment using low doses was conducted by Popov and coworkers [60], and it suggests that slight changes in thyroid function would be expected in workers exposed at 0.2 mg/cu m. This value is near the permissible exposure limit for cobalt metal fume and dust, and long-term effects at low levels have not been studied in humans for any cobalt compounds. This information suggests that alterations of thyroid function should be considered as a possible effect of workplace exposure to cobalt.

Carcinogenicity and Mutagenicity

Fibrosis, and not carcinogenicity, has received most of the attention of the occupational health community concerned with cobalt. The many reports available concerning fibrosis would not be adequate to demonstrate any carcinogenic effect, because none are epidemiologic studies concerned with incidence rates. The three case reports describing the development of benign or malignant tumors in hard metal workers [17,32,38] and two epidemiologic studies describing an increased risk of lung cancer in cobalt recovery areas of nickel refineries [162,163] are not useful in demonstrating a possible

carcinogenic effect of cobalt. Arsenic was also present in the air of some plants examined in the epidemiologic studies. Mixed exposures to substances known to be or suspected of carcinogenicity were involved in all cases. The case reports cannot distinguish between the role of occupational exposure and other factors, including normal incidence. Thus, information from human studies does not provide any answers about the possible carcinogenic potential of cobalt.

The two studies conducted in animals by routes of administration most applicable to workplace exposure did not demonstrate a carcinogenic effect for cobalt [45,164]. The incidence of tumor development was low and did not differ significantly from controls in male Syrian golden hamsters exposed for their life spans to aerosols of cobaltous oxide at 10 mg/cu m, 7 hours daily, 5 days a week [45]. Many of these animals did develop fibrotic changes. Hamsters injected intratracheally once a week for 30 weeks with 4 mg of cobaltous cobaltic oxide (Co_3O_4) failed to develop a statistically significant excess of tumors compared with control animals [164]. It should be noted, however, that the two tumors that developed in the 50 animals exposed to cobalt were alveolar in origin while the four tumors in controls were at sites unrelated to exposure. These studies provide little evidence to suggest that cobalt oxides are carcinogens, but no similar studies have been conducted in animals other than hamsters.

The results of studies of the carcinogenic potential of cobaltous chloride are conflicting. Gunn et al [165] reported that no tumors were observed for 10-16 months in Wistar rats given four simultaneous injections of cobaltous chloride (0.18 mg cobalt/site) into a vital organ (liver or kidney), a gland (salivary or ventral prostate), and two mesenchymal mesodermal structures (chest, interscapular area, thigh, or femur). Similarly, Shelley [166] reported that no tumors were observed in 10 ICR mice given cobaltous chloride (3.5 mg cobalt) in the dorsal earlobe, although the 2- to 5-month observation period was relatively short. On the other hand, Shabaan et al [167] found subcutaneous fibrosarcomas in 14 of 27 rats surviving 8-12 months following 10 injections of cobaltous chloride at 40 mg/kg into the central abdominal wall. Two tumors were at the injection site, and the remainder were at various distances from the abdominal region. Metastases were not found in any tumor-bearing animal. This study provides evidence that cobaltous chloride could be a carcinogen, and it argues for the need to perform chronic testing of cobalt salts in animals by routes of exposure more applicable to the workplace.

Several investigators have examined the carcinogenic potential of cobalt given parenterally. In one study, neither metallic cobalt nor cobalt sulfide induced tumors in rats when these substances were injected into the poles of the right kidney [168]. Heath and associates [169-174], in a series of papers from 1954 to 1972, examined the effects of cobalt metal powder or alloys injected into rats. Many animals developed injection site sarcomas 3-12 months after im administration of the powder in fowl serum. Sarcomas were also induced in cardiac muscle following the administration of cobalt metal powder by intrathoracic injection [175,176]. Gilman [177] and Gilman and Ruckerbauer [178] were also able to induce injection site sarcomas in rats following im injection of cobaltous oxide or cobaltous sulfide, but they did

not observe tumors in mice similarly injected with cobaltous oxide. In experiments with cobaltous naphthenate, five rabbits injected im developed rhabdomyomas at the injection site after 2-6 months [179]; similarly, one of three injected iv developed an osteochondroma at the site. A rabbit given cobaltous naphthenate by intrahepatic injection and another animal receiving the compound intrapleurally also showed tumor formation. In a similar study in mice, injection site tumors developed after what was apparently an im injection of cobaltous naphthenate [180].

Mutagenicity tests in Allium cepa cells [181], Vinca faba roots [182], bacteriophage T4 [183], and yeast [184,185] have indicated that cobalt interferes with mitosis and can cause cell death in sufficient concentrations. Four cobalt compounds ($CoCl_2$, $Co(OH)_3$, $CoSO_4$, and $2CoCO_3.3Co(OH)_2$) were weakly positive in rec assays, but cobalt chloride and cobalt hydroxide were negative in spot mutation induction tests with two strains of E coli and five strains of Salmonella [186]. Cobalt nitrate had no effect on the chromosomes of human leukocytes [187], but cobalt chloride has decreased the fidelity of DNA synthesis [188]. Cobalt salts have also enhanced transformation of hamster embryo cells exposed to simian adenovirus SAT [189]. These studies are insufficient to serve as any indicator of possible carcinogenicity.

Information on cobalt is inadequate to conclude that cobalt is a carcinogen. The information is also inadequate to conclude that cobalt is noncarcinogenic. In fact, limited data [167,175,176] provide suggestive evidence that at least some cobalt compounds may prove carcinogenic when subjected to long-term testing by currently accepted protocols. Until such testing is performed, no definitive guidelines can be given. Tumor induction at the injection site, however, would argue for the need to adequately clean any wound contaminated with cobalt.

Effects on Reproduction

Whether exposure to a substance in the workplace can result in adverse effects on reproductive capacity or harm to the developing fetus is of grave concern to workers and to all persons responsible for the health of workers. The information available on cobalt is conflicting and insufficient to draw definite conclusions on the effects of cobalt on reproduction. Although this information does not substantiate any effects, it is presented below.

Studies in humans [190-192] and animals [193,194] demonstrate that cobalt can cross the placenta. This effect does not appear related to the essentiality of vitamin B12 [193]. Whether or not cobalt compounds possess any teratogenic activity is not established. Only 1 of 41 hamster embryos exposed to cobaltous acetate through the iv injection of 5 mg/kg in the dam on the 8th day of gestation was resorbed [195]. No gross abnormalities were evident. This experiment, however, would only have detected teratogenic effects under very limited conditions because of the single exposure and the lack of any microscopic examination. The most frequent malformations observed in chick embryos exposed to cobaltous chloride through injection of 0.4 or 0.5 mg per egg were in the skeletal system and eyes [196]. No embryo exposed

through injection of 0.1-0.3 mg was malformed. The mortality of the embryos was high, 75.7% in those injected with cobaltous chloride and 54.3% in control embryos. This experiment is of questionable relevance because of the nonmammalian test system used.

The literature describing the effects of cobalt on testicular function is characterized by disagreement among investigators. Hoey [197] reported marked but reversible changes (including suppression of spermatogenesis, abnormal sperm, deformation of the epididymal tubules, and necrosis of the duct system) in rats administered cobaltous chloride by sc injection. Kamboj and Kar [198] injected cobaltous nitrate sc in mice or intratesticularly in rats, and they found no microscopic damage to the testes or effects on spermatozoa. Niebroj [199] injected cobaltous chloride ip, and considered the effects on the testes of these mice to be generally positive.

Other Effects

There are numerous studies of additional toxic effects attributed to cobalt. Some, such as the acute lethality studies in animals, have little impact on the occupational environment since such exposure conditions are rarely, if ever, encountered. Some effects, such as increased levels of plasma lipids, have been observed in humans, but only rarely in anemic patients receiving cobalt [145,150,200]. Some, such as experimental induction of epilepsy by implantation of cobalt in the brain of animals, appear irrelevant. Other effects, such as kidney and liver changes, may be relevant; but information on occupational exposure is quite limited.

(a) Kidney Effects and Hyperglycemia

Workers exposed for no more than 3 years to cobalt at 0.6-3.2 mg/cu m in a Soviet plant manufacturing tungsten bars and hard metal alloys showed evidence of disturbed kidney function and hyperglycemia [46]. About half of the 178 workers complained of some symptom, including labored breathing, coughing, pounding of the heart, headache, dizziness, nausea, loss of appetite, and olefactory disorders. Blood glucose, measured in 37 subjects, was elevated in 8 (22%). Glucose tolerance tests produced prolonged elevations of blood glucose in 8 of 14 (57%) individuals. Blood chloride levels were increased in press operators but decreased in reducers; both groups showed a reduced chloride concentration in the urine. In a separate study, a worker apparently acutely poisoned by exposure to cobalt acetate suffered from albuminuria [201]. A similar effect was observed in guinea pigs administered large doses of cobaltous chloride for 6-7 days [202]. Both the cortex and the glomeruli were damaged, and pronounced changes occurred in nearly all tubules of the kidney. This study [202] and another using cobalt oxides [161] were consistent with the limited information provided by Popov et al [60]. In this study [60], rats exposed to cobalt dust continuously at 0.5 mg/cu m for 3 months reportedly had slight degenerative changes in the convoluted tubules. Except for the statement that this effect was not seen at 0.001 mg/cu m, no additional information was provided.

Cobaltous chloride therapy for anemia has reportedly led to hyperglycemic reactions in patients [203]. This response is more clearly demonstrated in experiments with animals. Parenterally administered cobalt salts and trisethylenediamine cobaltic chloride have produced time- and dose-related rises in blood glucose levels (hyperglycemia). This effect was noted in rats [204-207], guinea pigs [208], rabbits [209], and dogs [210]. The typical increase in blood glucose level usually peaked after 1-2 hours and lasted up to 10 hours depending on the dose. The hyperglycemia induced by cobalt appeared to be independent of its effects in alpha cells of the pancreas (see section (c)), but the mechanism of action is not yet understood.

NIOSH considers the information available sufficient to conclude that cobalt metal and salts, and probably cobalt oxides and a number of organocobalt complexes, can damage the kidneys. These effects are thought to occur only at levels that also produce other toxic effects.

(b) Liver Effects

Hard metal workers exposed to cobalt at 0.6-3.2 mg/cu m had slight to moderate changes in liver function tests in 19 of 34 (56%) individuals examined [46]. Other workers, exposed at 0.8-12 mg/cu m, had enlarged livers [35], and a woman who died from massive fibrosis had liver congestion [50]. These reports would indicate that cobalt can affect the liver, either directly or indirectly. However, the lack of similar information at lower doses suggests that the liver is not the critical organ for cobalt toxicity.

Exposure to cobalt has produced liver damage in laboratory animals. Popov et al [60] noted that the hepatocytes of liver tissue of rats exposed continuously to cobalt dust at 0.5 mg/cu m had necrotic changes. This effect was reported to be dose-dependent, with no effect at 0.001 mg/cu m. At higher doses (10-18 mg/kg of cobaltous chloride in a single iv injection), rabbits examined for up to 7 days developed a transient but marked glycogen depletion, necrotic changes in a few liver cells, and moderate to marked fatty degeneration [209]. In a study on rabbits given sodium cobaltic nitrate or cobaltic oxide im at relatively high doses for up to 219 days, areas of focal necrosis and liver cell degeneration were observed [211]. This information, in experimental animals, supports the contention derived from human data that cobalt can adversely affect the liver but only at high doses.

(c) Pancreatic Effects

Parenteral administration of cobalt salts in high doses has induced degenerative changes in pancreatic tissue of experimental animals. The guinea pig pancreas appears to be very sensitive to the effects of cobalt, resulting in it often being used in research [212-223]. The characteristic effect noted after administration of cobalt salts at 10-80 mg/kg was alpha cell degranulation and necrosis. Beta cells were usually not affected. Changes reached a peak 24-48 hours after a single dose. Animals that survived regenerated pancreatic tissue. This phenomenon may not be occupationally relevant because of the high doses used. In addition, no human data are

available that indicate a potential problem with pancreatic function after cobalt exposure.

(d) Additional Studies

Cobalt solutions, unless they are strongly acidic or basic, probably do not pose a serious risk of damage to the eye from splashes or spills. Subconjunctival administration of 1 ml of a 0.1-0.2% cobaltous sulfate solution to three rabbits produced no irritation of the mucosa [224]. However, the greatest risk of damage to the eyes from cobalt is probably a physical effect caused by flying chips of cobalt or hard metal.

Kaplun [35] studied olfactory acuity in 37 workers employed in the manufacture of hard-metal alloys. Twenty-eight subjects worked with tungsten carbide and cobalt and tungsten, and the rest worked with tungsten carbide alone. The author concluded that 25 of 28 persons working with tungsten carbide and cobalt had impaired senses of smell when compared with individuals working with tungsten carbide alone. However, details of the experimental design were not provided.

Distribution and Retention

Since it is a constituent of vitamin B12, cobalt should be present in small amounts in the normal human body. In 1962, Yamagata et al [225] used neutron activation analysis (NAA) to calculate the whole body content of cobalt (1.1 mg in humans). Approximately 44% was stored in muscle, 32% in bone, and the remainder in soft tissue. In workers who died of pulmonary fibrosis, however, the few studies available present contradictory evidence of cobalt accumulation in the lung; most found little or no cobalt [12,15,19,22,26], but others found large amounts [16,50,226]. Two groups of investigators examined the urine of workers exposed to cobalt compounds, and found a substantial elevation in the amount of urinary cobalt [226,227].

Accidental inhalation of radioactive cobalt as the metal or the oxides has provided some data on the kinetics of cobalt elimination after entry into the lungs. Several reports [228-231] have shown that lung clearance occurs in at least three stages, a rapid component having a half-life of 0.5-2 days, an intermediate component of 3-42 days, and a long-term component of 60-120 days. The International Commission on Radiological Protection, in a 1959 report, estimated the biologic half-life of inhaled cobalt-60 to be 9.5 days [232], but investigators have since reported data indicating that some inhaled cobalt can be retained in the body for many years [233,234].

Controlled experiments on the distribution of cobalt in humans have considered only cobaltous chloride. When administered orally, most was eliminated in the feces [156]. Absorption through the gastrointestinal tract appeared to be reduced if cobalt was given after a meal, in an albumin complex, or as a carrier-free solution [235]. Cobaltous chloride, given iv, was rapidly cleared from the blood [236], but a substantial amount (5-16%) was retained in the body for a year or longer [236,237].

The results of animal studies confirm and supplement the reports in humans. Numerous studies in animals also demonstrate that most cobaltous chloride administered orally is eliminated in the feces [238-241]. When cobaltous chloride was administered repeatedly in the drinking water of rats [242] or mice [243] (an exposure more typical of general human consumption), cobalt accumulated to increasingly higher tissue levels until a steady state was reached after 30 days. Cobaltous oxide was poorly absorbed in hamsters; when administered by gavage, less than 0.5% accumulated in body tissues [244]. Cyanocobalamin, in contrast, showed a much greater absorption and retention than cobaltous chloride [245]. Several investigators [242,243] have noted the tendency of cobalt to accumulate in the liver following administration of cobaltous chloride, and two [238,242] also described its long-term accumulation in bone. Considering these sites of deposition, it is not at all surprising that a fraction of the administered dose is retained for a long time.

Retention of cobalt oxides after inhalation has been examined in animals. Wehner and Craig [244] reported that hamsters eliminated 90% of the total dose of cobaltous oxide, inhaled at 15.6 mg/cu m 7 hours a day for 2 days, within the subsequent 3 days (day 5 of experiment); however, the remainder was retained tenaciously in the body of the animal. Barnes et al [246] administered respirable-sized particles of cobalt oxides by inhalation to dogs. In 10 days, only 10% of the cobaltous oxide was retained, compared with 60% of the cobaltous cobaltic oxide. Cobaltous cobaltic oxide showed accumulation in the lymph nodes of the lung, a typical reaction of tissue-insoluble substances, while substantially more cobaltous oxide was found in the tissues and blood.

The information on distribution and retention of cobalt is typical of substances showing moderate to substantial tissue solubility. Information on the chloride salt is particularly revealing. It appears that enough of the salts can be absorbed through the gastrointestinal tract to warrant good sanitation and personal hygiene by workers so that they can avoid absorbing significant amounts of cobalt through ingestion. The long-term accumulation of cobalt in the liver may also be relevant.