III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Nickel (Ni), atomic number 28, is the 24th element in order of abundance in the earth's crust [4]. According to Ademec and Kihlgren [4], nickel was first isolated by Cronstedt in 1751, and relatively pure metal was prepared by Richter, who described its properties in 1804. Most inorganic nickel compounds contain the nickel ion in the +2 oxidation state; the +3 and +4 states are also possible, but occur infrequently [5]. Nickel compounds have diverse chemical and physical properties. Selected compounds of industrial or chemical importance are listed in Table XV-1 [4-9].

Nickel in its natural forms is found mainly as either oxide (laterite) or sulfide ore [10]. Deposits of oxide ore have been formed from the weathering of nickel-containing rock, resulting in areas of increased nickel concentration, whereas sulfide ore deposits were created from the settling of nickel in molten rock. The nickel ores mined in the United States are oxide ores and do not contain sulfur.

In the United States, primary nickel is produced at one mine-smelter complex and at one refinery [11]. The only US nickel mine, in Oregon, produced 13,000 tons of nickel in 1975, which was smelted in the ferronickel form [12]. Since 1974, a refinery in Louisana capable of producing 40,000 tons of nickel per year has refined imported nickel matte. In 1975, 58,900 tons of nickel were recovered as a byproduct and from scrap [12]. All other primary nickel used in the United States is imported, predominantly from Canada, with smaller amounts from Australia, New

19

Caledonia, and other countries.

US nickel consumption in 1975 was about 146,500 tons (US Bureau of Mines, written communication, December 1976), about 30% less than the record-high figure of 1974. The US Bureau of Mines [11] has projected a 1.8-3.4% increase in the annual consumption of nickel through the end of 20th century. The pattern of nickel consumption has changed little in recent years [12]. Nickel was consumed in 1975 in the following forms: unwrought nickel (68%), ferronickel (17.3%), nickel oxide (11.4%), nickel salts (1.2%), and other (2.1%); 43% of the nickel was used in ferro-alloys, 39% in other nickel-based alloys, 13% in electroplating, and the remainder as nickel chemicals or °catalysts (US Bureau of Mines, written communication, December 1976).

Combined with other metals in alloys, nickel provides strength and corrosion resistance over a wide range of temperatures and is therefore vital to the iron, steel, and aerospace industries. Nickel is also used in a variety of chemical and catalytic operations. Commercial ammonia and hydrogen production require the use of nickel catalysts [13 (pp 495-497)]. The synthesis of natural gas from coal probably will also involve the use of large quantities of nickel catalysts.

NIOSH estimated that 250,000 persons in the United States are exposed to inorganic nickel in the workplace. Occupations involving potential exposure to inorganic nickel are listed in Table XV-2 [14].

Historical Reports

Da Costa [15], in 1883, reported on the therapeutic effects of nickel salts. Nickel sulfate was reported to be effective in relieving rheumatism,

20

as was nickel bromide in reducing the frequency of epileptic attacks. The author stated that 65-195 mg of nickel sulfate given orally were well tolerated, whereas 650 mg caused occasional giddiness and nausea in some individuals. Doses of nickel bromide (325-487.5 mg) were also tolerated in the stomach. In 1885, Leaman [16] described additional instances of the use of nickel bromide to relieve epileptic seizures.

As early as 1889, Blaschko [17] described dermatitis resulting from exposure to chemicals used in nickel plating. He noted that plating solutions containing ammonium nickel oxide were much less harmful than those containing nickel chloride and that eczema was more severe in those who had worked longest. Blaschko recommended the use of rubber gloves and protective creams as methods to reduce eczema.

Bulmer . and Mackenzie [18], in 1926, discussed the processes associated with the development of nickel dermatitis in workers at a Canadian nickel refinery, the factors involved in the disease, and the measures taken to prevent it. The development of skin rashes was most closely related to working in hot environments where finely divided nickel dust was present. Those workers exposed to the heat of the furnaces or to the heat and humidity of the electrolysis shop and those who shoveled nickel salts were affected most often. In 1923, 43 cases of nickel rash had caused a total lost time of 4,016 hours in an unspecified number of workers. A medical program consisting of oral administration of calcium chloride and topical application of calamine lotion was then begun. In 1924, there were 22 cases of rash causing a total lost time of 408 hours and, in 1925, there were 23 cases of rash causing only 72 lost hours.

In 1931, DuBois [19] reported on an investigation of a Swiss factory where large metal discs were plated with nickel. In a 2-year period (1928-1929), 370 workers were employed in the nickel plating room but only about 20 had been able to continue work without interruption due to dermatitis. The plating solution contained 35% nickel sulfate, 18% magnesium sulfate, and 0.1-0.2% sulfuric acid. The plating tanks were kept at a temperature of 85 C; a thick cloud, reducing visibility in the room to less than 1 meter, was produced. Although the workers wore long-sleeved shirts, had scarves around their necks, and changed clothing or bathed at the end of the work shift, dermatitis was a continuing problem. Improved working conditions, the use of lanolin barrier creams, and a requirement for the immediate reporting of any rash were instituted, and the number of cases was reduced considerably. The results in this plant led DuBois to inspect plating plants where cold plating solutions were used. Although the total number of workers examined was not indicated, no cases of dermatitis were observed. DuBois concluded that this dermatitis was the result of exposure to nickel or its salts, perhaps accentuated by heat and humidity.

In a 1933 report on nickel dermatitis, Goldman [20] criticized the conclusions of DuBois [19] because, in the investigation reported by the latter author, patch-testing for sensitivity to nickel had not been performed. Goldman [20] found cases of dermatitis in two plating workers who had become sensitive to nickel within 1 week after beginning work. They had positive skin reactions when patch-tested for nickel sensitivity and negative reactions to cobalt and lime. Goldman [20] concluded that there was a specific skin disease characterized by sensitivity to nickel compounds.

In Great Britain, cases of lung cancer and nasal cancer in workers at a nickel works were listed in the Annual Reports of the Chief Inspector of Factories for 1932 [21] and 1949 [22]. In the earlier report, Bridge [21] noted that 10 cases of cancer of the nasal cavities and paranasal sinuses developed in workers at the nickel plant between 1921 and 1932. In the 1949 report, Barnett [22] indicated that 47 cases of cancer of the nose and 82 cases of cancer of the lungs had been reported. Workers who developed nasal cancer had been employed an average of 23 years, those with lung cancer an average of 25 years, before the onset of cancer. In a review of cases that occurred before 1946, Barnett found that none of the workers who developed nasal cancer and only two of those who developed lung cancer had started to work at the nickel works after 1924.

The nickel works mentioned in the above reports has been identified as the nickel refinery in Clydach, Wales [23]. Amor [24] suggested in 1938 that lung and nasal cancers in workers at the Clydach nickel refinery were associated with exposure to arsenic, present in process material at a concentration of about 2%. In 1949, the Ministry of Pensions of Great Britain designated lung and nasal cancers in workers employed in operations involving the "decomposition of a gaseous nickel compound" as compensable diseases, according to an NAS-NRC report on nickel [3]. Nickel carbonyl was not specifically mentioned, but it apparently was presumed to be the agent causing lung and nasal cancers in workers at the Clydach nickel refinery, because, at that time, no excess incidence of these cancers had been reported in workers at nickel refineries that did not use the carbonyl process.

Effects on Humans

The following effects have been reported in humans exposed to nickel: dermatitis [17-20,25-34]; cancer of the lungs [22,35-47], of the nasal sinus cavities [21,22,35-37,39,41,43-45,47,48], and of the larynx [41,43]; irritation [48-50] and perforation [49,50] of the nasal septum and loss of the sense of smell [48,49]; and asthma-like lung disease [51,52], pulmonary irritation [53], pneumoconiosis [54,55], and a decrease in lung function [55]. Information on the chemical compositions of nickel compounds to which workers were exposed and the concentrations and durations of exposure was not presented in most of the human studies reviewed. When process information useful for determining probable worker exposures is available, it is included in the appropriate section of Epidemiologic Studies. A glossary of terms used to describe the refining processes for nickel is included as Appendix V. Each word included in the glossary is followed by an asterisk (*) on its first appearance in the text.

(a)   Dermatitis

Two forms of nickel dermatitis have been described [3]. Early cases of dermatitis in nickel miners, smelters, refiners, and electroplaters were attributed to "nickel itch," a skin disease in which eruption began as an itching or burning papular erythema in the web of the fingers and spread to the fingers, the wrists, and the forearms. A second type of nickel dermatitis was described as a papular or papulovesicular dermatitis with a tendency for lichenification. The eruption was characteristic of atopic dermatitis, rather than eczematous contact dermatitis. Calnan [25] also described two patterns of nickel dermatitis; a primary eruption at the site of direct metal contact, and a secondary eruption or area of spread remote

24

from the metal-contact site. It was noted in the NAS-NRC report [3] that by 1975 nickel dermatitis was seen infrequently as an occupational disease. In addition, it was stated that no studies had been done to determine the incidence of nickel dermatitis in the general population.

The incidence of nickel dermatitis in the work force has not been reported in the literature with the exception of a report from the USSR by Sushchenko and Rafikova [26], who noted dermatoses in workers at a nickel refinery. In the electrolytic process, sulfide ore was refined in solutions containing 74-85 g of nickel/liter. Environmental concentrations of nickel for the years 1966-1970 were reported to have ranged from 0.021 to 1.65 mg/cu m. From medical and attendance records it was determined that, for the years 1967, 1968, and 1969, there were 1.8-6.2 cases of dermatosis/100 workers and lost time ranged from 13.7 to 59.4 days/100 workers. In 1970, 651 workers were examined for dermatosis and 36 cases were found. The authors stated that the incidence of dermatosis increased in the spring and summer months, when the temperature and humidity in the shops were high, exposure to ultraviolet radiation was minimal, and hypovitaminosis occurred.

Chaumont and Himmelsbach [27], in 1961, published the results of examinations for dermatitis in workers from three plating shops. In the first shop, none of six women stationed at a nickel plating tank operated at 34-45 C developed skin lesions, probably because they all wore gloves. Another woman, who occasionally did plating work, developed erythema and blistering which disappeared when she was not exposed to the plating solution. There were 10 workers in the second shop, none of whom had skin lesions. However, between 1950 and 1955, seven workers had been affected

and were transferred to other jobs. The third shop had five nickel plating tanks, one of which was operated at a temperature of 50-60 C. Eight workers in this shop were exposed to nickel salts. Two of them had only 15 days of exposure and showed negative reactions to nickel sulfate patch tests. The other six workers, who complained of severe itching and had been exposed 3.5-9 years, had positive reactions to patch tests with nickel sulfate; the extent of reaction varied from erythema alone to erythema with edema, papules, and blistering. The dermatitis vanished completely during the 18-day annual leave but returned within 1 day when work resumed. The authors thought that the elevated temperature of the plating solution in the third shop might have been responsible in part for the more severe problems there.

Tsyrkunov [28] examined 87 workers exposed dermally to nickel salts through electroplating and metal degreasing. Exposure occurred because the workers did not use gloves and aprons while lifting objects from the plating baths. Skin abrasions caused by the metal parts increased the risk of dermatosis. Of the 40 persons who developed dermatitis and eczema, only 14 did not have skin abrasions of some sort; 33 of them had positive skin reactions to 1% nickel chloride. Skin inflammations and rashes developed most frequently 2-5 months after the beginning of employment and were confined primarily to the forearms, hands, and fingers. The author concluded that skin damage induced by nickel salts was facilitated by the numerous skin lesions and by the degreasing agents used.

In 1961, Polipov and Mezentseva [29] reported their observations of 100 nickel workers who were exposed to nickel sulfate in the plating of strips and containers, to nickel sulfate and metallic nickel in the

preparation of electrodes, and to nickel oxide hydrate in a battery shop. Of the 38 workers engaged in strip plating, 26 had dermatitis and eczema; 4 of the 12 who plated containers, 3 of the 25 electrode workers, and none of the 25 battery workers were similarly affected. The increased frequency of dermatoses in workers involved in the plating of strips was attributed in part to poor work habits such as frequent wetting of hands and arms which caused a loss of skin oil, and the handling of freshly plated strips without gloves. More importantly, the authors reported that the hands and forearms of these workers were constantly traumatized (abrasions, cuts) in the course of their work. All 50 workers in the plating shop were patch-tested; 28 of 38 strip platers and 4 of 12 container platers reacted positively to nickel sulfate. Eighteen of the 26 dermatosis-affected strip platers were transferred to other jobs at the plant, and 13 of them had no recurrences, but the other five had to be removed from all contact with nickel. Of the 8 who returned to the plating shop after recovery, 6 were reaffected within 1-2 weeks and were then transferred. The authors concluded that timely transfer of sensitive workers to other work areas was important in the prevention of nickel dermatosis, but that observance of proper work practices was also essential.

In 1974, Skripkin et al [30] reported on 225 patients with eczema or dermatitis, all of them workers in metal shops, chemical plants, or printing houses, including 56 nickel electroplaters. The authors observed increased sensitivity to the salts of nickel and chromium in 178 of the subjects (79%) but they did not differentiate between the two compounds. The authors described the skin disease as having developed from repeated contact with these salts. Coombs tests, used to measure antibody levels,

27

indicated that 21 of the 67 workers with recurring dermatitis and eczema had increased antibody titers, which would have accounted for the persistence of the skin conditions even after the workers were transferred to different work.

Skog and Thyresson [31], in 1953, reported the results of 3 years of routine patch testing of Swedish patients suffering from eczema. Tests were performed on 1,774 women and 1,513 men to determine sensitivity to formalin, potassium dichomate, nickel sulfate, turpentine, and para-phenylendiamine. Nickel sensitivity was determined by a patch test with 5% nickel sulfate. Occupational histories were obtained from all the subjects. Overall, 120 (7.9%) of the men and 166 (9.4%) of the women showed positive reactions to nickel. When patients were classified by occupation, a statistically valid increase in sensitivity to nickel, compared to other allergens, was seen in men employed in the building trades (P<0.01), in men employed in shops and warehouses (P<0.02), and in women employed in offices (P<0.001). In their discussion of the results, the authors considered that the higher incidence of sensitivity to nickel in building trade and warehouse workers was due, in part, to the handling of nickel-plated tools, and that in shop employees to the handling of nickel-containing coins. The overall higher incidence in women was attributed to increased contact with nickel-plated "contrivances," both at work and in the home.

In 1967 and 1968, eleven dermatologists in six European countries jointly investigated 4,000 persons in whom contact dermatitis had been diagnosed [32]. Of these, 769 were considered to have occupational dermatitis described as "a pathological condition of the skin for which

28

occupational exposure could be considered to be a major causal or contributory factor." Nickel sulfate (5%) in petroleum jelly was one of 20 substances tested. Patches, placed in four vertical rows on the upper back, were occluded, and readings were taken 48, 72, and 96 hours after application. In the occupational dermatitis group, 53 of 769 patients (7%) had positive reactions to nickel sulfate; 216 of 3,231 nonoccupational patients (7%) also had positive reactions to nickel sulfate, indicating that the percentage of nickel sensitivity was the same in both groups.

Marcussen [33] reported on the occupations of 621 persons in Denmark who developed nickel dermatitis between 1936 and 1955. These cases were confirmed by a positive patch-test reactions to 5% nickel sulfate. Of the 621 verified cases of dermatitis, 24 cases (4%) were attributed to work in nickel plating shops, 59 cases (9.5%) were associated with other occupations, and 538 cases (86.5%) were reportedly of nonoccupational origin. Marcussen also stated that 14 of the persons with nonoccupational dermatitis later worked with nickel and developed dermatitis on their hands. The author concluded that the risk of sensitization was greater from the private use of nickel items than from workplace exposure. In addition, several dermatoses of the hands of workers in nickel industries were actually the result of sensitization prior to nickel exposure in the workplace.

Norgaard [34] used radioactive nickel sulfate to determine the amount of nickel absorbed by human skin over a 24-hour period. Ten μl of nickel sulfate in solutions of four strengths (5.0%, 2.5%, 1.25%, and 0.68%) was applied to the skin and allowed to evaporate. The radioactivity was then measured, and the areas were covered for 24 hours. After 24 hours, the

29

radioactivity was again measured to determine the amount of nickel absorbed into the skin. Absorption of all solutions was similar and ranged from 55% to 77%. Other trials were conducted in which the radioactivity was measured several times throughout the 24-hour period to determine how absorption was affected by time. It was found that most nickel was absorbed early in the 24-hour period. Nickel-sensitive individuals did not differ from others in the rate of nickel uptake.

(b)   Cancer

Cancer of the respiratory organs in nickel refinery workers has been studied extensively. Different terms have been used by authors to describe cancers in specific sites. In this review, "nasal cancer" denotes cancer of the nose, nasal cavities, nasal sinus cavities, and ethmoid sinuses. "Lung cancer" denotes cancer of the trachea, bronchus, and lung, or pulmonary cancer. "Cancer of the respiratory organs" is used for cancer in all organs of the respiratory tract combined, ie, nose, larynx, and lungs.

Cancer of the respiratory organs has been noted in workers exposed to nickel in Wales, Canada, Norway, the USSR, Japan, France, Germany, and the US. Increased risks of death from lung cancer and nasal cancer were first noted in workers at a nickel refinery in Clydach, Wales; the risks of death from lung and nasal cancer in these workers have been reported in four epidemiologic studies [35,37,39,40], in two of which were noted substantial decreases in these risks in workers first employed after 1925. In the most recent Clydach study, Doll et al [40] reported that the ratio of observed to expected deaths (O/E ratio of deaths) from lung cancer decreased from 7.0:1 in workers first employed before 1925 to 1.9:1 in workers first employed after 1925. The O/E ratio of deaths from nasal cancer was 329:1

in workers first employed before 1925, but only one worker first employed after 1925 has developed nasal cancer. The decrease in the risk of death from cancer of the respiratory organs in these workers appears to be closely associated with their use of gauze masks beginning about 1923 [41]. The 80 deaths from nasal cancer and the 176 deaths from lung cancer identified between 1920 and 1975 in Clydach nickel refinery workers are shown by year of death in Figures XV-1 (a and b).

In 1950, Loken [42] reported on three deaths from lung cancer in workers at a nickel refinery in Kristiansand, Norway. An epidemiologic study by Pederson et al [43] in 1973 showed that workers in that refinery had increased risks of developing cancers of the nose, larynx, and lungs. Workers in all four categories (roasting* and smelting*, electrolysis, other specified processes, and other work) had increased risks of developing cancer of the respiratory organs. The 22 cases of nasal cancer and 64 cases of lung cancer diagnosed up to 1975 in Kristiansand nickel refinery workers are shown by year of diagnosis in Figures XV-1 (c and d).

Two epidemiologic studies by Sutherland have shown that workers at a nickel refinery in Port Colborne, Ontario [44], and at a nickel sinter plant in Copper Cliff, Ontario [45], had an increased risk of death from cancer of the respiratory organs. A third study [46] has suggested that workers in four occupational groups at the Copper Cliff nickel smelter had a slightly increased but not statistically significant risk of death from cancer of the respiratory organs. The 36 cases of nasal cancer and 90 cases of lung cancer in Port Colborne nickel refinery workers identified by 1975, and the 6 cases of nasal cancer and 50 cases of lung cancer in Copper Cliff sinter plant workers identified by June 1976, are shown by year of

31

diagnosis or death in Figures XV-1 (e-h). McEwan [56,57] also has reported an excess of lung cancer in former Copper Cliff sinter plant workers, in a study primarily concerned with the usefulness of sputum cytology screening programs.

Studies from the USSR have indicated that nickel refinery workers have developed erosions, perforations, and ulcers of the nasal cavities [49,50], and that they have had an increased risk of death from cancer [58,59]. Increases in the number of deaths from lung cancer have also been noted in studies of nickel workers in Japan [60] and of workers who refined nickel-arsenide ores in Germany [61].

In the US, deaths from cancer of the respiratory organs in nickel alloy plant workers in Huntington, West Virginia, have been reviewed in two epidemiologic studies [47,41]. Both of these studies are preliminary, and their results are inconclusive. The epidemiologic studies and associated reports mentioned above are discussed in detail in the section on Epidemiologic Studies.

A few case reports also have suggested an association between workplace exposure to airborne nickel and the development of cancer of the respiratory organs. In 1965, Tatarskaya [48] observed two cases of nasal cancer in workers engaged in the electrolytic refining of nickel. The first case was that of a 39-year-old woman employed for 18 years in the electrolysis shop of a nickel plant. During an initial examination, a large perforation of the nose and mild atrophic pharyngitis were found, although the woman's only symptom was a poor sense of smell. Eight years later, squamous-cell carcinoma of the right half of the nose, accessory

32

sinuses, and eye socket was diagnosed. The second case was that of a 42-year-old man employed in an electrolysis shop of a nickel plant for 13 years. The worker's symptoms of swelling and flare of the antrum of the nose were originally diagnosed as a boil, but squamous-cell carcinoma was diagnosed after microscopic examination of the affected tissue. The tumor had apparently originated in the anterior corner of the maxillary sinus and had spread to the anterior and medial walls. Tatarskaya emphasized that, in both cases, the tumors were not detected until the later stages of development although the workers had received periodic medical examinations. The author suggested that workers engaged in the electrolytic refining of nickel have an X-ray of the accessory sinuses at least once a year, and that nasal polyps or any other anomalies detected should be promptly examined microscopically.

In 1966, Bourasset and Galland [62] reported a case of reticulosarcoma of the nose in a 59-year-old woman employed from 1922 to 1960 in a cutlery factory. The woman was a houseworker for 7 years before she was employed in the cutlery factory. She worked in various jobs at the factory from 1922 to 1955; from 1955 through 1960, her job entailed cleaning cutlery and electroplating it with nickel. The nickel sulfate and nickel chloride plating bath was maintained at 50 C and did not contain arsenic. Although she reportedly dipped her hands into the bath often, she did not wear gloves or use protective cream. Greenish-white vapors were given off by the bath, and the workspace was small and poorly ventilated. The woman also cleaned the sediments from the bottom of the nickel-plating bath every 3 months.

The authors [62] reported that the worker did not smoke, and, although no anomalies were found prior to 1955, rhinitis was noted after 1955. A tumor of the nasal fossa was diagnosed in 1960 after she reported symptoms of acute rhinitis. The tumor was identified microscopically as a primary reticulosarcoma with beginnings of angioendothelial differentiation. Since the worker was not exposed to other known irritants or carcinogens, and since both the location and the microscopic characteristics of this tumor were quite rare, Bourasset and Galland suggested that the development of the tumor was associated with exposure to nickel salts from electroplating baths.

In 1973, Sunderman [63] reported on a case of lung cancer in a 36-year-old man who had ground and polished nickel-plated material. The worker had smoked less than one pack of cigarettes a day since the age of 16 (FW Sunderman Jr, written communication, December 1976). The period between first employment and the diagnosis of lung cancer was 9 years. The tumor was identified by microscopic examination as an anaplastic large-cell adenocarcinoma in the left lung. Metastases to the mediastinal lymph nodes, intestine, and skin were also found. Atomic absorption spectrophotometry was used to determine the concentration of nickel in the lungs and heart of this worker and in four apparently healthy people not exposed to nickel in the workplace who had died suddenly from accidents or homicide. Sunderman [63] found that the concentration of nickel in the nickel worker's nontumorous lung was nearly 23 times greater than that in the lungs of the four control subjects. The concentrations of nickel in lung tissues were 197 μg/100 g dry weight in the nickel worker, 15 μg/100 g in a 44-year-old man, 12 μg/100 g in a 40-year-old woman, 3.3 μg/100 g in

34

an 18-year-old man, and 4.3 $\mu g/100$ g in a 23-year-old woman. The concentration of nickel in the heart tissue of the nickel worker was also elevated compared to that in the heart tissues of the four control subjects.

In 1977, Sunderman [64] described the case of a 35-year-old man who had developed squamous-cell carcinoma of the nasal cavity. From 1965 to 1970 and from 1973 to 1975, this worker had been employed in a nickel-stripping operation, where nickel plating was removed from objects by dipping them into a solution of hydrochloric and nitric acid at 180 F. Although he was continuously exposed to acid fumes over the stripping tank, the worker reported that he never wore a respirator. He also noted that the most noxious part of his job was cleaning out nickel sludge from the nickel-stripping tank about once a week. During nickel-stripping operations, the worker was exposed to copper and silver, but not to chromium [64]. In 1970, the worker had severe symptoms of nasal irritation and was transferred to the pressroom, where he was exposed to airborne methylene chloride, carbon tetrachloride, and trichlorethane from 1970 to 1973. In 1975, he worked for 8 months in a metal-grinding room where stainless steel was fabricated. He had reportedly smoked 5-10 cigarettes a day since the age of 14. The worker developed an inflammation of the right nostril and sinusitis; 3 months later, squamous-cell carcinoma was diagnosed from a biopsy of a polyploid lesion in the nasal cavity. Nearly 1 year after the diagnosis, the concentration of nickel in the urine of the patient was measured and was found to be within normal limits. This was expected by the author, since the patient had not had any significant workplace exposure to nickel for several months. Sunderman concluded that

there was a "strong likelihood" that this case of nasal cancer identified in a worker engaged in nickel-stripping operations was caused by exposure to nickel.

(c)   Other Effects on the Respiratory Organs

In 1956, Tolot et al [51] described an asthmatic-type lung disease in a worker who had contact with nickel-plating baths. After 4.5 months of exposure in the plating room, the worker was hospitalized with acute lung disease. Environmental concentrations of nickel were not stated. Although the authors noted that acute symptoms responded to therapy, paroxysmal bronchial symptoms marked by coughing, expectoration, and labored breathing persisted for 2 months. The chronic symptoms improved after a 3-week hospitalization and drug therapy with theophyllin; the patient then returned to work. In 2 weeks, he was hospitalized again because of shortness of breath and a marked dry cough. X-ray examination showed that the bronchial tree was congested, and the cough reactions were considered by the authors to be very significant. They [51] concluded that the worker had developed signs of chronic bronchitis due to exposure to mists from a nickel plating bath. The authors did not discuss the possibility that the symptoms might have been associated with exposure to airborne substances other than nickel, such as sulfuric acid mist.

In 1973, McConnell et al [52] described a case of asthma associated with nickel sensitivity. Dermatitis, shortness of breath, chest tightness, wheezing, and a nonproductive cough developed in a 24-year-old male employee who had worked at a nickel metal plating plant for only 3 weeks. The symptoms were present during and for several hours after each work shift. The symptoms were relieved after 5 days of hospitalization;

upon the patient's return to work, however, they recurred, and he was advised to change jobs. Inhalation of a mist containing 10 mg/ml of nickel sulfate (total volume delivered unspecified) under controlled conditions established the role of nickel salts in the development of the asthmatic symptoms. After a 15-minute exposure to nickel sulfate, progressive shortness of breath occurred, and five hours later, pulmonary function was reduced by 50%. Under the same conditions, a control subject did not develop any significant functional changes. A patch test with nickel sulfate was positive. The symptoms described in this patient were attributed to hypersensitivity to nickel.

Arvidsson and Bogg [53], in 1959, observed a case of nickel dermatitis that also involved lung lesions and marked eosinophilia. A 48-year-old woman was hospitalized with severe dermatitis and fever. In the course of the disease, eosinophilia (31-32% eosinophils) and transitory pulmonary lesions and edema were noted. The dermatitis was not of occupational origin, since it was attributed by the authors to contact with nickel-containing earrings, but this report again suggests the possibility of pulmonary involvement in instances of nickel sensitivity.

In 1969, Zislin et al [54] studied the respiratory functions of 13 persons in the USSR with what they described as nickel pneumoconiosis. The persons averaged 42.9 years of age and were exposed to nickel dust for 12.9-21.7 years. Although no quantitative data were given, the authors noted that residual lung capacity and what was described as oxygen retention in the blood were lowered. The respiratory rate was also increased. Chest X-rays revealed diffuse fibrosis in the lungs (pneumosclerosis), and the authors concluded that pulmonary emphysema, at a

37

stage undetectable by X-ray, was present in these persons.

Jones and Warner [55], in 1972, described the effects of oxides of iron, nickel, and chromium on workers employed in a steel mill. The deseaming and cutting of stainless steel produced a fume containing oxides of iron, nickel, and chromium in a ratio of 6:1:1. Fumes from nonstainless steels were almost pure (96.9%) iron oxide. Total airborne dust concentrations ranged from 1.3 to 294.1 mg/cu m. Radiographic examinations indicated that 7 of the 19 workers had pneumoconiosis. Initial pulmonary function tests of the affected men were all normal, but in followup examinations of four men, reductions in expiratory volume and vital capacity were noted in two workers. The authors concluded that, since none of the affected workers had been exposed to iron oxide alone, their diseases could not be described as pure siderosis, and suggested that three of the men showed mixed-dust pneumoconioses. The presence of impairments in pulmonary function, which are suggestive of fibrotic lung changes, was indicative of exposure to oxides other than those of iron, which reportedly did not produce fibrotic changes.

In 1972, Sushchenko and Rafikova [26] studied workers engaged in nickel sulfide ore hydrometallurgy. Electrolytic solutions in the shop contained 75-85 g of nickel/liter of solution. Trace amounts (0.005-0.9 g/liter) of copper, cobalt, and iron were also present. The concentrations of nickel in aerosols in the shop environment ranged from 0.035 to 1.65 mg/cu m in the years 1966-1970. In 1970, 37 of 151 workers reported nasopharyngeal illness. Nasal membrane erosion was seen in 14 of these affected workers.

(d)   Other Effects

In 1948, Friberg described renal effects found in workers exposed to nickel and cadmium dusts during the manufacture of alkaline storage batteries [65]. Evidence of kidney damage was found in most of the 19 workers employed for more than eight years, although proteinuria or other pathologic changes were not observed in 19 others employed for less than three years. A more extensive study of these workers was reported by Friberg in 1950 [66]. On the basis of information obtained from animal experiments and from other battery producers, Friberg [66] concluded that kidney damage in these workers was caused by exposure to cadmium. No other information concerning the possibility that exposure to inorganic nickel may also damage human kidney function was found. Information is needed to determine if nickel could primarily affect glomerular function, or if it could affect tubular function, as does cadmium. Without supporting data, the effects of workplace exposure to nickel on kidney function cannot be adequately assessed on the basis of Friberg's reports [65,66]. His findings are reviewed in detail in "Criteria for a Recommended Standard--Occupational Exposure to Cadmium."

In 1965, Nechiporenko reported on eye damage in nickel electrolysis workers in the USSR [67] who were exposed to aerosols of nickel sulfate and to sulfuric acid mist and chlorine gas when mixing hot solutions and monitoring open electrolysis tanks. Sensations of having a foreign body beneath the lid and sharp pains in the eyes were reported. Excessive tear flow was also found, but further studies apparently indicated that the function of the tear ducts was not impaired. Many workers had diseases of both the nose and the eyes. In these workers, hypertrophic rhinitis and

conjunctivitis, frequently with hemorrhage, were found in the anterior segments of the eyes. After engineering controls were introduced to lower worker exposure to aerosols and vapors, eye damage decreased from 6.2 to 2.6 cases/100 workers.

The extent of eye damage in workers exposed to aerosols from nickel electrolysis tanks cannot be adequately assessed on the basis of this study [67], since the extent of exposure to aerosols, the procedures and criteria used to determine the extent of eye damage, and the number of workers studied were not reported. In addition, the eye damage may have resulted from an allergic conjunctivitis rather than from exposure to nickel. The study does suggest, however, that damage to the nose and eyes may occur in workers exposed to aerosols from nickel electrolysis tanks, even though the role of nickel sulfate in producing these effects is not clear.

Epidemiologic Studies

Comparisons of mortality in the discussions of epidemiologic data that follow are expressed as ratios of observed (O) to expected (E) deaths. Probabilities have been calculated from the cumulative Poisson distribution when E was less than 5 and from the chi-square test when E was 5 or more. These ratios are considered significant at $P < 0.05$.

(a) Wales

The nickel refinery at Clydach, Wales, where nickel is purified by the Mond (carbonyl) process, began operations in 1902 [36]. The refining process at Clydach was originally divided into six stages: crushing and grinding of nickel-copper matte*; calcining* of the crushed matte at 800 C [41] to produce mixed oxides of copper and nickel; extraction of copper by

40