III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Nearly four million pounds of mercury are currently consumed annually in the United States, but the production and usage of mercury has fluctuated widely through the years. [1] (See Table XII-1 and Figure XII-1.) Although the general trend in its use has been downward since 1969, increased consumption has been noted for a limited number of uses as shown in Table XII-2. [1] The demand for mercury in the future is predicted to increase significantly through the year 2000 as shown in Table XII-3. [2] The proportions of mercury used by various industries are also shown in these tables.

Major uses for mercury are in electrical preparation of chlorine and caustic soda and in the manufacture of electrical apparatus. The properties of mercury, Table XII-4, [3] have made it particularly useful in a variety of industries and, at the same time, have made controlling exposure to it difficult. Among these are liquidity at ordinary temperatures, high density and surface tension, conductivity, and uniform thermal expansion.

A list of specific occupations or trades involving frequent exposure to mercury has been prepared by Gafafer [4] and is presented in Table XII-5. The variety of occupations listed in that table indicates why an exact measure of the extent of exposure to mercury is nonexistent. It should not be assumed that all persons in these

occupations are actually exposed to mercury; however, they are subject to exposure, and therefore, are subject to risk of mercury absorption. Estimations based upon a study of industries in Chicago indicate that a minimum of 150,000 individuals are routinely exposed to mercury. [5]

To the exposure which an individual receives by virtue of his occupation can be added that exposure which is contributed from nonoccupational sources. These sources of exposure to mercury are highly variable and include atmospheric sources. [6-8] The atmosphere contains small but measurable amounts of mercury from vaporization and dispersal into the atmosphere of mercury occurring naturally in the earth's surface. [9] Other sources of atmospheric mercury are from the burning of fossil fuels, such as oil and coal, and airborne discharges from mercury-using industries. [9] It has been estimated [10] that atmospheric concentrations in large industrial cities may approach a level of 1 microgram per cubic meter of air (1 μg Hg/cu m), although sufficient data to substantiate this estimate are not yet available. Also, varying amounts of mercury are found in food and water. [11,12] In addition, individuals may be exposed through dental and medical treatment. [13]

Because of the wide variability in the exposure individuals may receive, a "normal" level of mercury in the body is difficult to establish with certainty. To complicate factors further, many of the investigations reporting on "normal" levels of mercury in "nonexposed" individuals fail to give adequate consideration to the population

sampled, to all possible sources of exposure, to the sampling and analytical methods employed; thus, the data do not permit definite evaluation and comparison. [13]

Early Historical Reports

Archeologists have found that cinnabar (HgS), a sulfide ore, was used as a pigment by ancient Egypt and Babylon according to the history of mercury written by Goldwater. [14] The Greek physician Dioscorides recorded the use of mercury as a topical medicine but noted that the element was dangerous if swallowed. [15] Mercurials were used during the Middle Ages in the treatment of syphilis, and the concomitant gastrointestinal, urinary, nervous, and mental disorders were well known. [16] According to Almkvist, [17] it was not until the end of the 18th century that the symptom complex known as erethism, a peculiar form of emotional instability, was recognized as a specific effect of mercury intoxication.

Goldwater, [14] attributes a description of the earliest cases of occupational mercury poisoning to Jean Fernel in De lue venerea published in 1579. Significant contributions to the literature on occupational mercurialism were made by Agricola and Paracelsus in the 16th century. [14] The description of occupational mercury poisoning by these writers was similar to those of Ramazzini in the late 18th, by Kussmaul in the 19th, and Thompson in the 20th centuries. [14] The major symptoms which they recognized, erethism, tremor, and

gingivitis, are still the predominant ones associated with inorganic mercury poisoning.

The fur and felt hat industries were formerly the primary source of occupational mercury poisoning, and studies of the working conditions in these industries revealed a high incidence of mercury intoxication. [18-21]

The last major studies in these fur-felt industries were by Neal et al in 1937 [18] and 1941. [19] Shortly after they were published, a substitute for the mercuric nitrate used in carroting the fur was introduced in the felt industry, thus eliminating exposures to mercury. [22]

Effects on Humans

Mercury and compounds of mercury may be absorbed through the skin, the gastrointestinal tract, and the lungs. [16] The principal source of occupational mercury poisoning is mercury vapor, with exposure to mercury compounds occurring less frequently. [16] The discussion of mercury in this document will be limited to mercury vapor, inorganic mercury compounds, and organic compounds other than the short chain alkyl mercurials. Because alkyl mercurials (ethyl and methyl mercury compounds) are known to have a significantly greater toxic effect than other forms of mercury, [23,24] a separate criteria document, specific to alkyl mercury, is under consideration. Therefore, discussion of alkyl mercury compounds in this document will

be limited to occasional comparison with effects of other forms of mercury.

The adverse effects of mercury absorption have been investigated or reviewed by many researchers and are well documented. [16,21,23-32]

The appearance of gingivitis and stomatitis accompanied by excess salivation or a metallic taste, erethism, and tremor are identified by Bidstrup [16] as the classical signs of poisoning by mercury vapor and inorganic forms of mercury. Exposure to high levels of mercury vapor affects the respiratory system and is manifested by pneumonitis, bronchitis, chest pains, dyspnea or coughing. These symptoms may be accompanied by the classical symptoms mentioned above. Ingestion of some inorganic compounds, eg, mercuric chloride, causes irritation and corrosion of the body tissues contacted. [16,32,33] If high concentrations of the mercury reach the small intestine, severe abdominal pain and bloody diarrhea will result, with the likelihood of sudden death due to shock and circulatory collapse. [33,34].

The onset of symptoms of mercury toxicity from chronic exposure is insidious, [16,35] and with the exception of tremor, may be ignored by the individual or attributed to other causes. This is particularly true with erethism, which is characterized by irritability, outbursts of temper, excitability, shyness, resentment of criticism, headache, fatigue, and indecision. [16,32] Erethism is the most difficult manifestation of chronic mercury toxicity to evaluate, particularly

when tremor is absent and these symptoms may be attributed to anxiety or neurasthenia.

Tremor is one of the earliest signs of central nervous system involvement resulting from mercury exposure and occurs from exposure to both the inorganic and organic forms of mercury. [32,35] It is characterized by fine, rhythmical, static trembling, interrupted by sudden, coarse, jerking movements and aggravated by voluntary movement. It usually affects the hands first as a fine "intention" tremor but may also be observed in the face and arms. [16,18,19,31]

Some central nervous system effects as manifested by dysarthria, ataxia, and constricted visual fields, have been regarded as significant signs of organic mercury poisoning; however, these effects occur most prominently with alkyl mercury poisoning. [36]

Poisoning from organic mercury compounds such as phenyl or methoxyethyl mercury compounds, which are the specific ones of major occupational concern, is manifested by symptoms of fatigue, dyspnea, chest and abdominal pain, and vomiting. [37-39] In addition, symptoms of gingivitis, dysarthria, motor weakness, and abnormal reflexes have been noted in a limited number of cases of poisoning from organic mercury compounds. [40] In general, signs and symptoms of aryl and methoxyethyl mercury poisoning resemble those observed for inorganic mercury compounds.

Kark et al [41] reported that symptoms of organic mercury poisoning may occasionally simulate those of inorganic and elemental

mercury poisoning, and conversely, cases of elemental mercury poisoning may rarely manifest signs and symptoms usually attributed to organic mercury. In tabulating the signs and symptoms in 87 cases of organic mercury poisoning reported in the literature since 1940, these authors found considerable overlap between signs and symptoms of mercury toxicity from organic mercury compounds and those usually associated with toxicity from inorganic mercury compounds.

The kidney, in almost all situations, accumulates the highest concentrations of mercury as compared to other organs. [23] Kidney damage may result from excessive exposure to mercury as manifested by the nephrotic syndrome of edema, proteinuria, and the presence of casts or cells in the urine. Such damage may or may not be accompanied by an elevated mercury level in the urine. [16] The nephrotic syndrome may be the only manifestation of mercury intoxication and recovery from the nephrotic syndrome usually follows removal from exposure. In more severe cases of kidney damage, renal failure and oliguria may develop, leading to complete anuria. [42-44]

Dermatitis may occur as a result of exposure to mercury. [45-47] Reported cases have usually followed sustained exposure and have been associated principally with organic compounds but cases may also involve inorganic mercury exposure. [35] Absorption of mercury through the skin can occur [45] and may contribute to the systemic effects of mercury absorption via other routes.

The appearance of a greyish-brown or yellow haze on the anterior surface of the capsule of the lens has been reported by Atkinson, [48] following examination by slitlamp. It appears to be associated with exposure to mercury vapor of long duration, and the depth of color apparently depends somewhat upon the length of time and the amount of mercury to which an individual has been exposed. Its presence may or may not be accompanied by signs of toxic absorption of mercury.

A group of nonspecific signs and symptoms have been associated with intoxication by inorganic mercury. [16,26,28] These include weakness, unusual fatigue, loss of weight, loss of appetite, insomnia, and gastrointestinal disturbances. Their association with mercury poisoning is difficult to assess. However, they may be considered a prelude to the appearance of more specific or severe symptoms of mercury toxicity when they are manifested in individuals having known exposure to mercury. [28]

Epidemiologic Studies

In the industrial setting, exposure to mercury is usually from low levels for long duration, and there are a number of studies in the literature which relate exposure to effect. [8,16,18-21,25-28,35] The exposure has generally been evaluated by measurements of air concentrations; however, analyses of urine or blood for mercury are often reported. Most data are from exposure to mercury vapor by inhalation, but other forms of mercury and routes of exposure are frequently associated with the vapor form. [18,26,28,32,35]

It has not been possible to evaluate the different forms of exposure separately even though, in some cases, attempts were made to differentiate between vapor and aerosols.

Ladd et al [27] reported a study of 74 workers, both miners and smelters, in the cinnabar and native mercury mines of Idria, Yugoslavia. Sixteen workers (22%) exposed to total mercury concentrations from vapor and dust in the mine ranging from 0.16 to 4.89 mg Hg/cu m were found to have signs of mercury poisoning. These environmental levels were determined separately as dust and vapor and reported as combined results. Mercury vapor concentrations ranged from 0.1 to 2.0 mg Hg/cu m in the mines, with a reported range of 0 to 2.0 mg Hg/cu m in the smelter. It was not possible to relate air levels to individual worker exposure since workers were rotated from one work station to another. The workers complained of disturbed sleep, irritability, personality change, salivation, tremor, gingivitis, and tremulous handwriting. Three of the affected miners had lower urine mercury levels (2 - 12 μg Hg/liter) than asymptomatic exposed workers (0 - 1275 μg Hg/liter).

In the same paper, Ladd and co-workers [27] described a study of workers exposed at levels ranging from 0.1 to more than 2.0 mg Hg/cu m in an open-pit cinnabar mine in the Philippines. Mercury vapor concentrations were measured by Kitagawa detector tubes, but dust levels were not determined, although the author indicated that, at times, mercury-laden dust may have been present in high

concentrations. This fact and the knowledge that the upper range of the detector tubes was 2.0 mg Hg/cu m would suggest that the air concentration to which the miners were exposed may have been higher than the 2.0 mg Hg/cu m reported. In 1964, half of the exposed work force of 30 miners had various signs and symptoms suggestive of mercury toxicity, consisting of tremor, gingivitis, salivation, and irritability. These same observations had been noted two years earlier at the same mine in 17 of the workers. As in the Idria study, urinary mercury levels were lower in the symptomatic group of workers (3-1260 μg Hg/liter) than in the exposed asymptomatic workers (75-2175 μg Hg/liter).

West and Lim [49] have presented information on 96 workers in nine mercury mining or milling operations in California. Thirty-one of the 96 workers studied had definite or borderline cases of mercury poisoning. All of these occurred in millworkers and there were no cases in the miners. These findings tended to support the claim that environmental mercury vapor concentrations from mercury sulfide ore in the mines were "negligible", in contrast to those in the milling operations where workers were exposed to both high concentrations of mercury vapor and excessive skin contact with liquid mercury. Exposures to mercury vapor in the milling operations were measured from 0.3 to 1.2 mg Hg/cu m, the maximum reading of the measuring instrument. Therefore, the maximum exposure experienced by these workers is not known but possibly could have been in excess of 1.2 mg

Hg/cu m. The average length of employment for the 31 mill employees was only eight months. Two workers who had been employed more than two years had severe mercury intoxication. It was also found that some millworkers had unknowingly contaminated their living quarters with mercury from their boots and work clothes, and thus were most likely exposed to mercury while away from work.

McGill et al, [50] in a study of chlor-alkali workers routinely exposed to mercury vapor concentrations ranging from 0.08 to 0.10 mg Hg/cu m as measured by a mercury vapor meter, reported that physical examinations showed no evidence of dangerous absorption of mercury among the workers. During hot weather, mercury vapor levels occasionally reached 0.13 mg Hg/cu m. Urine levels for this group of workers were extremely low, ranging from a reported 0 to 157 µg Hg/liter for those who spent full time in the cell room.

Smith et al [28] reported the results of a comprehensive, one year study of 567 workers exposed to mercury in 21 chlor-alkali plants in the United States and Canada. The environmental and medical data for the study were collected by industrial hygienists and medical personnel in the plants and analyzed by the authors. Environmental measurement of airborne concentration of mercury was performed using mercury vapor meters. Instructions for calibration of the survey instruments were provided to all industrial hygienists participating in the study. Precautions were taken to prevent interference from the high magnetic fields found in chlor-alkali plants in the operation of

the mercury vapor meters. Air concentrations of vapor ranged from less than 0.01 to 0.27 mg Hg/cu m. No measurements of total airborne mercury were routinely performed.

Standardized medical examination procedures were developed to minimize inconsistencies between methods of examination, and all workers were examined at least once during the study year. No cases of mercury poisoning were diagnosed during the year at exposure levels ranging from less than 0.01 to 0.27 mg Hg/cu m. There were reports, however, of fifty workers (9%) who complained of loss of appetite, 74 (13%) of loss of weight, and 56 (10%) of insomnia. [51] In addition to these symptoms, an unstated number of workers with tremors was observed and reported by the examining physicians. These signs and symptoms, although not specific for mercury, are among those associated with the clinical picture of chronic mercury intoxication. The distribution of these complaints among different exposure groups was reported by the authors [28] to show statistically strong correlations with the mercury exposure levels. The objective tremors of fingers, eyelids, and tongue were significantly related to mercury exposure levels (reported as P values) ($P = 0.001$). The incidence of abnormal reflexes was the same among controls as among mercury workers as a group, but when exposure was greater than 0.10 mg Hg/cu m, there was an appreciably higher incidence of abnormal reflexes. [28]

A condition described as asthenic-vegetative syndrome, or "micromercurialism", has been reported by Trachtenberg [52] in a

monograph published in 1969. The condition was originally described by Stock [53] on the basis of psychological changes observed in persons chronically exposed to low concentrations of atmospheric mercury. The syndrome was characterized by decreased productivity, increased fatigue and nervous irritability, loss of memory, loss of self-confidence, and, ultimately, by miniature symptomatology of classical mercurialism: muscular weakness, vivid dreams, pronounced decrease of productivity, and depression.

Trachtenberg [52] concluded that clinical "micromercurialism" shows characteristic symptoms of its own in addition to the classical symptoms of chronic mercury poisoning. These symptoms of "micromercurialism" were attributed to disturbances in the cortical centers of the central nervous system and are manifested by functional changes in organs of the cardiovascular, urogenital or endocrine systems. More complete details of this syndrome are discussed by Friberg and Nordberg, [54] based on material taken partly from translations of Russian publications and from information obtained by personal communications with scientists in the USSR.

Of the studies reported by Trachtenberg [52], the study of workers in Kiev exposed to average airborne mercury levels ranging from 0.01 to 0.05 mg Hg/cu m is informative for learning of the effects among Russian workers exposed to low concentration of airborne mercury. See Table XII-6. Differences in incidence of effects between exposed workers and controls noted by Trachtenberg do not

appear to be significant except possibly for the incidence of hyperthyroidism, where a 4.4% incidence was observed in controls and about 14% in exposed workers. Trachtenberg diagnosed hyperthyroidism by observation of enlarged thyroid (probably by palpation) and by increased uptake of radioactive iodine.

It is difficult to evaluate the observations of hyperthyroidism in mercury exposed workers. In earlier studies [18-21] enlarged thyroids were noted but the authors concluded there was no relationship between thyroid disease and exposure to mercury. It has not generally been reported in other studies [28,55] involving careful evaluation of workers exposed to mercury. Possibly it was not considered and therefore not looked for in these studies, but it seems likely that it would have been looked for since so many of the symptoms of mercury could be accounted for by demonstrating hyperactive thyroids.

In the hatter's fur-cutting industry, Neal et al [18] found 43 workers with mercury poisoning classified generally as tremor, psychic irritability, vasomotor disturbances, and oral conditions in 529 employees exposed to mercury-in-air levels ranging from 0.06 to 0.72 mg Hg/ cu m. In this study, mercury vapor concentrations were measured by selenium sulfide mercury vapor detectors, while aerosol levels were measured by impingers, using a 25% alcohol and water mixture as a collecting medium. In a later study of the felt hat industry, [19] these same investigators reported 59 cases of

intoxication by mercury (tremor, psychic disturbances, headaches, drowsiness, insomnia) from among 534 workers examined. Extensive urine mercury determinations were made by a spectrographic method, and approximately 30% of the 59 cases of mercury toxicity showed no mercury in the urine. Forty-nine "borderline" cases of poisoning were reported at environmental mercury concentrations as low as 0.1 mg Hg/cu m. "Borderline" cases were those considered as having mild changes similar to those found with mercury intoxication, but, according to these authors, the number and gravity of the signs or symptoms did not warrant a diagnosis of mercury poisoning. In this study, air concentrations were also measured by a selenium sulfide mercury detector and impinger and workers' exposure ranged from a reported 0.0 to 0.5 mg Hg/cu m.

Studies by Smith and Moskowitz [20] and Smith et al, [21] which were conducted in 1936 but not reported until 1948-50, showed that 85 (39.9%) of the 213 workers exposed to total mercury from less than 0.1 to 0.81 mg Hg/cu m in the fur-felt industry had definite signs of chronic mercury poisoning. Another 58 who had certain characteristic signs or symptoms of mercury poisoning but not so definite to remove all doubt of the diagnosis were considered "borderline" cases by these authors. Of 35 workers exposed to less than 0.1 mg Hg/cu m, 4 had signs or symptoms of mercury poisoning and 10 were considered borderline cases by the authors. Environmental measurements were made

by a selenium sulfide apparatus and a large Greenburg-Smith impinger. The samples were analyzed by dithizone titration.

In contrast to the studies by Neal et al, [18,19] Smith and Moskowitz [20] and Smith et al [21] found that all exposed workers had mercury in their urine. Moskowitz, [56] in reporting a statistical analysis of the cases studied, [20,21] showed that cases of mercury poisoning (tremor, weight loss, gingivitis, headache, loss of appetite) developed in workers exposed for seven years or longer at environmental mercury concentrations of less than 0.1 mg Hg/cu m. He further showed that concentrations of approximately 0.8 mg Hg/cu m produced cases in some individuals within five months.

In Italy, a study by Baldi et al [57] of records of 1,173 hatters revealed 300 cases of mercury poisoning resulting from exposure to concentrations ranging from 0.5 to more than 2.0 mg Hg/cu m. One third of the cases in this exposure range resulted in permanent disability. Some cases of mercury poisoning were reported at levels below 0.5 mg Hg/cu m, however no cases were reported in workers exposed at levels below 0.1 mg Hg/cu m.

In Yugoslavia, Kesic and Haeusler [58] found that two-thirds of 70 female felt hatters, exposed to air levels from 0.25 to 1.0 mg Hg/cu m, showed pronounced symptoms of mercury poisoning. Hematological studies indicated no significant difference in the values of blood elements and hemoglobin levels between these workers and a nonexposed control group.

Clinically negative studies have been reported by Shoib et al [59] and Kleinfeld et al [60] for workers exposed, at levels from 0.032 to 0.40 mg Hg/cu m, to a variety of inorganic mercury compounds in combination with metallic mercury.

Ladd et al [46] studied three plants in which groups of workers were exposed to single phenylmercuric compounds. In two of these plants, workers were exposed to phenylmercuric benzoate (PMB), while in the other, workers were exposed to phenylmercuric acetate (PMA). In one of the plants using PMB, 23 workers were exposed to mercury in air at levels ranging from a reported 0.00 to 0.08 mg Hg/cu m (mercury vapor meter) and presumably to PMB dust on the skin. None of the workers had any signs or symptoms of mercury poisoning. However, virtually all the workers showed the presence of mercury in their urine (range 1 - 788 μg Hg/liter).

In the second PMB plant, air measurements were made for vapor using mercury vapor meters and for total mercury using a Unijet Sampler with potassium iodide and iodine as the collecting solution. The readings given by the two methods of measurement were practically the same, indicating that essentially all the mercury in air was in the form of mercury vapor, and was probably the most significant source of exposure. This would suggest that PMB, like other organomercurials, is unstable and partially decomposes in air to release mercury vapor. At 21 of 30 sampling sites, the air levels were below 0.1 mg Hg/cu m. No signs of mercury toxicity were found

upon examination of the 21 workers exposed. Urine mercury levels were reported to range from 0 to 240 μg Hg/liter.

In the plant using PMA, the 23 workers were not continuously exposed to a given level of mercury because they did not remain continuously at a given work location. Samples from nine of the 17 locations tested showed no detectable mercury, while the other areas sampled were found to have air levels ranging between 0.05 and 0.10 mg Hg/cu m. None of the workers at this plant showed signs of toxicity and all workers' urine mercury levels were below 150 μg Hg/liter.

The study of these three plants, involving a total of 67 workers, would suggest that PMA and PMB both have a low toxicity for humans, in terms of industrial exposure, and that what absorption does take place from the air is probably in the form of mercury vapor.

Dinman et al [61] conducted a 5 1/2 year study of 20 workers having a mixed exposure to ethylmercuric and phenylmercuric acetates. Environmental mercury levels were determined by a total mercury method with levels averaging, on a monthly basis, from 0.01 to 0.12 mg Hg/cu m. No significant objective findings of mercury poisoning were made during the entire study period, and the incidence of a variety of subjective symptoms commonly associated with mercury intoxication was not significantly higher than in nonexposed control workers.

Since the kidney is a critical organ for accumulation of mercury, the appearance of renal damage with or without the appearance

of proteinuria would not be an unexpected occurrence in exposed workers.

In reporting on four cases of renal damage among two groups of workers exposed to unspecified levels of inorganic and organic forms of mercury, Kazantzis et al [62] described the appearance of albuminuria and of the nephrotic syndrome. At the time the patients were first seen, all four cases were excreting over 1,000 μg Hg/liter of urine. The albuminuria cleared up, and mercury disappeared from the urine after the workers were removed from exposure.

These findings suggest that chronic exposure to levels of mercury may occur which are insufficient to produce gross albuminuria or signs or symptoms of mercury poisoning yet are sufficiently high to produce low levels of proteinuria. Such a possibility was investigated by Joselow and Goldwater. [63] A group of 52 workers exposed to several inorganic mercurials were examined for total urinary protein. The mean urinary protein of the group was significantly higher than that of a group of 34 nonexposed controls (9 mg protein/100 ml of urine for the exposed group and 5.3 mg protein/100 ml of urine for the controls). In the exposed group, the urinary protein correlated ($r = 0.41$) with the urine mercury levels but only weakly with blood mercury levels ($r = 0.24$). However, the authors concluded that this correlation was found only on a group basis. This would suggest that the amount of protein found in the

urine of individual workers would not be an accurate index of their exposure to inorganic mercury.

The estimation of worker exposure to mercury is usually through evaluation of the workroom air concentrations to which he is exposed. In addition to receiving exposure at work, individual workers may be subjected to mercury exposure beyond their normal workday as a result of their work activity. Such exposure has been reported by several investigators and may be from inhalation, skin absorption or ingestion. [26,49,54] This type of exposure contributes an unknown factor to the total worker exposure.

Benning [26] reported gross contamination of the workplace and of workers' clothing which was worn home. Poor personal hygiene and work practices also resulted in these workers taking a certain amount of mercury contamination home with them.

West and Lim, [49] in their investigation of workers milling cinnabar, found that some of the mill workers were exposed to mercury away from work because they had unknowingly contaminated their living quarters with mercury from their boots and work clothes.

In reporting a study of workers in scientific glassware manufacturing plants, Danzinger and Possick [64] found no cases of mercury poisoning among 75 workers exposed to mercury in air levels ranging from a reported 0.00 to 0.30 mg Hg/cu m. These investigators reported frequently observing mercury particles in workers' clothing, especially when made of knitted fabric. This also occurred if the

workers were not wearing aprons. Such particles would be shaken from their clothes at home. They also observed one female worker having particles of mercury imbedded in the makeup on her face.

It is recognized that workers' exposure to mercury may continue beyond the workplace because contaminated work clothes are worn home, or because of poor personal hygiene or work practices; however, these factors do not appear to have been given adequate consideration by investigators in relating exposure to levels of mercury in biological tissues or to the appearance of symptoms. Such exposure may be exceedingly difficult to assess with any degree of accuracy. It could, however, account for some of the lack of correlation between reported air levels and reported urine or blood mercury levels. This could partially explain the good correlation when comparing groups of workers with exposure, and poor or no correlation of individuals within the same exposure group.

Animal Toxicity

To help understand the toxicological effects of mercury, a number of investigators have studied the toxicological and biochemical actions of mercury in various animal species.

(a) Absorption and Transportation

Hughes [65] hypothesized that elemental, as opposed to ionic (ie, oxidized) mercury, is transported in solution in the blood lipids to diffuse readily through lipid cell membranes into the cells of such tissues as the brain, before being oxidized. This has been confirmed

in the rat by Magos [66] by the intravenous injection of radioactive metallic mercury. Diffusion occurred rapidly and twenty percent of the mercury was exhaled through the lungs within 30 seconds, and a high concentration rapidly developed in the brain. Intravenous injection of an equivalent amount of mercuric chloride was followed by exhalation of a much smaller fraction (2%) and one-tenth of the concentration in the brain of that obtained with exposure to the vapor form. Similar results were obtained in rats, rabbits, and monkeys. [67] Diffusion of elemental mercury into the tissues and across cell membranes is apparently facilitated by its lipid solubility and its lack of electrical charge. [65,68] After absorption by the body, elemental mercury is oxidized to the mercuric ion Hg^{++} and thereafter behaves toxicologically as that ion. [31,68]

The dust or aerosols of inorganic mercuric salts are absorbed via the respiratory tract in amounts or at sites dependent upon their particle size and solubility in biological fluids. [68] Mercuric salts are rather poorly absorbed from the gastrointestinal tract, either following direct ingestion or secondarily from dust in swallowed sputum from the lungs. Clarkson [69] has shown that only about 2% of inorganic mercury is absorbed from the gastrointestinal tract of the rat following ingestion.

Using rats and radioactive mercuric chloride injected intravenously, Cember et al [70] have shown that, initially, three-fourths of the mercury became bound to the red blood cells and one-

fourth was bound to the serum proteins, particularly the alpha globulins of the plasma. With the passage of time and at the higher of the two dose levels employed (1.2 mg Hg/kg and 0.12 mg Hg/kg), mercury transferred from the erythrocytes to the plasma so that the later distribution was one-fourth in the red blood cells and three-fourths in the plasma. At the lower dose level, the initial partition persisted unchanged. This differs from some results in humans; Lundgren et al, [71] in their studies of the distribution of mercury in the blood elements in human subjects occupationally exposed to mercury vapor, reported a ratio of whole blood mercury/plasma mercury of 1.3 (range 0.9 to 2.4). They claimed that this corresponds closely to the distribution of inorganic mercury salts.

Animal experimental work using oral, intravenous, and intramuscular administration in chicks, rats, and dogs indicates that phenylmercuric acetate (PMA) is absorbed unchanged and transported intact by the blood. [72] In the blood of rats, phenylmercuric chloride is initially largely bound to erythrocytes but within 4 days, about a third of the erythrocyte mercury content seems to transfer to the plasma. [73] PMA is absorbed from the gastrointestinal tract of the rat to a greater extent than inorganic mercury salts [74] and, in the diet, is more toxic on long-term feeding to the rat than is mercuric acetate. [75] However, Ladd and his co-workers [46] suggest from epidemiological studies that phenylmercurials constitute less of an occupational hazard to man than other forms of mercury.

Several investigators [76-78] report from animal work that the distribution and behavior of methoxyethyl mercury is very similar to that of phenyl mercurials.

(b) Distribution in Tissues

The differential distribution of mercury among the various tissues and organs of the animal body, following the administration of the different classes of mercury compounds, shows considerable interspecies variation and some observations in animals are supported by autopsy findings in human victims of either occupational or of accidental mercury poisoning. [79-83]

Comparative studies have been made of the amount of elemental mercury accumulated in different organs, especially the brain after exposure to mercury vapor, as opposed to an equivalent amount of inorganic mercury salt. [67,81-83] In these experiments, a mercury content of the animal brain about 10 times higher than that following administration of inorganic mercuric (ionic) salts was found after exposure to elemental mercury vapor in mice, [82] in guinea pigs, [83] and in rats, rabbits, and monkeys. [67]

Tissue and cell-type distribution of elemental mercury within the central nervous system, using a micro-autoradiographic technique, has been studied in rats and mice by Cassano et al. [84] This work showed a greater concentration of mercury in the gray than in the white matter, with the highest levels in certain neurons of the cerebellum, the spinal cord, the medulla, the pons, and the midbrain.

In the cerebellum, there was selective localization in the Purkinje cells and in neurons of the dentate nucleus.

Elemental mercury is slowly oxidized to ionic mercuric mercury in the organism, partly in the blood (mainly in the erythrocytes), and partly in the tissues, [85] and therefore, its tissue distribution partly resembles that of inorganic ionic mercury with high concentrations in the kidneys and liver, the mucous membranes of the intestinal tract, and in the testes.

The tissue distribution of mercury in various small mammals, following single-or multiple-dose administration of radioactive inorganic mercury salts, has been studied. Berlin and Ullberg [81] examined whole body sections of mice autoradiographically, following a single intravenous injection of radioactive mercuric chloride. They found that mercury accumulated in the kidney, liver, myocardium, intestinal mucosa, upper respiratory tract, oral mucosa, interstitial tissue of the testis, skin, bone marrow, and the placenta. The degree of accumulation was most marked in the kidney and liver. Accumulation also occurred in the brain, but the uptake was much slower than in other organs. Slow elimination and considerable retention were found in parts of the brain and in the interstitial tissue of the testes, the skin, the buccal mucosa, and in the kidney. These authors pointed out that many of these tissue localizations are consistent with clinical effects observed in man.

Similar results in rats were reported by Friberg [86] following prolonged daily subcutaneous injection of labeled mercuric chloride. In addition, he noted an increase in the initial concentration of mercury in liver, spleen, and brain when exposure was prolonged, but not in renal mercury content.

With a single oral dose of radioactive mercuric acetate in rats, the highest concentrations of mercury were found in the kidneys, next, in the liver, the lung, and the heart. [74] Accumulation in other organs was comparatively small.

Autoradiographic whole-body sagittal section study [87] of the distribution of radioactive PMA in mice was compared directly with the distribution of radioactive mercuric chloride, already described. [81] For the first few days, the distribution of the phenylmercury was more distinctive, persisting longer in the blood, and accumulating more in the liver and less in the kidneys than did the inorganic salt. More phenylmercury was retained in the skeletal muscles. However, after 16 days, the distribution came to resemble very closely that of inorganic mercury in most tissues, including a late and moderate accumulation in parts of the brain. This is consistent with the observation that, in the mammalian organism, phenylmercurials are metabolized to inorganic mercury. [72]

Similar results were observed by Gage [88] in the rat by chemical analysis of organs and tissues, at various time intervals, after repeated subcutaneous injections of an aqueous solution of PMA.

One important difference from the mouse, however, was that phenylmercury penetrated the brain so little that the level was too low to be measured.

In almost all instances, the observed tissue distributions of the different mercury compounds are consistent with the clinical manifestations of toxicity, both in man and other animals, giving support to the concept of different critical target organs for different classes of mercury compounds, as well as for acute as opposed to chronic exposure. [89]

Druckrey et al [90] have shown that metallic mercury can produce sarcomas in rats after intraperitoneal injection. The sarcomas developed without exceptions at those places which had been in direct contact with the metal which could be identified marcroscopically and microsopically in all the tumors. No tumors were observed in remote organs even though serious absorptive effects were present.

(c) Biotransformation of Mercury

It has been held for a number of years that the fundamental biologic activity of mercury stems from the strong affinity of ionic mercury for, or reactivity with, sulfhydryl or thiol groups, -SH. An extensive discussion of this activity has been presented by Hughes [65] and much of the following is based upon his discussion.

Sulfhydryl groups abound in biological material and occur so widely in protein that free ionic mercury can have only an ephemeral existence in any living organism, being bound almost continuously to

proteins. The affinity of different sulfhydryl groups or ligands for ionic mercury varies, influenced by adjacent structures of the protein molecule. If two sulfhydryl groups lie adjacent on the peptide chain at a suitable spatial interval, one mercury ion will become bound at both sites with or without deformation of the chain. Otherwise, the mercury ion will combine with two sulfhydryl groups on neighboring protein molecules, thereby binding them together. Ligands of different affinities will form mercury bonds of differing strengths and will compete for available mercury. According to Hughes, [65] this is the basis for the transfer of mercury from one binding site to another, and from one protein to another. The physiological disturbance caused by the binding of mercury to a protein will vary according to the site of binding, and the function of the protein. The binding of mercury to purely structural proteins, such as the keratin of the hair and nails, causes minimal functional disturbance, whereas, the binding of mercury to sulfhydryl groups in the prosthetic group of an enzyme may be expected to cause maximal disturbance with possible total blockage of the function of that enzyme.

A number of mammalian enzymes are known, from in vitro experiments, to be sulfhydryl-group-dependent for their activity. Their activity may be blocked by the addition of ionic mercury but may be regenerated by addition of an excess of cysteine or another -SH containing amino acid to the system, which has a greater affinity for the bound mercury. The detectable biochemical disturbances, resulting

from the mercury inhibition of certain -SH dependent enzyme systems, have been investigated as possible bases for biological monitoring of mercury absorption by occupationally exposed workers, at levels insufficient to cause symptoms or clinical signs of mercurialism.

Wada et al [91] studied inhibition of delta-aminolevulinic acid dehydratase (ALAD) and cholinesterase (ChE) among workers with no clinical symptoms of mercury poisoning. These authors concluded that there was a significant relationship (P = less than 0.01) between urinary levels of mercury and the values of the decrease of ALAD and ChE. However, the correlation found for ALAD activity was so weak as to be of no value in practical assessment of reponse of individuals to mercury. On the other hand, ChE activity was markedly decreased among workers who excreted more than 200 μg/gm creatinine of mercury, but there was poor correlation between ChE activity and duration of exposure. They concluded that the decrease in activity of these enzymes became prominent above 200 μg/gm creatinine of urinary mercury and suggested that this level would be the maximum permissible concentration of urinary mercury in chronic exposure to inorganic mercury.

Verity and Reith [92] studied the effects of mercury within cells for interference with the integrity of lysosome membranes which contain essential thiol groups. Exposure of lysosomal preparations to inorganic and organic mercurials induced an irreversible damage of the membrane with resulting enzyme activation. The lysosomal hydrolase

preparations reacted differently at constant mercury levels, suggesting a different pattern of binding, unique for each enzyme studied.

The affinity for thiol groups is not only exhibited by bivalent free mercury ions of inorganic mercury. In organomercurials, such as the alkyl, alkoxy and aryl series, although the carbon-mercury bond is nonionic (covalent) and of varying stability in biological systems, the mercury atom still retains a free valency electron, ie, the mercury halogen or other anion bond is ionic. Organomercury salts ionize to from monovalent cations. [93]

Thio-ligand binding of mercury may explain the toxic effects of mercury in the ultimate target tissues, and might suggest the reasons for the different modes of absorption, transport within the body, and excretion of the different chemical forms. Thus, the speed of absorption of nonionic elemental mercury vapor into the blood lipids might be explained by its lipid solubility, and by its relatively ready penetration into cells of the central nervous system, by diffusion through the lipid-rich cell membranes, unimpeded by electric charge or binding to large molecules.

Once inside cells, it slowly becomes oxidized to the ionic form which then binds with intracellular proteins, and can leave the cell only with difficulty. [65]

The relatively poor absorption of inorganic mercury from the intestine may be explained by its binding to proteins in the

intestinal contents, rather than to proteins in the first mucosal cells it penetrates. Once in the blood, inorganic mercury is bound both to plasma proteins and within the red cells, which are particularly rich in thiol groups, in approximately equal proportions in man. So tightly bound is the mercury that it can transfer only slowly into most tissues by exposure to tissue ligands of greater affinity than those in the blood. The fact that it cannot diffuse freely is indicated by the fact that only about 1% of the mercury in the plasma is "ultrafilterable". [94]

Organomercurials are readily absorbed from the gastrointestinal tract, perhaps helped by the lipid solubility of their hydrocarbon moiety. Miller et al [72] have shown, from experiments in chicks, rats, and dogs, that aryl (predominantly phenly) mercurials undergo biotransformation rather rapidly after absorption and suggest that this form of mercury has about the same order of toxicity as inorganic mercury. In the blood, organomercurials are bound to the extent of about 90% to the thiol ligands of hemoglobin, and of the red cell stroma, [95] and in the case of the alkyl compounds, are taken up to a lesser extent by the kidney and accumulate more in the brain than the aryl compounds. As mentioned before, the aryl (ie, phenyl) mercury compounds are metabolized fairly rapidly into inorganic mercury, as the aryl carbon-mercury bond seems to be relatively unstable under biological conditions. The different behavior of alkyl, as opposed to inorganic mercury, may be explained partly by the lipid solubility of

the hydrocarbon moiety and partly by differential affinity of the single available valency for thiol binding. [96]

(d) Excretion

After the first few days of exposure, little distinction can be drawn between the excretion of elemental mercury and ionized inorganic mercury, into which the elemental form is oxidized prior to excretion. [66,97]

Basically, mercury, in whatever form it enters the body, is potentially excreted by the kidney, by the liver in the bile, by the intestinal mucosa, by the sweat glands, by the salivary glands, by the lungs, in the hair, nails and in the feces, and from the skin both by volatilization and by desquamation. [66,94,95,97,98,100]

In cocks, rats, and dogs, kidney accumulation and urinary excretion of mercury, following administration of phenylmercury salts and methoxymethyl mercury hydroxide, are so similar to the fate of inorganic mercury salts that these types of organomercurials appear to be handled by the kidney in the same way. [72,78,100,101] Using PMA in rats, Gage [88] showed that after a single dose, organic mercury initially appears in the urine for about two days to be followed by the later appearance of inorganic mercury. He inferred that the circulating PMA which enters the kidney is, in part, rapidly excreted unchanged in the urine and, in part, converted to inorganic mercury which is subject to the delay in the renal tubular cells seen in other experiments.

Although mercury may be eliminated from the body by several routes, ie, lungs, urine, feces, sweat, skin, the principal routes of excretion of mercury from the body are through the urine and feces, with the bulk of the excretion in urine. As a consequence, renal retention and excretion of mercury has been the subject of interest of a number of investigators for several reasons. [86,88,97] First, renal excretion is an important route of elimination of mercury from the body of man and many other mammals. [8,45,86,88] Second, the fact that the kidney accumulates more mercury per unit weight than any other organ, following inhalation of mercury vapor or administration of inorganic mercury and organomercurials, has been demonstrated in several animal species. [86,88,89,100,102] Therefore, the speed with which the kidneys extract mercury from the blood must have a significant regulating effect on the blood level and, consequently, on the body distribution of mercury. [97] Moreover, the kidney is the critical organ after acute exposure to inorganic mercury salts, and an acute nephrosis is occasionally seen following occupational exposure in man, as well as acute anuria or nephrosis following accidental ingestion. [103-105] Third, the urine is the most conveniently collected of all human excreta, and attempts continue to be made to use urine mercury levels as a practical guide to absorption and total body burden of mercury in the occupationally exposed. However, there are severe limitations in the use of urine mercury levels for this objective. (See discussion in Correlation of Exposure and Effects).

Of the mercury carried by the blood to the kidneys, it is that part which is in the plasma which is most directly available for excretion. In rabbit experiments, only about 1% of the plasma mercury was passed on ultrafiltration. Experimental evidence from the dog indicates that the little mercury which may be filtered by the glomerulus is reabsorbed. [96] Similarly, most ionic mercury in the plasma of man is bound to the plasma proteins which do not pass the glomerular filtration mechanism in the normally functioning kidney.

The exact mechanism of uptake of mercury from the plasma and its subsequent release into the tubular lumen is not clear, although experimental work suggested that mercury is secreted by renal tubules. A higher affinity for mercury of tubular cell ligands than of the plasma ligands, coupled with passive diffusion along a concentration gradient, is postulated from work in cocks. [106] That the reabsorption of mercury from the tubular fluid into the tubular cells might be by a metabolic transport mechanism is indicated by the work of Clarkson and Magos [107] with rats given the metabolic inhibitor, sodium maleate, followed by injection of 100 μg Hg as the mercury-cysteine complex. These investigators found that tubular-cell-bound mercury was released, not only into the urine, but also into the blood and thence to other organs which accumulate mercury. The possibility that the extraction of mercury by the kidney from the blood in the peritubular capillaries is an energy-dependent metabolic process was

also strongly indicated by experiments in the rat using another metabolic inhibitor, 2,4-dinitrophenol. [108]

It appears that the net renal excretion of mercury by the kidney is the excess of glomerular filtration (very minor) plus tubular excretion over tubular and collecting tubule reabsorption. Whether the sites of excretion and reabsorption are the same, under different milieus of pH or mercury concentration gradients, or separate (eg, excretion by the proximal, reabsorption by the distal, tubules) is still undetermined. [96]

Gage [109] has shown that renal excretion of mercury involves two phases: (1) the removal of mercury from the blood (clearance) and its accumulation in the renal tissue, predominantly the renal tubular cells, and (2) the net excretion of mercury into the urine (elimination). The two processes do not necessarily proceed uniformly or synchronously. On commencement of initial mercury exposure, there is a delay of maximal excretion until the kidney has accumulated a certain burden. In intermittent exposures (as in most occupational exposure), this delay mechanism may result in the occurrence of peak excretion during periods of nonexposure. Gage [109] also postulated a mechanism whereby some mercury continues to be excreted for a considerable time after cessation of exposure, suggesting that the metal may undergo irreversible incorporation into cell proteins, after which the rate of excretion would be dependent upon the metabolic turnover of protein.

The complexities of renal excretory mechanisms for mercury, revealed by animal studies, lend support to the observed difficulties in relating urine mercury levels in man to levels of exposure, absorption, and the imminence of toxic accumulations in the critical organs. Such difficulties would be even more evident in the case of "spot" urine samples as opposed to composite or 24-hour samples. This could be one explanation of the reason for high urine mercury levels in workers who show no signs or symptoms of illness from mercury while low levels may be found in some workers with symptoms. Based on his experiments in the rat, Gage [109] suggests that an approximate assessment of the total mercury absorbed during a working week would be obtained if it were possible to make a total seven-day collection of urine. The practicality of this procedures on a routine basis is, of course, open to question.

Although measurement of mercury in urine has been a principal method for estimating absorption and excretion of mercury, that which is eliminated by other routes may account for some of the disparity between extent of exposure and the amount of mercury found in urine. For example, fecal excretion of mercury which enters the body in inorganic form makes up a significant portion of total body excretion. [110,111] It represents the excess of mercury excreted in the saliva and swallowed, plus mercury secreted in the bile and the succus entericus, plus mercury bound in epithelial cells of the entire alimentary tract which are shed into the gut lumen, over the total

mercury absorbed from the gut, principally the small intestine. In the first few days of de novo exposure of rats, both to inorganic mercury salts and mercury vapor, fecal excretion exceeds renal excretion. Renal excretion equals or surpasses fecal excretion only in the second and longer phase. [110,111] The importance of fecal excretion should not be overlooked.

Correlation of Exposure and Effect

(a) Acute Intoxication

Tennant et al [80] reported one death and symptons of chills, nausea and general malaise, tightness in the chest and vague respiratory symptoms among eight workers exposed to large quantities (several tons) of mercury following an accidental rupture of tubing in a mercury boiler. The workmen were exposed to the warm mercury for about five hours without respiratory protection. No measurement of levels of mercury vapor were made until five days later at which time levels ranging from 0.4 to 0.8 mg Hg/cu m were found in the area of the boiler. This would suggest that levels at the time of exposure may have been substantially higher and probably reached the saturation point.

Four workers exposed to mercury while cleaning a storage tank probably inhaled mercury vapor concentrations from 1.5 to 1.7 mg Hg/cu m at breathing zone height as determined by a simulation experiment performed following the accidental exposure. [112] It was estimated

that exposure for only 2.5 to 5 hours to between 1 and 3 mg Hg/cu m had caused the four cases of acute mercurial pneumonitis.

Environmental levels from accidental exposures are generally unavailable, as in the case of the poisoning of a family from a gas space-heater freshly painted with a mixture containing approximately 65% by volume of mercury, [79] and from a home attempt at gold extraction. [113] The mother involved in the space-heater accident excreted up to 1.31 mg Hg/liter of urine during her one month's stay in the hospital. The man involved in the gold extraction excreted 557 μg Hg/24 hours by the second hospital day and was still mildly dyspneic on exertion one year after exposure.

(b) Chronic Intoxication

Neal et al [19] studied the working conditions of workers in the fur-felt and felt hat industries in New England who were exposed to average levels of mercury in air ranging from 0.02 to 0.5 mg Hg/cu m. Workers were found to have a variety of signs or symptoms including tremor, psychic disturbances, headache, drowsiness, insomnia, and weakness. They concluded that 0.1 mg Hg/cu m "probably represents the upper limit of safe exposure". However, these investigators reported cases of intoxication at 0.1 mg Hg/cu m and at all higher levels. In addition, three cases had borderline symptoms at exposures of around 0.08 mg Hg/cu m, and 15 cases had borderline or first stage mercurialism (similar, but less severe symptoms) at concentrations ranging from 0.08 to 0.15 mg Hg/cu m. Also, their 1937 report [18]

found mercury intoxication in 6% of the workers exposed at approximately 0.09 mg Hg/cu m of air. Therefore, their conclusions might be open to challenge.

Kesic and Haeusler [58] found 47 of 70 female workers, exposed to air levels ranging from 0.25 to 1.0 mg Hg/cu m, in a felt hat factory, had pronounced symptoms of chronic mercury toxicity. Benning [26] has reported severe cases of mercury poisoning in 52 of 90 workers (gingivitis, irritability, tremor, weight loss) at exposure levels between 0.2 and 0.75 mg Hg/cu m, while Bidstrup and co-workers [25] observed clinical mercury poisoning (tremor, erethism) in 27 of 161 workers exposed to levels ranging from 0.003 to 1.67 mg Hg/cu m. One of the cases with tremor was reported to have been exposed at levels from 0.005 to 0.06 mg Hg/cu m.

Turrian et al [114] found signs or symptoms of central nervous system involvement (headache, impaired memory, low concentrating ability, mental disorders) in 33 of 58 factory workers exposed to environmental mercury vapor concentrations ranging from 0.01 to 0.6 mg Hg/cu m. In 15 of the cases, the exposure ranged between 0.01 to 0.06 mg Hg/cu m. See Table XII-7.

Rentos and Seligman [55] reported cases of mercury poisoning (sore gums, tremor, gingivitis, personality changes) in 18 of 83 workers with average daily exposures between 0.08 and 0.68 mg Hg/cu m (mean = approximately 0.5), but no symptoms in other workers exposed to average daily concentrations of less than 0.02 mg Hg/cu m. A high

incidence of cases of poisoning was observed in those workers (17 of 54) who received average daily exposure of 0.31 mg Hg/ cu m. No cases were observed in those workers who received average daily exposures of less than 0.2 mg Hg/cu m. These authors concluded that a threshold limit value of 0.1 mg Hg/cu m was supported, even though a safety factor of no more than 2 was present. Friberg and Nordberg [54] maintained, however, that the Rentos and Seligman data indicated that mercury poisoning occurred at exposure levels greater than 0.2 to 0.3 mg Hg/cu m, and that no conclusions could be drawn in regard to exposure at concentrations between 0.02 and 0.2 mg Hg/cu m.

A study of chlor-alkali plant workers, reported by Smith et al, [28] is noteworthy for its standardization and completeness and provides valuable information on correlation of exposure and effects. Correlations of symptoms with air, blood, and urine concentrations of mercury were presented.

The study [28] demonstrated a strong statistical group correlation between urine mercury levels and such signs or symptoms as weight loss, loss of appetite, tremor, insomnia, shyness, and nervousness. However, this correlation was not as strong as one demonstrated between urine levels and mercury air concentrations ranging from 0.01-0.27 mg Hg/cu m. The correlations for urine and air mercury levels are given in Table XII-8 and shown in Figure XII-2. On a group basis, a good correlation may be seen between the urinary

mercury concentrations and the environmental levels although a considerable individual variation is present.

From the data presented in Table XII-9, it can also be seen that a positive group correlation exists between exposure to mercury air concentration levels and worker blood levels. This is in agreement with similar findings reported by Goldwater et al. [115] Data, as shown in Figure XII-3, also taken from Smith et al, [28] show a ratio of approximately 0.3 between blood and urine mercury levels on a mg/liter basis. Such findings are in agreement with data presented by Benning [26] from which a median quotient of 0.31 between blood and urine levels was calculated by Friberg and Nordberg. [54]

The relationship between the prevalence of certain signs and symptoms (tremor, nervousness, loss of appetite, loss of weight, insomnia) and the degree of exposure observed in the Smith study can be seen in Figure XII-4. Although the symptom of loss of weight was not confirmed by actual weight measurement, the findings reveal a clear dose-related response to mercury exposure and demonstrate the potential effects of even minimal exposure to mercury. The authors concluded, "The data presented here show no significant signs or symptoms in persons exposed to mercury vapor at or below a level of 0.1 mg/m^3. However, the data do raise a question regarding the adequacy of the safety factor provided by a TLV of this magnitude."

McGill et al, [50] in a report on another study involving 60 men in a chlor-alkali operation, showed that urine mercury levels, over

the 6-year period of plant operation, were usually between 80 and 250 µg Hg/liter of urine. Exposure levels ranged from 0.08 to 0.1 mg Hg/cu m. These investigators reported finding no evidence of dangerous absorption of mercury under conditions prevailing in this plant. The distribution of urine mercury levels showed a consistent positive relationship to three exposure groups based on the average amount of time spent in the chlor-alkali cell room, ie, 30 to 40 hours per week, 2 to 10 hours per week, and a control group with no exposure. One worker who spent 20 hours per week in the cell room was included in the 2-10 hour per week exposure group. The overall range of urine mercury levels at the time of the study was a reported 0 to 157 µg Hg/liter of urine.

In a study of mercury mining and smelting operations, West and Lim [49] performed urinalyses on 83 of 96 California cinnabar millworkers exposed to mercury in air levels ranging from 0.3 to more than 1.2 mg Hg/cu m and showed 35 workers to have urine mercury levels above 300 µg Hg/liter as analyzed by the dithizone method. Of these 35, 23 had definite signs or symptoms of mercury toxicity (tremor, muscle weakness, weight loss, nervousness, insomnia, bleeding gums) and two had "borderline" symptoms. Severity of symptoms was roughly related to urine mercury levels. In 13 of the 23 symptomatic workers urine mercury levels ranged from 320 to 7,100 µg Hg/liter of urine (median = 1,200). However, nine workers without symptoms also had

high urine mercury levels ranging from 200 to 1,100 μg Hg/liter of urine (median = 460).

In contrast to the study by West and Lim, [49] Ladd and his co-workers [27] reported that cinnabar workers in the Philippines and Yugoslavia showed urine mercury levels to be lower, on the average, in workers with mild symptoms of mercury toxicity than in asymptomatic exposed workers. Fifteen symptomatic workers (tremor, gingivitis, irritability in the 1964 Philippine survey where exposure levels ranged from a reported 0 to more than 2.0 mg Hg/cu m showed urine mercury levels ranging from 3 to 1,260 μg Hg/liter (mean = 389). Urine mercury levels for asymptomatic workers ranged from 75 to 2,175 μg Hg/liter (mean = 652).

In miners in the Yugoslav study, [27] 16 symptomatic workers (irritability, personality change, salivation, tremor) and 57 asymptomatic workers who were exposed to total mercury (vapor and dust) concentrations ranging from 0.16 to 4.89 mg Hg/cu m had urine levels ranging from 2.0 to 601 μg Hg/liter (mean = 255) and 0 to 1,275 μg Hg/liter (mean = 276), respectively. These low urine mercury levels in symptomatic workers lend support to the hypothesis of Copplestone and McArthur [116] that "mercurialism might be due to an inability to excrete mercury rather than simply to exposure."

While this hypothesis does not seem to have been pursued by other investigators, it might explain the paradoxical situation with urine levels. However, it does not explain the lower blood levels

reported by Ladd et al [27] in the same study where blood determinations showed similar results with a range of 0.6-24.0 μg Hg/100 ml whole blood (mean = 10.6) in the symptomatic workers and a range of 0.9-30 μg Hg/100 ml whole blood (mean = 13.5) in the asymptomatic workers. This would suggest that one might suspect the accuracy of some of the analyses in the study, or it may point to the fact that blood mercury levels may not be directly related to toxicity or that mercury levels in critical tissues are not affected by blood levels.

Vostal [96] has noted that differences in the red blood cell-to-plasma distribution of mercury in whole blood play an important role in urinary mercury excretion, ie the higher the plasma levels, the greater the level in the kidney. This could explain the good correlation between the blood and urine levels of exposed workers found in the Smith et al study [28] Furthermore, humans exposed to elemental mercury vapor and to inorganic mercury compounds show red blood cell-to-plasma ratios which seldom vary more than by a factor of two, [71,117] whereas organic mercurials have ratios reportedly as high as twenty. [71] Friberg and Nordberg, [54] have also pointed out that the average ratio of urine mercury levels (μg Hg/liter) and atmospheric mercury (mg Hg/cu m) is of the same order of magnitude (about 2) as reported in early studies by Storlazzi and Elkins, [118] who found an average ratio between urinary mercury and atmospheric mercury of 2.6. for group exposure.

In spite of this relationship, individual urinary excretion of mercury fluctuates considerably, independently of exposure . Wide diurnal and day-to-day variations have been reported. [7,8,119] Figure XII-5, reported by Friberg, [119] shows variations in excretion of mercury during a 24-hour period. Threefold changes in mercury excretion over a 24-hour period were not uncommon and a nearly 5-fold change may also be noted. A concentration of about 0.1 mg/cu m in air for a 40-hour week exposure corresponds to about 0.2 mg Hg/liter of urine as shown for group exposure by Friberg and Nordberg [54] and Storlazzi and Elkins, [118] However, environmental concentrations of mercury cannot be confidently related on an individual basis to urine mercury levels because of the extreme fluctuations.

Moskowitz, [56] in commenting upon previous work reported by Smith and Moskowitz [20] and Smith et al, [21] stated that the mean urinary excretion of mercury is directly related to the concentration of mercury in the air to which workers are exposed. This applies to groups of large population, groups of 15 to 20 not being sufficiently large to use in making statistical comparisons. Moskowitz also noted that variations of excretion within any exposure group were exceedingly large so that individual findings or the findings of small numbers cannot be used to determine intensity of exposure or the presence of mercury toxicity. He also found that the average urine mercury levels tended to decrease with increase in duration of exposure. However, the difference was not statistically significant.

The above studies and those reviewed earlier demonstrate that the higher the concentrations of mercury in air the greater the likelihood that an exposed worker will develop signs or symptoms of mercury intoxication although one cannot be assured that toxicity will develop at high exposure levels.