THE RESULTS OF EPIDEMIOLOGICAL STUDIES OF THE BIOLOGICAL EFFECTS OF LEAD

In studying diseases due to a single environmental agent such as lead, three main stages in man's state of knowledge may be distinguished. The first is the recognition of the diseased state but without appreciating the nature of the causative agent. It is at this stage of man's knowledge that Paul of Aegina and Avicenna describe patients suffering from "colicky affections" accompanied by paralysis which may well represent descriptions of lead poisoning, but it is not until the 2nd century B.C. that man enters the second stage of his knowledge of the biological effects of lead when there is unequivocal evidence linking the disease to the causative agent - lead. At that time Nikander wrote his "Alexipharmaca" describing both colic and paralysis as the result of ingesting litharge (lead oxide). The third stage in our increasing knowledge of the biological action of an agent such as lead comes with the demonstration that the severity of the effect produced is directly related to the amount absorbed. This third stage of knowledge is often late in coming because only severe disease produced by massive doses is recognized at first and more subtle effects are missed. Such situations are illustrated by the sporadic and usually accidental lead exposures reported after 1500, at about which time the development of printing made the dissemination of such reports easier and their preservation more certain.

In 1572 an epidemic of lead poisoning occurred in the French province of Poitou due to drinking wine adulterated with litharge (lead oxide) and from that time on repeated epidemics of lead poisoning due to intentional or accidental adulteration of cider,(5) rum,(6) food(7) or caused by drinking water conveyed in lead pipes,(8) (9) were reported. In the more recent past there have been outbreaks of lead poisoning presumably due to airborne lead particulate derived from the burning of old automobile batteries to provide domestic heating.(10) (11)

It is with the beginning of the Industrial Revolution with the splitting up of the manufacturing process into discrete operations performed by separate groups of men with differing degrees of lead exposure that it becomes possible to study sickness rates and relate these to the level of lead in the men's environment.

One of the first studies to clearly show such a relationship between the level of the lead exposure and the amount and severity of the sickness produced was that of G. E. Duckering in 1908.(10a) As a result of his measurements of the amount of lead in the air breathed by workmen in a number of British factories and his records of the number of men showing signs of lead intoxication, Legge and Goadby suggested in 1912 that "if the amount of lead present in the air breathed contains less than 5 milligrammes per 10 cubic metres of air, cases of

encephalopathy and paralysis would never, and cases of colic very rarely occur. And this figure is a quite practical one in any process amenable to locally-applied exhaust ventilation. Somewhere about 2 milligrammes, or 0.002 gramme, of lead we regard as the lowest daily dose which, inhaled as fume or dust in the air, may in the course of years set up chronic plumbism.(10b)

With the demonstration that exposure to a certain amount of lead caused a certain biological response and that as the dose of absorbed lead diminished the clinical response became less, the prevention of the disease depended increasingly upon the ability of the engineer to control the level of lead in the workman's environment. This ability to control lead poisoning by a combined medical and engineering approach backed by government regulations is illustrated by the figures for notified cases of lead poisoning in Great Britain which fell from 1,058 in 1900 to 239 in 1928.(10c) Similar studies were carried out in the United States(14) (11) and confirmed that the number of cases of plumbism was positively correlated with the level of lead in the air as shown in Table I taken from Reference 14.

TABLE I

CASES OF PLUMBISM AMONGST BATTERY WORKERS IN AREAS HAVING DIFFERENT LEAD EXPOSURES

	Atmospheric Lead Concentration (Mgm Pb per 10 m^3 air)			
	0 - 0.74	0.75 - 1.4	1.5 - 2.9	Over 3
Men Exposed	97	84	168	125
Men with early plumbism	4	6	50	67
Percent affected	4.1	7.1	29.8	53.6

Because the major route of entry for lead in the industrial worker is through the lungs, information from the study of industrial populations commonly relates the clinical or biochemical findings to the level of lead in the air, but similar relationships between the amount of lead absorbed and the biological effect produced has been found for ingested lead[16] and for lead injected intravenously as a therapeutic agent.[17] It has also been found from such studies that the level of lead exposure is reflected in the level of lead in the blood and the amount of lead excreted in the urine of the exposed person. Such relationships may show a considerable degree of variation when the values from individual persons are considered, but this variation is much less when the average or median values for groups of persons are studied. (Table II) The values in Table II should be used only to show a general tendency for increasing levels of exposure to be reflected in increased blood lead concentrations since the lead exposure is not completely described in terms of particle size and this is known to play an important part in the deposition and absorption of lead in the lung. Another factor tending to reduce the degree of correlation in this study between the blood lead and the level of lead in the air is the medical control exerted by the physicians in charge of the battery workers. This control removed many of the men in the high exposure group and placed them in areas of lesser exposure where they appear in Table II under the heading "Exposure changed." A more recent study[18] that illustrates the relationship between lead exposure and urine and blood lead levels provides the data for Table III.

TABLE II

(Ref.14)

Average and median blood lead content (dithizone method) in mg. per 100 gm. of blood. Storage-battery workers classified by exposure and by duration of employment.

Years lead exposure		Exposure not definable	Exposure changed	Mg. lead per 1 m^3 of air			
				0 - 0.074	0.075-0.14	0.15 -0.29	Over 0.3
0 - 4. . . .	Number	26	12.	17	16	32	20
	Average	0.0352	0.0368	0.0187	0.0316	0.0378	0.0463
	Median	0.024	0.040	0.021	0.030	0.038	0.050
5 - 9. . . .	Number	30	46	10	13	40	24
	Average	0.0352	0.0475	0.0278	0.0405	0.0501	0.0505
	Median	0.033	0.046	0.033	0.040	0.043	0.050
10 - 14. . .	Number	5	22	23	24	30	32
	Average	0.0508	0.0344	0.0198	0.0375	0.0502	0.0481
	Median	0.036	0.037	0.018	0.038	0.046	0.048
15 +	Number	7	26	44	30	59	45
	Average	0.0341	0.0520	0.0293	0.0407	0.0457	0.0493
	Median	0.027	0.054	0.023	0.036	0.045	0.045

Departmental means and standard errors of eight-hour lead-in-air concentrations and blood and urine lead concentrations for workers working in an electric storage battery plant.

TABLE III
(Ref. 18)

JOB	n	Pb-in-Air (mg/m^3)		BL (ug./100 ml.)		UL (ug./l.)	
		Mean	S.E.	Mean	S.E.	Mean	S.E.
Machine pasting	6	0.218	0.025	74.2	4.7	163.8	21.2
Hand pasting	8	0.150	0.029	63.2	9.2	111.3	14.1
Forming	9	0.134	0.013	63.0	2.7	114.0	7.2
Casting	6	0.052	0.003	-	-	87.9	6.8
Plastics Dept. A	5	0.012	0.0008	27.2	1.4	34.5	3.2
Plastics Dept. B	5	0.009	0.0008	29.1	1.6	34.8	2.0

In this study by Williams although the number of men observed (39) was not large, the use of personal air samplers and the number of observations made gives the results a more than usual value. From this data Williams calculated correlation coefficients (γ) and regression equations XY of the biochemical value (Y) with the mean 8-hour lead-in-air concentration.(X). These results are shown below:

Y	γ	Y	X
Blood lead	0.90	30.1 + 201 X	- 0.0975 + 0.00399 Y
Urine lead	0.82	45.5 + 486 X	- 0.0277 + 0.00138 Y

Experimental exposures of human beings to known concentrations of airborne or ingested lead have provided graphic data describing the relationship between the exposure level and the blood and urine lead concentrations.(19)

All of the information so far discussed deals with occupational or experimental exposure but at levels of lead found in the urban environment a similar correlation between the concentration of lead in the air and lead in the blood has been found.(20)(21) With regard to lead as a community air pollutant, there have been no cases of characteristic lead poisoning due to lead as a community air pollutant. Therefore from this point on, attention will be centered on those studies concerned with health effects of lead other than classical lead poisoning. Three main epidemiological approaches have been used in seeking such health effects. The first has been to compare the health of occupational groups with documented lead exposures with the health of groups not so exposed. The second approach has been to study persons with a certain disease and compare their tissue levels of lead with persons who are otherwise similar but do not suffer from the disease. The third method is to study the geographical distribution of a disease and compare it with the geographical distribution of a type of lead exposure.

The first method, if properly carried out, probably offers the chance of the greatest precision but suffers from certain limitations which are inherent in the nature of an employed population such as being restricted to a certain age range and initial state of health. In the case of the lead industries it is also likely to be predominately a male group.

There have been very few epidemiological studies of groups occupationally exposed to lead in which a large number of factors were documented and the results in different exposure groups compared.

One of the earliest of such studies to use modern epidemiological methods was of persons exposed to lead arsenate as a result of the use of this compound as an insecticide.

In common with most epidemiological studies which may be looked upon as naturally occurring experiments in which the investigator has little or no control over the experimental design this study of the orchardists in the Wenatchee area of the state of Washington was complicated for the purposes of this discussion by dealing with an exposure to lead arsenate. This raises the question as to the relative importance of the lead compared with the arsenical portion of the lead arsenate molecule in the overall toxicity of the compound. An attempt to answer this was made by special studies in animals.

It was found in these animal studies that the more toxic portion of the molecule of lead arsenate is to be attributed to the arsenical radical rather than to the lead or a synergistic action of the lead and arsenic.(23)

11 2 Lead

TABLE IV

URINE LEAD VALUES OF PERSONS IN WENATCHEE STUDY CLASSIFIED BY SEVERITY OF EXPOSURE

(Ref. 22)

		Urinary Lead mg Pb per liter		
		No. of Analyses	Aver-age	SD
Low exposure group				
	Men	146	0.035	0.021
	Women	123	0.028	0.019
Intermediate exposure group				
	Men	102	0.043	0.301
	Women	25	0.027	0.014
High exposure group				
	Men	386	0.09	0.060
	Women	61	0.05	0.024
Children under 15				
	Boys	81	0.05	0.039
	Girls	65	0.05	0.405

While the lead values shown in Table IV are not as high as those sometimes seen in other industrial exposures, they are of particular importance for this reason since the urine lead concentrations range from those slightly more than are commonly found in urban communities to those found in moderate lead exposures in industry. Among the factors studied in assessing the health of the orchardists were weight, blood pressure, diseases of the cardiovascular system, skin disorders, eye irritation, chronic nervous diseases, blood dyscrasias, kidney disease, pulmonary tuberculosis, visual acuity, syphilis, neoplastic disease and fertility.

Each factor was studied to find out whether it had been modified by lead arsenate exposure. Insofar as comparative data for other populations were available, no evidence was found that any of these factors was altered by the lead arsenate exposure. Special attention was given to medical examination of children because, in the Wenatchee area where orchards surrounded the communities or the houses in which they lived, there were unusual opportunities for children to be exposed to lead arsenate insecticide sprays and spray residues on branches, leaves and grass in addition to lead arsenate spray residues they ingested on apples. There was only one respect in which these children differed from children in other districts their urinary lead and urinary arsenic values were nearly twice as high as the corresponding values for a group of 18 children taken at the same time in Washing-

ton, D. C. (who had a mean urine lead level 0.026 mgm/Pb/liter S.D. 0.0128.) There was no indication of adverse effects of lead arsenate exposure on the health of the Wenatchee children children.

While this study of persons exposed to lead arsenate has many deficiencies when used as a source of information on the possible biological effects of lead as an urban air pollutant it is particularly important for two reasons. Firstly, it is one of the few modern studies containing an appreciable number of women of childbearing age; and, secondly, it is one of the few studies having children with a lead exposure other than flaking lead paint.

A study of storage-battery workers previously referred to (14) and who showed the range of blood lead concentrations shown in Table III was also studied for the possible effect of the lead exposure upon the incidence of diseases other than plumbism. Seventy-five percent of the 766 men studied had been employed in electric storage-battery plants for more than five years and about 12 percent for 20 years or more. In this study the incidence of disease in the high-exposure group (exposed to more than .15 mg Pb per M^3) was compared with the incidence in the low-exposure group (exposed to less than 0.15 mg Pb per M^3). The prevalence of arteriosclerotic-hypertensive heart disease did not increase with increasing atmospheric lead concentration. In the age range 45 - 54

which covers the period when degenerative cardiovascular disease is making its appearance, 53 workers were exposed to atmospheric lead concentrations below 0.15 mg Pb per M^3 and 32 percent were found to have arteriosclerotic hypertensive heart disease as defined in the study. In the 66 workers in the same age range exposed to concentrations in excess of 0.15 mg Pb per M^3 also had a 32 percent incidence of this type of heart disease.

Another statistical treatment, shown in detail in Table V, is to use the population exposed to less than 0.15 mg per 1 m^3 as a basis for predicting the number of cases that would be expected if the same rates of incidence prevailed in all age groups of the more heavily exposed populations. Thus, if this assumption were correct, one could expect to find 35 cases of heart diseases of the arteriosclerotic-hypertensive group in 263 workers between 25 and 65 years of age exposed to atmospheric lead concentrations in excess of 0.15 mg per 1 m^3. Making allowance for the differences in age distribution, actually, 37 cases were found, a number that agrees closely with the expected value. The agreement is even closer for the 102 workers who changed jobs within 5 years of the time of study, the expected value of 13.7 checking the observed number of cases, 14. Thus, it may be concluded that an increase in lead exposure was not accompanied by any increase in the prevalence of this group of diseases of the cardiovascular system.

TABLE V

Computation sheet, showing the number of cases of arteriosclerotic-hypertensive heart diseases that could be expected in relatively heavily exposed workers[1] supposing the age incidence to be the same as in relatively lightly exposed workers.[2]

	Less than 1.5 mg. per 10 m^3			More than 1.5 mg. per 10 m^3			Exposure changed		
Age	Number in age group	Cases	Percent affected	Number in age group	Expected cases	Observed cases	Number in age group	Expected cases	Observed cases
a	b	c	d	e	d X e	f	g	d X g	h
25-34	31	1	3.2	94	3.0	3	31	1.0	0
35-44	51	3	5.9	84	4.9	5	38	2.2	4
45-54	53	17	32.1	66	21.2	21	22	7.0	5
55-64	19	6	31.6	19	6.0	8	11	3.5	5
Total					35.1	37		13.7	14

[1] Exposed to more than 1.5 mg Pb per 10 m^3 of air.

[2] Exposed to less than 1.5 mg Pb per 10 m^3 of air.

When lead-affected workers are compared in the same way as before with workers exposed to less than 0.15 mg Pb per 1 m^3 of air one would expect to find 27.3 cases of arteriosclerotic-hypertensive heart disease in the 169-lead-affected workers between the ages of 25 and 65. Actually, there were 34 cases but, considering the standard deviation (4.78) that attaches to such an estimate, the difference is not statistically significant. Application of a chi-square test confirms this conclusion.

Response to a standard exercise test was as good in men exposed to lead concentrations in excess of 1.5 mg Pb per 10 m^3 as it was in men of comparable age exposed to lower concentrations. Men who had changed jobs during the preceding 5 years also, as a class, had equally satisfactory returns to preexercise pulse rates and systolic and diastolic blood pressure values.

In two age groups of storage-battery workers, 35-44 and 45-54, the differences between preexercise values and the values prevailing 3-minutes after exercise were in close agreement.

Application of a probability test indicated that the differences were in all cases not significant.

Blood pressure values, measured with the mercury syphgmomanometer, agree closely with the average values for 6,667 industrial workers in 9 other industries studied by the Public Health Service.(24)

As an additional check, a tabulation was made of men with preexercise blood pressures in excess of 150 mm. Hg. The number and percentage with higher systolic pressures, here designated as cases of hypertension, appear in table 68 for storage-battery workers and for other industrial workers.(24) The percentage values agree closely, showing that hypertension of this degree is no more prevalent in the storage-battery industry than in other industries.

This information on the status of the cardiovascular system has been given in some detail because this system has been the thought to be affected by lead by many earlier writers but after reviewing these authors Aub concludes "Although the general clinical opinion holds that arteriosclerosis is a result of chronic plumbism, this idea is based entirely on the occurrence of this condition in many postmortum examinations. That arteriosclerosis is much more frequent in those exposed to lead than in other individuals of the same age, however, needs much more statistical proof before it can be accepted."(25) Cantarow and Trumper in their book on lead poisoning are inclined to believe that lead at high concentra-

tions such that lead poisoning has occurred or is likely to occur may be associated with degenerative vascular disease.

Support for the view that lead at high levels may be linked to degenerative vascular disease found in a British study of battery workers[27] in which three exposure grades were defined Grade A - no exposure, Grade B - negligible exposure and Grade C - exposure represented for the last 20 years by a mean lead in urine values between ·100 and ·250 mg/liter (but in the past these have not infrequently exceeded ·250 mg/liter.) The mean exposure period for the pensioners in Grades B and C was 35.3 and 32.3 years respectively, while for men dying whilst employed, the mean exposure for Grade B exposures was 26.8 years and that for Grade C 21.8 years. In studying the number of deaths from all causes amongst the pensioners there was found to be a significant excess in Grade C but not in either of the other Grades. When the deaths attributed to vascular lesions are studied in this series a highly significant excess of deaths due to cerebro-vascular catastrophies was found amongst Grade C pensioners. As can be seen in Table VI while the deaths of pensioners prior to 1950 showed an excess of those observed over those expected in both Grade B and C, after 1950 only Grade C shows an excess of deaths. This suggests that improvements

TABLE VI

EXPECTED AND OBSERVED DEATHS FROM CEREBRAL HAEMORRHAGE, CEREBRAL THROMBOSIS, AND CEREBRAL ATERIOSCLEROSIS IN PENSIONERS, 1926-1961, AND IN EMPLOYED MEN, 1946-1961

	Year of Death	Grade of Exposure						
		A		B		C		
		Expected	Observed	Expected	Observed	Expected	Observed	
Pensioners	1926-1950	0.7	0	0.2	3	0.8	5	
	1951-1961	7.2	6	3.2	3	8.5	19	
	1926-1961	7.9	6	3.4	6	9.3	24*	$\chi^2=21.7$
Employed	1946-1961	3.2	3	3.1	3	5.6	9	

* $p < 0.001$

in hygienic standards with a consequent decrease in the lead exposure may have resulted in the observed improvement in mortality experience. It is unfortunate that this study which was initiated to study the incidence of cancer amongst battery workers did not contain more information on the physiologic status of the men. For instance it would have been most interesting to have known the incidence of hypertension in the various exposure groups.

The apparent difference in the experience of European and North American investigators studying the effect of lead on the blood vessels is thought by Lane[30] to be probably a reflection of differing working conditions on the two sides of the Atlantic although he points out that the study of Dreesen[14] contained only 12 percent of men with more than 20 years' exposure and that no adequate study has been conducted of workers in the United States exposed to high levels of lead for one or two decades. Support for the view that lead workers in carefully supervised plants do not, even after long exposure have an increased risk of hypertension compared with nonlead workers comes from the study of Cramér.[34] Three-hundred and sixty-four workers were studied, 82 of whom had been employed for more than 20 years, and 265 for more than 10 years. The incidence rates of hypertension in the various age and exposure groups were then studied and compared not only within groups but against data gathered in an extensive Norwegian study of nonlead-exposed men. In none of these

comparisons was there any evidence of an effect of lead exposure either in duration or in severity upon the incidence of hypertension.

The same confusion of claims and counter claims for the effects of lead surround the subject of kidney disease and high blood pressure. Views on these topics appear to depend as they do with arteriosclerosis on the characteristics of the lead exposure of the workers studied. The earlier observers who saw many more cases of heavy prolonged exposure to lead than is possible today were convinced that chronic kidney disease and high blood pressure were direct although delayed consequences of exposure to lead. The extensive literature on this matter has been reviewed by Radosev.(32) It is pointed out by Browning(30) that no actual rise in blood pressure of workers in the electric storage battery industry has been demonstrated by Belknap,(31) Dreesen,(14) or Lane,(29) and that this absence of significant change shows that their exposure had not reached a dangerous level and that the disappearance of chronic renal disease in lead workers is probably due to the improvement of conditions in modern lead industries. Therefore looking at these controversial matters from this point in time it would appear that the modern lead worker, although still showing a higher lead absorption than the nonlead worker, does not run the risk of arteriosclerosis, hypertension or kidney disease due to his lead exposure. This conclusion would be supported by the Wenatchee study(22) with it's generally moderate level of lead exposure and the

studies of Baader[44] and Vigliani.[45] The epidemiological experience with groups of persons exposed to lead and other materials in consuming illicitly distilled alcohol is dealt with elsewhere in this publication, but in general it may be said that the kidney disease seen in such groups is associated with high lead absorption.[33]

In concluding this review of information from epidemiological studies of lead workers, it is important to raise the question of whether certain groups of workers are more susceptible than others to the effect of lead. As must be repeatedly emphasized, it is not sufficient to consider this question alone, but as with every consideration of the biological effects of lead/must always be considered. the level of the exposure It might be that differences in susceptibility would be shown under conditions of severe lead exposure that would not be found at lead levels commonly found in the general population while it is also possible that some persons would be found to be unusually susceptible even at "normal" levels of lead exposure. On balance the evidence available at this time would favor the former rather than the latter situation. There are two main groups that have been the subject of concern, controversy and legislation with regard to their exposure to lead. These groups are women and children and the controversy over whether or not they are more susceptible than adult men to lead poisoning contains many of the same problems that were touched

on in discussing the relationship of lead to kidney disease. One additional factor in the case of women and children that makes resolution of the controversy difficult is the banning of both groups from the lead trades in most western countries for the past 50 - 70 years. Thus, the only occupational data comes down to us from a time when severe and prolonged exposure to lead was common and the criterion of a lead effect was clinical lead poisoning. Oliver[35] said in 1902, "So far as occupational exposure to lead is concerned, my opinion is (1) that women are more susceptible than man; (2) that while female liability is greatest between the ages of 18 and 23 years, that of men is later; and (3) that while females rapidly break down in health under the influence of lead, men can work a longer time in the factory without suffering, their resistance apparently being greater." On the other hand, the Germans at this same period felt that the apparent susceptibility of women to lead poisoning is explained not by their sex, but by the fact that they are usually more poverty-stricken than the men, are undernourished, and obliged to do work for their families in addition to their factory work. Then, also, a women's skirt and hair collect the lead dust so that she carries it home with her after work.[36] Support for this view is presented by Hamilton[37] for the U. S. battery industry around the beginning of the century. In those areas where there were strong unions to which the men belonged, the men enjoyed good pay and living conditions while the nonunionized women were underpaid, poorly housed, poorly fed and subject to the worry and strain of supporting dependents on low wages. Under these conditions a much larger pro-

portion of women than of men were found suffering from lead poisoning while in the nonunionized pottery fields where both men and women were both making low wages and economic conditions were poor for both men and women, the rate of lead poisoning was slightly greater among men. Information supporting the greater susceptibility of women to lead is given by Lane[29] quoting a British departmental committee report on the dangers attendant on the use of lead in the manufacture of earthenware and china. This report makes it possible to compare the incidence of lead poisoning in men and women engaged on the same work - ware cleaners, dippers and dipping assistants. The female incidence rate was shown to be from two to three times that of the male. Of course factors such as work habits, labor turnover, AND general health might influence these statistics but the committee making the report was sufficiently impressed with the data before them to express their belief that women are more susceptible to lead poisoning than men.

While the statistics available on the relative susceptibility of men and women leave much to be desired, there is even less information on whether lead poisoning shows a significantly different clinical picture in men when compared with women. In one of the few such comparisons undertaken there is a suggestion that there may be such a difference. Prendergast[38] found the following incidence rates for

various expressions of lead poisoning among 640 cases of plumbism in the Staffordshire potteries.

	Men	Women
Colic	77.6	69.8
Paralysis	57.0	30.0
Convulsions	15.0	34.9
Blindness (total)	2.3	7.7
Blindness (partial)	3.5	10.2

From this admittedly sketchy data there is a suggestion that when there has been a sufficient exposure to lead to cause clinical poisoning women are more likely to show central nervous system manifestations and men, peripheral nervous system involvement. This latter finding might be related to the fact that men are more likely to be engaged in heavy work and the amount and type of physical effort has been thought to affect the incidence and location of the muscular paralysis.

In discussing the possibility of women being more sensitive than men to the same dose of lead, there are related topics which it is also necessary to consider. These are the effect of lead on fertility, gestation and neonatal health.

In the study of the earthenware and china workers previously referred to the committee found that the incidence of miscarriage per hundred mothers was almost three times as

great among those who continued on lead work after their marriage compared with women not occupationally exposed to lead. In a review of the effect of lead on reproductive capacity Lund[39] concludes from studies conducted prior to 1920 that "even when the mortality of that time is taken into account, the number of "productive" pregnancies is abnormally small" (in mothers occupationally exposed to lead). The earlier writers, Hamilton, Oliver, Legge, Cantarow and Trumper are unanimous in their view that lead in high concentrations affects the reproductive capacity of women and that having regard to the poor hygienic conditions in the lead trades at that time women should not work in these trades. As a result of these views, there was enactment of legislation in many countries barring women from occupations where they would be exposed to lead. Therefore, there is almost no data on the effect of the generally much lower concentrations of lead now prevailing in these industries upon reproductive capacity. The Wenatchee study[22] remains as the only evidence and in that study no effect on fertility was found. In summarizing their study of the fertility of men and women in the Wenatchee study the authors conclude "The instances reported in the literature of an effect of lead on human fertility appear to be limited to men and women who were far more heavily and much more regularly exposed to lead than the residents of Wenatchee. It would appear that a clinical state approaching that of frank lead poisoning

is necessary before the fertility of men or women is affected."

The other large group of particular interest with regard to the possibility of specially sensitivity to lead is children and here again despite the voluminous literature on childhood lead poisoning, there is little data bearing directly on the problem. Since childhood lead poisoning is dealt with in detail elsewhere in this publication, this matter will not be discussed further beyond the following quotation from Chisholm.(40) "The more frequent occurrence of encephalopathy in children as compared with adults may depend in part upon their more intense exposure rather than upon any inherent biologic differences between child and adult." The majority of the early writers on the health of lead workers have remarked on the individual variability shown by persons exposed to high levels of lead. Some men becoming intoxicated within a few weeks, whereas others can work for years in the same surroundings without apparent harm. Undoubtedly some of this variation in response was due to differences in working habits and even today similar variations can be found although now it is more likely to be confined to a difference in the amount of lead absorbed rather than to variations in overt toxicity. There is a good correlation between blood lead levels and air lead levels with relatively little variation from man to man when the major portion of the lead exposure is from the air but when the work involves jobs such

as hand pasting of battery plates with a much greater chance of "local" lead contamination the variability of lead absorption between men increases as much as four-fold.[18] Therefore, it is probable that at least some of the apparent individual resistance to lead poisoning seen by the earlier writers reflects variations in working habits and therefore of lead absorption. There remains however a likelihood that persons respond differently to the same dose of lead, but whether this difference would be of any practical importance at the levels of lead exposure now found in the general population seems unlikely[53] but merits further study. Such studies should first consider persons known to already have biochemical defects in systems of the body known to be affected by lead in adequate amounts. Examples of such defects would be sickle cell anemia, glucose-6-phosphate deficiency, the porphyrias and gout.

At the beginning of this section on the epidemiology of lead three main avenues for using epidemiological information to throw light on the effects of single environmental agents were outlined. After devoting most of the available space to studies of occupationally exposed populations because in this type of study the factors under study are usually easier to document consideration must now be given to the remaining two areas of study. Although[1] studying the tissue levels of lead in various diseases and[2] looking for a congruence between disease distribution and some measure of lead exposure are attractive concepts, when the results are positive, the investigator is faced with a formidable task in dealing with

the question of - Did lead cause the disease under study? This problem of deciding whether two variables are merely associated or whether one bears a causal relationship to the other is dealt with by Sir Bradford Hill in his presidential address to the section of occupational medicine of the Royal Society of Medicine.(41) Among the aspects to be considered in deciding for or against a causal relationship between the two variables, Professor Hill suggests: Strength of association, consistency, specificity, temporal relationship of the association, dose response curve, plausability from the biological standpoint, coherence with generally known facts, experimental evidence and judgement by analogy.

Two diseases other than classical lead poisoning have been studied for tissue levels of lead. These are renal disease in Queensland, Australia and multiple sclerosis in England. The Queensland study of bone lead levels in renal disease(42) showed that in 866 autopsies there were 160 cases of Bright's disease (chronic renal disease). If those aged 20 - 49 years of age at the time of their death are studied, 63 percent have no known cause for their renal disease and the remainder suffered from diseases recognized to involve the kidney. The bone lead levels of those persons with kidney disease of known causation were significantly lower than those having kidney disease of unknown causation, thus lending support to the belief (dealt with elsewhere in this publication) that long-standing absorption of lead in sufficient quantity can cause chronic kidney disease. The source of the lead in the Australian cases was childhood

ingestion of lead derived from exterior house paint. The authors of this study suggest that surveys of the lead content of tissues taken from persons dying of kidney disease of unknown cause might be useful in providing diagnostic clues at to the cause. This work derived from autopsy material has more recently been supported by Emerson[43] who was able to show that in a group of Australian patients with renal disease of undetermined origin, the mobilization of lead from the bone by a standardized infusion of Calcium EDTA gave evidence of a significant past exposure to high levels of lead in 12 out of 16 cases, thus suggesting that lead might have played a part in the causation of the renal disease.

The other example of high tissue levels of lead being correlated with a particular disease in a population was that of Campbell[46] who reported that teeth from patients with multiple sclerosis contained on the average significantly higher concentrations of lead than was present in the teeth of normal healthy people. This observation was followed up by Butler who observes that physiological changes accompanying chronic diseases may promote the deposition of metals in the skeleton as illustrated by the increased deposition of zinc in the teeth in tuberculosis. Butler then goes on to analyze the lead content of the urine, blood cerebrospinal fluid, and

and bone in 31 cases of multiple sclerosis and in 54 cases of neurological disease other than multiple sclerosis. When the lead levels in the two series were compared one with the other and with commonly accepted normal values no significant differences were found. An examination of the lead levels in necropsy tissue including brain and spinal cord from patients in whom the diagnosis of multiple sclerosis was confirmed histologically did not show significantly elevated levels. Butler concludes that his study does not support the view that lead plays a part in the etiology of multiple sclerosis. The final epidemiological relationship to be explored is that of the geographical distribution of a disease and the relationship of this distribution to some index of lead exposure.

Two diseases have been looked at in this particular manner in their relationship to lead. The first is multiple sclerosis and the second is cancer. Warren(48) has drawn attention to the great variation in the incidence of multiple sclerosis in different geographical areas of Norway, Scotland, Sweden, England and Canada while in some of those areas having a high incidence of the disease there are lead-bearing rocks. There are many reasons for not accepting this association to be a causal relationship at this time. The first is the difficulty of obtaining adequate statistics on the true

incidence of a disease whose prevalence is normally between 30 to 60 per 100,000 population and if deaths are the basis of the reporting, then death rates may vary from zero to 4 per 100,000. In the areas reported as having a high incidence such as the Orkney and Shetland Islands of Scotland with a total population of around 36,000, the addition of a single case in a disease that is particularly difficult to diagnose with certainty can increase the overall prevalence rate by as much as 25 percent. Additional impediments to accepting a causal relationshipare the strong North-South gradient in prevalence rates,(49) the lack of recognition of multiple sclerosis as a sequela to industrial lead exposure the failure to show elevated lead levels in the brain, blood or urine of multiple sclerosis patients,(47) and the evidence that multiple sclerosis is probably an auto-immune disease possibly related to an earlier viral infection.(50)* Warren(48) points out that if variations in cancer death rates are plotted on a geographic basis, striking differences appear in certain circumscribed areas. Allen-Price(51) in a survey in Devon in England claims that there is a higher incidence of cancer in persons living on the highly mineralized Devonian geological formation than on the adjoining carboniferous and granite formations. Warren then goes on to state that in some cases rocks containing more than 1000 ppm lead can be correlated with some of the high cancer areas encountered by Allen-Price but this was not a uniform finding. Warren mentions two other examples of the same rather tenuous nature and suggests that further studies should be carried out. Apart from the difficulties mentioned earlier of obtaining reliable mortality statistics for small

* See last page.

geographical areas the even larger problem of the reliability of the information upon which the cause of death is based is a well-recognized epidemiological problem. Although it is well recognized that lead at levels of one percent or more in the diet cause cancer of the kidney in rats, there is no evidence that this happens in other species including man. The study by Lane[15] referred to earlier among lead workers was undertaken to examine the incidence of cancer and no increase in cancer incidence was found. Although many human diseases have been alleged to have been caused by lead.

Cancer is one disease that, even in the days of heavy and prolonged exposure sufficient to cause renal disease, was *not* thought by clinicians to be linked to the causation of cancer. As Hammond says, "It is comforting to see evidence suggesting that something is <u>not</u> the cause of cancer." [52]

* (insert from page 30)
The epidemiological evidence that lead can cause cancer in man is mentioned more because of the seriousness of the disease than because of the strength of the evidence.

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Nov. 9, 1970

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Chisholm 40-50 in Scotch child
Children 1-2% of 100 000 children tested
Chicago 1100 poisoned

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