THE HEALTH

OF

WORKERS

EXPOSED TO

CADMIUM

THESIS PRESENTED IN FULFILMENT OF THE REQUIREMENTS
OF DOCTOR OF MEDICINE OF THE UNIVERSITY OF TASMANIA

BY

PETER FRANCIS GILL

M.B.B.S. (MELBOURNE) F.R.A.C.G.P.

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TABLE OF CONTENTS

Summary

Cadmium has been described as being toxic in all living species. At no level of intake does it appear to have a useful biological function.

Although it was not recognised until 1817 as a separate element man has been polluting his environment with it for centuries - from the time the early Greek metallurgist began working with "bronzes". Widely distributed in the earths crust in low concentrations it remains "locked in" unless other more important resources are extracted and refined. Erosion and weathering of the earths crust contributes little to the level of environmental cadmium.

In nature it is closely associated with zinc. It is also found in many other polymetallic ores, particularly those containing copper and lead. Fossil fuels, coal and oil, as well as phosphate rock also contain significant quantities of cadmium. When mankind refines and utilises and purifies these materials cadmium is released. It is a relatively unimportant resource, a by-product of far more important resources.

Whether needed or not it is being separated and recovered in greater quantities annually. Many uses have been found to make it marketable. Little recycling of the end product occurs. Consequently an increasing quantity of "free" cadmium is available for contamination of the environment. Water, air, food chains, foodstuffs are providing an increasing load to all living things. It has been claimed it poses a threat to all life on earth.

Almost 150 years passed from the time cadmium was recognised to the time it was generally accepted as a dangerous substance. 19th century industry provided many examples of its acute toxicity but it was the mid twentieth century before it was established that the metal could accumulate in the body over many years and ultimately reach a concentration which interfered with the function of the host cell.

Those most at risk are those who handle the material in their occupation. But heavy pollution of some Japanese waterways has resulted in death and chronic disability to the population living along the shores. Chronic obstructive airways disease and renal tubular disease are common in those whose working conditions expose them to high concentrations. Anaemia, bone disease, general malaise have also been found.

Animal experimentation has shown that cadmium, though poorly absorbed, can enter the body via the skin, lungs and alimentary canal. Its entry stimulates the formation of a special protein, Metallothionein, which acts both as a carrier and a receptacle. Cells of many tissues take up cadmium - in particular the liver, kidney, pancreas, gonads, salivary and intestinal glands. Because of its environmental ubiquity and its slow excretion - mainly via the kidney, lifelong accumulation occurs. How much can the body accumulate before signs of toxicity appear? Just how toxic is it to various organs?

I have compared the health of 34 workers at the Electrolytic Zinc Company of Australasia, Risdon, Tasmania who have spent many years working in a moderately contaminated atmosphere with fellow workers exposed only to environmental cadmium. I restricted my investigation

to the clinical field and avoided invasive investigational procedures.

I found no evidence of any serious ill health specific to the exposed group. In particular this group did not manifest any of the disabilities found in similar surveys by others. My group of workers were different in that they were working in levels well below accepted tolerable levels. This group therefore could be used as representatives of a middle group between those environmentally at risk and those seriously at risk because of heavy occupational exposure.

I found cadmium did cause chronic pulmonary symptoms even in these low concentrations but without objective pulmonary disease. Some of those with the longest exposure and presumably the largest body burden did show evidence of altered haemoglobin and protein synthesis without obvious clinical manifestations.

I found no evidence of any of the conditions - hypertension, malignancy endocrine disorders speculatively linked to cadmium by epidemiologists using results of animal studies on environmental studies and disease patterns. Though definitely toxic to cells cadmium can be tolerated up to a certain body burden for a "no effect". I was not able to establish this burden but the study may provide areas for further research into this very important question.

FOREWORD

Scope and General Plan of Thesis

This thesis reports on a once only survey of 34 workmen at the Electrolytic Zinc Company of Australasia's plant at Risdon who have been working in a cadmium contaminated atmosphere for long periods. It compares their health with 34 controls working in non cadmium contaminated sections of the plant. A survey of the literature dealing with cadmium, its environmental and occupational hazards is presented first followed by detailed analysis of the findings of the survey.

Obligatory Statement

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

P.M. Bell

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α	-	Alpha
β	-	Beta
Cd.	-	Cadmium
C.S.I.R.O.	-	Commonwealth Scientific and Industrial Research Organisation
d.f.	-	degrees of freedom
Dias.	-	Diastolic
E	-	Exposed
FEV_1	-	Forced expiratory volume at one second
FSH	-	Follicle stimulating hormone
FVC	-	Forced vital capacity
γ	-	gamma
g	-	gram
GM	-	gram
Hg	-	Mercury
Hr	-	Hour
Kg	-	Kilogram
LH	-	Luteinising hormone
m	-	Mole
M	-	Milligram (mole)
Meq	-	Millieqivalent
Mg	-	Milligram
mgm	-	Milligram
Min	-	Minute
ml	-	Millilitre
mls.	-	Millimetre
ml. U/mil	-	Milli unit per millilitre
m.m.	-	Millimetre

MMEF	-	Mid maximum expiratory flow
NACL	-	Sodium chloride
n.d.	-	None detected
neg.	-	Negative
n.m.	-	Nano metre
n mol	-	Nano mol
n.s.	-	Not significant
Pb	-	Lead
ppb	-	Parts per billion
ppm	-	Parts per million
occas.	-	Occasionally
r	-	Correlation coefficient
Sys	-	Systolic
U	-	Unexposed
Ug	-	Microgram
U.K.	-	United Kingdom
U/L	-	Units per litre
V.C.	-	Vital capacity
X_1	-	Chi.

CHAPTER 1.

Cadmium and the Environment

Historical Background

Despite its wide distribution in the earth's crust, cadmium was not recognised until the early 19th century. The ancient Greek metallurgists had noticed that certain "earths" lacking tin could produce a bronze when added to copper and that these earths resembled the flue dust of their zinc smelting furnaces but failed to detect a separate element. Pliny and Dioscorides (1st Century A.D.) named this earth Cadmia Fornacum in honour of Cadmos, son of the Phonecian king Agenon. The former was responsible for the introduction of zinciferous ores into metallurgy. (1)

In 1817 Strohmeyer, a Gottingen metallurgist working with zinc carbonate, noted a brilliant yellow pigment which he attributed to a new element. Hermann from Schonebeck isolated this pigment and confirmed the presence of a new element. Other workers soon verified these findings and noted its close association and relationship to zinc. Many different names were proposed but finally Strohmeyer's suggestion that it be called cadmium in honour of the early Greek metallurgist was accepted. (1)

Environmental Aspects

Cadmium is unique amongst the chemical elements in that nearly always it is found in nature in close association with zinc. In addition, it is present in the polymetallic ore sources of lead and copper whilst traces are found in the fossil fuels, coal and oil, and phosphate rock. (2)

Although closely associated in nature with zinc, cadmium, unlike zinc, serves no biological useful function at any level of intake or cellular

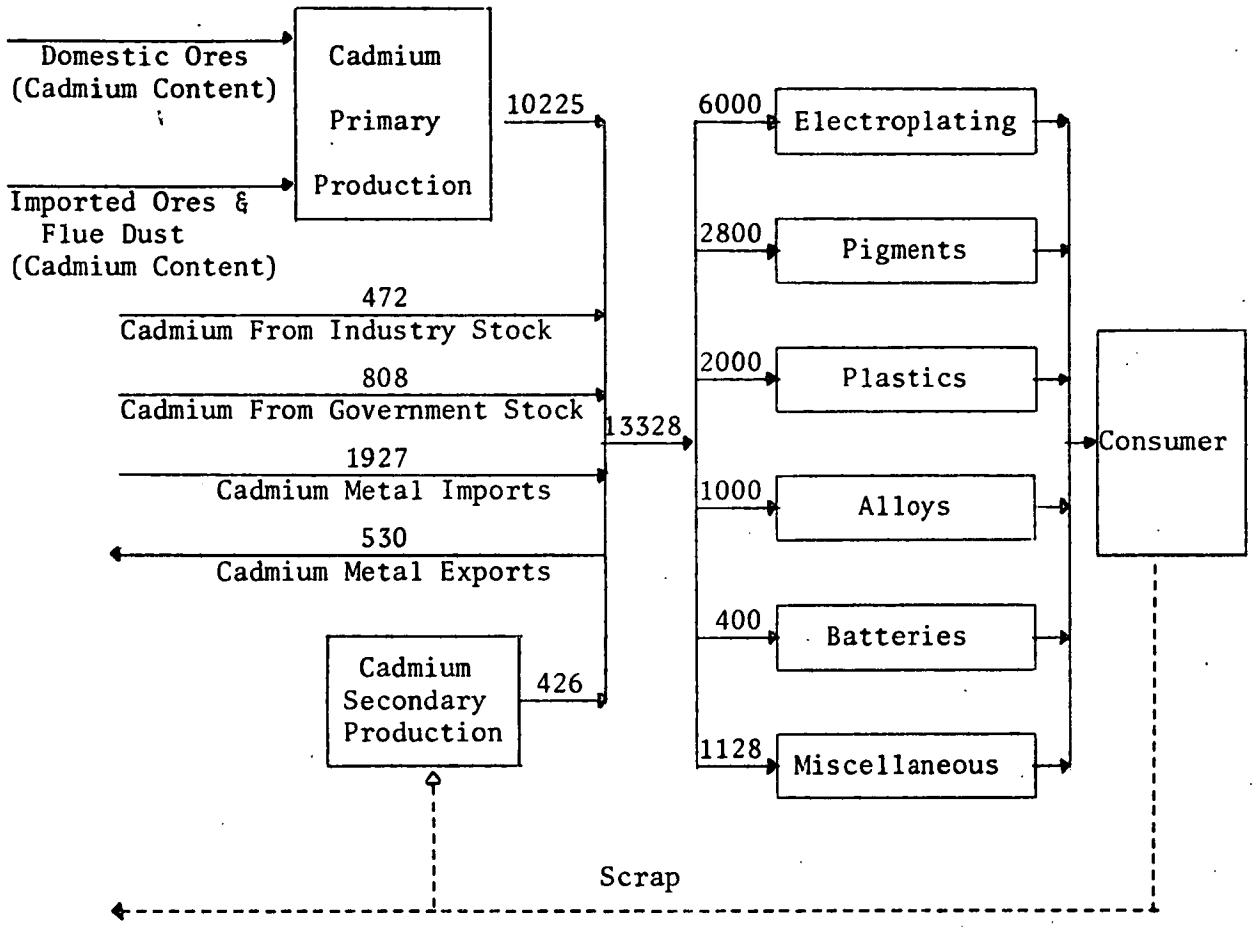
concentration. As more and more zinc, copper, lead, fossil fuels and fertiliser are consumed more and more cadmium is dispersed into the environment. Cadmium in low concentration can now be found as a constituent of all living things. Yet it is not essential to life; on the contrary, in all its chemical forms it is toxic to all living species. (2)

It is this ubiquitous toxicity and the increasing environmental concentration of readily accessible cadmium which has prompted extensive studies into the societal flow of cadmium and its effect on various ecosystems.

Cadmium is an unimportant by-product of the refining of zinc, copper or lead. Industry, both primary and secondary, has found many uses for it and is finding more as more and more cadmium is being separated and recovered because technology demands purer and purer zinc, lead, copper without even traces of impurities. (Figures 1 and 2, pages 3 and 4). Cadmium is not generally recycled and consequently is accumulating in the environment at an increasing rate.

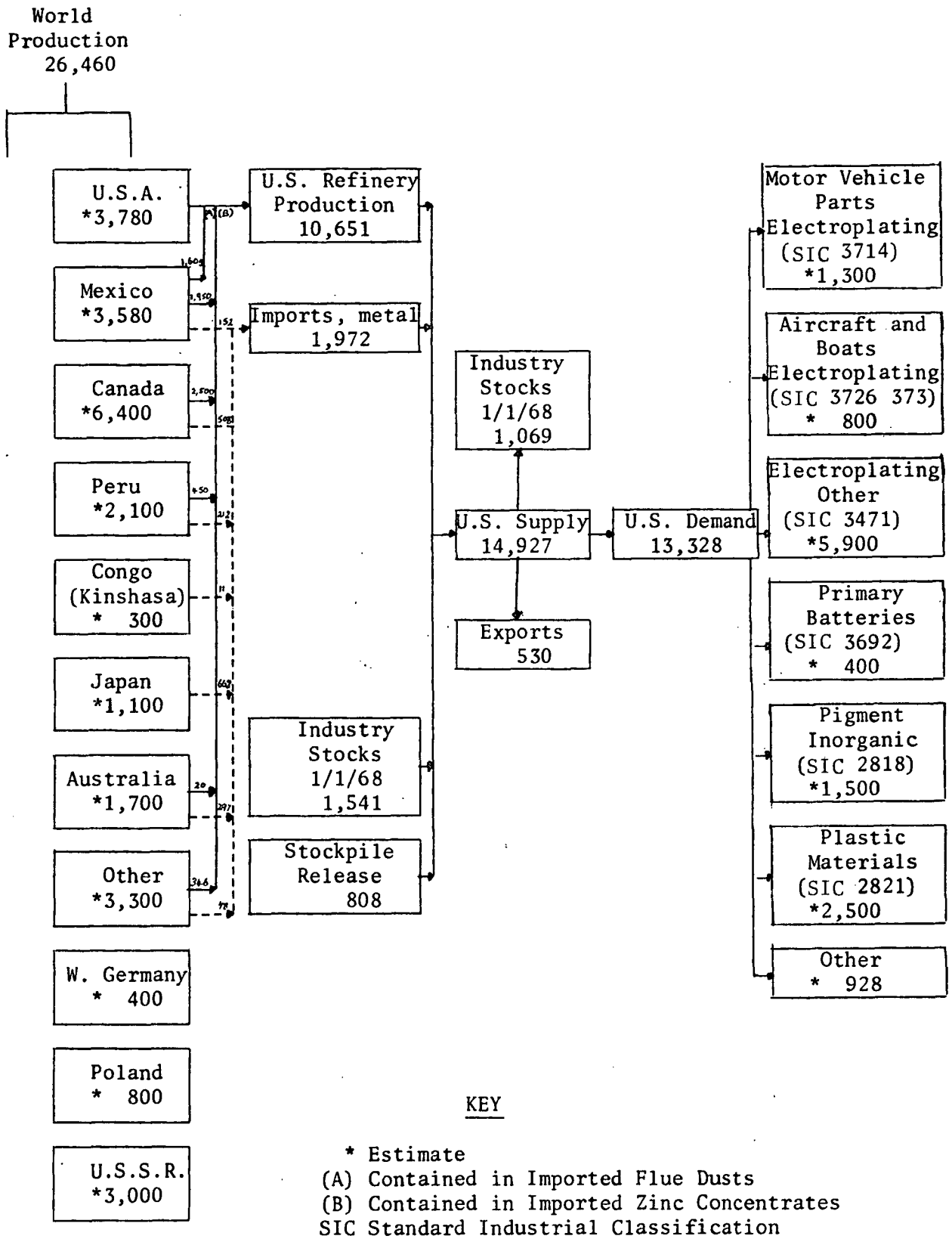
Some thirty different uses have now been developed for cadmium. In none does it appear to be essential or non substitionable. Adequate substitutes already exist or could easily be developed. Cadmium, therefore, is an unimportant resource and could be stockpiled like other trace contaminants such as arsenic or thalium without serious loss to society as a whole. (2)

Two different estimates of the material flow of cadmium in the U.S.A. in 1968 are shown in Figures 1 and 2, as given by Davis et al. (3) and by Heindl (4). The values for miscellaneous or other uses (Fig. 1) include uses in fungicides, nuclear control rods, phosphors, ceramics, and others.



Cadmium material flow chart, 1968 (thousands of pounds). Data of Davis et al. (3)

FIGURE 1



KEY

* Estimate
(A) Contained in Imported Flue Dusts
(B) Contained in Imported Zinc Concentrates
SIC Standard Industrial Classification
Unit Thousand Pounds of Cadmium (Cd)

Government Stockpile Balance - 12,940

Supply-demand relationships for cadmium, 1968. Data of Heindl (4)

FIGURE 2

The Cadmium System

Although relatively new to industrialists and chemists, cadmium has been entering the environment for many centuries - ever since man first started smelting zinc and working with copper and lead. Its flow through the environment is dependent on a multiplicity of factors. These include background levels due to natural occurrence and abundance; mining, refining, use, recycling of zinc, lead and copper ores as well as metals; coal, oil and phosphate utilisation. Many gaps exist in our understanding of the importance of these factors either in isolation or combination.

An ever increasing number of studies concerning cadmium in many biological areas have produced a wealth of data. Some is valuable in immediately increasing understanding in one area. Some is confusing and seemingly irrelevant whilst some is completely contradictory to existing accepted facts.

Though widely distributed in the rocks of the earth's crust, cadmium is generally in low concentration averaging 0.15 - 0.2 parts per million. Uncultivated soils contain between 0.01 - 0.7 parts per million. Higher levels are found near ore bodies or zinc smelters. (5)

Most fresh waters contain less than 1 Ug/litre. Sea water averages about 0.15 Ug/litre. Erosion and weathering of rocks and soils apparently contribute little to these figures, the major proportion coming from man's activities - mining, sewage disposal, soil fertilisation. (5)

In natural waters cadmium is found mainly in bottom sediments and suspended particles whilst that in solution is of low concentration. Decreasing the pH will increase the solubility. (5)

Studies in 1966 on 58 cities and 29 rural areas in the U.S.A. by the National Air Sampling Network showed a range of 2 - 370 nanograms/cubic metre for urban areas compared with 0.4 - 26 for rural. The higher concentrations were found in cities with considerable industry, especially metallurgical and smelting. Coal and oil burning plus exhaust gases, wear of cadmium plated bearings and tyres from automobiles, contribute to airborne cadmium. No accurate data is available on the fate of airborne cadmium. Presumably it is carried back to earth by rain and snow. (6) (7)

Soils enriched with phosphate or sewage sludge fertiliser may contain ten times the cadmium level of uncultivated soil. Williams and Davis of the C.S.I.R.O. Division of Plant Industry have found that 80% of the cadmium applied in fertiliser is retained in the top portion of the soil from which crops and pasture plants take their nutrient. The remaining 20% is leached into waterways adding to the existing cadmium content of streams, lakes and bays. (8)

Several controlled studies have shown that the cadmium content of crops and pastures rises proportionately to the soil cadmium content. Little is known about the exact mechanism of transfer from soil to plant. It is believed that micro organisms are involved, producing a readily assimable organic cadmium compound or compounds. So far no organism or organic compounds have been identified. Soil pH and the presence of other metals affect the transfer. Root systems concentrate the cadmium and so block the transfer to the plant. In this they resemble the human placenta - presumably protecting the growing structure (vide infra.).

Atmospheric concentration of cadmium affects plant concentration - particularly leaf crops. Lagerwerff, in a study of plants near highways showed

that approximately 50% of the cadmium content came from airborne sources and this cadmium content decreased with the distance from the highway. (9)

Plankton are able to concentrate cadmium by a factor of some 900. Though this is considerably less than for copper, lead and zinc, it does lead cadmium into the marine food chain. In addition, marine plants have a concentration factor of 1620 - again less than other heavy metals but significant enough to add to the cadmium content of marine life. (10)

Shell fish, particularly oysters - are able to accumulate cadmium from water that has only a small cadmium content (Thrower and Eustace). Some oysters can obtain a high cadmium level from such waters. (11).

Ayling has shown that it is the concentration of the metal in the mud of the bed site which determines this concentration emphasising the importance of the bottom sediment as well as the environmental water in the cadmium system. (12)

Cadmium in Food and Water

Cadmium is present in relatively small amounts in nearly all food and water used by man. Fish and meat show mean levels considerably higher than those for wheat, eggs, other cereals and vegetables. Oysters and anchovies have 3 - 5 times the concentration of other foodstuffs. (13)

Normal Human intake of Cadmium from Environmental Sources

Man is therefore exposed to cadmium from his food, water and air. The principal source would appear to be food though this may not be true of

smokers. There have been few accurate comprehensive studies on total cadmium balance in humans and the more reliable estimates from these studies would suggest a daily intake of 20 - 50 Ug of which only a small proportion is retained. Absorption into the body varies with the mode of entry (vide infra) and probably totals 2 - 3 Ug per day. (14)

Two studies of water supplies would indicate that, except in unusual circumstances of contamination, intake via water is negligible. (5)

Another significant source of cadmium in human beings is cigarette smoking (14). About 1.4 Ug of cadmium is present in each cigarette. Some 70% of this volatilised in the smoke. The respiratory intake from a packet of cigarettes would be 2 - 4 Ug per day, some 10 - 20 times the intake estimated from the air of a large city.

CHAPTER 2.

Analysis for Trace Concentration of Cadmium

Many methods can be used for the determination of cadmium in trace concentrations. Unfortunately none of these provide a sensitive, simple, accurate, reliable, inexpensive, rapidly reproducible result unaffected by the presence of other elements or compounds. Different observers have used different methods for the same or various types of material studied since cadmium became an important biological study. This lack of standard technique has produced confusing and conflicting data. This in turn has complicated interpretation and correlation of results.

Traditionally trace elements analyses of biological samples involved the use of a well established analytical method in conjunction with a suitable separation mechanism to purify and concentrate the element. This was an expensive laborious approach requiring precision in sample handling at all stages. In recent years newer instrumental techniques have been evolved which provide maximum information with minimum sample preparation. These have simplified to some extent the analysis of traces of cadmium. Unfortunately no study has collaborated the results of various laboratories engaged in research on the biological effects of cadmium. Such a study would facilitate comparisons in the future of cadmium in food, urine or blood.

Some of the more common methods used are:-

1. Spectrophotometic colorimetry after dithizone extraction
2. Emissions spectroscopy
3. Atomic absorption spectrophotometry
4. Neutron activation

5. Various electro-chemical techniques
6. Spark source mass spectrometry
7. Isotope dilution

The most generally used method is atomic absorption spectrophotemetry preceeded by a reliable separation method. Phosphate and sodium chloride, both common biological constituents can cause errors. Some earlier investigators using this method failed to appreciate this interference and their results have to be interpreted with caution. (14) This method is the basis for the cadmium analyses in this survey. (Chapter 7).

Spectrophotometric Colorimetry

The method is based on the measurement of the degree of absorption of light at a given wave length that is characteristic of a specific ion or complex. Thus, the maximum absorption of light by a solution of cadmium dithizonate (the most commonly used complex) occurs at the wave-length 518 nm, and the intensity of absorption is related to the concentration of cadmium dithizonate in solution which can be determined by appropriate calibrations with standard solutions.

Concentration by selective extraction by organic solvents of the cadmium dithizonate complex is a necessary step, which can remove many interfering elements with proper adjustment of pH during the extraction. The method is less sensitive than some of the others, except where concentration is comparatively easy, as for sea water, in which levels of parts per billion can be determined.

Special modifications, such as the use of ultraviolet spectrophotometry or fluorometric methods give promise of increased sensitivity of determination of cadmium.

Emission Spectroscopy

When elements are vaporized by means of a spark or an electric arc, the atoms present are energized to excited energy states; return of these energized atoms to the ground state is accompanied by the emission of light, the frequency of which is characteristic of each element. Resolution of these spectral lines and the determination of their intensities serve as the basis for estimating the concentrations of the trace elements present.

The method is most commonly used for direct analysis of solid samples, without pre-treatment, because it makes possible the determination of many elements simultaneously. The inherent variations due to varying composition of samples, variations of degree of volatility, etc. require careful standardization against known material of similar composition and the use of internal standards. The sensitivity for the direct method (generally 5 - 10 ppm) is not as good as in most of the methods discussed; it can be improved by concentration methods, followed by spark emission on solutions, or by arc emission of the evaporated dried solids. Such methods have not however, been used extensively.

Atomic Absorption Spectrophotometry

The basic principle of the method is that vaporized elements will absorb radiation of their characteristic frequencies by being activated from the

ground energy state to a higher electronic energy state. The concentration of the atomized element is measured by the degree of absorption of its characteristic frequency of light.

Atomic absorption is one of the most widely used methods for determining traces of cadmium, because of its relative simplicity, speed, and sensitivity. It is commonly preceded by a concentration procedure, most often by dithizone extraction, to improve the sensitivity and to eliminate interferences, especially the serious interference caused by the presence of NaCl; some of the early data on cadmium in biological samples may be seriously in error because this source of error was not then known.

Recent modifications of the method, such as atomic fluorescence flame spectrometry and flameless atomic absorption, give promise of lowering sensitivity limits for cadmium to well below 1 ppb Cd.

Neutron Activation

Many elements, when subjected to bombardment by neutrons in a reactor, form radioactive isotopes. The amount of a given isotope formed is proportional to the concentration in the original sample of the specific element, the neutron flux used, and the crossection of the parent nuclide. Instrumental analysis of the energy of radiation and the decay curve is used to identify the desired radioactive isotope, the amount of which is determined by comparison with standards that are irradiated simultaneously with the unknowns and which have been carried through the identical separation and counting procedures. Rarely is direct counting possible; usually separations must be made from other radioactive isotopes that

might interfere in the final counting procedure. The chemical separations are made after adding a known, generally much larger amount of the non-radioactive element after irradiation is completed. Although such separations may be quite complex, it is unnecessary to make quantitative recoveries of the element sought, because yields can be calculated from a knowledge of the amount of nonradioactive carrier added.

The neutron activation method is extremely sensitive. For cadmium the isotope ^{115}Cd is generally measured, with sensitivity in the ppb range if chemical separations are made. The principal disadvantage is the need for a nuclear reactor and a "hot" laboratory.

Electrochemical Methods (Polarography, Anodic Stripping Voltammetry)

The polarographic method is based on the current voltage curves obtained by the electrolysis of solutions under special conditions, using a dropping mercury electrode. With proper choice of electrolyte, it is possible to obtain separate steps in the curves for each element present, the height of each step (current) being proportional to the concentration of the ion, and the location (potential) being dependent on the ion and on the nature of the base electrolyte.

The method in its conventional form can be used to analyze solutions for cadmium at about $10^{-5}M$ concentrations and with special techniques for concentrations down to $10^{-7}M$.

Anodic stripping voltammetry is essentially a polarographic method in which the element is slowly plated out of a small volume of solution on a

small electrode (usually mercury-plated graphite) under carefully controlled conditions. After electrolysis is complete, a reversed voltage is applied, causing rapid dissolution of the plated element from the amalgam and thus producing a relatively large signal on the plot of current flow versus voltage.

The method is extremely sensitive and is especially useful for natural waters; its use may yield information on the nature of binding of cations in waters.

Spark Source Mass Spectrometry

Analyses for traces of metals by this method involves the volatilization and ionization of the material being analyzed by applying a radio-frequency spark, followed by measurement of the ions formed by their masses in a high-resolution mass spectrometer. The method is extremely sensitive, permits the simultaneous determination of many elements, and can be used for nearly all types of samples. The main problems are erratic variability of the emissions of ions from a spark source, which requires that an internal standard such as lutetium be used, and the formation of multiply charged ions. Precisions of about $\pm$10% have been reported for rock samples; further research should improve this.

Isotope Dilution

The method of stable isotope dilution, applicable to the determination of traces of any element composed of two or more stable isotopes, is based on the mass spectrometric determination of the proportions of two stable isotopes in a sample to which a known amount has been added of a "spike",

i.e., of a sample of known isotopic composition enriched in one of the isotopes that is of low natural abundance. The procedure requires the complete solution of the sample, addition of the spike with thorough mixing, separation of the element from possible interfering elements, and determination of the isotopic composition. For cadmium, the spike might be enriched in ^{106}Cd (normal abundance 1.22%) or ^{108}Cd (normal abundance 0.88%) and the ratio measured against ^{112}Cd (24.07%) or ^{114}Cd (28.86%).

The method is extremely sensitive, with very high precision and accuracy. It has the advantage that quantitative recovery in separation is unnecessary; also the yield does not have to be determined, because a ratio, rather than an absolute amount, is measured. Contamination by reagents can be determined by parallel experiments. Although the method has not often been used for cadmium, probably because it is relatively slow and expensive, it is to be considered one of the ultimate means of monitoring faster and less expensive methods. (5)

CHAPTER 3

The Metabolism of Cadmium

Most of our knowledge of the absorption, distribution and excretion of cadmium is derived from animal experimentation. Many different mammals have been given cadmium either by injection, inhalation, orally or through the skin. Single, multiple or constant dosage regimes have been employed. Independent of dosage or source of entry cadmium can be found in blood, internal organs, skin, hair and excreta in all species. A detailed analysis of the behaviour of cadmium in the animal body has emerged from the vast amount of data that has come from the research efforts of many investigators. Only a small number of controlled experiments on a few human beings have been performed. These and past mortem studies corroborate the suggestion that the metabolism of cadmium is the same in all animal species.

Single Dose Studies

There are numerous studies recording the fate of a single dose of radioactive cadmium taken either orally or by the respiratory tract or given by injection. Walsh and Burch 1959 (15) working with dogs; Kench, Wells and Smith 1962 (16) using rabbits and Perry et al 1970 (17) using rats have all shown the initial high plasma level after a single intravenous dose clears rapidly - usually within 30 minutes. By the end of twelve hours there is little cadmium in the blood and this cadmium is now in equal concentration in the plasma and in the red cells attached to protein.

Lucis, Lynn, Lucis 1969 (18) found equal blood and plasma concentration 12 hours after mice were given a subcutaneous injection.

Miller, Blackmon and Martin 1968 (19) working with goats and Fern, Hanlon and Urban 1969 (20) using hamsters showed a secondary rise of blood cadmium occurred between day one and day seven. This suggests a release from the storage sites responsible for the initial high clearance.

Decker, Byerrum and Hoppert 1957 (21) found that in the rat there was an increasing concentration of cadmium in the liver and this peaked at 8 hours. By 72 hours the concentration in liver and kidney were equal.

Miller et al (19) following the fate of single dose of over a period of days in their goats found after 14 days most of the cadmium had moved to the kidney.

These findings have been substantiated by many other workers using different species.

Although the liver and kidney are the major organs of cadmium storage, traces of the metal can be found in most body compartments at some time after a single dose. The pancreas, spleen, testis and bone have all been shown to be able to store significant amounts.

Harrison et al 1947 (20) exposed dogs to atomised cadmium chloride as a 25% aerosol for 30 minutes and subsequently measured the cadmium content of various organs from serial autopsies. By day five, most cadmium had left the lungs and the storage pattern showed a marked similarity to that described above after dosage by injection.

Single dose experiments also indicate a long biological half life for cad-

mium in most species. Cotzias et al 1961 (21) found it to be at least 100 days in mice, Friberg et al (14) 2 years in monkeys and Rahola et al 1971 (22) in one of the few human studies noticed a half time for body retention in excess of 100 days.

This long biological half life is due to a small daily excretion of cadmium. Only traces of the metal can be found in urine, faeces and hair. Of these excretion routes the major one appears to be the alimentary canal. The salivary glands - the glands of the stomach, duodenum, pancreas and small intestine all accumulate cadmium and ultimately excrete it into the gut - Berlin et Ullberg (23). The rates and routes of excretion will be discussed again both in the next section and in the section devoted to body burden.

Multiple Dose or Constant Exposure

There are no major differences in the distribution of cadmium when multiple dose or long exposure experiments are conducted. Cadmium can be found in the cells of many organs and the concentration - particularly in the kidney rises proportionately to the total dose. Despite the increasing kidney concentration there is no significant rise in cadmium excretion in the urine unless the kidney shows evidence of damage. Axelsson and Piscator 1966 (24). However, when renal dysfunction - as evidenced by proteinuria occurs, there is a sharp increase in urinary cadmium excretion. Friberg 1955 (25) gave rabbits firstly radioactive cadmium and then non-radioactive cadmium and compared renal excretion with that from a control group given radioactive cadmium for the full period. During the period of administration of non-radioactive cadmium the concen-

tration of radioactive cadmium in urine increased sharply when proteinuria appeared. This clearly demonstrates that when kidney damage occurred urinary cadmium came from accumulated renal deposits.

In some species there is 100% increase in urinary excretion associated with increasing renal concentration of cadmium and renal damage. Axelsson and Piscator 1970 (24). This finding has an important clinical significance which will be discussed in a later chapter.

Metallothionein

No matter the portal of entry cadmium ultimately achieves widespread tissue distribution. However, there is significant difference in the percentage amounts absorbed from each site. Despite this difference the mode of absorption is probably the same from each site.

In 1957 Margoshes and Vallee (26) discovered a low molecular weight protein in the equine kidney. This protein contained cadmium and other workers soon found similar proteins present in many tissues from other species including human tissue. This protein has many unique properties including a lack of aromatic amino acids, a high content of cysteine and an ability to bind certain heavy metals e.g. zinc, cadmium and mercury; for these reasons it was named metallothionein.

Nordberg et al 1972 (27) has shown that there are different forms of metallothionein associated with a different metal content. These are closely related structurally as are the various metallothioneins of the various species.

Cadmium and other heavy metals appear to stimulate the production of this protein in the liver. It is also found in the lung, intestinal mucosa, kidney, spleen and pancreas. The protein binds the metal, transports it to, and holds it in the storage sites. The exact mechanism of transfer from gut or lung to metallothionein is not known. It is presumed that the metal is temporarily converted into an organic form although no compound or organism capable of forming an organic cadmium compound have been isolated at these sites. Metallothionein has been identified in quantity in various organs in a male who suicided by swallowing large quantities of cadmium iodide - Wesniewska et al 1971 (28). Syversen (29) found metallothionein like protein in post mortem liver and kidney samples of non occupationally exposed males. No-one has found these proteins in human blood but Nordberg has in mice. (30).

The Absorption of Cadmium

Absorption via the lungs depends on the solubility and physico-chemical properties of the cadmium particles. Initially particle size determines the fate of cadmium aerosol. Those greater than 5 - 7 micron size will be either trapped by nasal hairs or swept up out of the pulmonary compartment by ciliary action into the alimentary canal. Subsequent digestion and absorption of these will occur complicating the assessment of primary lung absorption.

Friberg attempted to assess the actual pulmonary absorption by analysing Harrison's 1974 (14) data on single dose exposure with dogs. He suggested a figure of 40%. This figure is higher than that found by others in other species. Prodan 1932 (31) found a 30% retention in cats. Potts et al

1950 (32) 10% in mice and Friberg himself 1950 (14) using rabbits a 30% retention. There is no quantitative data on absorption and retention in the human and a range of 10% to 40% is possible.

In contrast most workers investigating oral absorption in animals appear to agree that only 1 - 2% of the ingested cadmium is retained. Rahola 1971 (22) found a 6% retention in human male volunteers given a single oral dose of radioactive cadmium. Many factors influence oral absorption. Larssons and Piscator (33), Kobayashi et al 1971 (14) found that when mice were given a low protein diet they had a higher absorption. Worker et al 1961 (34) found that Vitamin D increased cadmium absorption in chickens. Larssons and Piscator 1971 (33) noted a higher absorption when rats were on a low calcium diet.

The only long term study on humans by Tipton, Stewart and Dickson 1969 (35) has come in for considerable criticism on the ground of poor analytical technique. No attempt was made to extract cadmium from the various samples analysed and other electrolytes present probably gave erroneous readings. The study by these workers suggested a very high 75% dietary absorption. Kitamura 1972 (36) carried out a short term balance study on a 55 year old Japanese male using both cadmium contaminated rice and water. He found an absorption of 5.35% from the water and 1.55 from the rice.

Unknown aspects of Cadmium Metabolism and Toxicology

Considerable ignorance still exists in certain vital areas of cadmium metabolism. Much more information is required on the precise mechanism of cadmium absorption, especially with respect to chemical or physio-

logical factors which either enhance or inhibit intake. Little is known about how or in what molecular form the metal is transported from absorption site to tissue stores. In addition, we are ignorant on just how the metal traverses vascular endothelium just prior to tissue deposition. Some investigators believe specific organs possess innate biochemical systems which vary from one location to another.

Information is lacking concerning the chemical form or forms in which cadmium is deposited in various tissues. The specific effects of the metal on intermediary metabolism both in vivo and in vitro are not yet understood. Much has to be learnt about the inter-relationship between cadmium and other toxic compounds - drugs, pesticides, specific carcinogens within cells, on their metabolic processes. Until these and many other unknowns are understood, speculation on the exact role of cadmium in health and disease will predominate over scientific fact.

CHAPTER 4.

The Body Burden of Cadmium

Henke, Sachs and Bohn 1970 (14) from an analysis of kidney and liver samples of stillborn babies in West Germany found that the total cadmium content of the new born is less than 1 Ug. Piscator in Sweden noted that cadmium accumulates in the placenta during pregnancy. He found that an average 500 Gm placenta has 5 Ug. cadmium. Schroeder 1961 (37) from post mortem tissue analyses concluded that the standard American man of 30 - 50 years weighing 70 Kg. contains 30 milligrams of cadmium. There is therefore a huge increase in body cadmium during life.

But not all workers agree with Schroeder's figures. Smith et al (38) working with post mortem liver and kidney from three occupationally unexposed males in the United Kingdom suggest a figure of 15 mgm as total body burden. Ishizaki et al (14) found the renal concentration from some Japanese men in the Kanazawa area indicated a high 80 mgm accumulation. This area is not considered to give an excess exposure to cadmium.

About 50% of total body cadmium can be found in the kidneys and liver in normal non-exposed humans. Of this about 33% is present in kidneys if there is no renal damage. The remainder is in various organs - pancreas, spleen, testes, thyroid, muscle and fat. Many workers have shown a decreasing kidney content after 50 years. Several explanations have been offered. Schroeder et al (14) speculate that this might be due to an increased mortality for individuals with higher renal levels but Friberg et al (14) suggests it is due to increased exposure over the past 50 years with kidney damage and increased excretion of renal cadmium.

Liver and kidney content of cadmium of occupationally exposed subjects are much higher and suggest body burden of 100 to 1,200 mgm. Only 10% of this is usually found in the kidney if there is evidence of renal cortical damage. Friberg (39). Animal studies and studies on workers occupationally exposed to cadmium have repeatedly shown that there is probably a critical body burden beyond which overt tissue damage occurs. No study has conclusively established an exact figure for this burden.

No study has yet suggested either an accurate method for establishing body burden or a reliable indication of it. Yet this is the most critical point in the relationship between cadmium and health. It is quite clear that body cadmium increases with age, that it is stored with increasing exposure and that increasing environmental exposure is occurring. It is equally clear that the body can tolerate a certain cadmium level without demonstrable effect. The social, medical, economical and environmental implications of this vital missing link in the cadmium story are immense and far reaching.

Many attempts have been made to solve the dilemma. Animal studies have shown that blood cadmium does not reflect body content. Blood cadmium levels in exposed workers show that concentrations do increase with exposure, but only to a certain level. Friberg (39). These levels fluctuate and a single or group of readings may reflect recent or past exposure rather than tissue levels.

Similarly urinary excretion is more dependent on renal damage than renal concentration or can be linked to intercurrent illness, Bonnell et al 1959 (40), Smith et al 1960 (38). Faecal excretion is unreliable as it is not possible to distinguish between excreted cadmium and unabsorbed cad-

mium from the diet.

Workers in U.S.A., Japan, Sweden and Yugoslavia - Friberg (14), have attempted to correlate the cadmium content of hair and body burden. Schroeder and Nason (41) found that sex, hair colour, dust, hair lotion or sprays all effected the analysis to such an extent as to render this an unreliable marker.

Proteinuria and Cadmium

One early sign of excessive absorption of cadmium is an increase in protein excretion in the urine. Initially this may be intermittent and therefore not always detected. Later it becomes constant and may remain for many years without change. Sensitive analytical techniques have shown that this protein resembles the small amount of protein normally excreted by the kidney or urinary tract, but some fractions are in higher concentration. Electrophoretic examination following ultrafiltration reveals a distinct pattern with a low albumin content and a predominance of $\alpha 2$ and β globulin components-Kazantis et al 1963 (42), Piscator 1966 (43). The proteinuria is also characterised by an abnormally high clearance of low molecular weight protein.

Concentration of the urine by ultrafiltration followed by two dimensional electrophoretic separation may reveal the pattern of tubular proteinuria at a stage before proteinuria can be detected by the usual chemical tests. These tests must be based on precipitation with either salicylsulphonic acid - Henry 1964 (44), trichloracetic acid - Friberg 1950 (14) or other

reagents - Piscator 1962 (45). Impregnated paper strips e.g. Albustix may not be sensitive enough to detect these proteins nor will simple boiling of urine.

Nevertheless the significance of a small increase in urinary protein is difficult to interpret and of no reliable value as an indicator of total body burden. It may appear in some exposed workers after a short exposure or fail to appear after many years or even appear long after exposure has ceased.

A number of enzymes are also excreted with this protein which is believed to arise in the renal tubules - these include lysozyme, ribonuclease and muramidase. They correlate well with the proteinuria, so well that Adams et al 1969 (46) has suggested their presence indicates early biochemical change induced by cadmium.

Cadmium and Zinc

Zinc and cadmium are closely connected in nature. In the body their metabolism is similar. The one important difference is that zinc is an essential trace element and many enzymes are zinc dependent. Parisi and Vallee list 18 zinc metallo enzymes and 15 zinc enzyme complexes known in various biological systems. (47).

Cadmium has the ability to exchange with zinc in these enzyme systems. When this happens tissue levels of zinc increase - Schroeder (37). The toxic or adverse effects of cadmium are almost certainly due to this exchange and in certain animal experiments some of the acute toxic effects

of cadmium can be prevented by doses of zinc - Gunn et al 1961 (48) without altering tissue cadmium concentration.

The zinc to cadmium ratio relative to intake therefore may be important in finalising body burden. It is very probable also that the zinc-cadmium ratio in tissue is of importance in the total effect of the body burden of cadmium. As yet no research has produced a reliable method whereby changes in enzymatic or tissue zinc could be used as a marker of body cadmium despite the predominance of zinc enzymes available for study.

Cadmium and other minerals

Metals other than zinc and cadmium can be bound by metallothionein e.g. copper and mercury. Although it has been established that cadmium can displace copper readily from metallothionein in chickens - Starcher (49) no correlation between cadmium content and copper analysis has been demonstrated. Selenium and cobalt protect animal testes from damage by cadmium without effecting tissue content. Gunn et al (48).

Other trace elements probably also have an important role in modifying the effects of tissue cadmium. As yet this interrelationship between essential and non essential trace elements is not completely understood.

CHAPTER 5.

Cadmium and the Occupationally Exposed

Little industrial use was found for cadmium for sixty years after its discovery in 1817. But, by the end of the 19th century battery and pigment manufacturers were consuming increasing quantities with little realisation of the health hazards involved. Industrial consumption was given a great impetus in 1919 when M.J. Udy employed cadmium in the electroplating field. Today some thirty differing occupations in both primary and secondary indusry provide exposure to cadmium and pari passu with its increased industrial usage is the increased awareness of its established and potential effects on health.

In 1858 Sovet (50) recorded the first cases of cadmium toxicity. He reported severe respiratory symptoms in three men using cadmium carbonate as a silver polish. The effect on a respiratory function of acute exposure to cadmium, either as dust or fume, was subsequently noted by many workers both in Europe and America. By 1920 medical literature documented abundant evidence that acute overexposure to the metal or its salts could lead to a severe chronic or sudden fatal respiratory illness.

Initially the great majority of cases of acute cadmium toxicity reported were associated with absorption by inhalation but by 1940 it was well established that acute ingestion also produced severe chronic systemic disease or sudden fatality.

Acute exposure

Brief exposure to high concentration of cadmium fume leads to severe pul-

monary oedema. The clinical picture is usually one of intense respiratory irritation, precordial pain and severe dyspnoea coming on some hours after exposure. Generally those affected did not suffer sufficient initial discomfort to cause them to leave work - Bulmer and Rothwell (51). Death may be caused either by acute pulmonary oedema or later by acute renal failure. Dunphy (52), from a study of the literature has postulated three overlapping phases of pulmonary pathology - oedematous - proliferative-and fibrogenic. Death can occur in phase one or two from interference with blood gas exchange. Phase three is the chronic phase leading to emphysema and pulmonary vascular complications.

Chronic exposure

Occupational physicians, focusing on the effects of acute exposure, initially paid little heed to a suggestion in 1920 by Stephens (53) that constant exposure to cadmium in the working environment may lead to chronic ill health. It was not until 1940, when Mancioli (54) reported that men working in an electroplating shop suffered chronic rhinitis and pharyngitis, that the spotlight fell on the effects of long term absorption.

In 1942 Nicoud,Lafitte and Gros (55) investigated a group of workers in a French alkaline accumulator factory. No details are given about the number of people employed or the number investigated. Weight loss, iron deficiency, anaemia, and marked osteoporosis with pseudo fractures of long bones were ascribed to cadmium. The latter was cured with calcium and vitamin D suggesting nutritional deficiencies, due to the war, were an associated factor. Chronic bronchitis and emphysema were found occasionally but were not associated with cadmium exposure by these workers. Blood and urine

cadmium levels and the cadmium concentration in the working environment are not given in their report.

Princi, 1947 (56) studied twenty workers in an American cadmium smelter. The length of exposure varied from six months to twenty two years. Atmospheric cadmium varied from 40 micrograms to 31.30 milligrams per cubic metre. Blood cadmium level varied between 10 and 65 micrograms/100 gm., urine cadmium between 11 and 125 micrograms per litre.

Both blood and urine cadmium were established by Church's spectrophotemetric method. This is less sensitive than other methods. Vide chapter 2.

A complete history and physical examination was performed on each worker. Despite the high urinary levels, marked symptoms and signs of ill health were absent though the haemoglobin levels were slightly lower than the average for the altitude. The most characteristic finding was a yellow staining of the teeth in those long exposed. Chest x-rays showed no significant changes. Princi concluded exposure to cadmium did not cause chronic ill health.

In contrast, Friberg, 1948 (57) looking at 38 workers in a Swedish alkali storage battery plant found evidence of renal damage in men exposed to between 3 and 15 milligrams of cadmium per cubic metre for more than 8 years. He compared the health of nineteen workers exposed for less than 8 years to nineteen with 8 or more years exposure. Although both groups complained of fatigue, nervousness, irritability, thirst, cough and dyspnoea, he found

no pathological changes which could be definitely associated with cadmium exposure in the first group. The second group contained a significant number of men with objective renal damage, as measured by a proteinuria and inulin clearance and lowered respiratory function when tested by spirometry. A significant number of these men also complained of anosmia.

A subsequent report on an expanded group of forty three, 1950, (58) confirmed these findings. In addition, Friberg found a raised erythrocyte sedimentation rate and some suggestion of impaired liver function. He noted a lower average haemoglobin level amongst workers and a mild anaemia in animals experimentally exposed to cadmium by injection. Proteinuria was only evident in the Heller test, being absent in a boiling only examination of urine. Electrophoretic study of this urinary protein suggested it was of a special type with a molecular weight between 20,000 and 30,000

Baarder, 1951 (59) reported emphysema, proteinuria and weight loss amongst 11 workers in an alkaline accumulator factory in Germany. One worker who came to autopsy subsequently had large deposits of cadmium in both his liver and kidneys. Neither Friberg nor Baarder reported on blood or urinary cadmium levels in their exposed workers.

Bonnell, 1949, (60) examined two groups of British workers in two separate factories producing copper cadmium alloys and compared them with controls of the same age distribution. In all, 100 workers with an exposure range of 5 to 26 years were investigated.

104 controls worked in the same factory in jobs not exposing them to cadmium. No figures are given for blood cadmium but those in the exposed group excreted between 0 and 800 micrograms of cadmium per day. The working environment averaged 270 micrograms of cadmium per cubic metre. No figures are given for control group exposure.

Although 12 exposed workers had clinical and radiological evidence of emphysema, respiratory function, as measured by vital capacity, maximum ventilatory capacity, total lung volume and intrapulmonary mixing showed no significant differences between the groups. Haemoglobin, erythroctye sedimentation rate and haematocrit showed no significant differences either.

None of the workers with emphysema had proteinuria. A further seven without emphysema also had proteinuria. Three control workers showed proteinuria. Bonnell found the boiling test unreliable. 25% trichoroacetic acid or 3% sulphosalicylic acid gave positive reactions when added to the urine before boiling. Electrophoretic examination of 4 random sera showed that the α globulin was raised in all cases and the γ globulin high in two. Electrophoresis of urinary protein in two cases showed a large number of electrophoretic components sedimented in the 20,000 to 30,000 range.

Forty four men in the series (41 exposed - 3 controls) excreted more than 30 micrograms of cadmium per day (polarograph method). Less than 50% of these showed clinical or biochemical abnormalities. Specific enquiries failed to reveal loss of smell, yellow discolouration of teeth or abdominal pain.

Reporting on a follow up of these men Bonnell, 1954 (61) suggests that

symptoms and signs may develop and progress after a latent interval despite cessation of exposure.

Kazantzis et al, 1962, (42) extensively investigated 12 employees of a U.K. pigment factory handling cadmium seleno-sulphide. Although atmospheric levels of cadmium are not given, urinary excretion measured on two occasions varied from 1 - 109 micrograms/24 hours. Ten of the 12 workers excreted more than 30 micrograms per litre. Subjective respiratory symptoms - dyspnoea, cough, wheeze, were frequent but pulmonary radiology was not abnormal except in one case. 25% showed a low FEV_1. Other tests of respiratory function were normal.

No evidence of sterility was found nor was any anaemia or anosmia. Five subjects, all with a low FEV_1, had proteinuria indistinguishable on two dimensional electrophoresis from that found in renal tubular disorder. Two of this group had an increased aminoaciduria, creatinine clearance and calcium excretion was elevated in 7.

Serum sodium and potassium, protein, cholesterol, calcium and alkaline phosphatase were all within normal limits. The plasmas of those excreting protein generally showed a tendency to hypochloraemic acidosis. These workers concluded that chronic exposure to cadmium could produce emphysema and renal tubular dysfunction.

Adams et al, 1969 (46) reported on a twelve year supervision of men exposed to cadmium in a British alkaline accumulator factory. Cadmium in air levels varied depending on the department (range 50 micrograms per cubic metre to 5 milligrams). Many men excreting more than 30 micrograms of cadmium per litre

had proteinuria and renal dysfunction. They reported no other significant abnormality.

Horstowa et al, 1966 (62) attempted to develop diagnostic criteria for cadmium poisoning on the basis of observations made on plant operators in a Polish alkaline battery factory. Workers were exposed to an atmosphere of .13 to 1.17 milligrams cadmium/cubic metre. Of 80 workers involved, 26 were selected for intensive study because of symptoms (20 female - 6 male). The exposure time varied between 1 to 12 years.

The most frequent complaints were insomnia, anorexia, weakness, headaches and dyspnoea. Ten workers had a yellow discolouration of teeth. Twelve had a reduced vital capacity. The haemoglobin did not deviate from normal level but the erythrocyte sedimentation rate was elevated in 17. Proteinuria was present in 7 cases. Sodium and potassium in blood and urine were normal. Serum iron and cholesterol were normal but serum lipids elevated in 9 patients. Electrophoresis of serum protein showed an elevated $\alpha 1$ and $\alpha 2$ globulin in 14 cases. Radiological examination showed emphysematous changes in 17 patients (although only 12 had a diminished vital capacity). Bone films showed osteoporosis in 10 patients. In summary, these workers suggest that non specific symptoms, whilst they cannot serve as a basis for cadmium poisoning, occur frequently in long exposure workers.

Not all investigations have confirmed respiratory illnesses associated with chronic cadmium inhalation. Suzuki et al, 1965 (63) found proteinuria in Japanese workers in a vinyl chloride film plant exposed to cadmium stearate dust in concentration varying from 30 to 690 micrograms of cadmium but no significant difference in pulmonary symptoms or lung function

studies when compared with a control group.

Teculeseu and Stanescu, 1970 (64) in a Rumanian study of 11 workers with more than 7 years exposure to cadmium oxide fumes in concentration between 1.21 and 270 milligrams/cubic metre found neither proteinuria nor significant changes in extensive pulmonary function studies, blood gases or chest radiology.

Despite a few contrary reports, by 1970 it was generally accepted that long term exposure to cadmium was associated with both pulmonary and renal dysfunction and threshold limit values for cadmium both as dust or fumes had been set in various countries, e.g. America 200 micrograms/cubic metre for dust and 100 micrograms for fume; 20 and 10 micrograms/cubic metre in Finland. It was not long before there was debate about these levels. In 1973 Lauwerys et al (65) studied three groups in Belgium, one group - 31 females exposed to 31 micrograms/cubic metre for a period of 1 - 12 years - a second, 27 men to 134 micrograms/cubic metre for six months to 19½ years and a third group of 22 men to 66 micrograms/cubic metre for 21 to 40 years.

Cadmium in urine and blood, various enzymes, respiratory function and proteinuria were measured and compared with a number of controls. Although some cases of proteinuria were found in the first of two groups with lower years of exposure there was no significant difference in respiratory function studies between the exposed and controls. But in the group exposed for longer than 20 years both respiratory symptoms and respiratory function showed a significant difference when compared to the control. 68% of the exposed group had an abnormal electrophoretic pattern. There was a weak, but significant, correlation between urinary cadmium excretion and proteinuria.

These workers, discussing their findings, point out that the major uncertainty in any survey is the average concentration to which workers are exposed during their workday life. Isolated, or even repeated, samplings over a short time span probably do not fully represent total past exposure. Nevertheless, they concluded that the threshold limit value for cadmium dust in the working environment should be 50 micrograms/cubic metre if respiratory and renal dysfunction from cadmium absorption is to be avoided or minimised.

Smith et al, 1975 (66) conducted a study amongst workers in a cadmium production plant in Denver (U.S.A.). They endeavoured to determine the relationship between pulmonary function, respiratory symptoms and chronic exposure in workers with ten or more years in a high cadmium concentration atmosphere. All workers excreted more than 50 Ug cadmium/litre on one or more occasions. Two matched control groups - one with low cadmium exposure in the same plant and another with no exposure from outside the plant - were also examined. Cadmium air concentrations varied between 20.4 milligrams per cubic metre to 50 micrograms over the twenty year sampling period.

Pulmonary function was measured by Forced Vital Capacity (FVC), Forced Expiratory Volume (FEV) at one second, mid maximum expiratory flow (MMEF) arterial blood gases and chest radiology. No significant differences were found in respiratory symptoms or morbidity. The high exposure group had a significantly lower FVC but although the mean FEV and MMEF here were not of significance, smoking apparently made no difference to their findings. Chest film showed 29% of exposed workers had mild or moderate fibrosis.

Cadmium air concentrations varied between 20.4 milligrams per cubic metre to 50 micrograms over the twenty year sampling period. Diminished respiratory function correlared with both a urinary excretion greater than 25 micrograms per litre and time exposed. Additionally there was correlation between exposed time, airborne cadmium and urinary cadmium excretion. Urinary cadmium was measured by atomic absorption spectroscopy after dithizone extraction.

There are so many variables between the numerous surveys of the health of cadmium workers that it is difficult and perhaps not even relevant to compare one with another. Such factors as geographic and cultural situation, actual environmental exposure, chemical and physical form of cadmium involved, associated exposure to other toxins, analytical technique used for the assay of biological and atmospheric cadmium, are so diverse that it is not surprising there are considerable areas of disagreement in the various findings. Nevertheless cadmium has been associated with the following abnormalities detected in those occupationally exposed to it:-

1. Urinary Tract

   Renal tubular dysfunction

   Deceased glomerular function

   Renal calculi

   Carcinoma of bladder and prostate

   Glycosuria

2. Haemopoetic System

   Mild anaemia of the iron deficiency type

   Raised Erythrocyte Sedimentation rate

3. Respiratory System

Emphysema

Carcinoma of the lung

Anosmia

Chronic rhinitis and pharyngitis

4. Skeletal System

Osteomalacia

5. Reproductive System

Non specific histological change in testicular tissue. Smith et al 1960. (67).

6. Alimentary System

Liver damage

Gastritis

Dental changes

7. Vague ill health and reducted working capacity

In 1975 I carried out a survey at the Risdon works of the Electrolytic Zinc Company of Australasia comparing the health, physical findings and results of certain routine biochemical and other non invasive investigations of a group of workers exposed to cadmium with a matched group of controls. The survey was planned to be more extensive than any reported in this chapter being designed to look for all the known or suggested cadmium effects listed above.

No similar survey has been reported in the literature. My group of men,

in contrast to those discussed above were associated with the extraction and refining of cadmium. They were also exposed to other heavy metals at the same time. (Chapter 7).

CHAPTER 6.

Cadmium and the Non-occupationally Exposed

Itai-Itai Disease

In 1955 at a meeting of the Japanese Society of Clinical Surgeons, Dr. Nobura Hokino, a general practitioner from Fuchu in the Toyoma Prefectune Japan and Dr. M. Rono, assistant professor at the Kikei medical school reported on a "new disease" the former had been studying since 1946. Dr. Hokino called the disease Itai-Itai (meaning ouch ouch) because those patients afflicted cried out in pain when their bones were examined. All sufferers lived in the region of the Jintsu River system.
In 1961, Hokino and Yoshioka, an agricultural scientist, suggested that heavy metals, particularly cadmium, could play a part in the etiology. In 1968 the Japanese Ministry of Health and Welfare declared "the Itai-Itai disease is caused by chronic cadmium poisoning in the presence of other inducing factors, pregnancy, lactation, unbalanced internal secretion, ageing, deficiency of calcium etc." It also announced that the Kamika Mining Station of the Mitsui Mining Company polluted the Jintsu river and that cadmium pollution of the river caused polluted soil, rice, soybeans in areas irrigated by the river, as well as underground wells nearby.

In 1971, a district court in central Japan ruled that this bone ailment was caused by cadmium and that the Mitsui Mining Company must compensate the victims of the disease.

Because of several puzzling features of the disease as described by Hagino, Murata (14) and others these rulings have created considerable controversy and debate.

The disease was epidemic amongst elderly women who had borne many children (average 6). The outstanding features were lumbar pain and myalgia, spontaneous fractures with skeletal deformities. Pain was readily elicited when pressure was applied to bone. A hypochromic microctyic anaemia was present, serum calcium and phosphorus was low and the alkaline phosphatase level was high. Although serum proteins were normal there was proteinuria and glycosuria with increased amino acid excretion in the urine. Analysis of the proteins revealed them to be similar low molecular weight proteins to those described previously as being associated with industrial cadmium intoxication.

Cadmium in blood and urine was increased and zinc levels lower when compared to controls - Friberg (14). Histological studies showed renal tubular epithelial atrophy and bone changes consistent with osteomalacia. The cadmium content of the liver was about 5 times that in control specimens but that in the kidney was lower.

Epidemiological studies have shown that the disease is confined to a limited area around the Jintsu river and that it is not genetic but environmental. These studies have also revealed other contaminated river systems in Japan. There is a high incidence of the combination proteinuria plus glycosuria associated with high body cadmium levels in inhabitants of areas along all these rivers. But no cases of overt osteomalacia or Itai-Itai disease have been found elsewhere. This is the basis of the controvesy surrounding the findings of both the Health and Welfare Ministry, and the Court. Is there another factor besides cadmium?

Almost all cases of Itai-Itai disease have been females yet in the endemic area the incidence of proteinuria plus glycosuria has been almost as high in males as in females. Two French and two British reports on bone changes associated with industrial cadmium intoxication indicate that osteomalacia occurs in both sexes. Nicaud et al (55), Bonnell (60). Friberg (14) in discussing Itai-Itai disease suggests that vitamin D must also play a role. He postulates that either vitamin D deficient ricketts associated with certain cultural practices of the area or vitamin D resistant ricketts following on renal tubular disease is the basic cause of the Itai-Itai disease.

Professor Takeuchi from the Department of Internal Medicine, Kanazawa University has reviewed the debate in a long article in the Nippon Rhinso (68). He casts considerable doubt on the validity of the link between cadmium and the disease and also appears to doubt a link between cadmium contaminated water, soil and irrigated crops, and the high incidence of proteinuria and glycosuria in inhabitants of these regions. Initially he was a supporter of the hypothesis that cadmium is the responsible toxin but now he believes that Itai-Itai is ricketts and quotes many cures with vitamin D therapy.

Despite the Japanese Ministry and the Courts ruling there is still considerable scientific and emotional debate throughout the world on the environmental effects of cadmium. Within the past decade a number of investigators have theorised, based on acceptable scientific observations both in animals and man, that environmental cadmium may be intimately involved in various pathological processes in humans.

Toxicological Effects of Cadmium Poisoning on Experimental Animals

Cadmium has been shown to be highly toxic in numerous animal experiments. Its toxicity rating, 5, on a scale of 1 to 6 puts it in the category of extremely toxic - Gleason et al (69). The acute lethal dose by ingestion for man based on animal experiments is estimated to be between 5 and 50 micrograms per kilogram of body weight.

The following is a list of effects noticed in animals exposed to varying doses of cadmium:-

Amyloidosis

Anaemia

Cancer

Cirrhosis

Dental changes

Enteritis

Gastritis

Hypertension

Hypocalcaemia

Life span shortening

Nerve damage

Ovarian changes

Pancreatic atrophy

Proteinuria

Pulmonary emphysema

Renal damage

Teratogenic and embryotic effects

Testicular atrophy and lesions

Toxaemia of pregnancy

Weight loss

Many of these conditions have been found in workers exposed to cadmium, (vide chapter 5). Some however, have not been detected and some though found in exposed workers are also found to the same extent in controls or the population generally.

Epidemiological Speculations

(a) Cardiovascular Disease

Carroll 1966 (70) examined mortality ratios standardised for age, sex and race for heart disease except rheumatic disease in 28 cities in the United States and the concentration of cadmium in the air of these cities. The death categories included arteriosclerotic heart disease, hypertension with or without mention of heart, and other heart diseases attributed to non specific terms: congestive cardiac failure or myocardial degeneration. He found a positive correlation between the two but no correlation between vascular lesions of the central nervous system and atmospheric cadmium.

Schroeder 1965 (71) from an examination of renal tissue from subjects living both in the U.S.A. and outside the U.S.A. concluded that most patients dying from hypertensive complications showed either an increased concentration of cadmium or an increased cadmium to zinc ratio compared to subjects dying of a variety of other major diseases. In another study 1966 (72) he noted that soft or acid waters frequently contain cadmium in

excess of U.S. Public Health Standards and a positive correlation between soft water and hypertension.

Morgan 1972 (73) in a careful assessment of cadmium tissue levels in hypertensive patients and controls found no excessive renal cadmium in the former. Hammer (74) in an epidemiological survey of people industrially exposed to cadmium found no rise in blood pressure in this group. It has been suggested that occupationally acquired zinc acted as a protective in this group.

(b) Respiratory Disease

Lewis et al 1969 (75) found, from autopsies carried out in Glascow, an elevated liver cadmium level in those dying from emphysema and or bronchitis. No data were given on occupation or smoking habits.

(c) Malignant Disease

Cadmium has relatively strong carcinogenic properties when administered to animals. Morgan 1970 (76) reported significantly higher renal and hepatic cadmium concentrations in tissues taken from the general population dying of carcinoma of the lung. Earlier Tietz 1976 (77) had found increased liver and lung cadmium levels in persons with pulmonary, oesophageal, pancreatic and brain tumors.

Potts 1965 (78) reported a high incidence of cancer in 74 men exposed to cadmium for 10 years. Eight of the men died, three from carcinoma of the prostate, one from the lung and one where the primary was not identified.

Other workers have recorded similar figures. Lemen et al, have reported in a paper presented at a meeting on Occupational Carcinogenesis sponsored by the New York Academy of Science in March 1975 that their retrospective survey of deaths of 280 workers in a cadmium plant showed a higher incidence of lung and prostatic cancer as well as total malignancies than would have been expected in the general population.

d) Testicular Damage

Partizek 1957 (79) reported a rapid sterilising effect (within 4 - 6 hours) from a small injected dose of cadmium chloride or lactate in rats. Histological changes were seen in the seminiferous epithelium but none in liver or renal cells. After about a month endocrine function returned. Higher doses produced permanent sterility. Chiquoine 1964 (80) reviewing all the studies on various animals concluded that cadmium had a sterilising effect on species with scrotal testes but not on those possessing abdominal testes. Gunn et al (48) reported that zinc, selenium and thiols, e.g. cystein and British - Anti Lewesite prevented necrosis.

Favino et al 1965 (14) analysed the fertility of ten cadmium workers and their hormonal levels. He found no evidence of infertility and one case of low androgen level.

e) Teratogenesis

Pregnant experimental animals fed cadmium either abort, produce small litters, abnormal offspring, or small offspring - Schroeder (81). Friberg (14) quotes Cvetkova as having reported that women working in a cadmium accumulator factory in Russia produced lower birth weight male and female children than did the population generally. In addition some offspring

suffered from ricketts or delayed dentition.

f) Pancreatic Function

Although high concentrations of cadmium are found in the pancreas in the occupationally exposed, little work has been done on the effect of cadmium on pancreatic function. Friberg (14) quotes Murata as recording a decrease in pancreatic activity in Itai-Itai disease.

g) Mutagenesis

Conflicting reports have appeared in recent literature on the mutagenicity of cadmium compounds. Cadmium can bind to the phosphates and bases of Desoxy-ribonuclecic acid and as such could induce genetic alteration. Plants e.g. peas and beans treated with cadmium do show chromosomal abnormalities. However, neither the fruit fly, Drosophila nor the parasitic wasp, Habrobraeom produced mutations when given large doses of cadmium.

Shiraishi and Yosida (82) reported an increased frequency of cells with chromosome abnormalities in Itai-Itai patients. The-Hung Bul et al 1975 (83) could not find any evidence of chromosome damage in 4 cases of Itai-Itai disease or in 5 Swedish workers with a higher blood cadmium level than Itai-Itai patients. Very few genetic studies either in animals or humans have been performed. Many more studies are needed before it can be established that environmental cadmium is a health hazard.

The high concentration of cadmium in the silt and waters of the River Derwent and in the surface soil of some areas around Hobart has caused considerable speculation as to whether the health of the public is at risk because of this. One pointer might be the health of workers closest to the source of this environmental contamination.

CHAPTER 7

A Health Survey of Workers Exposed to Cadmium in Hobart

At its Risdon plant, on the Derwent River, Tasmania, the Electrolytic Zinc Company of Australasia recovers cadmium from a cadmium copper precipitate by-product of the purification stage of zinc.

Twenty seven men working on a three, eight hour shift per day basis are employed in the recovery operation which is conducted in a small multi-storied building.

In brief the recovery operation consists of:- (Anderson 1949 (84))

1. Oxidation and grinding of cadmium copper precipitate
2. Leaching and filtering
3. Precipitation of cadmium
4. Oxidising and grinding of the precipitated cadmium
5. Leaching oxidised cadmium precipitate and purification of the leach solution
6. Electrolysis of cadmium sulphate solution
7. Melting, casting and packing

Men working in this plant are exposed to cadmium both as dust and fume. Concentration of each of these varies considerably over the working day and throughout the various areas of the plant. Eight hour sampling of the working environment indicates that the average concentration of cadmium varies from 17 to 31 micrograms per cubic metre.

Situated close to the cadmium plant is a small building housing a compressed air station. Eight men are employed in this building working on a three, eight hour shift per day basis. The working environment of the building is subject to some fall out from the cadmium plant, mostly cadmium dust. An eight hour sampling of the atmosphere within the station reveals a concentration of 1 microgram per cubic metre.

Another section of the plant produces super phosphate by mixing acid with ground up phosphate rock. The phosphate rock may come from several world sources and can contain up to 200 parts per million of cadmium. The number of men working in this plant and the number of shifts worked per week fluctuates considerably depending on the demand for superphosphate. An eight hour sampling of the working environment of this section of the plant revealed a concentration of between 0.15 micrograms per cubic metre to 0.85 micrograms per cubic metre.

Each section of the plant at Risdon is visited by a medical officer at least once every six months. At each visit the working environment is examined. The company has given considerable attention to industrial hygiene and the past decade has seen the introduction of measures aimed at improving both working conditions and protection from excess exposure to cadmium.

The waters of the River Derwent and the sediment in the river show a high concentration of heavy metals including cadmium - Bloom (85). Soil in some areas around Hobart also reveals a higher cadmium content than others (86). This has been attributed to atmospheric pollution at least in part by the plant and subsequent wind dispersion. Commercial oysters in the river show a high cadmium content - Thrower (87).

In September, 1975, I conducted a health survey amongst workers in those areas where cadmium is a possible occupational hazard, and a control group from a general office well removed from cadmium sources.

The survey received the encouragement and backing of the Electrolytic Zinc Company. Company records, both employment and sickness were made available to me. Widespread promotion through Unions, Union representatives, employee social groups, and individual employees allayed any fears or misapprehension those who would be involved might have. Clerical staff were made available to facilitate the organisation and logistics of the survey. Employees taking part were given time off in working hours and transported by company vehicle to the various centres for the medical examination, radiology and pathology required.

With this background I wrote to every employee exposed to cadmium and a group of clerical workers for controls inviting them to participate.

Twenty two of the twenty seven men in the cadmium plant volunteered, four of the eight men working in the compressed air station and eight of the seventeen men working in the superphosphate plant - in all, a total of thirty four exposed workers. There is a slight bias towards younger men in the control group - thirty four office staff. (Figure 6, Page 76)

Objectives of the Survey

1. To elicit any individual or pattern of symptoms which could be attributed to working with cadmium.

2. To elicit any clinical signs or groups of signs which could be ascribed to cadmium effect.

3. To compare the overall health of workers exposed to cadmium with a non exposed control group with particular references to:-

   (a) the skin
   (b) the central nervous system
   (c) liver function
   (d) gastro-intestinal function
   (e) renal function
   (f) blood pressure
   (g) myocardial function
   (h) coronary and peripheral arterial disease
   (i) respiratory function
   (j) bone marrow function
   (k) gonadal function
   (l) bone structure and density

4. To examine a series of easily performed biochemical and radiological investigations which may indicate a covert cadmium effect on tissue or cellular function.

5. To examine any correlative effect of other industrial metals, e.g. zinc, lead, mercury.

6. To compare the findings of this survey with similar surveys elsewhere.

7. To investigate the significance of extra occupational cadmium absorption from diet, smoking, residence.

8. To develop a simple screening procedure which would indicate to the employer, employee and examining medical officers that body cadmium was at the danger level.

The Survey

Each participant completed, at his leisure, a questionnaire designed to give:-

a) Information about possible background cadmium exposure from: diet, previous occupation, smoking habits, residence past and present.

b) Information concerning past and present health.

c) An indication of symptoms suggesting effects of either acute or chronic exposure to cadmium on all bodily functions.

Later all received an extensive medical examination. At the time of the examination the completed questionnaire was discussed in detail. Answers were confirmed and clarified where necessary. Further information was also sought, particularly in the area of gonadal function (it was thought prudent not to include this in the written questionnaire). In addition those exposed occupationally to cadmium were questioned about workmates who had left or retired. The objectives of this was to see if a retrospective survey of the health of these men would prove worthwile. A sample questionnaire follows:-
(Pages 53 - 62)

MEDICAL IN CONFIDENCE (1)

SURNAME:

GIVEN NAMES:

Present Address: How many years have you lived there:

Previous Address(es) in Australia (If any): How many years did you live there:

Date of Birth:

Country of Birth:

Years in Australia:

Where have you lived before coming to Australia: How many years did you live there:

Years in Hobart:

Years worked at the Electrolytic Zinc Company:

Where:

Where have you worked previously: What did you do there: For how long did you work there:

MEDICAL IN CONFIDENCE (2)

Personal history

Single/Married:

Exposure to fertiliser/pesticides

At home:	☐	Never	☐	Sometimes	☐ Often
On farm:	☐	Never	☐	Sometimes	☐ Often

Smoking history

Started: Stopped: .....cigarettes/day
.....pipes/day
.....cigars/day

Alcohol intake

.....beers/day .....nips/day

Diet:

Sea fish	☐	Small	☐	Moderate	☐ Big eater
Shell fish	☐	Small	☐	Moderate	☐ Big eater
Meat	☐	Small	☐	Moderate	☐ Big eater

MEDICAL IN CONFIDENCE (3)

PERSONAL PREVIOUS MEDICAL HISTORY

Illnesses - requiring hospital treatment

Illnesses - requiring a week or more off work

Operations -

Medical Treatment, if any, at present -

Names of drugs taken previously -

MEDICAL IN CONFIDENCE (4)

FAMILY MEDICAL HISTORY

	Good Health	Poor Health:	Dead	When	Cause
Father: Age					
Mother: Age:					
Brothers: Age:					
Sisters: Ages:					
Children: Ages:					

MEDICAL IN CONFIDENCE (5)

Please tick appropriate box

In the past five years:

1. Has your weight -

- ☐ Increased by five pounds of more
- ☐ Increased, but less than five pounds
- ☐ Remained just about the same
- ☐ Decreased, but less than five pounds
- ☐ Decreased by five pounds of more

2. Has your appetite -

- ☐ Increased quite a bit
- ☐ Increased slightly
- ☐ Remained just about the same
- ☐ Decreased slightly
- ☐ Decreased quite a bit

3. Diet -

Have you been following any special diet

☐ Yes ☐ No

Do certain foodstuffs, or types of cooking upset you

☐ Yes ☐ No

If so, what foods and why

- ☐ Fatty or fried foods
- ☐ Spiced dishes
- ☐ Exotic cooking
- ☐ Any other foods

MEDICAL IN CONFIDENCE (6)

4. Existing habits

Do you eat three normal meals a day

☐ Yes ☐ No

Do you forgo meals each day

Consistently Spasmodically Seldom

5. In general, has the frequency of your bowel movements -

☐ Increased ☐ Decreased ☐ Not changed

6. Has the size of the movement, in general -

☐ Increased ☐ Decreased ☐ Not changed

7. Has the colour of the movements, in general -

☐ Increased ☐ Decreased ☐ Not changed

8. Have you passed any black, tarry looking stools -

☐ Several times ☐ Only once of twice ☐ Not at all

9. Do you have:-

Abdominal Pain -

☐ None ☐ Sometimes ☐ Often

Or Cramps -

☐ None ☐ Sometimes ☐ Often

10. Wind or belching -

☐ None ☐ Sometimes ☐ Often

When -

MEDICAL IN CONFIDENCE (7)

11. Have you had a cough -

- ☐ That continues rather regularly
- ☐ That shows up only once in a while
- ☐ Not at all

12. Have you coughed up any blood -

☐ Several times ☐ Only once or twice ☐ Not at all

13. Do you have shortness of breath -

☐ Yes ☐ No

14. Do you wheeze -

☐ No ☐ Sometimes ☐ Constant

15. Do you have sputum production -

☐ Slight ☐ Moderate ☐ Plenty

16. Do you have colds or bronchitis -

☐ Never ☐ Sometimes ☐ Often

17. Have you had a sore throat -

☐ Several times ☐ Only once or twice ☐ Not at all

18. If you have a sore throat is it usually -

- ☐ of a fairly long duration
- ☐ of rather short duration

MEDICAL IN CONFIDENCE (8)

19. Have you had any progressive or recurring hoarseness that was not associated with a cold -

☐ Several times ☐ Only once or twice ☐ Not at all

20. Sense of smell -

☐ Good ☐ Poor

21. Chest pain -

☐ None ☐ Slight ☐ Severe

When: ☐ At rest ☐ On exertion

22. Have you had dizzy spells -

☐ Yes ☐ No

Were they:

☐ Severe and frequent

☐ Severe but not frequent

☐ Mild and frequent

☐ Mild and not frequent

23. Have you had any headaches that were -

☐ Severe and frequent

☐ Severe but not frequent

☐ Mild and frequent

☐ Mild and not frequent

☐ Do not have headaches

24. In general, has the frequency with which you urinate during the day -

☐ Increased ☐ Decreased ☐ Not changed

MEDICAL IN CONFIDENCE (9)

25. Has the frequency with which you urinate at night -

☐ Increased ☐ Decreased ☐ Not changed

26. Do you have blood in urine -

☐ Yes ☐ No

27. Do you have scalding -

☐ Yes ☐ No

28. Do you have pain in kidneys -

☐ Yes ☐ No

29. Do you have groin pain -

☐ Yes ☐ No

30. Do you have any noticeable swelling of your ankles or legs -

Several times ☐ Only once or twice ☐ Not at all

31. Do you have bone pain -

☐ Yes ☐ No

Where:

32. Do you have joint pain -

☐ Yes ☐ No

Where:

MEDICAL IN CONFIDENCE (10)

33. Have you ever had any -

Fever	☐	Several times	☐	Only once or twice	☐	None	
Chills	☐	Several times	☐	Only once or twice	☐	None	
Unusual sweats	☐	Several times	☐	Only once or twice	☐	None	

34. Have you had any -

Earaches	☐	Several times	☐	Only once or twice	☐	None	
Ringing in your ears	☐	Several times	☐	Only once or twice	☐	None	
Diminished hearing	☐	Several times	☐	Only once or twice	☐	None	
Paralysis	☐	Several times	☐	Only once or twice	☐	None	
Nervous trouble	☐	Several times	☐	Only once or twice	☐	None	

35. Have you had any discharge of blood or pus from your -

Eyes	☐	Several times	☐	Only once or twice	☐	None	
Ears	☐	Several times	☐	Only once or twice	☐	None	
Nose	☐	Several times	☐	Only once or twice	☐	None	
Mouth	☐	Several times	☐	Only once or twice	☐	None	
Rectum	☐	Several times	☐	Only once or twice	☐	None	
Genitalia	☐	Several times	☐	Only once or twice	☐	None	

.....

SIGNATURE

Alcohol

Eighteen men in the exposed group answered that they rarely took alcohol; this represents 52.9% of this group. Five of these men admitted that they had averaged 80 grams per day in the past, but had not consumed alcohol for at least five years. In the control group 14.7% rarely drank alcohol. In both groups there were five men who consumed more than 80 grams of alcohol per day. It is generally accepted that there is a high risk of physical, social and mental damage if consumption exceeds 80 grams per day.

Smoking

No attempt has been made to distinguish pipe, cigar or cigarette smokers, nor to define smokers into light, medium or heavy. A non-smoker was defined as one who had not smoked for five years. Each group of non-smokers contained men who had smoked prior to 1970. These are identified where required. The majority of "non-smokers" in the exposed group were smokers at some stage of their lives.

The examination included:-

a) An E.C.G.

b) An assessment of respiratory function:-

i) Vital Capacity) measured on a Pulmotest
ii) Forced expiratory volume at one second) spirometer

c) Routine urine testing using:-

i) Bililabstic (Ames)

iii) A further examination for protein was made by boiling a measured quantity of freshly voided urine and adding acetic acid.

Special Investigations

a) Radiology

i) Forearm through a water jacket to examine ulnar cortical density - Doyle 1961 (88).

ii) Chest - if no recent chest film available.

There examinations were carried out by Dr. B. Fazackerley of Hobart.

b) Biochemistry

i) Metals in urine (24 hour specimen).

ii) Metals in blood.

The concentration of cadmium, lead, mercury and zinc in both these fluids was determined by Chemlabs - Hobart.

The description of their methodology, as supplied by the laboratory reads as follows:- (Pages 65 - 67).

HEAVY METALS

Methods of analysis

General

The methods selected for analysis of blood and urine were selected after a review of methods used in similar surveys reported in the literature. It was noted that many surveys led to results which could be partly attributed to the methods of analysis. Accordingly, we have in each instance used the method of addition of standards, together with correction for non-atomic background absorption effects, which are intended to take into account sample peculiarities which may either enhance or diminish the atomic absorption signal for each metal being measured. Each metal has been measured by atomic absorption spectrophotometric techniques. The reliability of these analyses has been confirmed by interlaboratory surveys in which different methods of analysis have been used, i.e. anodic stripping voltametry and atomic absorption flame and flameless techniques.

Mercury in blood and urine samples was determined by digestion then measurement of generated mercury vapour by atomic absorption spectrophotometry. Many procedures have been recommended for digestion of organomercury compounds under reflux. However, to avoid the losses of volatile mercury compounds, the digestion was carried out in a cold sealed flask of acid-permanganate over a 48 hour period.

Zinc was determined in both types of samples after perchloric acid digestion and suitable dilution. It is noted that many authors preferred in the case of urine to aspirate the sample directly into the flame. We preferred to remove all traces of organic matter from both types of samples to overcome the significant non-atomic absorption effects that would otherwise result.

Cadmium and lead were determined in both types of samples after a preconcentration step, which isolated the metals from the effects of sample matrix interferences. These metals were chelated with a mixture of sodium diethyldithiocarbamate and ammonium pyrollidine dithiocarbamate, at the appropriate pH, then extracted into a methyl isobutyl ketone organic phase which was subsequently aspirated into the flame.

Table (1)

Limits of detection and accuracies for analytical methods used

	Detection limit Urine Ug/l	Accuracy	Detection limit Blood Ug/100 ml.	Accuracy
Mercury	<0.2	±0.1 at 0.5	0.1	±0.2 at 1.0
Cadmium	0.3	±0.2 at 1.0	<0.2	±0.1 at 1.0
Lead	2.0	± 4 at 40	2.0	± 1 at 20
Zinc	20	± 10 at 500	20	± 10 at 500

Table (2)

Lead in blood - a comparative study

Sample	Conc^{n}. in Ug/100 ml anodic stripping voltametry (ASV)	Carbon rod AAS	Solvent extraction AAS
	Univ. of Tas.	Univ. of Tas.	Univ. of Tas.
1	10	9.7	11
2	12	9	12
3	10	10.2	6
4	8	15.3	12
5	20	20	18
6	25	29	28
7	12	13	13
8	10	16	10
9	8	7	6
10	28	24	24

	Univ. of Tas. (ASV)	Chemlabs
M. Bowerman	30	26
J. Folder	14	13
R. Edwards	13	16
B. Watson	15	16
K. Young	16	16
I. Richards	26	27

Table (3)

Analysis of cadmium in urine, cited by Berman (1) using a solvent extraction procedure similar to that used in this project. Westerlund-Helmerson (2) has used this method successfully for analysing cadmium in blood down to 0.2 Ug/100 ml.

No. of samples	Cadmium added Ug/100 ml	Cadmium recovered Ug/100 ml
5	5	5-5.5
5	10	10-11
5	20	20-21
5	30	29-32
5	40	41-42
5	50	49-54

1. Berman, Eleanor (1967) "Determination of cadmium, thallium and mercury in biological materials by atomic absorption." At.Absorp.Newsl., 3(6), 57-60.

2. Westerlund-Helmerson, Ulla "Determination of Lead and cadmium in blood by a modification of the Hessel method." At.Absorp.Newsl., 9(6), 133-134

Table (4)

Analysis of lead in blood in conjunction with Chemistry Department of University of Tasmania who participated in an International Survey

Conc^{n}. Ug/100 ml found by this laboratory	Average conc^{n}. found by different laboratories using a variety of methods
59	62.9 $\pm$9 Ug/100 ml by solvent extraction/flame atomic absorption

c) The following biochemical, haematological and bacteriological studies were performed by Dr. Parson's Laboratory, Hobart. Where appropriate a short description of the technique is given. The normal range for the laboratory is also presented.

Serum bilirubin

Determined by reaction with diazotised sulphanic acid in aqueous (conjugated) or methanolic-aqueous (total) solution. Normal range is up to 1 mg/100 ml.

Alkaline phosphatase

Measured by fixed-time hydrolysis of phenolphthalein phosphate at 37^{o}. Normal range is 9 - 35 units.

Serum glutamic pyruvic transaminase

Determined by a kinetic method using a Boehringer kit. Normal values up to 27 u/1.

Serum cholesterol

Determined by the Liebermann-Burchard reaction. Normal values range from 150 - 250 mg/100 ml.

Serum triglycerides

Triglycerides are separated from other lipids by partition between nonane: isopropanol and water. The triglycerides are saponified and the liberated glycerol determined by the Hantsch condensation. Normal fasting range is 30 - 135 mg/100 ml.

Blood urea nitrogen

Determined by urease-catolysed hydrolysis to ammonia, followed by reaction with phenol and hypochlorite. Normal range in this laboratory is 20 - 40 mg/100 ml.

Serum creatinine

Determined by the Joffe reaction with alkaline picrate. Normal range in this laboratory is 0.8 - 1.3 mg/100 ml. The creatinine clearance (ml/min) can be calculated by the formula:

$$\text{Creatinine Clearance} = \frac{U \times V}{S} \quad \text{ml/minute}$$

where U = urine concentration (mg/100 ml.), V = urine vol. per minute, and S = serum or plasma concentration (mg/100 ml.) Normal value is 120 - 130 ml/min.

Serum sodium

Determined by manual flame photometry. Normal range in this laboratory is 136 - 149 mEq/1.

Serum potassium

Determined by manual flame photometry. Normal range in this laboratory 3.8 - 5.2 mEq/1.

Serum chloride

Determined by titration with mercuric nitrate/diphenylcarbozone without deproteinization. Normal range in this laboratory is 98 - 108 mEq/1.

Blood glucose

Determined by reaction with 0 - toluidine plus acetic acid. Normal values in this laboratory are 70 - 220 mg/100 ml.

Blood uric acid

Determined by reaction with phosphotungstic acid after deproteinization. Normal range is 2.5 - 7.0 mg/100 ml.

Serum protein

Total protein determined by EDTA-chelated biuret method.

Electrophoretic pattern of serum proteins

Proteins separated by electrophoresis on cellulose acetate at pH 8.6.

Serum thyroxine

Determined by the Oxford T4 - by Column Kit. Normal values are 3.0 - 6.6 ug/100 ml.

Serum calcium

Determined by complexation with methylthymol blue plus 8 - hydroxyquinoline followed by colorimetry. Normal range for this method is 4.2 - 5.3 mEq/1.

Serum Phosphous

Determined by reduction of phosphomolybdic acid to molydenum blue. Normal range (as phosphorus) is 2.5 - 4.5 mg/100 ml.

d) Sex hormones

i) Serum testosterone

ii) Serum luteinising hormone

iii) Serum follicle stimulating hormone

Measurements of these hormones were done at the Medical Research Centre, Prince Henry's Hospital, Melbourne, by Dr. H. Burger using radio-immuno assay. Normal ranges are shown in Figures 3, 4 and 5. Pages 71 - 73.

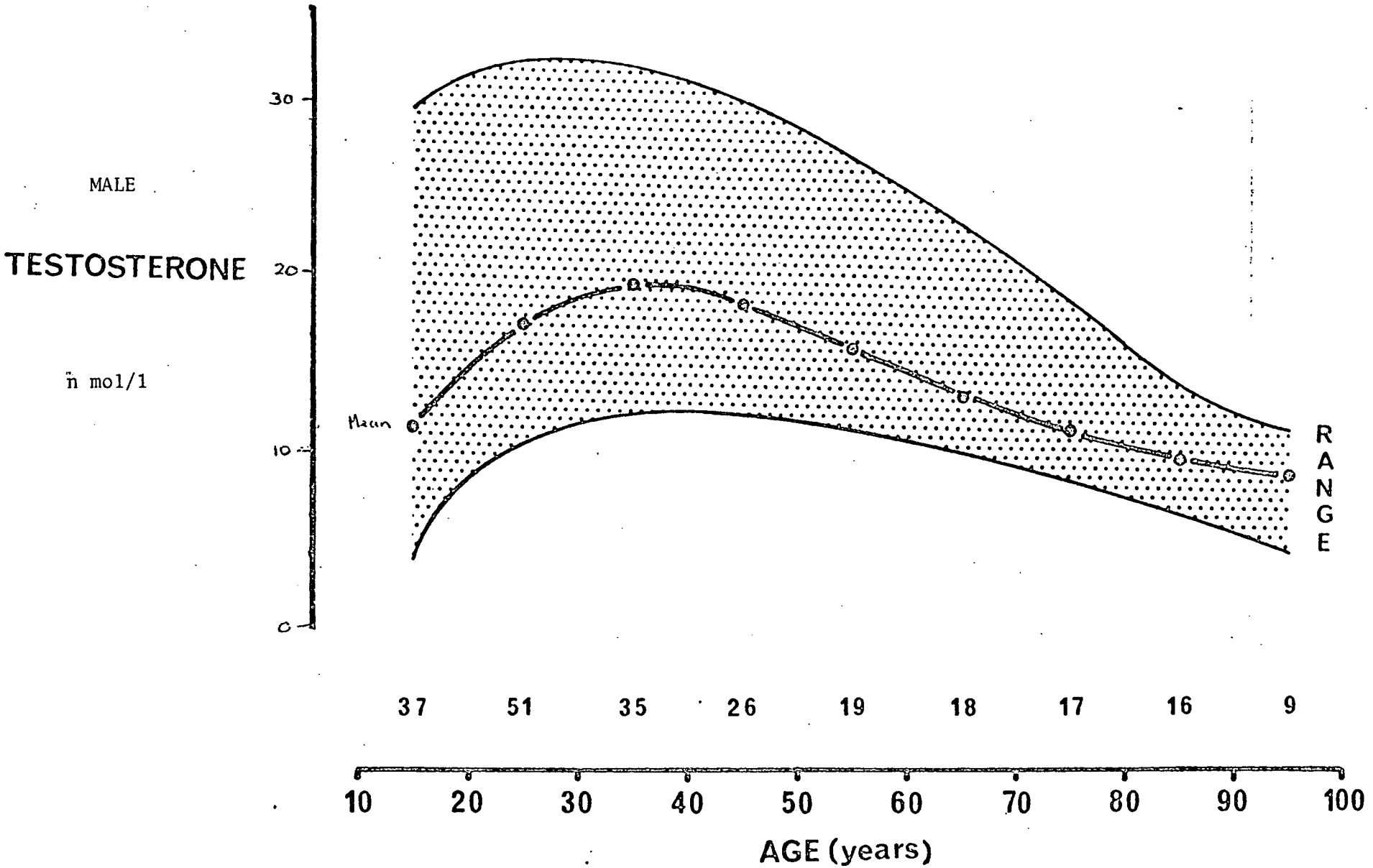

MALE
TESTOSTERONE
n mol/1
30
20
10
0
Mean
RANGE
37
51
35
26
19
18
17
16
9
10
20
30
40
50
60
70
80
90
100
AGE (years)

FIGURE 3

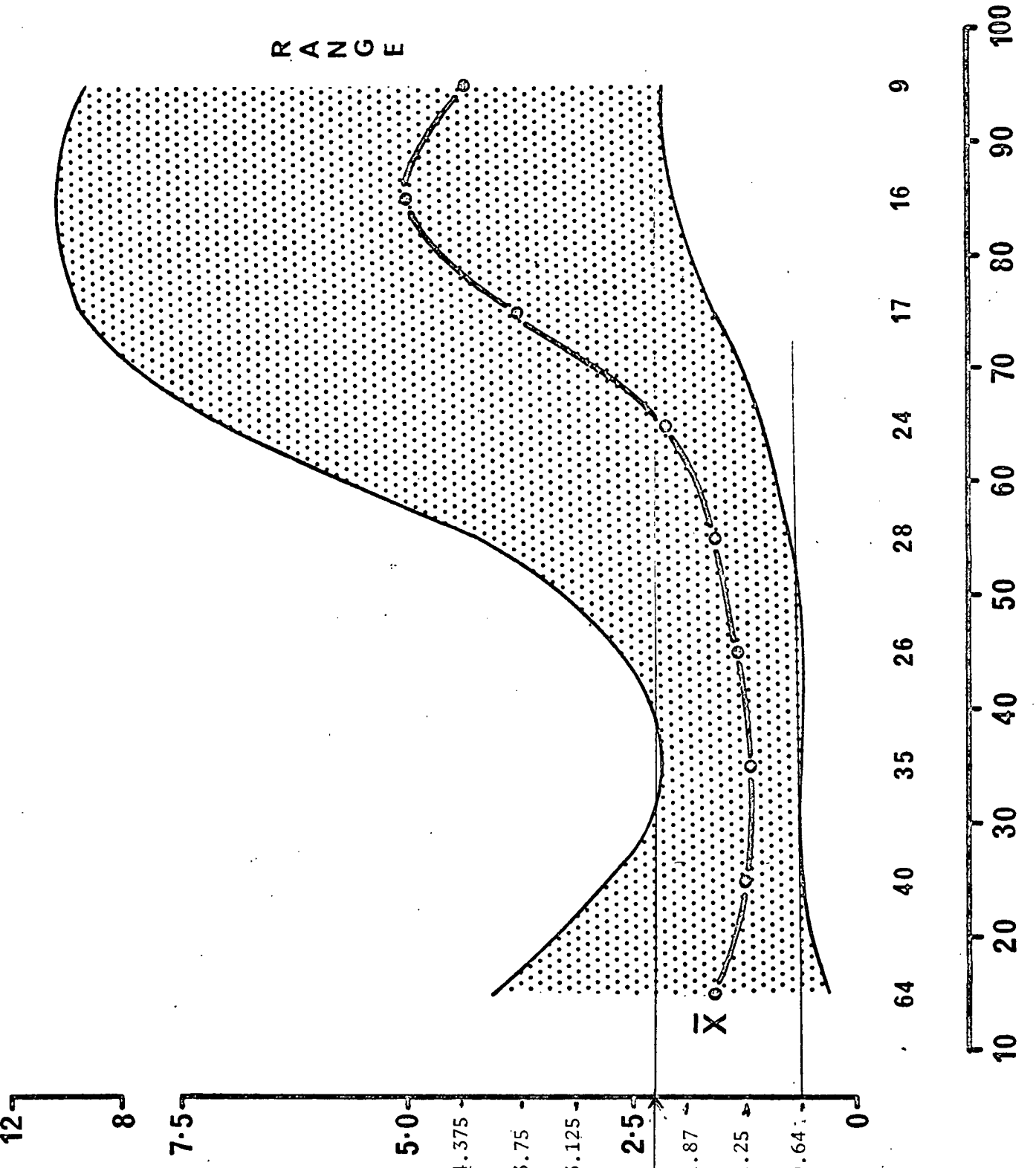
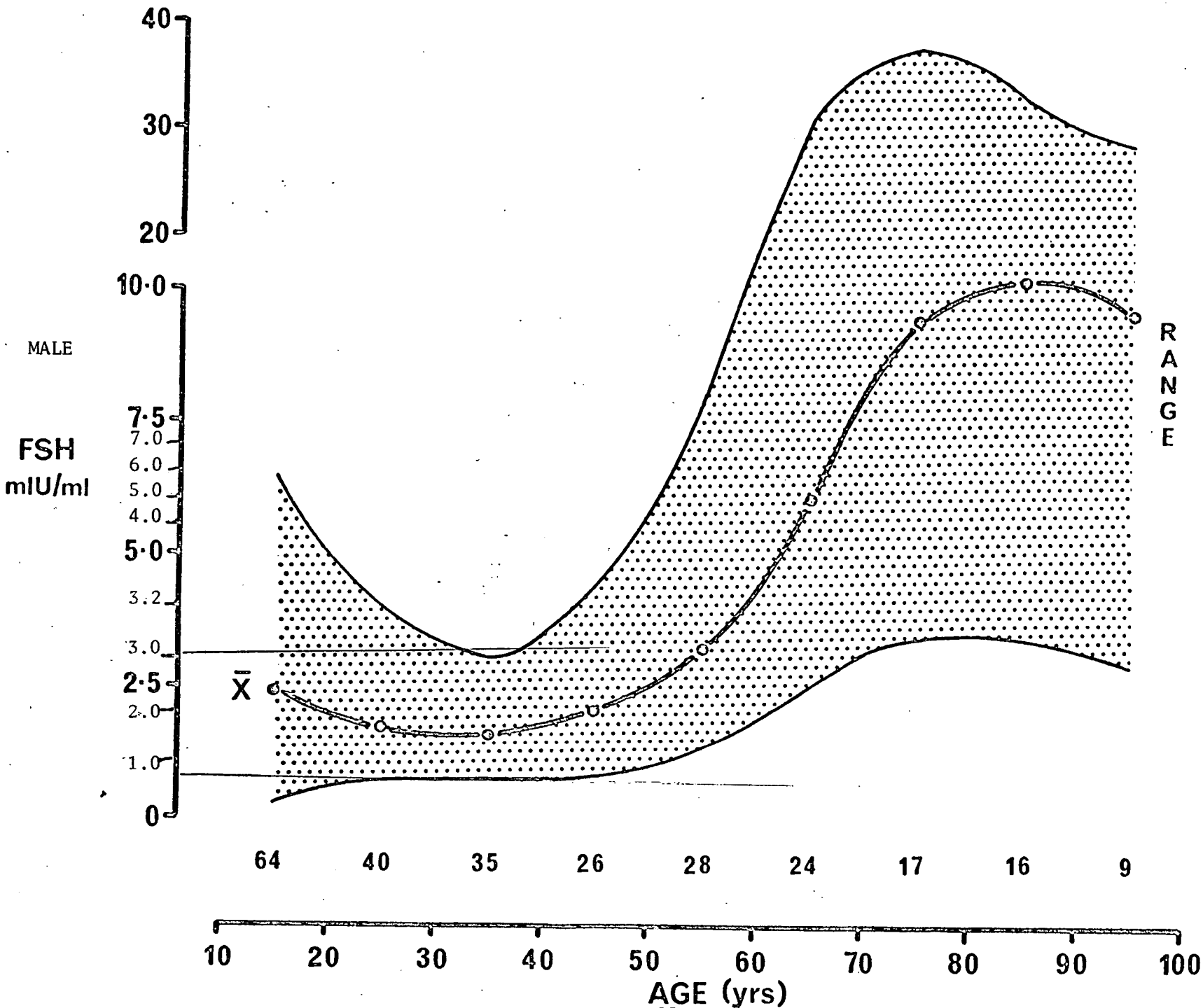

RANGE
MALE
LH
mIU/ml
12
8
7·5
5·0
4.375
3.75
3.125
2·5
2.25
1.87
1.25
0.64
0
$\bar{X}$
64
40
35
26
28
24
17
16
9
10
20
30
40
50
60
70
80
90
100
AGE (years)

FIGURE 4

SERUM FSH WITH AGE



e) Haematology

Haemoglobin

Packed cell volume

White cell count

Platelet count

Relative viscosity

Differential white cell count

f) Urine

Microscopy and culture

Examination of 24 hour specimen

Creatinine

Determined by the Joffé reaction with alkaline picric acid. The normal values given in standard texts are:

0.4 - 1.8 g/24 hr. (Wootton); 1.0 - 1.5 g/24 hr. (Boehringer);

1.1 - 2.5 g/24 hr. (Merck); 1.0 - 2.0 g/24 hr. (Tietz).

Amino acids screening test

Determined by formation of a charge-transfer complex with benzoquinone - Lorentz, K. and Flatter, B. Clinical Chemistry, 20, 1553 (1974). These authors quote a range of 73 - 260 mg/24 hr. Most standard texts quote higher values: 200 - 700 mg/24 hr. (Tietz); 175 - 530 mg/24 hr. (Merck).

The History

After consideration of the written and oral replies it became apparent that only significant sources for body burden of cadmium would be occupational exposure and smoking. Diet and residence in a higher soil cadmium locality showed no significant variation between the groups.

Many of the signs, symptoms and biochemical findings could have been effected by a high intake of alcohol. As both groups contain the same percentage of men with an excess alcohol consumption it was felt that any influence of alcohol on the statistical findings would be balanced and could be ignored. Accordingly the survey results were arranged and are presented in four groups as follows:-

CONTROL GROUP		EXPOSED GROUP	
No	34	No	34
Smokers	22	Smokers	23
Non-smokers	12	Non-smokers	11

Figure 6, page 76 shows the years worked for each individual in each group. Figure 7, page 77 illustrates the smoking history.

Statistical Analysis of Results

Dr. D. Ratkowski from the Division of Mathematical Statistics, C.S.I.R.O., Hobart, analysed the survey findings.

The survey data were subject to analyses of variance using the F test, correlation coefficients and X^2 tests of contingency. The text identifies the method used to arrive at a conclusion.

CORRECTION

Page 76, line 9, Unexposed Smokers column, the figure 32 should read 15.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		1		8
		6		
25 - 30		5		6 *
		8		5
		11		
		9		
30 - 35	3 A	16	2 C	16
		7 **		
		32		
35 - 40	9 A	23 **		19
	5 A	16		1
	4 A	22		
	15 B			
	3 A			
	11 C			
	7 A			
40 - 45	11 A	5		26
	9 A	13		25
	23 A	17		
	9 A			
	11 B			
45 - 50	24 A	6	3 * A	33
	28 C	46	20 A	
			10 * A	
50 - 55	15 A	8	13 A	37
	19 C	11	23 * A	23
		38		
55 - 60	20 A	9	12 C	
	27 C	40	8 * C	
	24 A		18 * A	
60 & OVER	37 A		37 * B	19 *
	26 A		22 * A	
	27 A			

YEARS WORKED

AT THE ELECTROLYTIC ZINC COMPANY

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 6

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		4		-
		11		
		10		- *
25 - 30		13		-
		12		
		11		
	16 A	16	- C	-
30 - 35		14 **		
		15		
	19 A	20 **		-
35 - 40	18 A	23		-
	21 A	23		
	25 B			
	18 A			
	22 C			
	19 A			
	29 A	24		-
40 - 45	15 A	26		-
	32 A	26		
	30 A			
	27 B			
	30 A	27	16 * A	-
45 - 50	26 C	25	- A	-
			9 * A	
	39 A	35	- A	-
50 - 55	37 C	38	37 * A	-
		26		
	26 A	41	- C	
55 - 60	41 C	38	30 * C	
	41 A		32 * A	
	40 A		42 * B	- *
60 & OVER	41 A		7 * A	
	41 A			

SMOKING YEARS

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 7

CHAPTER 8

Body Burden of Mercury, Lead, Zinc and Cadmium

The blood levels for these four heavy metals expressed as Ug/ml. and the amount excreted in a 24 hour urine collection expressed as Ug/litre were determined once for each participant. The findings were used as a guide to body burden. Additionally the findings were subject to further statistical analyses to check whether the presence of lead, zinc or mercury might influence any possible cadmium effect.

All blood specimens were collected in the laboratory. Exposed workers, in order to remove accidental occupational skin contamination showered beforehand. The 24 hour urine specimen was collected at a weekend, or in the case of shift workers on their "days off" - again to remove possible occupational contamination. Each participant received two separate detailed instructions on the collection of a 24 hour specimen - one in writing and the other orally when they were given the specimen bottle. This was a glass 2 litre bottle cleaned with concentrated nitric acid and containing 10 mls. of hydrochloric acid as a preservative. Participants were warned not to use plastic material in the collection process. Arrangements were made to provide the laboratory with each specimen almost immediately after collection.

Mercury

Laboratory results for blood and urine levels are shown in figure 8, page 80 and figure 9, page 81 for each sub-group. Table 1, page 82 and table 2, page 82 indicate the mean, minimum and maximum concentration for each group. Statistically there is no significant difference between the groups using

an analysis of variance. Body burden of mercury is considered to be the same throughout the groups and will therefore be ignored as a possible influence on any cadmium effect.

Lead

Figure 10, page 83 shows individual results for blood lead for each group. No member of either group had a blood level above the accepted danger level for lead (70-80 Ug/ml.). There is a significant difference in blood lead levels between the combined exposed groups and controls - (table 3, page 85). The mean for this group, (23.65) is significantly higher than that of the combined unexposed group, (19.29), ($p<0.05$). This higher blood level was not expected when the survey was planned as lead in residue from the zinc plant is removed before the cadmium residue is treated in the cadmium plant. The possible association between lead, cadmium and haemoglobin levels is discussed in a later section. Figure 11, page 84 shows the individual figures of a 24 hour lead excretion concentration. There is no statistical difference between the groups - (table 4, page 85).

Zinc

Figures 12, page 86 and 13, page 87 and tables 5, page 88 and 6, page 88 show the results and statistical analyses for each group for this metal. Again statistically there is no significant difference between the groups.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		1.2		0.3
		0.1		
25 - 30		nd.		0.4 *
		nd.		0.3
		0.3		
		0.3		
30 - 35	nd. A	0.1	0.1 C	0.4
		nd. **		
		0.1		
35 - 40	nd. A	nd. **		0.4
	0.4 A	0.4		nd.
	0.8 A	0.7		
	0.3 B			
	nd. A			
	nd. C			
	0.1 A			
40 - 45	0.4 A	nd.		0.4
	0.1 A	nd.		nd.
	0.1 A	nd.		
	0.4 A			
	0.3 B			
45 - 50	0.1 A	nd.	0.3 * A	nd.
	nd. C	0.7	0.3 A	
			0.1 * A	
50 - 55	nd. A	nd.	0.7 A	0.1
	0.3 C	0.3	0.4 * A	0.9
		1.2		
55 - 60	nd. A		0.7 C	
	0.4 C	nd.	nd. * C	
	0.9 A	nd.	0.7 * A	
60 & OVER	0.3 A		nd. * B	0.9 *
	0.4 A		0.1 * A	
	0.4 A			

BLOOD MERCURY (UG/100 MLS.)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 8

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		1.6		3.7
		2.0		
25 - 30		2.8		4.6 *
		0.3		1.3
		2.0		
		0.5		
30 - 35	0.7 A	2.5	nd. C	2.6
		0.3 **		
		4.3		
35 - 40	1.0 A	0.3 **		2.1
	4.0 A	4.6		nd.
	1.0 A	1.5		
	0.3 B			
	nd. A			
	1.3 C			
	4.3 A			
40 - 45	2.5 A	1.3		1.0
	0.7 A	0.7		1.3
	nd. A	0.7		
	2.2 A			
	0.3 B			
45 - 50	0.2 A	0.3	1.3 * A	1.3
	0.3 C	2.6	4.6 A	
			0.3 * A	
50 - 55	0.4 A	2.0	1.0 A	4.3
	3.6 C	2.0	1.0 * A	nd.
		0.3		
55 - 60	0.4 A	0.7	8.9 C	
	2.6 C	0.7	0.3 * C	
	nd. A		6.7 * A	
60 & OVER	2.4 A		4.0 * B	2.0 *
	nd. A		1.0 * A	
	0.2 A			

URINARY MERCURY (UG/LITRE)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 9

Blood Hg - (Ug/100 mls.)

	Mean	Min	Max
Unexposed smokers	0.245	0	1.2
Unexposed non-smokers	0.342	0	0.9
Exposed smokers	0.248	0	0.9
Exposed non-smokers	0.309	0	0.7

TABLE 1

Groups not significantly different.

Urine Hg - (Ug/litre)

	Mean	Min	Max
Unexposed smokers	1.55	0.3	4.6
Unexposed non-smokers	2.02	0	4.6
Exposed smokers	2.92	0	4.3
Exposed non-smokers	2.65	0	8.9

TABLE 2

Groups not significantly different.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		19		19
		16		
25 - 30		24		16 *
		16		16
		16		
		22		
30 - 35	24 A	13	30 C	24
		19 **		
		13		
35 - 40	27 A	22 **		22
	22 A	22		16
	24 A	24		
	16 B			
	27 A			
	22 C			
	13 A			
40 - 45	56 A	16		27
	19 A	22		19
	16 A	16		
	27 A			
	16 B			
45 - 50	24 A	16	19 * A	30
	22 C	22	24 A	
			22 * A	
50 - 55	27 A	13	22 A	19
	22 C	16	36 * A	22
		22		
55 - 60	13 A	16	24 C	
	22 C	19	16 * C	
	19 A		22 * A	
60 & OVER	22 A		33 * B	22 *
	30 A		24 * A	
	22 A			

BLOOD LEAD (UG/100 MLS.)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 10

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		24		16
		30		
25 - 30		26		20 *
		11		31
		15		
		26		
30 - 35	26 A	117	33 C	41
		40 **		
		31		
35 - 40	39 A	2.9**		20
	20 A	48		17
	33 A	22		
	11 B			
	26 A			
	34 C			
	31 A			
40 - 45	62 A	11		39
	26 A	51		31
	26 A	11		
	53 A			
	26 B			
45 - 50	33 A	23	60 * A	43
	23 C	<2	65 A	
			2.9* A	
50 - 55	17 A	110	83 A	60
	2.9 C	20	30 * A	74
		17		
55 - 60	46 A	31	150 C	
	14 C	0.8	2 * C	
	14 A		43 * A	
60 & OVER	30 A		43 * B	17 *
	77 A		22 * A	
	17 A			

URINARY LEAD (UG/LITRE)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 11

Blood Pb - (Ug/100 mls.)

	Mean	Min	Max
Unexposed smokers	18.36	13	24
Unexposed non-smokers	21.00	16	30
Exposed smokers	23.13	13	56
Exposed non-smokers	24.73	16	36

TABLE 3

Significant difference between groups ($p<0.05$).

Urine Pb - (Ug/litre)

	Mean	Min	Max
Unexposed smokers	30.4	0	117
Unexposed non-smokers	34.1	16	74
Exposed smokers	29.9	3	77
Exposed non-smokers	48.4	0	150

TABLE 4

Groups not significantly different.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		640		430
		490		
25 - 30		440		420 *
		420		540
		630		
		1,300		
30 - 35	540 A	520	680 C	480
		720 **		
		550		
35 - 40	570 A	750 **		550
	600 A	530		590
	530 A	450		
	270 B			
	670 A			
	700 C			
	550 A			
40 - 45	510 A	430		600
	650 A	740		510
	530 A	530		
	500 A			
	570 B			
45 - 50	450 A	470	680 * A	470
	480 C	510	560 A	
			640 * A	
50 - 55	510 A	1,200	630 A	600
	610 C	500	460 * A	620
		570		
55 - 60	320 A	570	460 C	
	510 C	620	650 * C	
	420 A		580 * A	
60 & OVER	400 A		700 * B	600 *
	510 A		470 * A	
	500 A			

BLOOD ZINC (UG/100 MLS.)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 12

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		540		180
		670		
25 - 30		940		350 *
		300		550
		110		
		220		
30 - 35	770 A	515	190 C	160
		270 **		
		300		
35 - 40	580 A	90 **		275
	165 A	450		120
	390 A	690		
	370 B			
	95 A			
	220 C			
	300 A			
40 - 45	150 A	520		320
	85 A	550		350
	80 A	370		
	600 A			
	1,100 B			
45 - 50	570 A	160	690 * A	590
	760 C	580	780 A	
			200 * A	
50 - 55	670 A	400	540 A	740
	800 C	560	440 * A	50
		240		
55 - 60	370 A	790	310 C	
	320 C	380	960 * C	
	200 A		1,000 * A	
60 & OVER	410 A		380 * B	700 *
	140 A		620 * A	
	230 A			

URINARY ZINC (UG/LITRE)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 13

Blood zinc - Ug/100 mls.

	Mean	Min	Max
Unexposed smokers	617	420	1300
Unexposed non-smokers	534	420	620
Exposed smokers	517	270	650
Exposed non-smokers	592	460	700

TABLE 5

No significant difference between groups.

Urinary zinc - Ug/litre

	Mean	Min	Max
Unexposed smokers	438	90	940
Unexposed non-smokers	365	50	740
Exposed smokers	408	80	1100
Exposed non-smokers	555	190	1000

TABLE 6

No significant difference between groups.

Cadmium

Blood and urine cadmium levels are shown in figure 14, page 90 and figure 15, page 91.

Blood cadmium (Ug/100 mls.) - very highly significant differences were shown between the groups ($p<0.001$). The combined exposed group had a higher mean than the combined unexposed group, e.g. .727 micrograms per 100 mls. compared with .129 micrograms per 100 mls. The mean, minimum and maximum for each group are shown in table 7, page 92.

However, when blood cadmium, as an index of years of exposure, was examined by calculating the correlation coefficient between these two variables, there was no significant correlation (table 8, page 92).

A contingency table, (table 9, page 93) based upon whether people in the combined exposed group had more than 15 years of exposure or not and whether people had 1.0 microgram per 100 mls or more of cadmium in their blood was formed. This suggests that there is some evidence that some people exposed to cadmium for more than 15 years are more likely to have blood cadmium in excess of 1 microgram per 100 mls than people exposed for shorter periods.

Urine Cadmium (Ug/litre)

Again there was highly significant differences between the groups ($p<0.01$) and the combined exposed mean 8.69 is higher than the mean for the combined unexposed group (1.79) (table 10, page 93). However, when a correlation coefficient between urine cadmium and years of exposure is formed there was no significant correlation. (Table 11, page 94).

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		0.3		nd.
		0.2		
25 - 30		0.5		<0.2 *
		nd.		nd.
		nd.		
		nd.		
30 - 35	0.3 A	0.2	0.2 C	0.2
		nd. **		
		0.2		
35 - 40	2.0 A	0.2 **		<0.2
	0.3 A	0.2		nd.
	0.7 A	0.2		
	0.2 B			
	0.5 A			
	<0.2 C			
	0.2 A			
40 - 45	2.3 A	nd.		nd.
	0.9 A	0.5		0.2
	0.5 A	0.2		
	0.9 A			
	nd. B			
45 - 50	0.7 A	0.2	<0.2 * A	nd.
	nd. C	0.2	1.1 A	
			0.4 * A	
50 - 55	0.3 A	nd.	1.1 A	0.2
	<0.2 C	nd.	0.3 * A	0.3
		<0.2		
55 - 60	2.0 A	0.2	0.2 C	
	0.2 C	0.2	0.2 * C	
	1.1 A		1.6 * A	
60 & OVER	2.6 A		nd. * B	<0.2 *
	1.6 A		0.9 * A	
	1.6 A			

BLOOD CADMIUM (UG/100 MLS.)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 14

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		0.6		4.2
		2.0		
25 - 30		4.8		11. *
		0.6		0.6
		1.2		
		0.3		
30 - 35	1.4 A	2.8	0.9 C	1.6
		1.9 **		
		0.8		
35 - 40	27 A	0.3 **		2.8
	6.0 A	3.2		0.8
	7.8 A	2.0		
	1.9 B			
	1.9 A			
	0.8 C			
	0.8 A			
40 - 45	18 A	0.8		3.7
	3.6 A	1.7		0.3
	4.2 A	1.7		
	15 A			
	0.8 B			
45 - 50	19 A	1.4	4.7 * A	nd.
	1.4 C	1.1	24 A	
			1.1 * A	
50 - 55	2.6 A	2.9	17 A	0.6
	0.8 C	0.3	3.2 * A	0.6
		1.1		
55 - 60	6.9 A	0.8	3.8 C	
	0.6 C	0.8	0.3 * C	
	7.5 A		21 * A	
60 & OVER	28 A		1.4 * B	1.7 *
	13 A		29 * A	
	20 A			

URINARY CADMIUM (UG/LITRE)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 15

Blood Cadmium - (Ug/100 mls.)

	Mean	Min	Max
Unexposed smokers	0.159	0	0.5
Unexposed non-smokers	0.075	0	0.3
Exposed smokers	0.822	0	2.6
Exposed non-smokers	0.527	0	1.6

TABLE 7

Highly significant differences between groups ($p < 0.001$).

Blood Cadmium and Years of Exposure

	r	d.f.
Unexposed smokers	0.0095^{ns}	20
Unexposed non-smokers	0.4306^{ns}	10
Exposed smokers	0.3196^{ns}	21
Exposed non-smokers	0.1997^{ns}	9
All groups combined	0.1926^{ns}	63
Exposed groups combined	0.2850^{ns}	31

TABLE 8

NOTE - ns means "not significantly different"

d.f = degrees of freedom.

Blood Cadmium and Years of Exposure

		Blood Cadmium ≤1.0	Blood Cadmium >1.0	
Years of Exposure	<15	16	3	19
	>15	8	7	15
		24	10	34

$X_1^2 = 3.849^*$ ($p<0.05$; just significant)

TABLE 9

Urine Cadmium - (Ug/litre)

	Mean	Min	Max
Unexposed smokers	1.50	0.3	4.8
Unexposed non-smokers	2.33	0	11.0
Exposed smokers	8.22	0.6	28.0
Exposed non-smokers	9.67	0.3	29.0

TABLE 10

Highly significant differences between the groups ($p<0.01$).

Urine Cadmium and Years of Exposure

	r	d.f.
Unexposed smokers	-0.2035^{ns}	20
Unexposed non-smokers	-0.3984^{ns}	10
Exposed smokers	0.3285^{ns}	21
Exposed non-smokers	0.2664^{ns}	9
Exposed group combined	0.3045^{ns}	31

TABLE 11

NOTE - d.f. means degrees of freedom

ns = not significant

Urine Cadmium and Years of exposure

		Urine Cadmium ≤5	>5	
Years of Exposure	<15	13	6	19
	>15	6	9	15
		19	15	34

$X_1^2 = 2.746^{ns}$

TABLE 12

Blood Cadmium - years of smoking

	r.	d.f.
Unexposed smokers	-0.1199^{ns}	20
Exposed smokers	0.2506^{ns}	21

TABLE 13

No significant relationship

Blood and Urine - Cadmium and Zinc

The following correlation coefficients have been calculated:

d.f. = 66 All subjects

	Urine Cd	Urine Zn.	Blood Cd.	Blood Zn.
Urine Cadmium	1.0			
Urine Zinc	0.13	1.0		
Blood Cadmium	0.80***	-0.02	1.0	
Blood Zinc	-0.21	-0.11	-0.24*	1.0

* = $p<0.05$; *** = $p<0.001$

TABLE 14

d.f. = 32 Using only the combined exposed group

	Urine Cd.	Urine Zn.	Blood Cd.	Blood Zn.
Urine Cadmium	1.0			
Urine Zinc	0.13	1.0		
Blood Cadmium	0.78***	-0.14	1.0	
Blood Zinc	-0.26	0.03	-0.37*	1.0

* = $p<0.05$; *** = $p<0.001$

TABLE 15

Examination of a contingency table based upon urine cadmium greater than 5 micrograms per litre and greater than 15 years exposure showed no significant difference. (Table 12, page 93).

Blood Cadmium and Years of Smoking

Table 13, page 94 shows the correlation coefficients based on years of smoking and blood cadmium levels. From these results there is no evidence of a relationship between the two.

Body Burden of Zinc and Cadmium and Mercury

Zinc and cadmium are closely related in nature and in body metabolism. Although blood and urine zinc levels were not significantly different in the control and exposed groups, correlation coefficients between the blood and urine levels of these two metals were formed (table 14, page 95 and table 15, page 95). These reveal a high positive correlation between blood and urine cadmium levels and a significant negative correlation between blood zinc and cadmium levels.

There was no significant correlation between blood and urinary zinc or urinary cadmium and zinc.

Statistically, therefore, body burden of mercury and zinc as measured by blood and urinary levels would not affect any findings.

Blood Lead

The higher blood lead levels found in the exposed group should not, on todays accepted knowledge of lead and body metabolism, affect any of the

clinical or biochemical parameters measured. This will be examined further in a later chapter, (chapter 15).

Conclusions

(1) Body content of mercury, zinc and lead were not significantly different between the exposed and control groups and therefore should not affect any findings.

(2) Blood cadmium and urinary cadmium measurements were not good markers of body burden.

Discussion

It has been shown in previous chapters that cadmium accumulates in the human body over the life span. The body content is, because of a low and seemingly fixed excretion rate unrelated to intake, a good index of total exposure. Several workers have constructed mathematical biological models which relate total cadmium accumulation to exposure from all sources. There is no general agreement as to the exact body burden of a 70 year old man. However, figures produced by these models range from 15 to 120 mgm. It has also been pointed out in earlier chapters that daily exposure is increasing and there is a critical renal concentration beyond which permanent renal damage occurs. There are also differing figures suggested for this critical figure by other models.

Comparison of atmospheric levels and urinary excretion figures from this survey and those performed elsewhere (chapter 7) would suggest a lower body burden for my group than most other surveyed. This group of exposed workers, therefore, would appear to be representative of a middle group

between those environmentally exposed to low body burden and those occupationally exposed to high levels. The survey should, therefore, provide useful information on just how much cadmium can be tolerated before adverse effects appear. This, in turn, could help in deciding controls for environmental contamination.

It was not possible to attempt to answer the question posed by many investigators - "does zinc have a protective effect against cadmium?". One can only speculate on the importance, if any, of the fact that in this small group of workers exposed to both zinc and cadmium there is a negative correlation between the blood levels of both metals.

CHAPTER 9

Cadmium and General Health

The Medical Examination -

The questionnaire and physical examination revealed a wide variety of medical and surgical conditions amongst the members of each sub-group of exposed and control workers. There was no common pattern to either group or sub-groups or group difference except in the area of respiratory function - vide chapter 10. Figure 16, page 100 illustrates the findings of previous or existing medical conditions either treated or receiving treatment.

The medical questionnaire was designed particularly to elicit symptoms referable to organs or systems particularly involved in the metabolism of cadmium. There was no difference in symptomatology between the control group and the exposed group in answers to questions referable to:-

(a) The alimentary system including liver and pancreas
(b) Genito-urinary system
(c) The skin
(d) The central nervous system
(e) The cardiovascular system

Participants in the survey were asked to judge their own sense of smell. Six exposed workers thought their sense of smell was poor and five controls did likewise.

All participants were also asked if they had bone or joint pain. Those who answered yes to this question were asked further details at the time

	EXPOSED	CONTROL
Hypertension	2	5
Coronary artery disease	1	3 (Confirmed) 1 (Not confirmed)
Renal calculus	2 (diagnosed and treated before exposure to cadmium in both cases.)	0
Prostatomegaly	2	0
Papilloma of the bladder	0	1
Peptic ulcer	4	3
Hiatus-hernia	1	2
Acute pancreatitis	1	0
Gout	3	1
Diabetes	1	0
Chronic airways disease including asthma	2	2
Silicosis	1 (diagnosed and treated before exposure to cadmium).	

FIGURE 16

Previous or existing medical conditions either treated or receiving treatment.

of the examination. In many cases a cause was found, e.g. post traumatic, gout, spondylitis etc. In the case of eleven exposed workers no obvious cause for the bone pain was found, and thirteen controls also had inexplicable bone pain.

At the time of the medical examination all participants were questioned about their sexual function. There were no questions referable to this in the questionnaire. One exposed worker had been investigated for infertility. No worker, either in the control group or the exposed group had sought treatment for any sexual problem and no worker in either group had expectations of a higher than his present sexual function.

The Clinical Examination

A wide variety of minor and major physical abnormalities were found in both groups. Some were to be expected in view of the previous or existing medical history. Some however, were unmasked. Again, as with symptoms, there was no common pattern to the group or group differences.

1. Skin - No skin tumors, ulcers, rashes or pigmentary changes were found in any individual. Some members of both groups had mild acne and the usual minor skin conditions e.g. warts, moles etc.

2. Nasal mucosa and sputum - One member of the exposed group had a perforated nasal septum and another had a very crusted nasal mucosa. With these two exceptions, no difference was noted between the exposed and the control group.

3. Teeth and gums - No pigmentary changes were noted in the gums of any individual in any group. No staining or colouring on the teeth was noticed in either the exposed or the control group.

   Four members of the group of exposed smokers had considerable dental caries or gingivitis. No major dental abnormalities were noted in the control group or the group of exposed non-smokers.

4. Cardio vascular system - One man in the sixty to sixty five age group, an exposed smoker, had moderate peripheral vascular disease. No other cases of unknown arterial disease were found. Excluding those known to have coronary artery disease, the only electrocardiographic abnormalities found was one case of right bundle branch block in the exposed group and ventricular extrasystoles in three members of the exposed group and three members of the control group.

Effects of acute exposure to high concentration

Many workers in the cadmium plant could remember occasions when high concentration of either dust or fumes caused them to stop work temporarily until the working environment returned to normal. Four workers suffered anorexia, nausea, dyspnoea and cough and subsequent night sweats after these episodes. None found it necessary to seek medical attention and all were back to work at the next shift.

One worker with grade 4 dyspnoea, though able to return to work immediately after acute exposure, believed his dyspnoea was worse for three to four

days afterwards. He is receiving treatment for obstructive airways disease.

The "time lost" records for each exposed worker in the cadmium plant were examined. These records show time lost through sickness, with diagnoses, injury, or without reason since he started work. The mean time lost for this group of 24 from sickness or unknown reason is 20 days with a minimum of no days to a maximum of ninety four. Similar records are not available for the control group but plant workers elsewhere have as much, or more, time off for non injury reasons than this group of exposed workers.

Because the work force in the cadmium plant has always been small in number and the turnover small also compared with other Company activities it was possible to obtain a considerable amount of information on the health of ex fellow workers from present day long term workers at the time of their questionnaire interview. An attempt at a retrospective survey of the health of workers who had left the cadmium plant was made using Company records supplemented by the memories of the long term present day workers. As Company records did not allow an accurate analysis and human memory is fallible, this survey could not produce data on which scientific or statistical conclusions could be based. The following is a summary of the material that this small survey produced.

Deaths in Tasmania related to Cadmium

The Deputy Commonwealth Statistician, who is responsible for recording and coding the causes of death in Tasmania, was unable to retrieve material which would precisely link cadmium with the cause of death.

However, one of the coders in the Department, whose experience spanned twenty five years, was certain that he never saw a death certificate with any mention of cadmium. Other coders with shorter experience agreed with this.

Mortality amongst ex workers

A sample of 22 new names of ex cadmium workers who had left Company employment in the last twelve years was given to the Registrar of Births, Deaths and Marriages. Only 3 of these 22 were registered as deaths. All had died from cardio-vascular disease.

Of other ex workers known to be dead to their fellow workers, only one was known to have a malignancy; carcinoma of the lung. According to their fellow workers most appeared to have died from cardiovascular disease.

Morbidity amongst ex workers

(a) An insignificant number of men had to be either retired or transferred from the cadmium plant as the result of the findings made at the compulsory biennial medical examination over the years. No specific cause could be identified for these.

(b) Long term ex workers are invited back to the Company for a reunion annually. According to present day workers, many ex workers enjoyed, or still are enjoying a long retirement.

(c) The long term workers, particularly, believe that renal disease,

malignancy, serious lung disease had not figured prominently amongst the maladies of the ex colleagues. They anticipate a long and reasonably health retirement basing their expectations on the experiences of their ex colleagues.

Conclusion

No individual symptom or pattern of symptoms or signs could be identified as due to working with cadmium.

Discussion

Several surveys (chapter 5) have suggested that vague ill health - insomnia, anorexia and fatigue are the lot of a worker exposed to cadmium. This survey found no evidence of this. No worker expressed any desire for a different job nor any reluctance to resume after a holiday.

Company records indicate there is little labour turnover in the cadmium plant where most exposure occurs. This is confirmed by analysis of the length of service in the plant, (figure 6, page 76). This would suggest that both, on an individual and collective basis, there is no employee recognition of a health problem working with cadmium.

CHAPTER 10

Cadmium and the Respiratory System

The questionnaire sought information on the following symptoms:-

(a) cough and sputum production

(b) exertional dyspnoea

(c) wheeze

(d) frequency of colds or bronchitis

At the time of medical examination the subjective symptoms were graded according to the patients estimate of severity.

Cough with sputum production - (Figure 17, page107)

This was graded roughly according to the daily volume of sputum. Eighteen members of the exposed group complained of cough and sputum, fourteen were smokers and four non-smokers. Thirteen were graded as grade one, one grade two and four grade three. Twelve members of the control group, nine smokers and three non-smokers complained of these symptoms, eleven were graded one and one was graded two. Table 16, page109compares the findings of the various groups.

Exertional dyspnoea -(Figure 18, page 108)

This was graded in accordance with the Medical Research Council formula. Twenty two exposed workers complained of dyspnoea; six grade one, thirteen grade two, two grade three and one grade four. Eleven controls complained of dyspnoea, eight grade one, three grade two. All those graded three or

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		-		-
		1		
25 - 30		1		- *
		-		-
		1		
		-		
30 - 35	- A	-	- C	2
		- **		
		-		
35 - 40	1 A	- **		1
	1 A	-		-
	- A	1		
	1 B			
	- A			
	- C			
	- A			
40 - 45	2 A	-		-
	1 A	1		-
	1 A	1		
	3 A			
	1 B			
45 - 50	- A	1	1 * A	1
	1 C	1	3 A	
			- * A	
50 - 55	1 A	1	- A	-
	1 C	-	- * A	-
		-		
55 - 60	1 A	-	1 C	
	- C	-	- * C	
	- A		1 * A	
60 & OVER	3 A		- * B	- *
	- A		- * A	
	3 A			

COUGH WITH SPUTUM PRODUCTION

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 17

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		0		0
		1		
25 - 30		0		0 *
		0		0
		0		
		0		
30 - 35	1 A	0	0 C	1
		0 **		
		0		
35 - 40	0 A	0 **		1
	0 A	0		0
	2 A	1		
	1 B			
	1 A			
	0 C			
	1 A			
40 - 45	3 A	0		0
	1 A	0		0
	2 A	0		
	2 A			
	0 B			
45 - 50	0 A	0	0 * A	1
	1 C	0	2 A	
			0 * A	
50 - 55	2 A	2	2 A	2
	0 C	1	2 * A	1
		1		
55 - 60	3 A	0	0 C	
	2 C	0	2 * C	
	0 A		2 * A	
60 & OVER	4 A		2 * B	2 *
	2 A		0 * A	
	2 A			

EXERTIONAL DYSPNOEA

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 18

Cough with Sputum Production

	Mean	Min	Max
Unexposed smokers	0.409	0	1
Unexposed non-smokers	0.333	0	2
Exposed smokers	0.913	0	3
Exposed non-smokers	0.545	0	3

TABLE 16

Groups are not significantly different, although the means for the exposed group of workers are somewhat higher.

Exertional Dyspnoea

	Mean	Min	Max
Unexposed smokers	0.27	0	2
Unexposed non-smokers	0.67	0	2
Exposed smokers	1.30	0	4
Exposed non-smokers	1.09	0	2

TABLE 17

Highly significant differences between the groups ($p<0.01$). The combined exposed group of thirty four had a mean score of 1.23 where as the unexposed group of thirty four people had a mean score of 0.41. There was no significant difference due to smoking.

below did not feel seriously inconvenienced by dyspnoea and were able to work and enjoy recreational activity without any distress. One man graded four was inconvenienced by his dyspnoea, both at work and at leisure. Table 17, page 109 shows the statistical analysis of this symptom.

Respiratory Infection - (Figure 19, page 111)

These were graded according to the number of attacks per year. Grade 0, one or two attacks, grade one, three attacks, grade two, four attacks per year. Twelve exposed workers, ten smokers and two non-smokers were graded one, whereas, three control workers, two smokers and one non-smoker were graded one. Table 18, page 113 compares the findings of the group.

Wheeze - (Figure 20, page 112)

This was graded according to the estimate of severity by the individual. Grade one - wheeze on moderate exertion, grade two - wheeze at rest. Thirteen of the exposed workers complained of wheeze, eleven smokers, two non-smokers, three controls had this symptom, two smokers, one non-smoker. Table 19, page 113 analyses this symptom.

Respiratory Function - (Figures 21 and 22, pages 114 and 115)

Each applicant's vital capacity and forced expiratory volume at one second was tested using a Pulmotest spirometer until there was 5% or less difference between the two highest readings. These measurements were repeated after bronchodilation with salbutamol inhalation. The vital capacity is expressed as a percentage of the predicted vital capacity as expected from height and age. A figure of 80% or less for this result is considered abnormal.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		-		-
		-		
		-		- *
25 - 30		-		-
		-		
		-		
	- A	- **	- C	-
30 - 35		-		
		-		
	- A	- **		-
35 - 40	- A	-		-
	- A	1		
	- B			
	- A			
	- C			
	- A			
	1 A	-		-
40 - 45	- A	-		-
	1 A	-		
	1 A			
	1 B			
	- A	-	- * A	1
45 - 50	1 C	-	- A	
			- * A	
	1 A	1	- A	-
50 - 55	1 C	-	- * A	-
		-		
	1 A	-	- C	
55 - 60	- C	-	- * C	
	- A		- * A	
	1 A		- * B	- *
60 & OVER	- A		- * A	
	1 A			

RESPIRATORY INFECTION PER ANNUM

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 19

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		-		-
		-		
25 - 30		-		- *
		-		-
		-		
		-		
30 - 35	- A	-	- C	-
		- **		
		-		
35 - 40	1 A	- **		-
	1 A	-		-
	- A	1		
	- B			
	- A			
	- C			
	- A			
40 - 45	1 A	-		-
	1 A	-		-
	1 A	-		
	1 A			
	- B			
45 - 50	- A	-	- * A	1
	1 C	-	1 A	
			- * A	
50 - 55	1 A	1	- A	-
	- C	-	- * A	-
		-		
55 - 60	1 A	-	- C	
	- C	-	- * C	
	- A		1 * A	
60 & OVER	1 A		- * B	- *
	- A		- * A	
	2 A			

WHEEZE

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 20

Respiratory Infection

	Mean	Min	Max
Unexposed smokers	0.091	0	1
Unexposed non-smokers	0.083	0	1
Exposed smokers	0.435	0	1
Exposed non-smokers	0.182	0	1

TABLE 18

Significant differences between the groups ($p<0.05$). The exposed smokers have a higher mean than the two unexposed groups.

Wheeze

	Mean	Min	Max
Unexposed smokers	0.091	0	1
Unexposed non-smokers	0.083	0	1
Exposed smokers	0.522	0	2
Exposed non-smokers	0.182	0	1

TABLE 19

Highly significant differences between groups $p<0.01$. The exposed smokers have a higher mean than the unexposed workers.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		110%		102%
		84%		
		98%		104% *
25 - 30		88.6%		100%
		97.1%		
		88.6%		
	84% A	90%	82% C	97%
30 - 35		105% **		
		113%		
	98.8% A	97.5% **		125%
35 - 40	97% A	92%		104%
	104% A	104%		
	87% B			
	86% A			
	110% C			
	105% A			
	88% A	90%		105%
40 - 45	115% A	120%		108%
	109.3% A	97%		
	92% A			
	105% B			
	86% A	113%	78% * A	125%
45 - 50	86% C	126%	83%	
			87% * A	
	108% A	94%	86% A	105%
50 - 55	107% C	100%	82% * A	102%
		86%		
	84% A	63%	132% C	
55 - 60	111% C	91%	88% * C	
	105% A		113.8% * A	
	72% A		108% * B	102% *
60 & OVER	92% A		111% * A	
	100% A			

VITAL CAPACITY

PREDICTED VC

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 21

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		84%		88%
		78%		
25 - 30		100%		82% *
		92%		80%
		86%		
		90%		
30 - 35	86% A	84% **	93.75% C	81%
		42%		
		46%		
35 - 40	75% A	96.9% **		80%
	67.5% A	68%		84%
	69.8% A	83%		
	44% B			
	93% A			
	77% C			
	78% A			
40 - 45	50% A	73.6%		82%
	74% A	74%		83%
	75% A	94%		
	80% A			
	66.6% B			
45 - 50	81% A	81%	73% * A	72%
	75% C	71%	83% A	
			84% * A	
50 - 55	75% A	73%	87% A	72.92%
	61% C	78.9%	71% * A	67.57%
		80.6%		
55 - 60	71% A	58%	64% C	
	94% C	96%	52% * C	
	71% A		61% * A	
60 & OVER	38.5% A		59% * B	75% *
	40% A		69% * A	
	68% A			

FEV_1

VITAL CAPACITY

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 22

Two members of the exposed group, one a smoker and one a non-smoker were below this figure while one member of the control group, a smoker, did not reach this figure. The forced expiratory volume at one second was expressed at a percentage of the actual vital capacity. A figure of 75% or lower for this is considered abnormal Nineteen exposed workers, twelve smokers and seven non-smokers failed to reach this figure whilst eleven of the unexposed workers, eight smokers and three non-smokers also did not reach this figure.

There was no correlation between the abnormal respiratory function test findings and symptoms. Some with marked or moderate reduction in the $FEV_1/VC\%$ had no complaints of dyspnoea or wheeze whilst others who did complain had no reduction in this figure.

Statistically there is no significant difference between the exposed and the control group when respiratory function was measured objectively. - Tables 20 and 21, page 117.

On clinical examination ten exposed workers, eight smokers, two non-smokers exhibited rhonci in the lung fields on auscultation. Two members of the control group, (both smokers) did also. This clinical sign is not considered to be of any significance in this study.

Radiology

1. Chest Film -

Each participant in the survey has had a chest x-ray every two years. This is a compulsory requirement under an act governing employment in the mining

VC/Pred VC%

	Mean	Min	Max
Unexposed smokers	97.6	63	126
Unexposed non-smokers	106.6	97	125
Exposed smokers	97.0	72	115
Exposed non-smokers	95.5	78	132

TABLE 20

Groups not significantly different.

FEV_1/VC%

	Mean	Min	Max
Unexposed smokers	78.6	42	100
Unexposed non-smokers	79.0	68	88
Exposed smokers	70.0	39	94
Exposed non-smokers	72.4	52	94

TABLE 21

Groups not significantly different although mean for the combined exposed group (70.78) is somewhat lower than the mean for the combined unexposed group (78.74) Statistically there is no significant difference between the exposed and the control group when respiratory function was measured objectively.

industry in Tasmania. These films are examined by the same radiologist who reports either linear or nodular abnormalities suggestive of a pneumoconiosis or progress, or otherwise, of any changes notified previously. Only one exposed worker had changes consistent with silicosis and these changes were present on entry into the workforce. These were acquired whilst mining in Europe. Apart from this worker, no radiological abnormalities were reported in either group.

Conclusion

Individuals working with cadmium are more likely to complain of dyspnoea, cough, repeated respiratory infections and wheeze than non exposed individuals.

Although these workers had more respiratory symptoms than the non exposed there were no clinical signs or groups of signs or changes in simple measurements of respiratory function that could be definitely ascribed to cadmium effect.

Discussion

The literature (vide chapter 5) contains many surveys of respiratory function and disease of cadmium workers. Although some, like this one, failed to find objective evidence of a pulmonary effect of cadmium it is generally accepted that chronic airways disease with significant loss of function is produced by this metal. The unresolved questions are just how much, in what form and for how long cadmium must be present to have an

effect. Most Western countries accept a threshold limit value of 200 Ug/ cubic metre of dust and 100 Ug/cubic metre of fume. Some workers, e.g. Lauwerys (65) believes these figures should be halved. If workers are to avoid subjective symptoms this study indicated that a figure below 30 Ug/cubic metre of dust should be the aim of the occupational hygienist.

It was not possible to ascertain the effect of intermittent exposure on symptoms as there are no employees whose job provides a rotation through the cadmium contaminated plants and elsewhere. It would be of interest and value to study the effects of job rotation on those workers who do have symptoms. I have suggested this to the Company but there are problems to be overcome, e.g. job training, inter union co-operation, team variation, etc.

Most employees when questioned about their symptoms after an absence from exposure for holidays did not appear to notice any change. A study of pre and past holiday symptoms and signs would provide evidence of the health value of job rotation.

CHAPTER 11

Cadmium and Blood Pressure

Blood pressure was recorded standing and after being recumbent for a quarter of an hour. Using the figure of 140 on 90 as the upper limit of normal for any age group, fourteen members of the exposed group had an elevated blood pressure not already diagnosed compared with thirteen members of the control group - Figure 23, page 122. Statistical analysis of both the systolic and diastolic pressures is shown in tables 22 and 23, page 123.

Conclusion

There is no relationship between body burden of cadmium and blood pressure levels in exposed workers.

Discussion

This is an important and significant finding. Several workers, e.g. Schroeder (71), Carrol (70), have linked hypertensive disease to environmental cadmium - (Chapter 5). Morgan, (73) and Hammer (74) have produced evidence refuting such a link. Many advocates with both medical and non medical backgrounds frequently use the alleged association between the two as one of the fundamental reasons for stricter controls on environmental cadmium. The media also portray the linkage as an established fact. The public in general as a consequence now seem to believe that there is a cause and effect relationship between the two.

It has been suggested that the occupationally exposed are protected from hypertension by the concomitant exposure to zinc. If blood and urinary zinc levels can reflect body burden of zinc this would not appear to be the case in the groups of workers for there is no difference between the exposed and controls. None of the surveys recorded in chapter 5 revealed any suggested link between cadmium and hypertension. Many involved workers who were exposed to cadmium only so there could be no suggestion that occupationally acquired zinc might be a protective. Hypertension is frequently associated with chronic renal disease. Cadmium may produce chronic renal disease. In chapter 12 the results of renal function studies will be analysed. No cases of chronic renal disease were found.

There was no correlation between blood pressure and years exposed. If there is a relationship between cadmium and hypertension there is no evidence from this survey of a direct dose or an increasing dose effect. However, the possibility of a relationship between the presence of cadmium in a sensitive individual and hypertension is not negated by this survey. This sensitivity could be based on individual enzyme structual differences, differing immunological complexes or protective actions by other substances in trace proportions. Environmental cadmium per se is not likely to be a cause of hypertension. Therefore other factors must also be involved.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		140/80		140/80
		170/80		
25 - 30		160/95		150/100 *
		130/80		130/75
		150/90		
		130/80		
30 - 35	130/80 A	170/90	140/85 C	150/100
		120/85 **		
		140/85		
35 - 40	150/100 A	140/75 **		150/100
	140/90 A	140/90		130/85
	180/80 A	190/100		
	130/80 B			
	150/80 A			
	140/85 C			
	130/85 A			
40 - 45	190/100 A	140/100		120/80
	120/85 A	130/ 80		160/100
	140/85 A	110/80		
	130/85 A			
	160/90 B			
45 - 50	140/95 A	130/90	140/100* A	140/100
	130/80 C	120/90	170/115 A	
			150/85 * A	
50 - 55	150/110 A	140/85	130/80 A	150/95
	130/80 C	130/80	120/80 * A	140/90
		110/70		
55 - 60	160/90 A	140/90	170/100 C	140/95 *
	130/90 C	200/110	150/80 * C	
	130/75 A		180/105 * A	
60 & OVER	140/85 A		*190/90 * B	
	180/90 A		180/90 * A	
	130/80 A			

HIGHEST BP READING

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 23

Blood Pressure (Sys) - mm Hg.

	Mean	Min	Max
Unexposed smokers	142.3	110	200
Unexposed non-smokers	141.7	120	160
Exposed smokers	143.9	120	190
Exposed non-smokers	156.4	120	190

TABLE 22

Groups not significantly different.

Blood Pressure (Dias) - mm Hg.

	Mean	Min	Max
Unexposed smokers	86.4	70	110
Unexposed non-smokers	91.5	75	100
Exposed smokers	86.8	75	110
Exposed non-smokers	92.1	80	115

TABLE 23

Groups not significantly different.

CHAPTER 12

Cadmium and Renal Function

Cadmium accumulates in the kidney and its accumulation there contributes significantly to body burden. A raised body burden of cadmium, in both experimental animal studies and observations on humans occupationally or environmentally exposed, is frequently associated with impaired renal function particularly tubular function. (Vide chapters 3, 4, 5, 6)

In this study the following investigations were used to assess various aspects of renal function.

1. Tests for proteinuria
   (a) Bililabstix (Ames)
   (b) Boiling fresh urine followed by the addition of trichloracetic acid.

Only two exposed workers showed proteinuria, with both the Ames Bililabstix test and boiling followed by the addition of acetic acid. These men were exposed to low concentrations of cadmium outside the cadmium plant itself. One had a 24 hour excretion of 0.3 micrograms per litre whilst the other had an excretion of 1.4 micrograms per litre. No proteinuria was detected in the urine of men who had a high (greater than 20 micrograms per litre) excretion of cadmium. (Figure 24, page 125)

2. Microscopy of Urine

Red cells in significant numbers were found in the urine of two exposed workers. No obvious clinical explanation was found to account for these.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		nil		nil
		nil		
25 - 30		nil		nil *
		nil		nil
		nil		
		nil		
30 - 35	nil A	nil	nil C	nil
		nil **		
		nil		
35 - 40	nil A	nil **		nil
	nil A	nil		nil
	nil A	nil		
	nil B			
	nil A			
	nil C			
	nil A			
40 - 45	nil A	nil		nil
	nil A	nil		nil
	nil A	nil		
	nil A			
	nil B			
45 - 50	nil A	nil	nil * A	nil
	nil C	nil	nil A	
			nil * A	
50 - 55	nil A	nil	nil A	nil
	nil C	nil	nil * A	nil
		nil		
55 - 60	nil A	nil	nil C	
	nil C	nil	60mgm*C	
	nil A		nil *A	
60 & OVER	nil A		50mgm*B	nil *
	nil A		nil *A	
	nil A			

PROTEINURIA

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 24

in other workers from both the exposed and control groups an occasional red cell was reported. No worker showed a significant leucocyte count, epithelial cells or casts and all urines were negative on culture. (Figures 25, 26, 27, 28, pages 127, 128, 128 and 130).

3. Urinary pH - (Figure 29, page 131)

The mean, mimimum and maximum pH values are shown in table 24, page 133. There is no significant difference between the groups.

4. Blood Urea - (mgm/100 ml. Normal range 20 - 40)

Five exposed workers, three smokers and two non smokers exceeded the normal level. One control had a raised level. (Figure 30, page 132).

Statistically, (table 25, page 133) there was a significant difference between the groups. The combined exposed group had a higher mean (35.35) than the combined unexposed group (30.82). The clinical significance of this finding will be considered in a later discussion.

5. Blood Creatinine - (mgm/100 ml. Normal 0.8 - 1.3)

The groups were not significantly different, although the mean for the combined exposed group (1.156) is somewhat higher than the mean for the combined unexposed group (1.076). (Figure 31, page 134 and table 26, page 140).

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		-		-
		-		
		3		- *
25 - 30		-		-
		-		
		-		
	- A	occas.	- C	-
30 - 35		- **		
		-		
	- A	- **		-
35 - 40	- A	-		-
	>100 A	-		
	- B			
	- A			
	- C			
	- A			
	20 A	-		-
40 - 45	- A	-		-
	- A	4		
	- A			
	- B			
	- A	-	- * A	-
45 - 50	2 C	-	- A	
			- * A	
	- A	-	- A	-
50 - 55	- A	-	- * A	-
		-		
	- A	-	- C	
55 - 60	- C	3	- * C	
	1 A		- * A	
	- A		Occas.* B	- *
60 & OVER	1 A		- * A	
	- A			

RED BLOOD CELLS IN URINE

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 25

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		-		-
		-		
25 - 30		occas.		occas. *
		-		-
		occas.		
		-		
30 - 35	occas. A	15	occas. C	occas.
		- **		
		-		
35 - 40	occas. A	- **		-
	- A	-		-
	- A	-		
	- B			
	- A			
	- C			
	- A			
40 - 45	occas. A	occas.		-
	- A	-		-
	occas. A	occas.		
	- A			
	- B			
45 - 50	1 A	1	- * A	-
	occas. C	-	- A	
			1 * A	
50 - 55	2 A	-	- A	-
	occas. C	-	- * A	-
		-		
55 - 60	10 A	occas.	occas. C	
	- C	occas.	- * C	
	2 A		- * A	
60 & OVER	- A		- * B	- *
	occas. A		- * A	
	- A			

LEUCOCYTES IN URINE

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 26

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		-		-
		-		
25 - 30		occas.		- *
		-		-
		-		
		occas.		
30 - 35	occas. A	occas.	- C	-
		- **		
		-		
35 - 40	- A	- **		-
	- A	-		-
	- A	-		
	- B			
	- A			
	- C			
	- A			
40 - 45	- A	-		-
	- A	occas.		-
	occas. A	occas.		
	- A			
	- B			
45 - 50	1 A	occas.	- * A	-
	- C	1	- A	
			occas.* A	
50 - 55	- A	-	- A	occas.
	occas. C	-	- * A	-
		-		
55 - 60	- A	occas.	- C	
	- C	-	- * C	
	occas. A		- * A	
60 & OVER	occas. A		occas.* B	- *
	occas. A		- A	
	- A			

EPITHELIAL CELLS IN URINE

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 27

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		neg		neg
		neg		
25 - 30		neg		neg *
		neg		neg
		neg		
		neg		
30 - 35	neg A	neg	neg C	neg
		neg **		
		neg		
35 - 40	neg A	neg **		neg
	neg A	neg		neg
	neg A	neg		
	- B			
	neg A			
	neg C			
	neg A			
40 - 45	neg A	neg		neg
	neg A	neg		neg
	neg A	neg		
	neg A			
	neg B			
45 - 50	neg A	neg	neg * A	neg
	neg C	neg	neg A	
			neg * A	
50 - 55	neg A	neg	neg A	neg
	neg C	neg	neg * A	neg
		neg		
55 - 60	neg A	neg	neg C	
	neg C	neg	neg * C	
	neg A		neg * A	
60 & OVER	neg A		neg * B	neg *
	neg A		neg * A	
	neg A			

CULTURE OF URINE

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 28

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		6.8		6.6
		5.3		
25 - 30		5.6		5.4 *
		5.7		5.6
		6.6		
		5.6		
30 - 35	6.9 A	6.2	6.3 C	6.7
		5.2 **		
		5.9		
35 - 40	7.5 A	6.2 **		6.7
	5.2 A	8.1		5.4
	6.4 A	6.6		
	5.4 B			
	6.0 A			
	5.4 C			
	6.0 A			
40 - 45	7.8 A	6.0		6.1
	6.9 A	5.8		-
	5.4 A	5.4		
	5.0 A			
	5.4 B			
45 - 50	5.6 A	5.6	5.2 * A	6.6
	5.3 C	7.7	5.8 A	
			7.0 * A	
50 - 55	5.4 A	5.2	- A	6.5
	5.5 C	6.2	- * A	6.5
		5.0		
55 - 60	5.4 A	6.6	5.3 C	
	5.4 C	5.3	5.4 * C	
	5.5 A		5.3 * A	
60 & OVER	6.3 A		5.5 * B	- *
	5.9 A		6.3 * A	
	6.8 A			

URINARY pH

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 29

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		36		29
		36		
25 - 30		30		33 *
		26		30
		29		
		30		
30 - 35	37 A	25	34 C	33
		29 **		
		21		
35 - 40	31 A	38 **		20
	27 A	37		28
	31 A	24		
	25 B			
	31 A			
	34 C			
	25 A			
40 - 45	22 A	25		33
	24 A	35		34
	50 A	42		
	36 A			
	39 B			
45 - 50	37 A	28	35 * A	28
	35 C	36	22 A	
			47 * A	
50 - 55	47 A	38	29 A	29
	40 C	28	36 * A	36
		33		
55 - 60	40 A	23	35 C	
	26 C	35	36 * C	
	33 A		62 * A	
60 & OVER	35 A		39 * B	31 *
	47 A		37 * A	
	38 A			

BLOOD UREA

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 30

Urinary pH -

	n	Mean	Min	Max
Unexposed smokers	22	6.027	5.0	8.1
Unexposed non-smokers	10	6.210	5.4	6.6
Exposed smokers	23	5.930	5.0	7.8
Exposed non-smokers	9	5.790	5.2	7.0

TABLE 24

No significant difference between the groups.

Blood Urea -

	Mean	Min	Max
Unexposed smokers	31.09	21	42
Unexposed non-smokers	30.33	20	36
Exposed smokers	34.35	22	50
Exposed non-smokers	37.45	22	62

TABLE 25

Significant differences between groups ($p<0.05$). The combined exposed group has a higher mean (35.35) than the combined unexposed group (30.82).

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		1.20		0.9
		1.1		
25 - 30		1.0		1.1 *
		0.9		1.1
		1		
		1.10		
30 - 35	1.10 A	0.9	1.0 C	1.00
		1.0 **		
		0.8		
35 - 40	0.95 A	1.2 **		1.0
	1.1 A	1.2		1.05
	1.00 A	1.2		
	1.0 B			
	1.0 A			
	1.10 C			
	1.00 A			
40 - 45	0.9 A	1.0		1.1
	1.0 A	1.20		1.2
	1.50 A	1.30		
	1.20 A			
	1.20 B			
45 - 50	1.20 A	1.1	1.4 * A	1.0
	1.20 C	1.1	1.00 A	
			1.2 * A	
50 - 55	1.3 A	1.25	1.00 A	1.00
	1.0 C	1.0	0.9 * A	1.1
		1.1		
55 - 60	1.35 A	0.9	1.30 C	
	1.1 C	1.3	1.2 * C	
	0.9 A		1.5 * A	
60 & OVER	1.05 A		1.6 * B	1.10 *
	1.40 A		1.3 * A	
	1.2 A			

BLOOD CREATININE

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 31

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		1.73		1.4
		2.77		
		1.46		1.74 *
25 - 30		1.87		1.80
		1.75		
		1.58		
	2.09 A	1.16	2.0 C	1.11
30 - 35		1.98 **		
		1.90		
	1.15 A	1.62 **		1.57
35 - 40	0.89 A	2.00		1.17
	2.48 A	1.43		
	1.54 B			
	1.48 A			
	2.86 C			
	1.49 A			
	0.58 A	2.22		2.24
40 - 45	0.94 A	1.79		1.64
	0.92 A	1.69		
	1.92 A			
	2.10 B			
	3.22 A	2.00	1.92 * A	2.42
45 - 50	2.21 C	1.20	2.04 A	
			2.00 * A	
	1.70 A	2.15	1.83 A	1.64
50 - 55	2.46 C	1.58	1.85 * A	1.41
		1.74		
	2.40 A	1.47	2.42 C	
55 - 60	2.09 C	2.10	2.34 * C	
	1.38 A		2.15 * A	
	2.28 A		1.72 * B	2.0 *
60 & OVER	0.98 A		1.75 * A	
	1.57 A			

URINE CREATININE (GM/24 HR.)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 32

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		880		1,700
		1,750		
25 - 30		800		1,860 *
		850		1,060
		1,670		
		1,970		
30 - 35	960 A	1,700	2,500 C	2,030
		1,800 **		
		1,250		
35 - 40	1,050 A	2,050 **		920
	940 A	1,760		1,060
	1,380 A	1,170		
	770 B			
	2,550 A			
	1,950 C			
	1,460 A			
40 - 45	1,670 A	930		2,050
	3,600 A	1,700		830
	2,300 A	1,140		
	920 A			
	850 B			
45 - 50	1,840 A	1,910	920 * A	1,850
	1,170 C	1,330	950 A	
			1,620 * A	
50 - 55	1,480 A	1,670	1,410 A	1,080
	1,250 C	1,100	1,850 * A	3,000
		1,340		
55 - 60	950 A	900	1,240 C	
	1,280 C	1,800	1,650 * C	
	2,300 A		1,630 * A	
60 & OVER	940 A		2,100 * B	980 *
	1,440 A		870 * A	
	1,850 A			

24 HOUR VOLUME URINE (mls)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 33

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		0.61		1.18
		1.22		
25 - 30		0.56		1.29 *
		0.59		0.74
		1.16		
		1.37		
30 - 35	0.67 A	1.18	1.74 C	1.41
		1.25 **		
		0.87		
35 - 40	0.73 A	1.42 **		1.33
	0.65 A	1.22		0.74
	0.96 A	0.81		
	0.53 B			
	1.77 A			
	1.35 C			
	1.01 A			
40 - 45	1.16 A	0.65		1.42
	2.50 A	1.18		0.58
	1.60 A	0.79		
	0.64 A			
	0.59 B			
45 - 50	1.28 A	1.33	0.64 * A	1.28
	0.81 C	0.92	0.60 A	
			1.13 * A	
50 - 55	1.03 A	1.16	0.98 A	0.75
	0.87 C	0.76	1.28 * A	2.08
		0.93		
55 - 60	0.66 A	0.63	0.86 C	
	0.89 C	1.25	1.15 * C	
	1.60 A		1.13 * A	
60 & OVER	0.65 A		1.46 * B	0.68 *
	1.0 A		0.60 * A	
	1.28 A			

URINE (mls/min.)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 34

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		197.		86.47
		158.2		
		182.5		93.55 *
25 - 30		220.		169.
		104.7		
		80.2		
	217.7 A	68.23	80 C	54.67
30 - 35		110. **		
		152.		
	109.52 A	79.02 **		81.7
35 - 40	94. A	113.		110.37
	179. A	122.		
	200. B			
	58. A			
	146.6 C			
	102.5 A			
	34.73 A	238.		118.
40 - 45	26.1 A	105.29		260.
	40. A	148.		
	208.69 A			
	248. B			
	- A	104.7	208.69 * A	110
45 - 50	188. C	90.2	214.7 A	
			123.4 * A	
	114.86 A	128.7	129.78 A	151.85
50 - 55	196.8 C	143.6	100. * A	47
		129.		
	252.6 A	163.	195.16 C	
55 - 60	163.28 C	116.	141.8 * C	
	60. A		131.9 * A	
	242. A		81.90 * B	204.08 *
60 & OVER	68.05 A		201.1 * A	
	84.6 A			

URINE CREATININE (mg/100mls)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 35

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		100.		113.37
		175.		
25 - 30		101.38		109.85 *
		144.2		113.6
		121.53		
		99.74		
30 - 35	131.9 A	89.5	138.8 C	81.14
		137.5 **		
		164.9		
35 - 40	84.15 A	93.74**		108.45
	56.18 A	115.		71.3
	172. A	82.75		
	106.9 B			
	102.7 A			
	180. C			
	103.4 A			
40 - 45	44.75 A	154.		152.
	65.2 A	103.5		125.
	42.5 A	89.		
	111.1 A			
	122.1 B			
45 - 50	186 A	126.26	95.2 * A	168.
	127.8 C	75.7	141.66 A	
			115.74* A	
50 - 55	90.8 A	149.3	127. A	151.85
	110. C	109.1	142.7 * A	89.0
		109.7		
55 - 60	123.45 A	113.42	129.27 C	
	131.9 C	112.17	135.4 * C	
	106.48 A		99.53* A	
60 & OVER	150. A		149.3 * B	126.26 *
	48.6 A		93.48* A	
	90.85 A			

CREATININE CLEARANCE (mls/min)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 36

Blood Creatinine - (mgm/100cc . Normal 0.8 to 1.3 mgm /100 ml.)

	Mean	Min	Max
Unexposed smokers	1.086	0.8	1.3
Unexposed non-smokers	1.058	0.9	1.2
Exposed smokers	1.126	0.9	1.5
Exposed non-smokers	1.218	0.9	1.6

TABLE 26

Groups not significantly different, although the mean for the combined exposed group (1.156) is somewhat higher than the mean for the combined unexposed group (1.076).

Creatinine Clearance - (Normal value is 120 - 130 ml/min.)

	Mean	Min	Max
Unexposed smokers	116.7	75.7	175.0
Unexposed non-smokers	117.5	71.3	168.0
Exposed smokers	108.2	42.5	186.0
Exposed non-smokers	124.4	93.5	149.3

TABLE 27

No significant difference between the groups.

6. Creatinine Clearance - (expressed as mls/minute. Normal 120 - 130)

Figures 31, 32, 33, 34 and 35, pages 134 - 138 depict the survey data on which the creatinine clearances (figure 36, page 139) were determined.

Eighteen exposed workers had a value less than 120 mls/minute whilst twenty one control workers failed to reach this figure. As this test is generally regarded as one of the best if not the best indicator of glomerular function, several statistical exercises were carried out on the results.

Table 27, page 142 shows the mean, minimum and maximum figures for each group. There is no significant difference between these groups.

Table 28, page 142 is a contingency table considering clearances above and below 120 mls/minute. Again there was no significant group difference.

In table 29, page 142 the calculation was repeated using 100 mls/minute as the cut off figure. Again there is no significant difference.

7. 24 Hour Amino Acid Nitrogen - (mgm/24 hours. Normal 200 - 700)

No worker in any group had an abnormal level. (Figure 37, page 143). Statistically (table 30, page 147) there is no difference between the groups.

8. Serum Electrolytes

Renal tubular function was also evaluated by determining serum sodium, potassium and chloride, (figures 37, 38, 39, pages 144 - 146). Tables 31, 32, 33, pages 147, 148 indicate there is no statistical difference between the groups.

	Creatinine Clearance	
	> 120	< 120
Unexposed smokers	8	14
Unexposed non smokers	5	7
Exposed smokers	9	14
Exposed non-smokers	7	4

U	13	21	34
E	16	18	34
	29	39	68

$$X_1^2 = 0.54^{ns}$$

TABLE 28

n.s. - not significant

The calculation was repeated using 100 ml/mm as the cutoff value:

	> 100	< 100
Unexposed smokers	16	6
Unexposed non-smokers	9	3
Exposed smokers	15	8
Exposed non-smokers	8	3

U	25	9	34
E	23	11	34
	48	20	68

$$X_1^2 = 0.28^{ns}$$

TABLE 29

n.s. - not significant

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		380		70
		600		
25 - 30		290		410 *
		310		310
		440		
		350		
30 - 35	330 A	360	470 C	190
		470 **		
		475		
35 - 40	310 A	250 **		415
	190 A	510		420
	385 A	290		
	210 B			
	240 A			
	400 C			
	240 A			
40 - 45	130 A	270		406
	340 A	240		240
	295 A	380		
	390 A			
	280 B			
45 - 50	610 A	450	252 * A	320
	300 C	460	400 A	
			365 * A	
50 - 55	460 A	430	510 A	470
	336 C	270	390 * A	210
		255		
55 - 60	440 A	390	410 C	
	280 C	320	330 * C	
	410 A		336 * A	
60 & OVER	480 A		310 * B	630 *
	225 A		420 * A	
	305 A			

AMINO ACID NITROGEN (mg/24 Hr.)

Normal 200 - 700

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 37

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		130		142
		138		
25 - 30		142		136 *
		136		136
		139		
		140		
30 - 35	140 A	136	134 C	135
		135 **		
		140		
35 - 40	140 A	140 **		135
	136 A	140		136
	138 A	137		
	138 B			
	137 A			
	142 C			
	129 A			
40 - 45	139 A	140		134
	142 A	136		135
	137 A	139		
	136 A			
	140 B			
45 - 50	140 A	135	142 * A	137
	135 C	136	138 A	
			138 * A	
50 - 55	134 A	137	141 A	134
	135 C	138	140 * A	139
		136		
55 - 60	144 A	138	139 C	
	141 C	140	137 * C	
	141 A		135 * A	
60 & OVER	140 A		135 * B	140 *
	140 A		135 * A	
	136 A			

SERUM SODIUM (meq/100 mls)
Normal 136 - 149

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 38

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		3.6		3.8
		3.5		
25 - 30		4.2		3.8 *
		3.9		4.0
		3.7		
		3.6		
30 - 35	3.7 A	3.6	3.9 C	4.0
		3.3 **		
		3.5		
35 - 40	3.7 A	4.1 **		4.0
	4.2 A	3.7		3.6
	4.0 A	4.1		
	4.0 B			
	3.6 A			
	4.6 C			
	4.7 A			
40 - 45	3.7 A	4.4		3.8
	3.6 A	3.4		4.0
	4.1 A	4.5		
	3.5 A			
	3.9 B			
45 - 50	4.2 A	3.7	3.5 * A	4.1
	3.5 C	3.7	3.7 A	
			4.0 * A	
50 - 55	3.3 A	4.0	4.2 A	3.6
	3.8 C	3.6	4.1 * A	3.8
		4.0		
55 - 60	4.2 A	4.0	3.7 C	
	4.0 C	3.2	3.9 * C	
	4.5 A		4.3 * A	
60 & OVER	4.0 A		3.2 * B	4.0 *
	3.9 A		4.2 * A	
	3.4 A			

SERUM POTASSIUM (meq/100 mls.)

Normal 3.8 - 5.2

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 39

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		96		102
		99		
25 - 30		104		101 *
		102		105
		103		
		104		
30 - 35	107 A	105	100 C	-
		98 **		
		106		
35 - 40	106 A	103 **		102
	101 A	-		101
	102 A	100		
	104 B			
	103 A			
	102 C			
	99 A			
40 - 45	101 A	108		-
	104 A	101		101
	98 A	102		
	102 A			
	103 B			
45 - 50	- A	100	102 * A	103
	98 C	104	102 A	
			- * A	
50 - 55	100 A	102	- A	99
	104 C	105	105 * A	104
		101		
55 - 60	103 A	103	- C	
	- C	105	99 * C	
	102 A		103 * A	
60 & OVER	103 A		98 * B	103 *
	102 A		111 * A	
	103 A			

SERUM CHLORIDE (meq/100 mls.)

Normal 98 - 108

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 40

24 hour Amino Acid Clearance - (mgm/24 hrs. Normal 200 - 700 mgm)

	Mean	Min	Max
Unexposed smokers	372	240	600
Unexposed non-smokers	341	70	630
Exposed smokers	330	130	610
Exposed non-smokers	381	252	510

TABLE 30

Groups not significantly different

Sodium - (Normal range in the laboratory is 136 - 149 mEq/1)

	Mean	Min	Max
Unexposed smokers	137.64	130	142
Unexposed non-smokers	136.58	134	142
Exposed smokers	138.26	129	144
Exposed non-smokers	137.64	134	142

TABLE 31

Groups not significantly different

Potassium - (Normal range in the laboratory 3.8 - 5.2 mEq/1)

	Mean	Min	Max
Unexposed smokers	3.786	3.2	4.5
Unexposed non-smokers	3.875	3.6	4.1
Exposed smokers	3.917	3.3	4.7
Exposed non-smokers	3.882	3.2	4.3

TABLE 32

Groups not significantly different

Chloride - (Normal range in the laboratory is 98 - 108 mEq/1)

	n	Mean	Min	Max
Unexposed smokers	21	102.43	96	108
Unexposed non-smokers	10	102.10	99	105
Exposed smokers	21	102.24	98	107
Exposed non-smokers	8	102.50	98	111

TABLE 33

Groups not significantly different

Other indices of tubular and glomerular function; glycosuria, serum calcium and phosphorus, serum proteins, were measured and are discussed in later chapters. The results of these investigations support the following conclusion.

There was no difference in renal function of the control and exposed groups using the parameters discussed above. The statistical significance between the actual blood urea levels of the groups is considered clinically unimportant and has been ignored because the more sensitive and more reliable indication of glomerular function, the creatinine clearance, did not correlate with this finding. It is generally accepted that a raised blood urea, in isolation, is a little value in assessing renal function.

Discussion

There is abundant evidence that a large percentage (33% or more) of body burden of cadmium is stored in the cells of the renal tubules. It is also clear that once a critical cellular concentration is reached permanent irreversible damage occurs resulting in both increased excretion of cadmium and clinical and biochemical manifestation of tubular damage. Urinary cadmium levels therefore do not reflect either renal concentration or total body burden. But it may be of value in detecting or assessing current exposure and intake as it rises and falls with exposure

Levels of 30 microgram/litre or more are necessary before early signs, e.g. transient proteinuria, of altered renal function appears. Because this

figure has been consistently associated with signs of renal damage an arbitrary figure of 25 micrograms/litre (where there is no evidence of renal damage) has been suggested as an indication of excessive exposure. This survey confirms the suggestion that renal damage does not occur with a urinary excretion of less than 30 Ug/litre but does not provide evidence for or against the selection of 25 Ug/litre as an indication of excessive exposure.

Urinary cadmium estimation are tedious and subject to many possible sources of error from incorrect sample collection to errors in actual assay. Some body burden of cadmium can be tolerated by renal tissues without producing damage therefore. How can the clinician decide when this burden has been reached?

Unfortunately the only markers of renal tubular dysfunction at present easily recognisable are those which indicate irreversible damage. What is needed is an easily identifiable indicator of high renal tubular cadmium which in itself is not the result of irreversible cadmium toxicity. Considerable experimental work is going on at present to determine whether increased excretion of certain enzymes in the urine will provide the answer to this problem. This survey showed that the usual tests of renal function either singly or in groups were not useful markers of non toxic renal tissue burden of cadmium.

The survey result must offer considerable consolation to the general public who, from mathematical models predictions, have been led to believe that critical renal levels will be reached before middle age if current exposure trends continue. If workers occupationally exposed to high

concentrations of cadmium for long periods do not reach the danger level there must be far less chance of the general population doing so from environmental exposure.

CHAPTER 13

Cadmium and the Digestive System

The intestinal mucosa and pancreas have an important role in the absorption, storage or excretion of cadmium. My survey looked at possible significant functional changes in these structures due to their involvement in cadmium metabolism.

1. The Pancreas and Alimentary Canal

Because elaborate or extensive investigations were deliberately excluded from the survey, digestive, absorptive and excretory function was assessed by history and clinical examination. However, certain investigations e.g. blood sugar, serum protein, lipids, triglycerides, cholesterol, uric acid, though performed primarily for other reasons discussed in later chapters were of assistance in finalising conclusions based on the above premises.

Acute exposure following accidental plant malfunction and short term high atmospheric contamination produced nausea and vomiting in several workers on occasions. These symptoms were of short duration and no participant admitted either in the questionnaire or at the subsequent interviews to being seriously incapacitated by them. No worker could remember having to lose time from work because of an "overdose" and no medical certificates presented for any lost time by any employee implicated the working environment as a cause of illness. In high enough doses cadmium appeared to be an emetic of temporary duration.

The questionnaire was designed to highlight symptoms associated with digestive disorders, malabsorption and altered intestinal motility. In

all these areas there was no differences in the response pattern between the groups. As mentioned previously there was no significant difference in the incidence of diagnosed gastro-intestinal conditions between the groups.

Physical examination of the abdomen revealed no abnormalities in any group. No member of any group exhibited associated stigmata of malabsorption, e.g. finger clubbing, pallor, cachexia.

Several workers e.g. Princi (56), Horstowa et al (62) have reported a yellow staining of teeth in the occupationally exposed. No member of the exposed group showed staining of natural teeth. There was no significant difference in the number in each group with either partial or full dentures.

Four workers in the exposed group, three smokers and one non smoker had marked caries and gingivitis. No member of the control groups had any serious dental condition. The company provides an on-site dental clinic and these findings may simply reflect both the easier access and hygiene conscience of clerical workers in contrast to the problems of access of a shift worker and a labourer's standards of hygiene.

Conclusion

No differences in the functioning of the digestive system of exposed workers and controls were found.

Discussion

Some investigations have linked vague ill health, anaemia, nausea and disordered digestion or intestinal motility with chronic cadmium intake. There is good and abundant experimental evidence that both the pancreas and the gut, as well as salivary glands are very actively involved in handling body cadmium. It is not surprising therefore that such a linkage has been frequently suggested. No worker has proven that cadmium concentration in the cells of these organs is responsible for the symptoms. No worker has found pathological changes in these organs that could be correlated with cadmium in the cells.

The symptoms generally ascribed to cadmium are often associated with disease elsewhere in the body. Perhaps renal or pulmonary disease in the cadmium exposed workers was responsible for the production of these symptoms and not cadmium itself.

CHAPTER 14

Cadmium and Liver

The liver plays an important role in the transport and storage of cadmium. A large percentage of body burden - possibly 20 - 25% is stored in here. Metallothionein - the protein responsible for cadmium binding in the tissues and transport in the circulation is produced in part if not in toto by hepatic cells.

The following list of tests of liver function were employed to investigate possible hepatic dysfunction:-

(a) Total Bilirubin
(b) Conjugated Bilirubin
(c) Serum Protein
(d) Serum Albumin
(e) α 1 Globulin
(f) α 2 Globulin
(g) β Globulin
(h) γ Globulin
(i) Alkaline Phosphatase
(j) Serum Glutamic Pyruvic Transaminase
(k) Serum Cholesterol
(l) Serum Triglycerides

(a) Serum Bilirubin - No member of either the exposed or the control group had a serum bilirubin higher than 0.5 mgm per 100 ml. Figure 41, page 156.

(b) No member of either group had any conjugated bilirubin in the specimen of serum analysed. Figure 42, page 157.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		0.5		0.5
		0.5		
25 - 30		0.5		0.5 *
		0.5		0.5
		0.5		
		0.5		
30 - 35	0.5 A	0.5	0.5 C	0.5
		0.5 **		
		0.5		
35 - 40	0.5 A	0.5 **		0.5
	0.5 A	0.5		0.5
	0.55 A	0.5		
	0.5 B			
	0.5 A			
	0.5 C			
	0.5 A			
40 - 45	0.5 A	0.5		0.5
	0.5 A	0.5		0.5
	0.5 A	0.5		
	0.5 A			
	0.5 B			
45 - 50	0.5 A	0.5	0.5 * A	0.5
	0.5 C	0.5	0.5 A	
			0.5 * A	
50 - 55	0.5 A	0.5	0.5 A	0.5
	0.5 C	0.5	0.5 * A	0.5
		0.5		
55 - 60	0.5 A	0.5	0.5 C	
	0.5 C	0.5	0.5 * C	
	0.5 A		0.5 * A	
60 & OVER	0.5 A		0.5 * B	0.5 *
	0.5 A		0.5 * A	
	0.5 A			

TOTAL BILIRUBIN
mgm /100 ml.

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 41

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		nil		nil
		nil		
25 - 30		nil		nil *
		nil		nil
		nil		
		nil		
30 - 35	nil A	nil	nil C	nil
		nil **		
		nil		
35 - 40	nil A	nil **		nil
	nil A	nil		nil
	nil A	nil		
	nil B			
	nil A			
	nil C			
	nil A			
40 - 45	nil A	nil		nil
	nil A	nil		nil
	nil A	nil		
	nil A			
	nil B			
45 - 50	nil A	nil	nil * A	nil
	nil C	nil	nil A	
			nil * A	
50 - 55	nil A	nil	nil A	nil
	nil C	nil	nil * A	nil
		nil		
55 - 60	nil A	nil	nil C	
	nil C	nil	nil * C	
	nil A		nil * A	
60 & OVER	nil A		nil * B	nil *
	nil A		nil * A	
	nil A			

CONJUGATED BILIRUBIN %

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 42

(c) Serum Protein - Four members of the exposed group, three smokers with lengthy exposure to cadmium and one non-smoker with limited exposure to cadmium had a total protein below the laboratory normal of 6.5 grams per 100 mls. One member of the control group did not reach this level. However, when subject to statistical analysis, there was no significant difference between the groups as a whole. (Figure 43, page 160, table 34, page 166).

(d) Serum Albumin - The four members of the exposed group with a low serum protein all recorded a level of albumin less than 3.5 grams per 100 mls. (lower normal for the laboratory). In addition another member of the exposed group with limited exposure to cadmium also failed to reach this figure. The only member of the control group with low serum protein also had a low serum albumin. Again, however, statistically there is no difference between the groups. (Figure 44, page 161, table 35, page 166).

(e) α 1 Globulin - No member of either the exposed group or the control group showed a value lower than the laboratory normal, (normal 0.1→0.4 Gm. 100 mls.). (Figure 45, page 162, table 36, page 167).

(f) α 2 Globulin - Twelve members of the exposed group, eight smokers and four non-smokers had a level of α 2 globulin higher than 0.8 grams percent (the laboratory normal). Six members of the control group exceeded this figure, three smokers, three non-smokers. However, statistically there was no significant difference between the groups. (Figure 46, page 163, table 37, page 167)..

(g) β Globulin - Seven members of the exposed group had a level greater than 1.0 grams percent, four smokers and three non-smokers. Three members of the control group also had elevated figures, two smokers and one non-smoker. However, statistically there was no difference between the groups. (Figure 47, page 164, table 38, page 168).

(h) γ Globulin - Five members of the exposed group, two smokers and three non-smokers had an elevated level compared with three in the control group, two smokers and one non-smoker. Again statistically there is no significant difference between the groups. (Figure 48, page 165 table 39, page 168).

(i) Alkaline Phosphatase - (Normal 9.35 IU/Litre). Three members of the exposed group had a level higher than the laboratory normal of 35 units/litre; all were smokers. Two members of the control group had elevated figures also. Statistically there was no difference when all the levels were considered between the groups. (Figure 49, page 169, table 40, page 171).

A contingency table formed from people with values above and below the level of 35 IU showed that these numbers with raised levels were not significant. (Table 41, page 171).

(j) Serum Glutamic Pyruvic Transaminase - (Normal range < 27 units per litre). (Figure 50, page 170, table 42, page 172). Thirteen people, four unexposed and nine exposed had a level higher than the laboratory normal. A contingency table to examine this was formed. (Table 43, page 172). Again these numbers were not significant.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		6.80		7.20
		7.10		
25 - 30		7.50		7.70 *
		7.20		6.90
		7.20		
		6.70		
30 - 35	7.30 A	7.70	5.80 C	7.00
		7.50 **		
		7.60		
35 - 40	6.70 A	7.00 **		7.50
	7.30 A	7.80		6.90
	7.10 A	6.80		
	7.20 B			
	7.40 A			
	7.60 C			
	7.20 A			
40 - 45	7.30 A	7.60		7.10
	7.70 A	7.60		6.30
	7.0 A	7.40		
	7.0 A			
	7.20 B			
45 - 50	6.70 A	6.90	7.50 * A	7.30
	7.40 C	6.80	7.20 A	
			7.90 * A	
50 - 55	7.00 A	6.50	6.90 A	6.70
	7.20 C	7.00	7.30 * A	6.50
		6.80		
55 - 60	7.50 A	6.00	6.70 C	
	7.10 C	7.20	6.50 * C	
	6.30 A		7.60 * A	
60 & OVER	6.00 A		7.20 * B	7.20 *
	6.70 A		6.90 * A	
	6.40 A			

TOTAL PROTEIN (gm PER 100 ml,)
(Normal 6.5 - 8)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 43

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		4.20		4.30
		4.61		
25 - 30		5.27		4.76 *
		4.44		4.35
		4.05		
		4.26		
30 - 35	4.52 A	5.15 **	2.91 C	4.04
		4.79		
		4.86		
35 - 40	4.28 A	3.97 **		4.24
	3.90 A	4.79		3.74
	4.25 A	4.02		
	4.60 B			
	4.29 A			
	4.69 C			
	4.03 A			
40 - 45	4.35 A	4.40		4.76
	5.10 A	4.63		3.76
	3.79 A	4.71		
	3.63 A			
	4.51 B			
45 - 50	4.09 A	4.33	4.05 * A	4.58
	4.03 C	5.32	4.10 A	
			4.27 * A	
50 - 55	4.26 A	4.38	3.89 A	4.08
	3.91 C	3.80	4.46 * A	3.99
		3.54		
55 - 60	4.65 A	3.49	4.17 C	
	3.72 C	4.54	3.35 * C	
	3.44 A		4.85 * A	
60 & OVER	3.24 A		4.46 * B	4.22 *
	4.19 A		4.39 * A	
	3.43 A			

SERUM ALBUMIN (gm/100 ml.)
(Normal 3.5 - 5.2)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 44

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		0.20		0.13
		0.15		
25 - 30		0.15		0.10 *
		0.26		0.19
		0.24		
		0.24		
30 - 35	0.21 A	0.17	0.18 C	0.15
		0.16 **		
		0.20		
35 - 40	0.15 A	0.12 **		0.19
	0.19 A	0.33		0.22
	0.18 A	0.21		
	0.22 B			
	0.29 A			
	0.18 C			
	0.20 A			
40 - 45	0.16 A	0.17		0.30
	0.20 A	0.16		0.17
	0.18 A	0.10		
	0.21 A			
	0.22 B			
45 - 50	0.14 A	0.18	0.12 * A	0.15
	0.30 C	0.11	0.18 A	
			0.22 * A	
50 - 55	0.20 A	0.12	0.15 A	0.17
	0.24 C	0.20	0.21 * A	0.12
		0.22		
55 - 60	0.17 A	0.30	0.09 C	
	0.45 C	0.13	0.18 * C	
	0.23 A		0.18 * A	
60 & OVER	0.18 A		0.11 * B	0.19 *
	0.25 A		0.13 * A	
	0.18 A			

α 1 GLOBULIN (gm /100 ml.)
(Normal 0.1 → 0.4)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 45

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		0.80		0.73
		0.70		
25 - 30		0.58		0.58 *
		0.70		0.66
		0.91		
		0.77		
30 - 35	0.68 A	0.55 **	0.74 C	0.81
		0.76		
		0.67		
35 - 40	0.65 A	0.93 **		0.90
	0.94 A	0.76		0.88
	0.68 A	0.77		
	0.68 B			
	0.72 A			
	0.79 C			
	0.69 A			
40 - 45	0.68 A	0.80		0.48
	0.65 A	0.71		0.63
	0.84 A	0.60		
	0.84 A			
	0.72 B			
45 - 50	0.81 A	0.67	0.87 * A	0.76
	0.95 C	0.59	0.85 A	
			0.84 * A	
50 - 55	0.76 A	0.50	0.80 A	0.75
	0.91 C	0.73	0.76 * A	0.68
		0.73		
55 - 60	0.69 A	0.59	0.59 C	
	0.61 C	0.86	0.90 * C	
	0.83 A		0.58 * A	
60 & OVER	0.82 A		0.67 * B	0.70 *
	0.69 A		0.65 * A	
	0.74 A			

α 2 GLOBULIN (gm /100 ml.)
(Normal 0.4 → 0.8)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 46

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		0.80		0.97
		0.76		
25 - 30		0.67		0.94 *
		0.88		0.83
		1.04		
		0.77		
30 - 35	0.93 A	0.96	1.06 C	1.00
		0.85 **		
		0.82		
35 - 40	0.79 A	0.85 **		1.01
	0.94 A	0.96		0.95
	0.90 A	0.90		
	0.76 B			
	0.95 A			
	0.93 C			
	1.08 A			
40 - 45	0.91 A	0.91		0.68
	0.85 A	0.98		0.79
	1.05 A	0.92		
	1.09 A			
	0.72 B			
45 - 50	0.88 A	0.86	1.14 * A	0.89
	1.06 C	0.83	0.97 A	
			0.98 * A	
50 - 55	0.76 A	0.75	0.95 A	0.85
	0.91 C	0.85	0.75 * A	0.68
		1.15		
55 - 60	0.86 A	0.74	0.78 C	
	0.91 C	0.86	1.14 * C	
	0.87 A		0.86 * A	
60 & OVER	0.82 A		0.98 * B	1.00 *
	0.73 A		0.77 * A	
	0.81 A			

β GLOBULIN (gm/ 100 ml.)
(Normal 0.5 - 1.0)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 47

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		0.80		1.07
		0.88		
25 - 30		0.83		1.32 *
		0.92		0.87
		0.94		
		0.66		
30 - 35	0.96 A	0.87	0.91 C	1.00
		0.94 **		
		1.05		
35 - 40	0.83 A	1.13 **		1.16
	1.33 A	0.96		1.11
	1.09 A	0.90		
	0.94 B			
	1.15 A			
	1.01 C			
	1.10 A			
40 - 45	1.20 A	1.32		0.88
	0.90 A	1.12		0.96
	1.14 A	0.97		
	1.23 A			
	0.98 B			
45 - 50	0.78 A	0.86	1.32 * A	0.92
	1.06 C	0.95	1.10 A	
			1.49 * A	
50 - 55	1.02 A	0.75	1.11 A	0.85
	1.23 C	1.42	1.13 * A	1.03
		1.16		
55 - 60	1.13 A	0.88	1.07 C	
	1.41 C	0.90	0.93 * C	
	0.93 A		1.13 * A	
60 & OVER	0.94 A		0.98 * B	1.09 *
	0.84 A		0.86 * A	
	1.24 A			

σ GLOBULIN (gm/ 100 ml.)
(Normal 0.6 - 1.3)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 48

Serum Protein -(Normal 6.5 - 8 Gm/100 ml.)

	Mean	Min	Max
Unexposed smokers	7.123	6.0	7.8
Unexposed non-smokers	7.025	6.3	7.7
Exposed smokers	7.057	6.0	7.7
Exposed non-smokers	7.045	5.8	7.9

TABLE 34

No significant difference between the groups.

Serum Albumin - (Normal 3.5 - 5.2 Gm/100 ml.)

	Mean	Min	Max
Unexposed smokers	4.434	3.49	5.32
Unexposed non-smokers	4.235	3.74	4.76
Exposed smokers	4.126	3.24	5.10
Exposed non-smokers	4.082	2.91	4.85

TABLE 35

No significant difference between the groups.

α 1 Globulin - (Normal 0.1 - 0.4 Gm/100 mls.)

	Mean	Min	Max
Unexposed smokers	0.187	0.10	0.33
Unexposed non-smokers	0.173	0.10	0.30
Exposed smokers	0.214	0.14	0.45
Exposed non-smokers	0.159	0.09	0.22

TABLE 36

No significant difference between the groups.

α 2 Globulin - (Normal 0.4 -> 0.8 Gm/100 ml.)

	Mean	Min	Max
Unexposed smokers	0.713	0.50	0.93
Unexposed non-smokers	0.713	0.48	0.95
Exposed smokers	0.755	0.61	0.90
Exposed non-smokers	0.685	0.58	0.90

TABLE 37

No significant difference between the groups.

β Globulin - (Normal 0.5 - 1.0 Gm/100 ml.)

	Mean	Min	Max
Unexposed smokers	0.869	0.67	1.15
Unexposed non-smokers	0.882	0.68	1.01
Exposed smokers	0.892	0.72	1.09
Exposed non-smokers	0.944	0.75	1.14

TABLE 38

No significant difference between the groups.

γ Globulin - (Normal 0.6 - 1.3 Gm/100 ml.)

	Mean	Min	Max
Unexposed smokers	0.964	0.66	1.42
Unexposed non-smokers	1.022	0.85	1.32
Exposed smokers	1.063	0.78	1.41
Exposed non-smokers	1.094	0.86	1.49

TABLE 39

No significant difference between the groups.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		20		14
		28		
25 - 30		25		19 *
		31		20
		25		
		18		
30 - 35	21 A	26	17 C	14
		22 **		
		23		
35 - 40	53 A	29 **		32
	13.7 A	15		27
	27 A	15		
	25 B			
	20 A			
	25 C			
	31 A			
40 - 45	58 A	19		21
	25 A	31		36
	19 A	22		
	20 A			
	33 B			
45 - 50	15 A	27	34 * A	18
	30 C	29	24 A	
			15 * A	
50 - 55	20 A	22	15 A	14
	25 C	22	- * A	27
		15		
55 - 60	118 A	76	17 C	
	23 C	24	24 * C	
	21 A		27 * A	
60 & OVER	25 A		25 * B	15 *
	21 A		15 * A	
	18 A			

ALKALINE PHOSPHATASE IU/LITRE
(Normal 9 -35)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 49

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		20		9
		33		
25 - 30		11		7 *
		18		20.25
		27		
		36		
30 - 35	4 A	13	18 C	108
		25 **		
		7		
35 - 40	61 A	17 **		27
	9 A	4		9
	9 A	7		
	8 A			
	11 B			
	6 C			
	20 A			
40 - 45	34 A	13		13
	12 A	16		14
	36 A	7		
	20 A			
	11 B			
45 - 50	227 A	9	43 * A	6
	20 C	13	28 A	
			6 * A	
50 - 55	13 A	37	22 A	11
	45 C	11	7 * A	13
		18		
55 - 60	16 A	22.5	18 C	
	11 C	16	40.5*C	
	20 A		11 * A	
60 & OVER	29 A		7 * B	27 *
	20 A		9 * A	
	9 A			

SERUM GLUTAMIC PYRUVIC TRANSAMINASE
(Normal 27 Units/Litre)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 50

Alkaline Phosphatase - (Normal 9 - 35 IU)

	Mean	Median	Min	Max
Unexposed smokers	25.45	23.5	15	76
Unexposed non-smokers	22.17	20.5	13	36
Exposed smokers	29.65	24.0	13	118
Exposed non-smokers	21.00	20.5	14	34

TABLE 40

No significant difference between the groups.

Number of people with Alkaline Phosphatase values above and below 35 IU/litre

	<35	>35	
Unexposed	32	2	34
Exposed	30	3	33
	62	5	67

$X_1^2 = 0.25^{ns}$

TABLE 41

n.s. = not significant

Serum Glutamic Pyruvic Transaminase - (Normal range 27 units per litre.)

	Mean	Median	Min	Max
Unexposed smokers	16.57	16	4	37
Unexposed non-smokers	22.33	13.5	6	108
Exposed smokers	29.26	20	4	227
Exposed non-smokers	19.09	18	6	41

TABLE 42

No significant difference between the groups.

Number of people with Serum Glutamic Pyruvic Transaminase values higher than normal

	< 27	> 27	
Unexposed	30	4	34
Exposed	25	9	34
	55	13	68

$X_1^2 = 2.38^{ns}$

TABLE 43

n.s. = not significant

(k) Serum Cholesterol - (Normal range 150 - 250 mgm/100 mls.)
Thirteen members of the control group, six smokers and seven non-smokers had a cholesterol level over than 250 mgm percent. Seventeen of the control group had a higher level, eleven smokers and six non-smokers. (Figure 51, page 174). There is no statistical significance between the groups (table 44, page 176).

(l) Serum Triglycerides - (Normal 30 - 135 mgm/100 mls.) Twenty four members of the exposed group, sixteen smokers and eight non-smokers had an elevated level. Twenty eight members of the control group, eleven non-smokers and seventeen smokers had a raised level. (Figure 52, page 175). However, table 45, page 176 shows there is no significant difference between the groups.

Conclusion

There is no evidence from this study to indicate any significant clinical variation in liver function between exposed workers and controls.

Discussion

The results of the serum protein and its components, serum alkaline phosphatase and serum glutamic pyruvic acid showed some departures from normal values. As has been pointed out there was no statistically significant variation between the groups. However, these abnormalities are worthy of comment. They could be dismissed as a manefestation of infectious hepatitis which was epidemic in Southern Tasmania at the time. From specific questioning and clinical examination, I could not

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		160		215
		267		
25 - 30		274		257 *
		296		290
		253		
		148		
30 - 35	233 A	298	282 C	261
		192 **		
		212		
35 - 40	204 A	200 **		186
	242 A	309		202
	226 A	208		
	260 B			
	232 A			
	219 C			
	234 A			
40 - 45	212 A	215		220
	250 A	277		296
	253 A	221		
	202 A			
	200 B			
45 - 50	290 A	258	364 * A	276
	286 C	267	242 A	
			252 * A	
50 - 55	268 A	248	268 A	186
	177 C	222	260 * A	212
		304		
55 - 60	296 A	198	210 C	
	236 C	298	277 * C	
	202 A		200 * A	
60 & OVER	216 A		331 * B	254 *
	209 A		193 * A	
	192 A			

CHOLESTEROL (mgm /100 ml.)
(Normal 150 - 250)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 51

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		136		125
		209		
25 - 30		149		275 *
		135		179
		209		
		149		
30 - 35	163 A	530	1,380 C	145
		159 **		
		250		
35 - 40	129 A	133 **		136
	381 A	209		170
	179 A	168		
	210 B			
	95 A			
	106 C			
	560 A			
40 - 45	252 A	210		145
	340 A	163		499
	173 A	80		
	422 A			
	126 B			
45 - 50	527 A	55	210 * A	173
	379 C	254	109 A	
			145 * A	
50 - 55	145 A	665	172 A	138
	119 C	205	181 * A	136
		436		
55 - 60	310 A	119	109 C	
	154 C	450	219 * C	
	90 A		132 * A	
60 & OVER	146 A		385 * B	312 *
	236 A		163 * A	
	99 A			

TRIGLYCERIDES (mgm/100 ml.)
(Normal 35 - 135)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 52

Serum Cholesterol - (mgm / 100 ml. - Normal 150 - 250)

	Mean	Min	Max
Unexposed smokers	242.0	148	309
Unexposed non-smokers	237.9	186	296
Exposed smokers	232.1	177	296
Exposed non-smokers	261.7	193	364

TABLE 44

No significant difference between the groups.

Serum Triglycerides - (Normal 30 - 135 mgm/100 mls.)

	Mean	Min	Max
Unexposed smokers	231	55	665
Unexposed non-smokers	203	125	499
Exposed smokers	232	90	560
Exposed non-smokers	291	109	1380

TABLE 45

No significant difference between the groups.

link any survey participant with either the disease or close contact with known sufferers. As the hepatitis virus is almost certainly more widely distributed throughout the community than the number of diagnosed cases would suggest, altered tests of liver function could be produced by sub-clinical infection. Unfortunately there is no specific test for this condition.

Another explanation could be they reflect the drinking habits of the individual. There is a close correlation between heavy drinking and some abnormal results in the non exposed groups but not all heavy drinkers in either exposed or control groups showed one or more abnormal results. Two almost teetotal controls showed an abnormality in one or more tests compared with eleven almost teetotal exposed workers.

These figures have not been subject to statistical analysis for several reasons. The majority of abnormal results were not very different from normal and could well be laboratory error. Also there is no consistent pattern to the variation. Most were a single deviation only.

But three of the "teetotal" exposed group showed three or more abnormal tests and these men had long periods of exposure, (25 years or more). As a similar picture emerged when haemoglobin levels were examined. (Chapter 15) correlation matrices were calculated to see if there was any correlation between blood lead, blood cadmium, haemoglobin, total protein, albumin α 2 globulin and years of exposure for the twenty two men in the cadmium plant only. (Tables 46, 47, 48, pages 180 - 181. The statistician reports as follows -

"The most significant correlation coefficients between the measured variables and years of exposure are those for haemoglobin and total protein, both of these showing a highly significant decline ($p<0.001$) for workers in the cadmium plant (the exposed non-smokers group is too small for significance to be easily detected). Blood cadmium is positively correlated with years of exposure ($p<0.05$). Albumin is significantly depressed ($p<0.05$) in the exposed smokers group, but not in the non-smokers group. The total protein, haemoglobin and albumin are highly intercorrelated in the exposed smokers group. There is no evidence, however, that $\alpha 2$ globulin is significantly raised, the correlation coefficient 0.2831 being far from significant.

An interesting result is the highly significant correlation between $\alpha 2$ globulin and haemoglobin ($r = 0.8873$) for the exposed non-smokers. This would tend to rule out any possibility that an increase in α 2 globulin would be expressed as a result of long exposure in the cadmium plant. However, the sample size is too small to be emphatic about any conclusions; this is unfortunate because any effect observed in the exposed smokers groups may be due to smoking rather than due to exposure to cadmium."

My investigations were directed towards the health hazards of cadmium and I have concluded that there is no harmful effects on liver function to those with body burdens of the range my group of exposed workers have attained. It would be of interest, however, to investigate protein metabolism in a much bigger group of workers with long and higher exposure and therefore higher body burdens to see if there was a significant variation from normal in this group. Metallothionen is a protein apparently

specifically associated with heavy metals and changes in the serum proteins might reflect its formation and tissue levels thus providing an easily identifiable marker for cellular cadmium levels.

a) For the exposed smokers group (d.f. = 15):

Yrs. Exp.	1.0						
Blood Pb	-0.1449	1.0					
Blood Cd	0.5406*	0.3596	1.0				
Haem.	-0.8889***	0.2430	-0.4201	1.0			
Tot. Prot.	-0.7539***	0.0443	-0.4187	0.7624***	1.0		
Albumin	-0.5514*	0.1060	-0.1612	0.5469*	0.8127***	1.0	
α 2 Glob.	0.2831	-0.1923	-0.2276	-0.1795	-0.3363	-0.6667**	1.0
	Yrs. Exp.	Blood Pb	Blood Cd	Haem.	Tot. Prot.	Albumin	α 2 Glob

TABLE 46

b) For the exposed non-smokers group (d.f. = 5):

Yrs. Exp.	1.0						
Blood Pb	0.6818	1.0					
Blood Cd	0.4800	-0.1831	1.0				
Haem.	-0.5503	-0.1960	-0.3990	1.0			
Tot. Prot.	-0.4423	-0.1672	-0.2787	0.1837	1.0		
Albumin	0.4741	0.2829	0.3709	-0.6858	0.3523	1.0	
α 2 Glob.	-0.5575	-0.1199	-0.6376	0.8873**	0.1405	-0.8237*	1.0
	Yrs. Exp.	Blood Pb	Blood Cd	Haem.	Tot. Prot.	Albumin	α 2 Glob

TABLE 47

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

c) For the combined exposed group (d.f. = 22):

	Yrs. Exp.	Blood Pb	Blood Cd	Haem.	Tot. Prot.	Albumin	α2 Glob
Yrs. Exp.	1.0						
Blood Pb	-0.0357	1.0					
Blood Cd	0.5145*	0.2810	1.0				
Haem.	-0.7890***	0,1485	-0.4054*	1.0			
Tot. Prot.	-0.6421***	0.0102	-0.4324*	0.5765**	1.0		
Albumin	-0.3828	0.1240	-0.1201	0.2636	0.7455***	1.0	
α2 Glob	0.0667	-0.1664	-0.3326	0.2102	-0.1521	-0.6402***	1.0

TABLE 48

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Relative Viscosity - (Normal 1.5 - 1.72 centrepoises)

	Mean	Min	Max
Unexposed smokers	1.689	1.56	1.84
Unexposed non-smokers	1.734	1.59	1.94
Exposed smokers	1.702	1.58	1.85
Exposed non-smokers	1.738	1.56	1.91

TABLE 49

No significant difference between the groups.

CHAPTER 15

Cadmium and the Haemopoetic System

Cadmium is found in both serum and red cells, Perry et al (17), Lucis et al (18). Some investigations have found anaemia amongst cadmium workers, others have not. (Vide Chapter 5). Eosinophilia also has been described - Nicaud et al (55), Princi (56). Friberg (14) examined the bone marrow of nineteen cadmium workers in 1950 and noted no pathological changes.

In this survey the following investigations into the haemopoetic system were carried out.

(a) Relative viscosity
(b) Haemoglobin
(c) Packed cell volume
(d) White cell count
(e) Platelet count
(f) Examination of blood film
(g) Differential white cell count
(h) Uric acid estimation

1. Relative viscosity - (Figure 52, page 186) This test was performed as an alternative to the erythrocyte sedimentation rate. It is a non-specific test which accurately and quickly reflects changes occurring in the plasma proteins. The normal range for the laboratory is 1.5 to 1.72 centrepoises. It was thought that this might reflect changes that are reputed to occur in proteins as the result of cadmium triggering off the production of metallothionen. Seventeen of the exposed group, ten smokers and seven

non-smokers had an elevated figure compared with thirteen controls, five non-smokers and eight smokers. However, statistically there was no significant difference between the groups. (Table 49, page 181). A contingency table (table 50, page 188) examines these results also.

2. Haemoglobin - (Normal range 13.5 - 18 Gm/100 mls.)

Six members of the exposed, four smokers and two non-smokers, all with lengthy exposure to the most contaminated atmosphere had a haemoglobin level less than 14 grams percent. Two members of the control group, one a non-smoker and the other a smoker had a low level. (Figure 53, page 187). However, there is no significant difference in actual levels between groups. (Table 51, page 188).

Several statistical exercises were carried out in relation to the number of men with haemoglobin above and below 14 Gm and years of exposure. A contingency table (table 52, page 189) considers all workers with 20 or more years exposure and shows there is a significant link between exposure time and low levels. A similar table (table 53, page 189) considering only those working in the most contaminated atmosphere reinforces the idea of a definite relationship between high body burden and lower haemoglobin levels.

Examination of a correlation coefficient between years of exposure and haemoglobin suggests that an added factor, smoking,may be of significance in the relationship.

	r	d.f.
Exposed smokers	-0.8014^{***}	21
Exposed non-smokers	-0.1896^{ns}	9

The correlation coefficient between haemoglobin levels and years of exposure, r = -0.6940 (d.f. 21) is highly significant as is years of smoking and years of exposure r = 0.7966 (d.f. 21). Both years of exposure and years of smoking are highly confounded with age.

Removing the effect of years of exposure using a partial correlation coefficient between haemoglobin and years of exposure produced the following: $r = -0.5711^{xx}$ (d.f. 20). A similar calculation giving a partial correlation coefficient between haemoglobin and years of smoking, removing the effect of years of exposure showed $r = 0.1538^{ns}$ (d.f. 20).

It therefore can be correlated that haemoglobin is negatively correlated with years of exposure even after the effect of smoking as accounted for whereas the correlation between haemoglobin and years of smoking does not stand after years of exposure have been equalised.

Tables 46, 47 and 48, pages 180 - 181 show the relationship between blood lead and haemoglobin. They do not provide any evidence for a significant correlation between the two.

Conclusion

Workers with at least 20 years of exposure have a significantly lower haemoglobin level than those employed for 20 years or more in unexposed areas.

3. Packed cell volume - (Normal 40 - 54 percent)

Figure 54, page 192 and table 54, page 190 indicate there is no significant difference between the groups.

4. White cell count - (Normal, 4,000 - 11,000 per cubic m.m.) Figure 55, page 193 and table 55, page 190 indicate no statistical significant difference between groups.

5. Platelets - (Normal 150,000 - 450,000 per cubic m.m.) Figure 56, page 194 shows no member of any group had an abnormal platelet count.

6. Differential white cell count - Figures 57, 58, 59, 60, 61, pages 195 - 199. There is no significant group variation.

7. Blood film examination - With three exceptions, all of whom subsequently were found to have a positive screening test for infectious mononucleosis, all blood films were essentially normal.

8. Uric acid - (Normal level 2.5 - 7 mgm per 100 mls.) Figure 62, page 200. Serum uric acid was measured for all participants. This examination primarily a marker of purine metabolism can also be used as an aid to assess bone marrow function or renal function. Although only four members of the survey, three in the exposed and one in the control group gave a history of being treated for clinical gout, twenty two participants in the survey had an elevated uric acid level. (Seven exposed smokers, four exposed non-smokers, two unexposed non-smokers and nine exposed smokers). Statistically there was no difference when the groups were analysed. Table 56, page 201.

Conclusion

Some abnormality of haemoglobin synthesis is associated with increased body burden of cadmium. No other bone marrow effect is evident in this survey.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		1.56		1.66
		1.79		
25 - 30		1.64		1.83 *
		1.61		1.68
		1.65		
		1.58		
30 - 35	1.66 A	1.72	1.80 C	1.94
		1.65 **		
		1.81		
35 - 40	1.65 A	1.66 **		1.85
	1.85 A	1.71		1.59
	1.59 A	1.66		
	1.58 B			
	1.80 A			
	1.71 C			
	1.71 A			
40 - 45	1.83 A	1.73		1.74
	1.66 A	1.84		1.92
	1.80 A	1.65		
	1.68 A			
	1.62 B			
45 - 50	1.75 A	1.59	1.80 * A	1.67
	1.80 C	1.69	1.76 A	
			1.91 * A	
50 - 55	1.75 A	1.69	1.67 A	1.66
	1.80 C	1.68	1.77 * A	1.61
		1.76		
55 - 60	1.67 A	1.68	1.65 C	
	1.70 C	1.81	1.74 * C	
	1.63 A		1.66 * A	
60 & OVER	1.60 A		1.80 * B	1.66 *
	1.67 A		1.56 * A	
	1.64 A			

RELATIVE VISCOSITY
(Normal range 1.5 - 1.72 centrepoises)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 52

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		15.7		14.4
		15.6		
25 - 30		14.9		15.6 *
		14.2		14.5
		14.8		
		15.0		
30 - 35	16.0 A	13.9	15.4 C	16.0
		14.3 **		
		15.3		
35 - 40	15.5 A	14.9 **		15.1
	15.9 A	16.2		13.5
	15.4 A	14.8		
	14.0 B			
	16.4 A			
	15.2 C			
	14.5 A			
40 - 45	15.4 A	14.3		14.8
	15.6 A	15.7		15.1
	14.8 A	15.4		
	16.0 A			
	16.0 B			
45 - 50	13.2 A	15.8	16.5 * A	15.0
	15.0 C	15.5	16.5 A	
			14.9 * A	
50 - 55	14.9 A	15.1	15.2 A	15.8
	15.0 C	15.4	14.5 * A	13.0
		14.7		
55 - 60	14.0 A	15.7	14.7 C	
	14.3 C	15.1	14.6 * C	
	12.4 A		13.3 * A	
60 & OVER	12.7 A		15.7 * B	15.6 *
	13.5 A		12.3 * A	
	12.5 A			

HAEMOGLOBIN
(gm/percent)
Normal 13.5 - 18

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 53

Relative Viscosity

Contingency Table - Prepared from those above and below the normal range.

	Normal	Above Normal	
Unexposed smokers	16	6	
Unexposed non-smokers	7	5	
Exposed smokers	15	8	
Exposed non-smokers	4	7	
Unexposed	23	11	34
Exposed	19	15	34
	42	26	68

$X_1^2 = 1.00^{ns}$

No significant difference.

TABLE 50

Haemoglobin - (Gm/100 ml. Normal 13.5 - 18)

	Mean	Min	Max
Unexposed smokers	15.10	13.9	16.2
Unexposed non-smokers	14.87	13.0	16.0
Exposed smokers	14.75	12.4	16.4
Exposed non-smokers	14.87	12.3	16.5

TABLE 51

No statistical difference

Haemoglobin Level

Workers with twenty of more years exposure -

	Normal	Below Normal	
Unexposed smokers	6	0	
Unexposed non-smokers	4	1	
Exposed smokers	4	5	
Exposed non-smokers	3	1	
Unexposed	10	1	11
Exposed	7	6	13
	17	7	24

$X_1^2 = 3.96^*$ ($p<0.05$ - significant)

TABLE 52

Workers with twenty or more years exposure in the most contaminated atmosphere -

Unexposed	10	1	11
Exposed	5	6	11
	15	7	22

$X^2 = 5.24^*$ ($p<0.05$ - significant)

TABLE 53

Packed cell volume - (Normal 40 - 54 percent)

	Mean	Min	Max
Unexposed smokers	44.91	41	48
Unexposed non-smokers	44.25	39	47
Exposed smokers	44.00	38	52
Exposed non-smokers	44.18	40	49

TABLE 54

No significant difference between the groups.

White cell count -

	Mean	Min	Max
Unexposed smokers	8000	6000	13000
Unexposed non-smokers	7000	5000	13000
Exposed smokers	8304	5000	12000
Exposed non-smokers	7364	6000	10000

TABLE 55

No significant difference between the groups.

Discussion

Although none of the exposed group with lower haemoglobin levels could clinically be regarded as anaemic an attempt was made after the survey was completed to investigate this small group in greater detail. Only one member presented for further examination after invitation. It was not possible to place him in any of the recognised categories of anaemia from the serum iron level, iron binding capacity, and repeat blood film. One explanation could be a cadmium effect on haemoglobin synthesis rather than iron metabolism. No attempt was made to pursue this line of thought. Investigation of a larger group of long exposed individuals with lower haemoglobin levels may provide the answer to this abnormality which has been a finding in other surveys also.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		46		43
		47		
25 - 30		45		46 *
		42		43
		46		
		43		
30 - 35	49 A	41	44 C	47
		44 **		
		46		
35 - 40	45 A	45 **		46
	47 A	48		42
	45 A	45		
	41 B			
	52 A			
	47 C			
	41 A			
40 - 45	46 A	42		44
	48 A	47		44
	45 A	46		
	46 A			
	47 B			
45 - 50	39 A	47	48 * A	44
	43 C	45	49 A	
			45 * A	
50 - 55	45 A	43	43 A	46
	44 C	46	44 * A	39
		43		
55 - 60	41 A	47	42 C	
	43 C	44	44 * C	
	40 A		40 * A	
60 & OVER	39 A		46 * B	47 *
	41 A		41 * A	
	38 A			

PACKED CELL VOLUME/PERCENT
(Normal 40 - 54%)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 54

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		7,000		5,000
		10,000		
25 - 30		6,000		8,000 *
		6,000		6,000
		7,000		
		6,000		
30 - 35	11,000 A	6,000	8,000 C	13,000
		7,000 **		
		12,000		
35 - 40	7,000 A	6,000 **		7,000
	10,000 A	12,000		6,000
	8,000 A	7,000		
	9,000 B			
	9,000 A			
	6,000 C			
	12,000 A			
40 - 45	7,000 A	7,000		7,000
	9,000 A	11,000		6,000
	8,000 A	13,000		
	11,000 A			
	11,000 B			
45 - 50	10,000 A	8,000	7,000 * A	6,000
	9,000 C	8,000	6,000 A	
			8,000 * A	
50 - 55	7,000 A	7,000	8,000 A	8,000
	5,000 C	6,000	8,000 * A	5,000
		7,000		
55 - 60	5,000 A	10,000	6,000 C	
	7,000 C	7,000	10,000 * C	
	9,000 A		7,000 * A	
60 & OVER	6,000 A		7,000 * B	7,000 *
	8,000 A		6,000 * A	
	7,000 A			

WHITE CELL COUNT
(Normal 4,000 - 11,000 per cubic mm)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 55

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		241,600		158,400
		245,000		
25 - 30		206,000		344,000 *
		170,000		237,600
		208,000		
		194,000		
30 - 35	285,000 A	209,000	240,000 C	212,000
		240,000 **		
		322,000		
35 - 40	243,000 A	240,000 **		240,000
	248,000 A	276,000		296,000
	273,000 A	264,000		
	272,000 B			
	264,800 A			
	175,000 C			
	317,600 A			
40 - 45	143,000 A	248,000		192,000
	173,000 A	288,000		190,000
	240,000 A	296,000		
	248,000 A			
	308,000 B			
45 - 50	283,000 A	216,000	200,000 * A	225,000
	256,800 C	250,000	280,000 A	
			196,000 * A	
50 - 55	220,000 A	224,000	308,000 A	206,000
	150,000 C	252,000	260,000 * A	240,000
		328,000		
55 - 60	123,200 A	312,000	224,000 C	
	228,000 C	272,000	252,000 * C	
	310,000 A		220,000 * A	
60 & OVER	344,000 A		259,000 * B	208,000 *
	328,000 A		228,000 * A	
	224,000 A			

PLATELETS
(Normal 150,000 - 450,000 per cubic mm)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 56

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		52		59
		60		
25 - 30		54		56 *
		56		52
		55		
		53		
30 - 35	50 A	62	71 C	72
		55 **		
		69		
35 - 40	61 A	47 **		71
	60 A	65		47
	57 A	50		
	59 B			
	66 A			
	50 C			
	58 A			
40 - 45	67 A	44		54
	58 A	64		61
	50 A	56		
	70 A			
	64 B			
45 - 50	63 A	62	70 * A	53
	65 C	72	55 A	
			35 * A	
50 - 55	71 A	42	67 A	63
	57 C	49	52 * A	69
		56		
55 - 60	62 A	55	56 C	
	53 C	55	53 * C	
	54 A		67 * A	
60 & OVER	59 A		64 * B	56 *
	56 A		53 * A	
	58 A			

NEUTROPHILS PERCENT
(Normal 25 - 75)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 57

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		10		7
		4		
25 - 30		6		3 *
		2		4
		2		
		4		
30 - 35	1 A	1	- C	2
		6 **		
		-		
35 - 40	- A	2 **		-
	1 A	1		7
	3 A	1		
	1 B			
	4 A			
	1 C			
	- A			
40 - 45	- A	5		4
	4 A	3		1
	2 A	-		
	3 A			
	2 B			
45 - 50	2 A	2	- * A	-
	1 C	3	1 A	
			1 * A	
50 - 55	1 A	3	2 A	-
	1 C	2	2 * A	1
		8		
55 - 60	2 A	4	3 C	
	2 C	-	2 * C	
	4 A		3 * A	
60 & OVER	4 A		2 * B	2 *
	3 A		1 * A	
	2 A			

EOSINOPHILS PERCENT
(Normal .4 - 4.4)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 58

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		-		-
		-		
		-		- *
25 - 30		-		-
		-		
		-		
	- A	-	- C	-
30 - 35		- **		
		-		
	- A	- **		-
35 - 40	- A	-		-
	- A	-		
	- B			
	- A			
	- C			
	- A			
	- A	-		-
40 - 45	- A	-		-
	- A	-		
	- A			
	- B			
	- A	-	- * A	-
45 - 50	- C	-	- A	
			- * A	
	- A	-	- A	-
50 - 55	- C	-	- * A	-
		-		
	- A	1	- C	
55 - 60	- C	-	- * C	
	1 A		- * A	
	- A		- * B	- *
60 & OVER	- A		- * A	
	- A			

BASOPHILS PERCENT
(Normal 0 - 1)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 59

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		34		29
		30		
25 - 30		38		38 *
		39		42
		35		
		38		
30 - 35	43 A	33	26 C	22
		33 **		
		24		
35 - 40	33 A	45 **		27
	32 A	30		33
	35 A	41		
	35 B			
	26 A			
	43 C			
	40 A			
40 - 45	28 A	43		42
	35 A	27		36
	42 A	37		
	21 A			
	32 B			
45 - 50	27 A	31	29 * A	37
	32 C	33	39 A	
			61 * A	
50 - 55	25 A	52	20 A	34
	34 C	42	44 * A	26
		32		
55 - 60	28 A	34	35 C	
	42 C	41	39 * C	
	38 A		23 * A	
60 & OVER	26 A		31 * B	32 *
	40 A		41 * A	
	32 A			

LYMPHOCYTES PERCENT
(Normal 15 - 35)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 60

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		4		5
		6		
25 - 30		2		3 *
		3		2
		8		
		5		
30 - 35	6 A	4	3 C	4
		6 **		
		7		
35 - 40	6 A	6 **		2
	7 A	4		13
	5 A	8		
	5 B			
	4 A			
	6 C			
	2 A			
40 - 45	5 A	8		-
	3 A	6		2
	6 A	7		
	6 A			
	2 B			
45 - 50	8 A	5	1 * A	11
	2 C	2	5 A	
			3 * A	
50 - 55	3 A	3	11 A	3
	8 C	7	2 * A	4
		4		
55 - 60	2 A	6	6 C	
	3 C	4	6 * C	
	3 A		7 * A	
60 & OVER	11 A		3 * B	10 *
	1 A		5 * A	
	8 A			

MONOCYTES PERCENT
(Normal 2 - 6.5)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 61

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		9.5		6.9
		6.2		
25 - 30		7.2		8.5 *
		6.1		6.9
		6.4		
		8.5		
30 - 35	5.6 A	6.5	3.6 C	6.5
		6.4 **		
		6.5		
35 - 40	4.9 A	5.3 **		6.3
	6.0 A	7.2		2.8
	6.9 A	4.7		
	5.7 B			
	6.0 A			
	6.8 C			
	5.3 A			
40 - 45	7.9 A	7.0		4.4
	7.6 A	7.3		7.3
	5.4 A	6.0		
	8.3 A			
	4.6 B			
45 - 50	5.0 A	5.4	7.9 * A	6.8
	7.4 C	8.7	5.0 A	
			7.3 * A	
50 - 55	8.3 A	7.6	6.3 A	6.9
	7.9 C	6.9	5.5 * A	4.0
		6.4		
55 - 60	8.1 A	7.6	6.0 C	
	4.6 C	7.5	9.2 * C	
	4.1 A		7.2 * A	
60 & OVER	5.1 A		6.9 * B	5.5 *
	3.0 A		4.4 * A	
	4.6 A			

URIC ACID
(mgm/percent)
Normal 2.5 - 7

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 62

Uric Acid - (Normal level 2.5 - 7 mgm/100 mls.)

	Mean	Min	Max
Unexposed smokers	6.86	4.7	9.5
Unexposed non-smokers	6.07	2.8	8.5
Exposed smokers	6.05	3.0	8.3
Exposed non-smokers	6.30	3.6	9.2

TABLE 56

No significant difference between the groups.

Serum Calcium - (Normal 4.2 - 5.3 MEQ/Litre)

	Mean	Min	Max
Unexposed smokers	4.532	3.2	5.3
Unexposed non-smokers	4.642	3.5	5.2
Exposed smokers	4.643	3.8	5.2
Exposed non-smokers	4.627	3.5	5.1

TABLE 57

No significant difference between the groups.

CHAPTER 16

Cadmium and Bone Metabolism

Animal experiments indicate that cadmium, unlike lead does not accumulate to any extent in bone. Kitamura et al 1970 (89) have shown that less than 1% of human body burden resides in osseous tissue and that there is accumulation with age.

Bone metabolism was investigated in this survey by measuring:-

1) Serum calcium
2) Serum phosphate
3) Serum alkaline phosphatase
4) A radiological survey for bone density using the ulna bone

1. Serum calcium - (Normal 4.2 - 5.3 meq/litre) Figure 70, page 204, table 57, page 201. All measurements are within normal range and there is no significant group difference.

2. Serum phosphate - (Normal range 2.5 - 4.5) Figure71, page 205, table 59, page 206. All measurements are within normal range and there is no statistical difference between the group.

3. Serum alkaline phosphatase - (Chapter 14) Figure 49, page 169, table 40, page 171.

4. Radiology - This was performed by Dr. B. Fazackerly of Hobart. The ulna bone mineral content was examined using a method described by Doyle (88). Macroscopic cortical thickness measurements only have been reported.

A microdensitometer reading for these films was initially proposed but no desitometer available in Tasmania has proved suitable for the task.

Dr. Fazackerly reports that there are no significant changes in any subject in any group. There is no evidence of bony metabolic disease in any film. A significant number (24) participants in the survey complained of vague bone pain for which no obvious explanation could be found at the clinical examination. This group comprised eleven exposed workers and thirteen controls.

Conclusion

No evidence of disordered calcium metabolism was found.

Discussion

Several reports of bone changes in the occupationally exposed (Nicaud et al (55), Bonnell (61), and the well documented changes in Itai-Itai disease are believed to result from renal tubular damage by cadmium in association with dietary deficiency of either calcium, vitamin D or both.

Bone changes have not been a feature of other surveys, similar to this even when there has been evidence of altered calcium or phosphate metabolism.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		4.5		4.8
		4.5		
25 - 30		4.1		4.5 *
		4.4		4.8
		5.0		
		5.3		
30 - 35	4.5 A	4.5	4.9 C	5.0
		5.1 **		
		4.6		
35 - 40	4.7 A	3.4 **		5.2
	4.7 A	5.2		3.5
	5.2 A	4.8		
	4.7 B			
	5.0 A			
	4.4 C			
	4.9 A			
40 - 45	4.9 A	4.8		4.8
	4.3 A	3.2		4.9
	4.8 A	4.7		
	4.7 A			
	4.6 B			
45 - 50	4.9 A	4.4	4.5 * A	4.3
	5.0 C	4.6	3.5 A	
			4.7 * A	
50 - 55	4.2 A	4.7	5.1 A	4.2
	3.8 C	4.6	4.5 * A	5.1
		4.7		
55 - 60	4.9 A	4.3	4.8 C	4.6 *
	4.9 C	4.3	4.9 * C	
	4.6 A		4.6 * A	
60 & OVER	3.9 A		4.7 * B	
	4.3 A		4.7 * A	
	4.9 A			

CALCIUM (meq/litre)
Normal 4.2 - 5.3

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 70

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		4.0		3.6
		2.7		
25 - 30		3.8		5.0 *
		4.1		2.8
		4.0		
		2.0		
30 - 35	3.2 A	3.7	5.2 C	3.6
		4.0 **		
		2.8		
35 - 40	2.2 A	4.8 **		2.9
	3.3 A	3.0		3.7
	2.7 A	4.5		
	3.2 B			
	4.1 A			
	2.8 C			
	3.0 A			
40 - 45	3.1 A	2.8		2.9
	3.2 A	3.4		3.7
	4.5 A	3.5		
	4.5 A			
	4.5 B			
45 - 50	3.0 A	3.8	2.7 * A	2.6
	2.5 C	3.4	3.2 A	
			3.3 * A	
50 - 55	4.0 A	3.6	3.2 A	5.0
	4.5 C	3.3	4.7 * A	3.0
		4.2		
55 - 60	3.6 A	4.5	3.2 C	
	2.9 C	2.5	3.0 * C	
	4.5 A		2.8 * A	
60 & OVER	3.8 A		3.5 * B	3.7 *
	3.5 A		4.5 * A	
	3.0 A			

PHOSPHATE (mg/ml)
Normal 2.5 - 4.5 mgm/100 ml

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 71

Phosphate -(Normal 2.5 - 4.5 mgm/100 mls.)

	Mean	Min	Max
Unexposed smokers	3.564	2.0	4.8
Unexposed non-smokers	3.542	2.6	5.0
Exposed smokers	3.461	2.2	4.5
Exposed non-smokers	3.573	2.7	5.2

TABLE 58

No significant difference between the groups.

T4 - (Normal 3.0 - 6.6 mg/100 mls.)

	Mean	Min	Max
Unexposed smokers	4.85	3.7	7.0
Unexposed non-smokers	5.47	3.8	7.4
Exposed smokers	5.29	4.0	6.7
Exposed non-smokers	5.49	4.3	6.7

TABLE 59

No significant difference between the groups.

CHAPTER 17

Cadmium and Endocrine Function

The pancreas and gonads are well known storage sites for cadmium. Thyroid, adrenal, pancreatic and testicular function were also examined clinically and biochemically as part of the survey. No clinical abnormality was found.

1. Thyroid function - (Normal 3.0 - 6.6 Mg/100 mls.)

   This was measured by determining the serum thyroxine content. (Figure 63, page 210). No member of the control or exposed group showed either a higher or lower level than the normal nor was there any significant difference between the groups when compared as a whole. (Table 59, page 206).

2. Adrenal function - As measured by 17 Keto Steroids excretion/24 hrs.

   17 Keto Steroids - (Normal 5-25 mgm/24 hrs.) Figure 64, page 211.

   No member of either group exhibited an abnormal value for this test. Statistically there was no significant difference between the groups. (Table 60, page 212).

3. Gonadal function -

   An estimation of serum testosterone, follicle stimulating hormone and luteinising hormone was made, (figures 65, 66, 67, pages 213 - 215). The laboratory normals for these groups vary with age. (Vide chapter 7). Two members of the exposed group, both smokers, had a testosterone level that was either low or border line for their age compared with three members of the control group. Five members of the exposed group, all smokers, had a slightly low or abnormally low follicle stimulating hormone level; only two of them worked in the most contaminated area.

One member, an exposed smoker, has an increased level. Three members of the control group, one a smoker and two non-smokers, have a raised follicle stimulating hormone level. Two members of the exposed group, both smokers, had a slightly raised LH level, as did two members of the control group. Only one member, a non-exposed worker had elevated FSH and LH with a low serum testosterone level, suggesting impaired testicular function. There was no correlation between blood cadmium, urinary cadmium excretion or length of exposure to cadmium with the abnormal results found.

4. Pancreatic function -

The endocrine function of the pancreas was assessed using a blood sugar level in association with a test for glycosuria. (Ames Bililabstix).

Four exposed workers, two smokers and two non-smokers showed glycosuria as did two controls. (Figure 68, page 216). When these findings were examined in association with blood sugar levels (figure 69, page 217) only one, an exposed worker in a low cadmium environment area would definitely be regarded as new diabetic. One other exposed worker known to be a diabetic receiving treatment had a normal blood sugar reading. Two exposed workers and one control with a trace of sugar (0.01%) and a normal blood sugar reading were invited to have further investigation but did not accept. One control worker with 0.75% glycosuria was found, after a glucose tolerance test to have renal glycosuria.

Conclusion

There was no evidence of a harmful effect from cadmium on thyroid, adrenal, gonadal or pancreatic endocrine function.

Discussion

Most surveys on cadmium and health have not reported investigations into endocrine function. This is surprising in the light of the knowledge that cadmium is stored in both gonadal and pancreatic cells.

Cadmium does have a temporary or permanent sterilising effect. Parizek (79). At one time it was under investigation as a male contraceptive. This study would suggest that its use in this area would be ineffectual. Furthermore, adequate dosage for long periods would probably be associated with undesirable renal and haemopoeitic effects. Cadmium had no effect on sexual function of those exposed.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		7.0		4.1
		5.3		
25 - 30		4.1		4.9 *
		4.2		4.5
		6.0		
		5.1		
30 - 35	6.0 A	3.8	4.3 C	6.7
		3.9 **		
		4.4		
35 - 40	5.4 A	5.0 **		7.0
	5.8 A	6.4		4.1
	4.7 A	5.0		
	5.7 B			
	4.8 A			
	5.6 C			
	5.2 A			
40 - 45	5.1 A	5.0		5.5
	4.0 A	5.4		7.4
	4.8 A	4.2		
	6.0 A			
	- B			
45 - 50	4.9 A	3.7	5.2 * A	3.8
	4.1 C	4.8	5.5 A	
			5.3 * A	
50 - 55	5.7 A	3.9	6.1 A	4.8
	5.2 C	6.3	5.0 * A	5.8
		3.8		
55 - 60	5.0 A	4.4	6.7 C	
	5.0 C	5.0	4.3 * C	
	6.7 A		5.9 * A	
60 & OVER	4.5 A		6.6 * B	7.1 *
	5.8 A		5.5 * A	
	6.4 A			

HORMONES
THYROXINE (mg/100 ml.)
Normal 3 - 6.6

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 63

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		6.0		9.5
		12.6		
25 - 30		7.0		7.5 *
		13.4		20.0
		10.5		
		13.3		
30 - 35	13.2 A	6.7	10.6 C	6.0
		18.0 **		
		9.4		
35 - 40	6.1 A	19.0 **		7.0
	8.3 A	11.9		8.0
	10.4 A	5.9		
	8.4 B			
	7.4 A			
	15.0 C			
	9.2 A			
40 - 45	7.6 A	13.8		14.1
	11.3 A	11.3		9.4
	7.5 A	11.0		
	11.0 A			
	8.6 B			
45 - 50	4.1 A	16.1	10.0 * A	10.9
	7.2 C	7.9	8.2 A	
			7.7 * A	
50 - 55	14.0 A	11.0	8.0 A	14.1
	6.2 C	7.4	14.6 * A	9.3
		9.0		
55 - 60	9.4 A	6.6	8.0 C	
	9.8 C	9.7	8.5 * C	
	17.0 A		14.5 * A	
60 & OVER	11.0 A		14.7 * B	9.0 *
	10.8 A		5.8 * A	
	9.1 A			

HORMONES
17 KETO STEROIDS
(mg 24 hrs)
Normal 5 - 25

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 64

17 Keto Steroids -

	n	Mean	Min	Max
Unexposed smokers	22	10.80	5.9	19.0
Unexposed non-smokers	12	10.40	6.0	20.0
Exposed smokers	21	9.68	4.1	17.0
Exposed non-smokers	11	10.05	5.8	14.7

TABLE 60

No significant difference between the groups.

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		21.6		22.3
		11.7		
25 - 30		19.2		17.1 *
		23.1		11 0
		22.7		
		24.5		
30 - 35	13.1 A	15.9	16.8 C	8.9
		17.8 **		
		21.3		
35 - 40	23.3 A	18.6 **		22.2
	21.6 A	15.9		21.1
	11.8 A	17.6		
	insuff.B			
	29.2 A			
	21.6 C			
	9.8 A			
40 - 45	16.8 A	25.3		14.3
	insuff.A	15.1		16.3
	16.3 A	21.6		
	19.2 A			
	17.2 B			
45 - 50	14.7 A	21.1	14.1 * A	13.9
	12.4 C	18.6	17.0 A	
			15.2 * A	
50 - 55	18.6 A	6.5	22.2 A	11.4
	24.9 C	21.6	18.0 * A	4.9
		11.7		
55 - 60	18.5 A	26.1	13.4 C	
	15.6 C	11.4	13.0 * C	
	3.4 A		20.5 * A	
60 & OVER	21.3 A		14.0 * B	16.4 *
	19.8 A		12.7 * A	
	26.4 A			

HORMONES
TESTOSTERONE (mol/L)

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 65

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		3.5 ± 0.2		2.5
		2.2 ± 0.2		
25 - 30		2.3 ± 0.2		1.0 ± 0.1 *
		2.3 ± 0.2		1.0
		1.7 ± 0.1		
		0.9 ± 0.1		
30 - 35	2.0 ± 0.2 A	3.4 ± 0.2	2.8 ± 0.2 C	1.4 ± 0.1
		1.4 ± 0.1 **		
		2.0 ± 0.2		
35 - 40	2.1 ± 0.2 A	1.3 **		2.7 ± 0.2
	1.4 ± 0.1 A	2.1 ± 0.2		3.5
	2.2 ± 0.2 A	2.4		
	0.4 B			
	3.6 A			
	6.4 C			
	2.3 A			
40 - 45	1.6 ± 0.1 A	3.6		2.0 ± 0.2
	4.3 A	3.4 ± 0.2		3.4 ± 0.2
	1.4 ± 0.1 A	2.9 ± 0.2		
	0.3 ± 0.1 A			
	1.0 B			
45 - 50	3.2 ± 0.2 A	1.9 ± 0.2	1.7 ± 0.1 * A	7.1 ± 0.4
	0.7 ± 0.1 C	1.6 ± 0.1	1.0 A	
			5.2 ± 0.3 * A	
50 - 55	2.0 ± 0.2 A	1.6 ± 0.1	2.5 ± 0.2 A	2.4 ± 0.2
	0.8 ± 0.1 C	1.2	1.5 ± 0.2 * A	21.2 ± 1.9
		3.2 ± 0.2		
55 - 60	4.5 A	1.4	3.6 ± 0.4 C	
	0.8 C	1.8 ± 0.1	4.0 ± 0.3 * C	
	2.7 ± 0.2 A		3.9 ± 0.3 * A	
60 & OVER	2.8 ± 0.2 A		2.3 * B	0.7 ± 0.1 *
	3.6 A		5.6 ± 0.5 * A	
	0.2 ± 0.5 A			

HORMONES
FOLLICLE STIMULATING HORMONE
ml U/ml

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 66

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		1.7 ± 0.1		2.3 ± 0.2
		1.5 ± 0.09		
25 - 30		2.0 ± 0.1		2.3 *
		1.8 ± 0.1		1.5 ± 0.1
		2.1		
		1.6		
30 - 35	3.0 ± 0.1 A	2.1 ± 0.1	1.4 ± 0.08 C	1.8
		1.8 ± 0.1 **		
		2.2 ± 0.1		
35 - 40	1.7 A	2.4 **		3.0
	2.5 ± 0.1 A	2.1		1.9
	1.5 A	1.9		
	2.1 ± 0.2 B			
	2.0 ± 0.1 A			
	3.4 ± 0.2 C			
	1.8 ± 0.1 A			
40 - 45	2.4 ± 0.1 A	2.3 ± 0.2		1.3 ± 0.08
	2.7 ± 0.2 A	2.7 ± 0.1		1.8 ± 0.1
	2.7 ± 0.1 A	2.5		
	1.0 A			
	1.6 ± 0.1 B			
45 - 50	3.1 ± 0.2 A	1.8 ± 0.1	1.6 *A	3.3 ± 0.2
	0.7 C	1.5 ± 0.1	2.0 A	
			2.4 ± 0.2 *A	
50 - 55	1.9 ± 0.1 A	1.4 ± 0.08	3.0 ± 0.1 A	1.9 ± 0.1
	1.2 C	2.6 ± 0.2	2.1 *A	8.1 ± 0.5
		2.1 ± 0.1		
55 - 60	4.9 ± 0.4 A	1.5	2.6 C	
	1.9 C	1.5	2.8 ± 0.1 *C	
	1.9 ± 0.1 A		2.6 ± 0.1 *A	
60 & OVER	2.6 A		2.2 *B	1.0 *
	4.3 A		5.5 ± 0.3 *A	
	1.3 A			

HORMONES
LUTEINISING HORMONE
ml U/ml.

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 67

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		nil		nil
		nil		
		nil		nil *
25 - 30		nil		nil
		nil		
		nil		
	nil A	pos++	nil C	nil
30 - 35		nil **		
		nil		
	nil A	trace **		nil
35 - 40	nil A	nil		nil
	nil A	nil		
	nil B			
	nil A			
	nil C			
	nil A			
	nil A	nil		nil
40 - 45	nil A	nil		nil
	nil A	nil		
	nil A			
	trace B			
	nil A	nil	nil * A	nil
45 - 50	nil C	nil	nil A	
			nil * A	
	nil A	nil	nil A	nil
50 - 55	nil C	nil	nil * A	nil
		nil		
	nil A	nil	nil C	
55 - 60	nil C	nil	nil * C	
	nil A		trace*A	
	nil A		+++ * B	nil *
60 & OVER	pos++ A		nil * A	
	nil A			

GLYCOSURIA

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 68

	Exposed Smokers	Unexposed Smokers	Exposed Non smokers	Unexposed Non smokers
UNDER 25		84		77
		96		
25 - 30		81		69 *
		110		90
		87		
		80		
30 - 35	87 A	85	80 C	78
		74 **		
		82		
35 - 40	100 A	100 **		85
	96 A	73		89
	80 A	90		
	97 B			
	81 A			
	76 C			
	93 A			
40 - 45	107 A	123		85
	92 A	88		96
	93 A	90		
	97 A			
	91 B			
45 - 50	75 A	87	90 * A	95
	80 C	85	92 A	
			83 * A	
50 - 55	96 A	108	86 A	111
	82 C	100	100 * A	107
		103		
55 - 60	102 A	79	117 C	
	86 C	124	89 * C	
	88 A		83 * A	
60 & OVER	80 A		368 * B	85 *
	100 A		88 * A	
	103 A			

BLOOD GLUCOSE
(mgm/100 ml)

Normal 70 - 110

* - Previous smokers over five years
** - Previous smokers under five years
A - Cadmium Plant
B - Compressed Air Station
C - Superphosphate Plant

FIGURE 69

CHAPTER 18

CONCLUSIONS

Using blood cadmium and 24 hour urinary excretion levels as markers, workers in a cadmium contaminated environment at the Electrolytic Zinc Company of Australasia's plant at Risdon, Tasmania, exhibit evidence of a higher body burden of cadmium than do controls from other areas of the plant. This cadmium burden appears to be tolerated very well for they show no evidence of serious health problems when compared to the controls. Only minor abnormalities of cellular or organ function were found in a wide variety of clinical, biochemical and radiological investigations performed. These have been detailed in previous chapters.

Pulmonary disease is a common finding amongst those occupationally exposed to cadmium (chapter 5). Bonnell et el (61) have reported that it may appear or increase in severity some years after removal from exposure. The cadmium workers had a higher incidence of subjective respiratory symptoms than the controls. However, simple screening tests of respiratory function showed no measurable difference between the two groups. Radiologically also there were no significant changes or differences in chest films. The first manifestations of chronic airways disease are those symptoms which were more prevalent in my group of exposed workers - cough, wheeze, dyspnoea and repeated respiratory infections. I am therefore not excluding the possibility that this cadmium effect will appear later, although Bonnell reviewed a group who had worked with a much higher level of atmospheric cadmium than my group (270 micrograms/cubic metre compared to 31). Clincally there was no serious respiratory disease found as a consequence of working with cadmium.

Most surveys show the other major hazard of a high body burden

of cadmium is impaired renal function. No evidence of an adverse effect on renal function from occupational exposure to cadmium has been demonstrated in this survey. As Bonnell also has reported that proteinuria can occur after removed from exposure, I am not excluding a later appearance of this finding.

Unlike most other surveys (chapter 5) I found no evidence of subjective or objective ill health arising from working with cadmium. Again this could be due to the low working environmental level. No figures are available for this level over the preceeding years but it should have been higher in the past when little attention was paid to industrial hygiene and many industrial practices now considered unsafe were in operation at Risdon.

In particular hypertension, neoplasia, liver disease, disorders of bone metabolism, endocrine malfunction, renal calculi and bladder tumors were not found amongst the exposed. Animal experimental studies and epidemological surveys have implicated cadmium as a causative agent in these conditions. This in turn has led to speculation by environmentalists that the general public are at risk from the increasing environmental levels of cadmium. If these conditions are not more prevalent in those with a body burden of the order of the group of exposed workers one can postulate that either they are not dose related if they are produced by tissue cadmium and/or if there is a dose relationship it is extremely unlikely that the public are seriously at risk from present environmental levels. There is no evidence from the findings of both groups that environmental cadmium in and around Hobart has any deleterious effect on health.

The survey shows cadmium may produce changes in the synthesis of both haemoglobin and plasma proteins. These changes have been discussed in previous chapters. They were of no clinical significance in my group of workers. Their real significance may be furthering both knowledge of metabolism and assessment of body burden. This would require a study of a much bigger group over a longer period. Several other surveys, but not all, have found similar changes but there are no reports of a more detailed examination of these changes.

No individual or group of symptoms and/or signs appeared from my investigations which might assist in the diagnosis of a cadmium effect. No simple non invasive investigation procedure produced any evidence of a direct cellular effect. There appears to be no synergistic or antagonistic effect from other metals on the health of cadmium workers. No simple screening procedure appeared from the survey results as a satisfactory indication of danger levels of body burden. Nevertheless the findings as a whole may be of assistance in deciding safe working levels.

Further monitoring of both groups would provide valuable evidence for those who have the responsibility of determining a figure for a safe, no effect level of total body cadmium, tissue, particularly renal tissue, level; and more importantly total intake levels. Industrial hygienists are particularly concerned with working environmental levels and there is still debate on just what these levels should be. Working in concentration up to 31 micrograms at least for long periods has proved to be safe for the group of workers I examined. (Vide infra).

The cadmium compounds normally encountered in industrial environments

may be divided into three categories in respect to the hazards to those exposed to them.

1. 'Fume' usually submicron (less than 0.5 um diameter) agglomerates of small (less than 0.1 um diameter) cadmium oxide particles. Such fume may be classed as wholly 'respirable', that is capable of reaching and depositing in terminal bronchioles and alveoli, to give localised effects and possibly complete systemic absorption.

2. 'Soluble dusts' defined as those soluble in N/10 HCl. They include cadmium oxide and chloride and cover all normal airborne sizes. It should be emphasised that with regard to its biological action, it is the solubility of the deposited dust in body fluids which needs to be considered for this may be quite different from its solubility in water. Certain cadmium compounds such as cadmium oxide are virtually insoluble in water but their solubility in such acid conditions represents the behaviour in the body of compounds such as cadmium oxide more closely in this respect than solubility in water at neutral pH. While with such dusts only the respirable fraction will be avilable for alveolar deposition, some of the larger particles may go into solution on the surface of the upper respiratory tract and also be absorbed systematically. The remaining larger particles, together with the proportion of the particles deposited on the ciliated epithelium of the tracheobronchial tree which are translocated will, finally, be swallowed to give only a low contribution to the systemic absorption.

3. Insoluble dusts, relatively incoluble in body fluids such as cadmium sulphides and sulphoselenides.

In 1971 the American conference of Government Industrial Hygienists recommended a Ceiling Value for cadmium oxide fume of 100 Ug per cubic metre and a Threshold Limit Value of 200 Ug/cubic metre for cadmium metal dust and soluble salts. These figures have produced considerable debate and lower figures have been suggested or applied by others.

Chronic lung disease, probably due to direct action from inhaled matter and renal disease from increasing renal concentration are generally accepted as the only major industrial hazards of cadmium. The setting of safe working limits to protect from these is complicated by the healthy kidneys ability to store cadmium, the small and relatively fixed cadmium excretion no matter what the renal tissue concentration and the increasing background exposure from increasing environmental concentrations.

Recent figures, based on certain assumptions of absorption, distribution and deposition of cadmium in the organism and the use of mathematical biochemical models have indicated that a renal concentration of 300 Ug/gm wet weight is associated with proteinuria. Friberg has suggested that 200 Ug be regarded as the tentative critical concentration for a no effect result. A 50 year old man would reach this level with either an ambient concentration of 2 Ug/cubic metre over a 24 hour day or 20 Ug/cubic metre in the working environment over an eight hour day.

The British Occupational Hygiene Society Committee on Hygiene Standards have recommended a figure of 50 Ug/metre as the figure for total respirable cadmium. My survey would suggest a figure of 30 Ug is safe and it is not necessary to aim for the relatively low figure suggested by Friberg.

Statistical analysis of my results indicates that exposed workers who smoke are more likely to suffer the abnormalities found than those who do not. As has been detailed earlier, smoking - particularly cigarette smoking contributes significantly to body burden. Bruckman et el (90) from their model have suggested that a smoker (20 cigs/day) has a 50% increase in body burden at the age of 70 than a non-smoker.

Independently, Friberg has concluded that a non-exposed 50 year old who smokes has probably exceeded a renal concentration of 200 Ug/gm wet weight. There is no evidence from my survey to suggest that the combination of smoking and exposure to cadmium produces serious effects. There is evidence that this combination is undesirable, for biochemical changes, as yet of no significance, are common with the combination. Further study of large numbers with this combination is required. It may be due to an additive effect of two different agents or an increased total burden of cadmium derived from two sources.

Cadmium has produced death and disability in both the occupationally and environmentally exposed. It has no useful biological function and consequently it must receive strict biological and environmental monitoring. But there is evidence from this work that the body can tolerate it to some degree. This should provide a stimulus to further research into both allowable environmental levels and controls as well as tolerable body burden.

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