CADMIUM

The importance of this non-essential trace metal in urology.

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CONTENTS

		PAGE
List of Tables		4
List of Figures		8
Acknowledgements		12
Summary		14
CHAPTER NO.		
1	Introduction.	20
2	History of cadmium.	25
3	Uses of cadmium.	33
4	Statutory regulations governing use of cadmium.	36
5	Environmental aspects of cadmium.	39
6	Effects of cadmium on various biological systems	58
7	Effect of cadmium on kidney.	90
8	Establishment of stone prevalence.	102
9	Study of coppersmiths exposed to cadmium.	107
10	Comparison of different groups exposed to cadmium.	119
11	Prospective study of coppersmiths 1975 - 1981.	134
12	Studies of different work groups in 1981 - 1982.	142
13	Study of general workers in factory with cadmium pollution problem.	150
14	Studies of cadmium in post mortem kidneys.	160
15	Studies of renal cadmium in various U.K. centres and in 2 coppersmiths.	169

CONTENTS (Contd).

		PAGE.
16	Conclusion.	179
	Appendices.	186
	References.	196

LIST OF TABLES.

TABLE NO.	TITLE
1	Physico-chemical data of cadmium.
2	Chronological table of major important dates.
3	Use of cadmium in different industries.
4	Production of cadmium worldwide.
5	Air pollution with cadmium.
6	Renal stone prevalence in random population.
7	Site of calcified renal stones found in random population.
8	Initial biochemical measurements in coppersmiths.
9	Comparison of biochemical parameters between coppersmiths and controls.
10	Comparison of blood cadmium values in 5 groups of workers.
11	Comparison of urine calcium values in 5 groups of workers.
12	Comparison of serum urea in 5 groups of workers.
13	Comparison of serum creatinine in 5 groups of workers.
14	Comparison of urine sodium in 5 groups of workers.
15	Comparison of serum copper in 5 groups of workers.
16	Comparison of serum zinc in 5 groups of workers.
17	Comparison of urine copper in 5 groups of workers.

TABLE NO.	TITLE.
18	Comparison of urine zinc in 5 groups of workers.
19	Value of Biochemical parameters which can be used to diagnose cadmium poisoning.
20	Paired analyses of blood cadmium values 1975 - 1981 in coppersmiths.
21	Mean blood cadmium values in coppersmiths 1975 - 1982.
22	Mean blood cadmium in 9 different factory groups.
23	Blood cadmium values in factory group with hypercalciuria 1976 - 1981.
24	Blood cadmium values in original group 1975 - 1981.
25	Proteinuria in workers with hypercalciuria 1976 - 1981.
26	Proteinuria in original control group 1975 - 1981.
27	Urine cadmium mean values in different factory groups 1981 - 1982.
28	Urine cadmium (mean values) in different factory groups 1981 - 1982.
29	Proteinuria in different factory groups in 1981 - 1982.
30	Previous respiratory problems in general factory scan.
31	Previous renal disease in general factory scan.
32	Previous stone disease in general factory scan.
33	Previous stone disease in general factory scan non-attenders.

TABLE NO.	TITLE
34	Cadmium values v age v smoking habits in general factory scan - males.
35	Cadmium values v age v smoking habits in general factory scan - females.
36	Mean blood cadmium v duration of employment in general factory scan - male non smokers.
37	Mean blood cadmium v duration of employment in general factory scan - male smokers.
38	Biochemical parameters in general factory scan - males.
39	Biochemical parameters in general factory scan - females.
40	Mean blood cadmium levels v type of employment in general factory scan - male employees.
41	Mean blood cadmium levels v type of employment in general factory scan - female employees.
42	Cadmium, zinc and calcium in renal cortex and medulla.
43	Cadmium in renal cortex related to disease category.
44	Significant differences between renal cadmium and zinc and different disease categories.
45	Renal cortical cadmium related to age.
46	Renal cortical cadmium related to age in subjects between 31 and 40 years of age.
47	Significant differences in renal cadmium zinc and calcium related to age.
48	Significant differences in renal cadmium zinc and calcium related to smoking habits.

TABLE NO.	TITLE
49	Significant differences of renal cortical cadmium in 4 groups of disease.
50	Comparison of renal cortical cadmium values in different countries.

LIST OF FIGURES.

FIG. NO.	TITLE
1	Periodic table showing essential and non essential trace elements.
2	World production of cadmium since First World War.
3	Production of cadmium in Western European Countries v Eastern bloc countries 1950 - 1959.
4	Production of cadmium in Western European countries v Eastern bloc countries 1960 - 1969.
5	Major cadmium producing countries within the EEC.
6	Geological specimen of Greenockite.
7	Common domestic products containing cadmium.
8	Effect of cadmium effluent on sediments in a river system.
9	The effect of sewage sludge on cadmium content of soil.
10	The variable cadmium content in different geological formations.
11	The variation of cadmium content in wheat from a variety of different countries.
12	Brazing process using silver rods containing 22% cadmium.
13	Completed compressor unit for domestic refrigeration unit.
14	Production line system illustrating large number of brazing procedures.
15	Sample of dust from factory roof.
16	Atmospheric levels of cadmium before and after cessation of brazing operations.

FIG. NO.	TITLE
17	Cadmium values found on individual samplers.
18	General pattern of blood and urine biochemical measurements on initial screening of coppersmiths.
19	Relationships of blood cadmium levels to proteinuria on initial screening.
20	Relationship of urine cadmium to proteinuria on initial screening.
21	The prevalence of stone disease in coppersmiths in 1975.
22	Relationship of blood cadmium to urine calcium in coppersmiths.
23	Comparison of coppersmiths and sheet metal workers on initial examination - general differences.
24	Comparison of coppersmiths and sheet metal workers - biochemical differences.
25	In patient studies of coppersmiths showing results of liver function tests.
26	In patient studies of coppersmiths showing abnormalities of urea electrolytes and creatinine.
27	In patient studies of coppersmiths showing abnormalities of calcium and phosphate parameters.
28	In patient studies of coppersmiths indicating renal function and prevalence of renal tubular acidosis.
29	In patient studies of coppersmiths showing renal patterns of calcium and phosphate and other abnormalities.
30	In patient studies of coppersmiths showing correlation between iron and copper.
31	Comparison of initial blood cadmium values in 5 groups of workers.

FIG. NO.	TITLE
32	Comparison of urine calcium excretion in 5 groups of workers.
33	Comparison of serum calcium in 5 groups of workers.
34	Comparison of serum inorganic phosphate in 5 groups of workers.
35	Progressive development of proteinuria in coppersmiths.
36	The progressive increase in B_2 microglobulinuria in coppersmiths.
37	The changes in urine zinc in coppersmiths.
38	The changes in urine calcium in coppersmiths.
39	The changing pattern of stone disease in coppersmiths.
40	Blood cadmium (mean values) in coppersmiths 1975 - 1982.
41	Blood cadmium values in different factory groups 1981 - 1982.
42	Blood cadmium (mean values) in factory groups with correction for previous occupation in Group 6 subjects.
43	Urine cadmium (mean values) in factory groups with correction for previous occupation in Group 6 subjects.
44	Urine cadmium (mean values) in factory group 1981 - 1982.
45	Urine cadmium (mean values) in different factory groups 1981 - 1982.
46	Low molecular weight proteinuria in different factory groups.
47	Large molecular weight proteinuria in different factory groups.

FIG. NO.	TITLE
48	Whole body calcium reduction related to duration of employment.
49	General factory scan - failure of smoking habits to affect blood cadmium levels - male subjects.
50	General factory scan - failure of smoking habits to affect blood cadmium levels - female subjects.
51	Repeat blood cadmium values in subjects in general factory scan.
52	Repeat serum inorganic phosphate at 1 yearly intervals in coppersmiths.
53	Serum inorganic phosphate values in male factory workers v general population.
54	Serum inorganic phosphate values in female factory workers v. general population.
55	Comparison of stone prevalence in general factory workers.
56	Repeat blood cadmium values in general factory workers.
57	Distribution of renal cortical cadmium in male and female.
58	Median values of reanl cortical cadmium related to age.
59	Renal cortical cadmium by age group.
60	Cortical and medullary cadmium by age group.
61	Renal cortical cadmium related to smoking habits.
62	Cortical cadmium related to disease category.
63	Cortical and medullary cadmium related to disease.
64	Cortical and medullary cadmium values in different disease

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SUMMARY

Improved biochemical techniques have resulted in a better appreciation of the role of trace metals in essential and non essential biological function.

Cadmium has been shown to be a non essential toxic trace element with a biological half life of between 20 and 30 years.

Since the time of the isolation of the metal in the early part of the 19 century there was very little appreciation of its toxic effects since isolated episodes of acute cadmium poisoning were very rarely encountered.

The development of mechanized transport during the first world war led to a major upsurge in the use of cadmium which was found to be a valuable element in the prevention of corrosion in the smaller parts of internal combustion engines.

It was in 1950 however before Friberg in Sweden gave the first description of chronic cadmium poisoning in a workforce. Various statutory legislations have been introduced and modified since that time with the hope that work forces can be protected from the effects of cadmium. The acceptable levels vary in different countries and are regarded by many overseas experts as being too high in the United Kingdom.

It is necessary to be aware that cadmium has been shown in man and animals to have an effect on a variety

of different systems and although it was considered initially to affect the pulmonary system it is now realised that it is the renal system which is most likely to be affected by cadmium.

Considerable attention has been paid in the past few years to the type of proteinuria caused by cadmium. Some authors consider that the principle damage within the kidneys occurs in the renal tubules and this results in low molecular weight proteinuria, specifically B_2 microglobinuria.

There is evidence which shows that medium to large molecular weight proteinuria occurs and from my own experience and in agreement with other workers in other countries it is clear that both large and low molecular weight proteinuria are to be found in chronic cadmium poisoning.

However, if too much emphasis is placed on the type of proteinuria found in chronic cadmium poisoning it is likely that other biochemical abnormalities which result from cadmium can be missed. This work gives an insight into the damaging effects which cadmium produces in terms of altered calcium metabolism resulting specifically in a steady rise in the prevalence of renal stone disease in a group of workers who were monitored annually from 1975 to 1982.

The men in question were very heavily exposed to cadmium and when compared to a reference population it can be seen that the mean levels of blood cadmium in the

group were always at least five times greater than the normal population. By careful annual follow up it was also possible to show that despite a complete and instant cessation of exposure to the metal the blood cadmium levels, like the urine cadmium levels did not immediately return to normal but remained constantly elevated. At the levels of exposure this must indicate a very large body burden of cadmium and what is more, despite the large amounts being lost by excretion in the urine, a mobilisation of cadmium must be taking place from large deposits in bones and other sites.

In order to assess the significance of the biochemical parameters found in the group under study, it was necessary to look at a variety of different groups of workers who were involved in different occupations within the factory under particular study or who were involved in different cadmium processes in a variety of different factories. The study of these different groups has enabled me to examine the different biochemical parameters across a wide spectrum of workers and has resulted in the clear demonstration that the workers in the principal study group had clearly been the most seriously affected with respect to exposure to cadmium. It has also been possible to demonstrate that workers beyond the immediate location of cadmium exposure appear to have a greater than normal risk of having higher blood cadmium levels than normal subjects and also a greater likelihood of having

damaged cells as a potential nucleus for renal stone formation. When such foci are present and are combined with altered calcium and phosphate excretion then it should be less than surprising to discover that stone formation is a major effect of chronic cadmium poisoning.

Because of the random population survey which had been undertaken by myself along with other helpers it was possible to demonstrate that the prevalence of stone disease in this area is 3.5%. At the initial examination of the coppersmiths in 1975 it was immediately obvious that the prevalence of stone disease in the group was 18.5% - a figure which is comparable to other reports. It is surprising therefore that there does not seem to be any follow up by those other workers specifically to discover whether or not the rate of stone disease remains the same or as has been found in the present study steadily increases with time. In the coppersmiths group in 1982 the prevalence of stone disease reached over 40%. Interestingly the subjects most likely to develop stone disease were those who initially were found to have subnormal or low normal serum inorganic phosphate values.

Apart from the clinical problems of stone disease, the presence of an unexplained and persistent hypercalciuria is highly significant to the long term welfare of the individual. In rather specialized circumstances in Japan it has been demonstrated in post menopausal

women in whom the effects of repeated pregancies have already presumably reduced skeletal calcium that excess cadmium can result in a severe osteo malacia described as itai-itai disease.

Although our studies have not found such severe skeletal effects nevertheless there is evidence that a whole body deficiency of calcium does occur in the workers examined as evidenced by the in vivo neutron activation study. It is therefore considered essential that in the general assessment of possible metabolic abnormalities likely to be found in the examination of a stone subject the demonstration of idiopathic hypercalciuria should alert the examiner to the possibility that a cause for the hypercalciuria could be chronic cadmium exposure. The latter can be excluded by a careful industrial history together with measurements of blood and urine cadmium along with estimations of serum calcium, inorganic phosphate and urinary protein estimations.

Finally in the assessment of potential episodes of chronic cadmium poisoning from whatever sources it is considered that a fundamental examination must be a plain abdominal radiograph.

Where there is a calcified focus in the region of either or both kidneys then a full intra venous urogram is indicated to ascertain whether or not a renal stone is present. When a work force is being followed on a

long term basis and, having established the stone prevalence at the outset of investigations, it is essential to be aware that, as has been shown in this work, renal stone formation is of paramount importance in the long term supervision of subjects and coupled with chronic hypercalciuria may result in subsequent significant reduction in skeletal calcium. Proof of the high renal levels of cadmium in kidneys in two of the cadmium exposed workers was obtained by analysing their kidneys and comparing these with a survey of renal cadmium content in this area. The levels in the two individuals were almost 6 times as high as the normal population. Highly significantly one of these individuals developed a renal carcinoma which adds further importance to the taking of an occupational history in upper urinary tract disease as presented to the practising urologist.

INTRODUCTION.

CHAPTER 1

INTRODUCTION

There has, in the past 10 years, been a considerable revival of interest in trace element metabolism. This can be attributed to three main factors (Underwood, 1970).

1 Improved analytical methods (Eaton, 1976).

2 The stimulus resulting from the work done on the mechanism of action of elements such as zinc, selenium, copper and cobalt in human, animal and agricultural biological systems.

3 An increased awareness that environmental or industrial pollution may occur as a result of the use of trace substances in manufacturing industries.

Biologists recognise essential and non essential trace elements, the latter being toxic or non toxic. Although most work on trace element metabolism has been in fields other than human metabolism, trace elements are very relevant in human biology.

Fourteen elements are essential for animal life and these include iron, iodine, copper, zinc, manganese, cobalt, molybdenum, selenium, chromium, nickel, tin, silicon, fluorine and vanadium (Masironi, Kiortyohann and Pierce, 1977). Other elements are known to be toxic at low levels of intake and include arsenic, lead, cadmium and mercury.

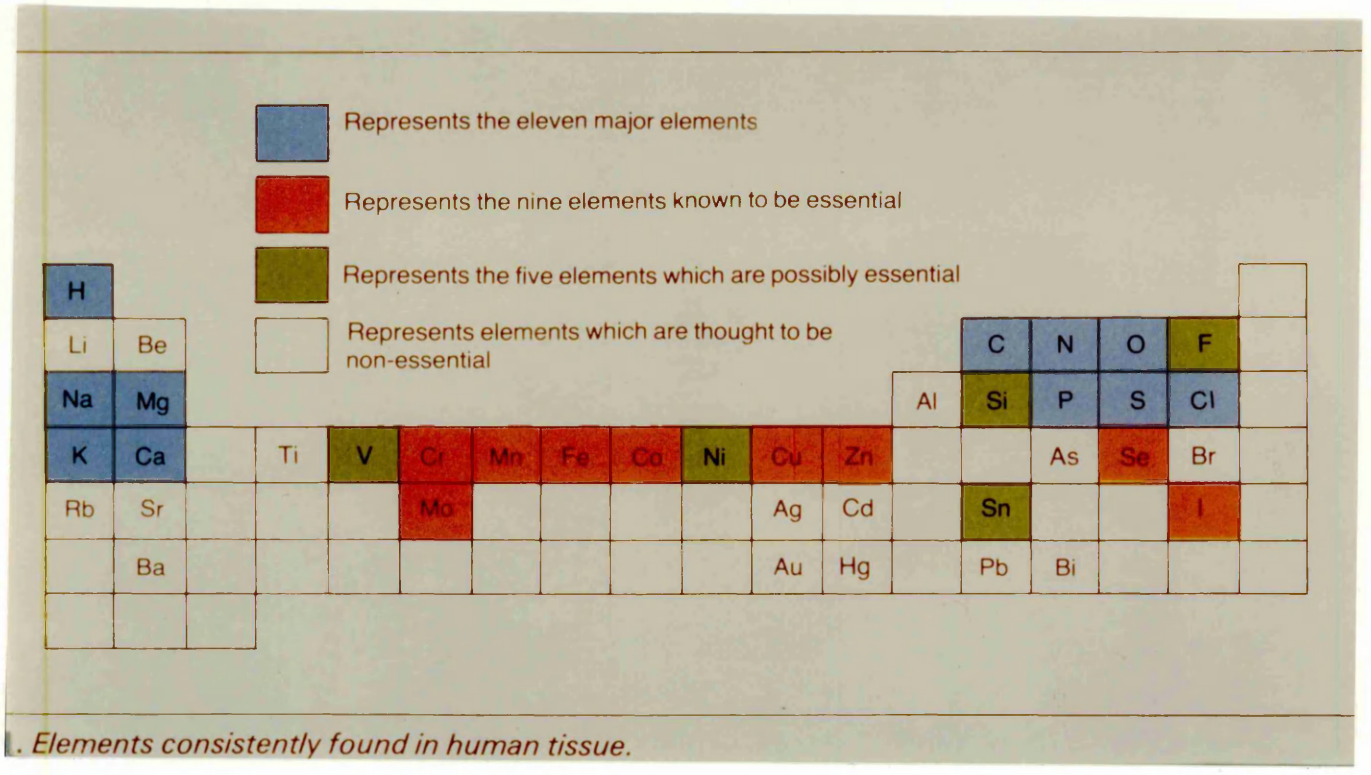

Fig. 1. The periodic table showing the essential elements and the non essential elements found in human tissues.
(By permission of Dr. P.J. Aggett).

Most trace elements of biological significance tend to occur in the same part of the periodic table. It is significant that calcium is placed in this part of the ionic spectrum and, if the calcium which is present in bone is excluded, then the element may justifiably be considered as a trace element in its own right (Fig. 1).

GENITO URINARY SYSTEM.

The genito urinary system both in man and animals requires trace elements for normal function and the balance can be affected by the introduction of excess amounts of essential trace elements, the accumulation of toxic non essential trace elements or as a result of the unusual circumstances created in the application of dialyses in the management of renal filaure (Knudson and Persson, 1977).

The most common trace element, apart from calcium, found in the genitourinary system is zinc. In animals zinc depletion results in a reduction of body weight, skin changes and in a diminution in reproductive capacity. In man a syndrome of zinc deficiency has been described and is characterized by reduction in stature, hypogonadism, mental sub normality and relative infertility (Prasad et al, 1963).

The other trace elements of importance in genito-urinary pathophysiology are magnesium, copper, aluminium and cadmium. Of these last elements cadmium is a non

essential toxic element. It is recognised as being nephrotoxic and possibly carcinogenic in prostate. The element is widely used in industry and its effect on a workforce which had been chronically exposed to cadmium forms the major part of this study.

Commercially used cadmium is obtained from zinc ores and from it's initial discovery in 1817 it was almost 100 years before the metal was used in quantity. The most important factor which increased the demand for cadmium was the development of mechanised transport with the onset of World War 1. As can be seen (Fig. 2) there has been a steady increase in world production of the element (Chadwick, 1976) as it has gained wider industrial application.

The main producing countries are U S A , Belgium, Canada, Australia, Poland, Italy, U K, Japan, Norway, France, West Germany, U S S R and Mexico.

The increased use of cadmium is shown by the fact that in 1976 the annual U S A output was 3.67 million pounds (Mining Review, 1977). Of the total, 20% is used in the nickel battery industry and 40% in electroplating. In 1977 the output was 4.4 million pounds in the U S A (Baker, 1978). Despite the large local production one half of all the cadmium used in the U S A is imported from overseas (Streatfield, 1976), the U S A in 1977 importing 5.0 million pounds. The sources included Canada, Australia, Yugoslavia, Mexico, Belgium

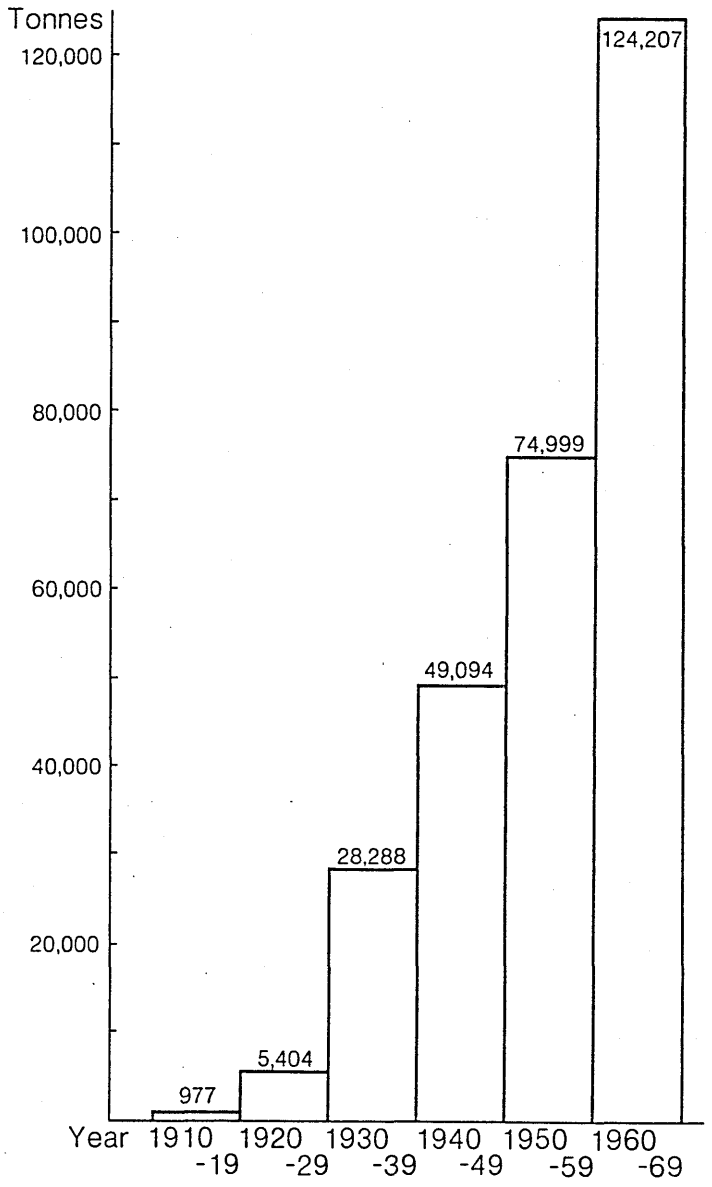

Fig. 2

The increase in world production of cadmium since the time of the first World War due to the use of the metal in prevention of corrosion in mechanised transport. (Criteria for Cadmium. Commission of the European Communities, 1978).

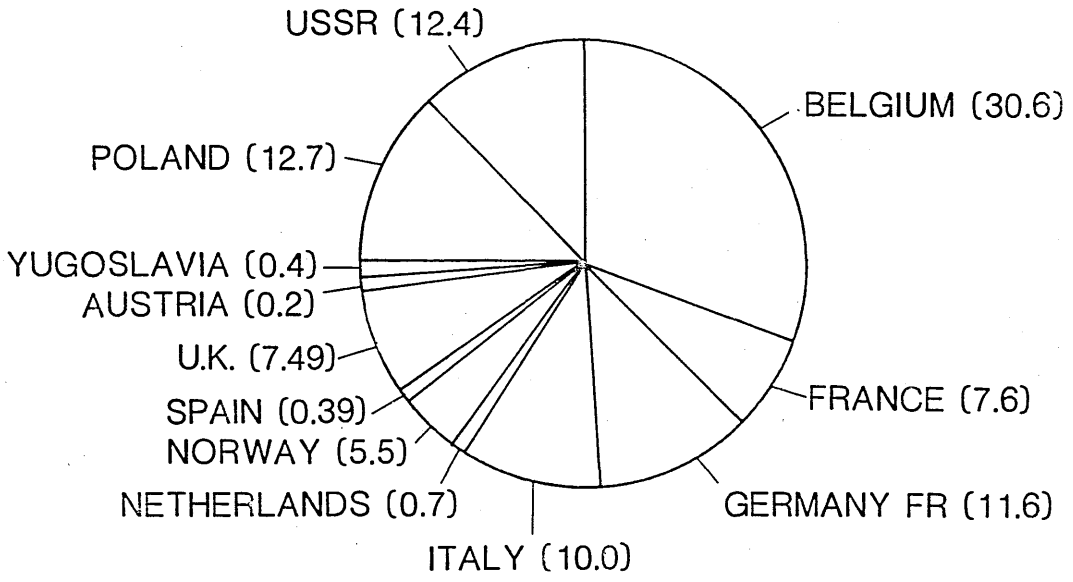

Fig. 3

The production of cadmium in E.E.C. countries compared with Eastern bloc producers between 1950 - 1959. Tons % (Criteria for Cadmium. Commission of the European Communities, 1978).

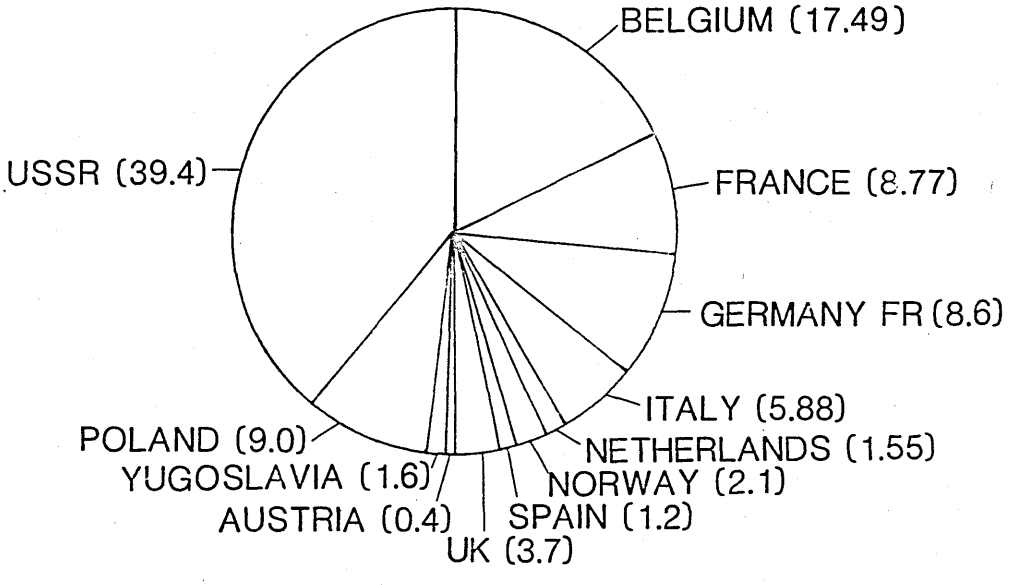

Fig. 4.

The changing pattern of cadmium production showing the marked increase in Eastern bloc countries as compared with E.E.C. countries between 1960 - 1969. Tons %

(Criteria for Cadmium. Commission of the European Communities, 1978).

and Luxemburg.

The production of cadmium in the twenty year period 1950 - 1970 records some very interesting facts. In the first half of the period the U S S R was a relatively low producer of cadmium (Fig. 3).

In the second half of the period it had become the major producer and overall the Eastern block countries outstrip the Western nations in the production of the metal (Fig. 4).

If one considers the importance of the metal in the aircraft industry, in electronics and in the prevention of corrosion then it is not unreasonable to draw certain conclusions about the general economy of countries from the cadmium production figures. It is also very interesting to note that Belgium - in the cockpit of Europe - is the leading producing country within the Western European countries (Fig. 5).

Because of the growing use of the metal it is realised that in the U S A there is a necessity to discover new sources of cadmium by geologic exploration (Mining Review, 1977; Baker, 1978). The main source of the metal is from the refining of zinc ores. For every ton of zinc produced there is also produced 5 pounds of cadmium as a byproduct (Streatfield, 1976) and therefore increased production of the metal will occur by exploiting known or new seams of zinc ores.

Although commercially used cadmium is derived from zinc smelting, cadmium is found in nature in the rock

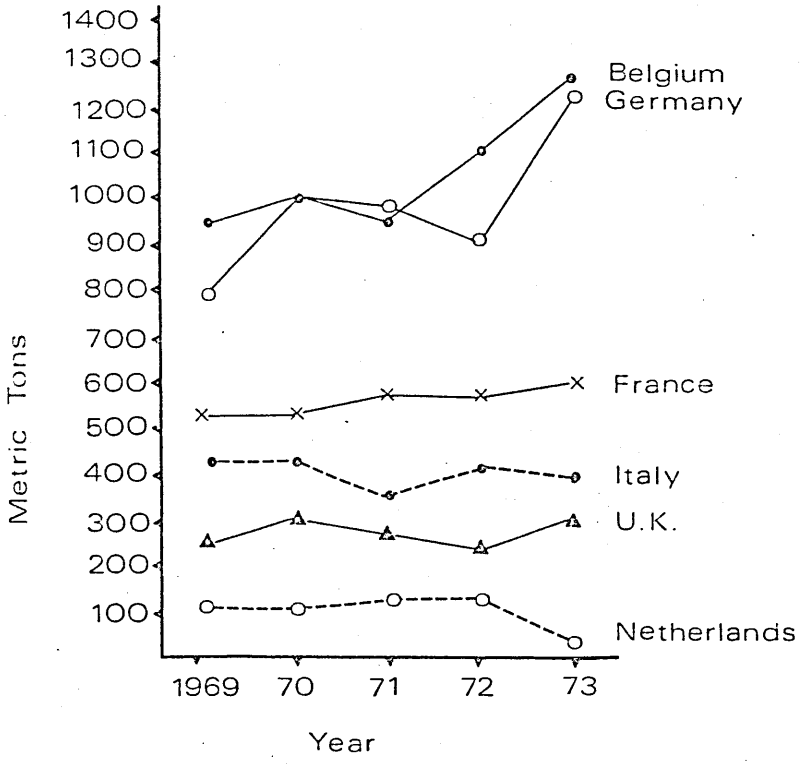

Fig. 5.

The production of cadmium within the E.E.C. community showing the output from the different major producers between 1969 and 1973.

(Criteria for Cadmium. Commission of the European Communities, 1978).

Greenockite (Fig. 6).

Cadmium is the 67th most abundant element and lies between zinc and mercury in the periodic table both of which are found in great quantities in the earth's crust. The physico-chemical data are summarized in Table 1.

From this data it can be seen that cadmium has a very low melting point and equally a very low boiling point. This means that it can be 'fumed' at very low or working temperatures.

Fig. 6.

A piece of greenockite ore showing the yellow cadmium deposits in the specimen.

(Courtesy of Geology Dept. University of Glasgow).

TABLE 1

ATOMIC NUMBER	48
ATOMIC WEIGHT	112
STABLE ISOTOPES	^{106}Cd ^{108}Cd ^{110}Cd ^{111}Cd ^{112}Cd ^{113}Cd ^{114}Cd ^{116}Cd
ELECTRONIC CONFIGURATION	2, 8, 18, 2, 6, 10, 2.
DENSITY	8.64 g/cm^3
IONIZATION ENERGY	864 Kilo joules/mol
MELTING TEMP.	$321^{o}C$
BOILING TEMP.	$765^{o}C$
ELECTRONEGATIVITY	1.7 Paulings
Cd E.D.T.A. COMPLEX	16.6 $\log_{10}$ (K stats) md^{-3} dm^3

Table 1. Major physico-chemical data of cadmium.

HISTORY OF CADMIUM.

CHAPTER 2

HISTORY.

The word 'Cadmium' probably derives from Cadmos a son of a Phoenician king whose brother Europa introduced the use of zinciferous earth at Thebes in Greece. Pliny in the first century A D was aware of the peculiar earthlike substance called 'Cadmia' a term used in classical terminology to describe zinc ore. In modern times Cadmium for commercial purposes is derived from zinc ores.

Cadmium was known to Aristotle (320 BC) who commented upon a particular bronze with a peculiar characteristic glossy yellow colour made without the incorporation of tin from the melting of copper along with a peculiar black earth at Mossynoecia. (Prodan, 1932).

References such as the above are scanty in the literature but it is generally accepted that in purely chemical terms cadmium was first discovered in 1817 by Friederich Strohmeyer of Gottingen at Salgitter in Germany and almost simultaneously by K S L Hermann in 1818 at Schonbeck. The former isolated the metal from zinc carbonate while investigating the yellowish banding in zinc ore.

Following its initial discovery little use was made of the metal and it was 41 years later in 1858 that the first cases of acute cadmium poisoning were reported. This first recorded incident involved a group of domestic

servants from a house near Brussels. The servants had unwittingly been using a cadmium powder to polish silver and had been acutely poisoned. It was A M Thirg who discovered that the cleaning powder used to clean the silver contained cadmium carbonate and noted that cadmium sulphate ion used therapeutically could cause vomiting, abdominal cramps and 'dysentery' which were the symptoms found in the unfortunate servants (Sovet, 1858).

The first reference concerning the effect of cadmium on kidneys came when, in 1867 Marne (quoted by Prodan, 1932) recorded that cadmium, among other effects, caused "a diffuse inflammation of the kidneys".

The next major report of a group of humans being subjected to cadmium poisoning came from the U S A in 1876 when a group of women who had purchased ammonium bromide at a local chemist shop subsequently suffered vomiting and abdominal pain. Samples sent to a professor of chemistry in the State of Maine confirmed the medicine to be cadmium bromide (Wheeler, 1876) and he commented that 'gross and wicked carelessness probably lies at the door of the French who prepared the medicine'. The bottle containing the cadmium salt would appear to have been wrongly labelled in Paris.

Purification of the metal enabled animal studies to be undertaken and the effects of cadmium in these early studies were compared to those of zinc. In 1895 the symptomatology of zinc and cadmium poisoning were clearly

identified as separate entities (Athanasiu and Langolis, 1895).

By 1896 Severi had so studied the effects of cadmium that he likened the renal effects to those produced by mercury and in his studies had clearly recognised tubular lesions, casts and irregular granulations being produced as a result of the administration of cadmium but interestingly made no reference to changes in the glomeruli. In the same year a deliberate attempt was made to compare cadmium and zinc salts in a more specific fashion. These latter experiments resulted in the observation that cadmium could affect the heart rate of experimental animals (Athanasiu and Langolsis, 1896).

In studies of the more general effects of cadmium it was noted in 1904 (Matthews, 1904) that in fish, growth of the embryo could be inhibited and the fish suffered from pigment deposition when injected with cadmium. The metal was considered by this observer to be 'as toxic as copper'. This is the first observation of a possible teratogenic effect of the metal.

After the turn of the century there was a series of reports describing acute cadmium poisoning in humans but it was much later, almost 50 years, before it was realised that chronic cadmium poisoning was a distinct clinical entity.

In 1920 there was a very interesting observation that many cases of so called lead poisoning could have been

caused by cadmium or zinc or a combination of both metals (Stephens, 1920). The rationale of such hypothesis was due to the finding that in so called 'lead deaths' - lead was not found in liver but cadmium was clearly present in large quantities. The same author referred to the diffuse nephritis found at post mortem in the subjects studied.

One of the very original and important observations in animals at this time was that cadmium induced a 'blue' testicle in rat (Alsberg and Schwartze, 1919). This clearly is a reference to the testicular necrosis subsequently observed by Gunn and workers in 1956.

Stephens (1920) noted that cadmium was used in soldering processes and he emphasised the volatility of the metal when it was heated - of considerable importance in the present study.

Apart from the renal effects, animal experimental work progressed to such an extent that it was appreciated that a number of trace metals interacted with each other and this could be detected clinically because of the effect on iron metabolism as indicated by haemolysis, agglutination and colour changes in serum (Purdy and Walbum, 1921). Shortly afterwards it was realised that, in chronic feeding experiments with toxic trace elements, the dose of cadmium administered affected the time of death and interestingly a longer survival time occured in female animals compared with males given similar doses of cadmium (Johns,Finks and Alsberg,1923). When given cadmium

at levels as small as 1000 ppm it was found that death occurred in 30 days in rats. This helped to emphasise the 'trace' element aspect of the metal along with its toxicity.

Cadmium had long been known to have a powerful emetic action (Schwartze and Alsberg, 1923) but it was not until 1923 that it was speculated that cadmium solder on food containers could cause problems not found when tin was used (Schiftner and Mahler, 1943). It was 20 years however before a food poisoning incident was directly attributed to cadmium leaching off cadmium plated utensils when in 1944 there was a classic report of an outbreak of cadmium food poisoning which originated from the metal leaching off the inside of a beverage container. The authors equated the symptoms with those of staphylococcal enterotoxin (Lufkin and Hodges, 1944).

Prior to 1938 all reports of cadmium poisoning had involved only small groups of individuals but in that year there was an important observation of an incident involving 15 cases of acute poisoning from which two subjects subsequently died. The problem arose in a plant where 300 pounds weight of cadmium plated rivets were being heat treated (Bulmer and Rothwell, 1938). This incident helps to highlight the relatively low temperature at which cadmium melts.

One interesting episode occurred in 1946 when a group of firemen were poisoned by irritant fumes. At first the cause of the toxicity was not understood but eventually

a box of bearings was found in the debris of the building and these were shown to contain 96% cadmium (Shiels and Robertson, 1946). The same authors made comparisons with animal deaths and alluded to changes in the glomeruli of guinea pigs and specifically commented upon the changes observed in the capillary tufts.

By 1941 it was observed that there were no studies of the chronic effects of cadmium but it was noted that anaemia, anorexia and retarded growth could be produced in animals receiving minuscule amounts of the metal (Wilson, De Eds, and Cox, 1941). As little as 0.0062mg per cubic metre of air breathed by animals caused a drop in haemoglobin in 1 - 3 months. The same authors noted that oral cadmium produced little effect on lungs but it was noted to cause swelling of epithelial cells of kidney tubules and accompanying these changes casts appeared in the renal tubules. Most previous histological examinations of kidney had suggested fatty degeneration of cells as the chief histological abnormality occurring on cadmium exposure (Prodan, 1932).

Chronic cadmium poisoning in humans was first considered as a possibility in 1942 (Nicaud, Lafitte and Gros, 1942). In formulating this hypothesis Nicaud and his team observed that symptoms could be very diverse and appeared to affect the respiratory tract, caused general toxaemia, bone problems, central nervous systems and blood disorders (Nicaud, et al, 1942). These statements were based upon observations

of workers who had been subjected to 12 - 16 years exposure to the metal in a nickel-cadmium battery factory where they were involved in the manufacture of the negative plates used in batteries. The plates were prepared at between 370°C-420°C which resulted in cadmium oxide fumes being produced. The discussion of the subjects in this study included observations such as 'the subjects tended to be yellow in colour; anaemia was frequent; intermittent dyspnoea occurs; vertigo is a feature; and that variable paraplegia has been observed.' Many of these observations have subsequently been substantiated but are so subtle as to be missed by most clinicians.

In 1947 comment was made that there were 200 references to cadmium intoxication in the literature but very few if any reports on the subject of chronic exposure (Princi, 1947). Princi undertook a deliberate study at three month intervals of a group of 20 workers. His researches were mainly related to the possible pulmonary effects and he noted that symptoms were non existent and no obvious pulmonary changes were observed. He concluded that this indicated rapid elimination of cadmium from the system with no sustained effects. He did however demonstrate a rise in blood and urine cadmium values which did not appear to be related to the duration of exposure experienced by any one individual.

By contrast Paterson considered that after inhalation chronic toxic effects occurred and were confined to the

lungs. It was noted that if an individual survived the acute state, then hyperplasia was found in the lung cells i.e. in the alveolar lining cells (Paterson, 1947).

In 1947 the suggestion was again made (Hardy and Skinner, 1947) that chronic cadmium poisoning was a distinct entity. This followed a study of cadmium contamination in a factory in Massachusetts where it was noted that levels of 0.1 mg/cubic meter were present in the air. The workers were involved in a tinning process which was used to cover small bearings. The temperature at which the process was being undertaken was 800-850^{0}C which is well above the melting point of cadmium. Five men were found to have fatigue, dental problems, gastro intestinal symptoms and on damp days respiratory symptoms. Two of the men had a reduced haemoglobin concentration. This latter was considered to be particularly significant in that it was a measurable parameter. The author quotes "some French work" which had commented on an association between cadmium exposure and anaemia and observed that the feeding of cadmium chloride to rats caused anaemia thought to be of an iron deficiency type.

In 1950 Friberg made the first positive statement that chronic cadmium poisoning had occurred in a group of battery workers. In his description he paid particular attention to the pulmonary,haematological and renal effects in the form of proteinuria encountered in the workers studied.

TABLE 2.

ARISTOTLE	320 BC	-	Bronze - yellow colour.
PLINY	1st Century AD	-	Zinciferous earth.
STROHMEYER	1817	-	Isolation of cadmium.
SOVET	1858	-	1st case of acute poisoning.
MARME	1867	-	Renal toxicity.
SEVERE	1896	-	Cadmium effects similar to mercury.
STEPHENS	1920	-	Cadmium effects similar to mercury.
BULMER	1938	-	First description of group poisoning.
NICAUD	1942	-	Chronic cadmium poisoning.
FRIBERG	1950	-	Chronic cadmium poisoning.

Table 2. Chronology of Cadmium - Important dates.

USES OF CADMIUM.

CHAPTER 3

USES OF CADMIUM

The earliest commercial application of cadmium after its discovery was as an artist's pigment (Schofield, 1976) and from this early beginning it was subsequently used to produce red and yellow pigments and a variety of paints and ceramic materials. Cadmium is particularly valuable as a pigment (Rade", 1979) because of the high stability of the sulphide compound. There is a growing tendency to substitute cadmium pigments with molybdenum based colouring materials (Dickenson, 1977). Cadmium pigments have been used to colour vulcanized rubber, printing inks, glazes, glasses, epoxyresins and in plastics.

The importance of corrosion as a major problem in industry is illustrated by the fact that over 5 billion dollars is lost annually by corrosion in cars in U S A alone and it was in this context that cadmium made its first major impact on industry (Kennedy, 1976). The metal became very important in the protection of small components particularly nuts and bolts.

In general corrosion each year destroys one fifth of the world production of ferrous metals. To give some indication of the extent in cost terms it is estimated that corrosion in 1971 was£1,365 million in U K (Committee Report, Dept. of Industry, 1976). Cadmium has several major advantages in this field including the protection of steel (Murnane, 1977) and since it has

a low co-efficient of friction along with the possibility of giving an attractive finish it is in great demand. A more specialised type of anti-corrosive can be undertaken using a mixture of cadmium and tin (Coch, 1979); this process allows the deposition of two metals thereby having a greater chance of preventing corrosion.

In 1909 the first nickel cadmium batteries were manufactured in Sweden (Technical Report, 1976). In the 1930's cadmium was first used in the form of sintered plates in nickel cadmium batteries a use which persists in air force satellites and aircraft where they are known as a sintered plate nickel cadmium battery. (Sintering is a process whereby a mass of particles having approximately the same composition are transformed into a ridged body without reaching the melting point and this in physical/chemical terms probably depends on surface mobility).

Cadmium is in the negative plate of a nickel cadmium battery. Small nickel-cadmium batteries are to be found in a wide variety of domestic and commercial products such as calculators, tape recorders and many modern electronic aids. (Fig. 7).

Apart from battery manufacture cadmium in modern industry has been widely used in plastics, plating, welding and brazing operations and as a method of increasing the tensile strength of copper wire. Cadmium is also employed in case materials within nuclear reactors.

In a recent review of the industrial uses of the

Fig. 7.

Common domestic objects where cadmium may be found and which have in the past caused cadmium poisoning either during production or in the home.

TABLE 3

Electronics	26.3%
Industrial fasteners	19.6%
Automotive parts	20.4%
Aircraft and aerospace	12.6%
Ordinance	5.6%
Hardware e.g. keys	3.1%
Household appliances	2.3%
Ship building	2.5%
Other industrial uses	7.8%

Table 3. Use of cadmium in different industries. (Marce, 1978)

element (Marce, 1978) it would appear that the proportion of usage is plating 34%, pigments 26%, stabilizers 15%, batteries 14% and others (including alloys) 11%. The proportion used in individual industries is shown in Table 3.

The automobile industry which initially gave the greatest impetus to the use of the metal still uses the metal to prevent corrosion of smaller parts of the vehicle. The association with cars is maintained as is shown by the fact that recently 70 kilo nickel cadmium batteries (Bell, 1977) have been used to power cars and this method of propulsion could increase in future.

One economical aspect of plating processes which is hardly noted is that recovered chemicals from a plating process are valuable as they do not require to be modified for further plating (Swalheim and McNutt, 1977). Until the beginning of World War II most industrial wastes were deposited without regard to solubility or recovery (Weiner, 1976). Since cadmium is a valuable industrial element it is considered essential to recover the element from effluents and plating processes are controlled to allow recycling of the element (Marce, 1978).

The importance of controlling industrial cadmium emmision or effluents is emphasised by the growing belief that cadmium toxicity may extend to the general population (Kendry and Roe, 1969).

STATUTORY REGULATIONS GOVERNING USE OF CADMIUM.

CHAPTER 4.

STATUTORY REGULATIONS ON FUME POISONING.

The realization that cadmium could cause a problem in an industrial situation resulted in a variety of regulations and governmental notes to guide employers and employees in the use and hazards of the metal.

The 1937 Factories Act was specifically designed to prevent dust or fume inhalation of toxic substances. For practical purposes it is well nigh impossible to exclude toxic substances from factories. The general principle recommended is that local exhaust systems should be introduced where a fume cupboard approach cannot be employed. In early guidance notes permissible levels of cadmium recommended in the atmosphere was 0.1 mg per cubic metre of air.

The National Insurance Act 1946 did not include cadmium as a prescribed poison but in a special report of the Industrial Injuries Advisory Council in 1956 it was commented that the evidence then available supported the existence of chronic cadmium poisoning as a definite entity. Most of this report dwelt upon the possible appearance of emphysema, anosmia and proteinuria as the specific clinical manifestations of chronic cadmium poisoning.

After the above report it was commented by another government agency that the presence of proteinuria did NOT by itself justify the diagnosis of chronic cadmium poisoning (Notes HMSO, 1972). Perhaps one of the most revealing facts about control of cadmium is that under

the Factories Act (1961) no specific regulations existed to deal with cadmium exposure (Technical Data Note, 1975).

Reports published in the form of Technical Data notes by the Department of Employment give good practical information on such matters as the management of work areas affected by hazardous fumes (Technical Data Note, 1974). Cadmium like other toxic substances has a recognised Threshold Limit Value (T.L.V.) which defines the maximum tolerable levels in the working environment.

The growing awareness of the potential hazard of cadmium resulted in the T L V in 1972 of 0.1 mg per cubic metre of air being reduced to 0.05 mg per cubic metre in 1976. The current value of the T L V for cadmium is now 0.01 mg per cubic metre.

The Commission of the E E C note that people in industrial areas have a higher dietary intake of cadmium than those in rural or non industrialized areas and the intake is also higher in smokers (Lauwreys, 1977). The Commission indicates that since some epidemiological work suggest a possible cancer/cadmium link, as well as its other likely effects, then T L V should be such that the daily intake should not exceed 10 - 12 ug. Cadmium levels in the atmosphere should in the opinion of the W H O, be continually under review (Friberg, 1977), and especially that proportion which is absorbed from food (W H O, 1977).

When comparison is made with other national

regulating authorities it is interesting to find that in the U S A the National Institute for Occupational Safety recommends a T L V value of 200 ug per cubic metre for a 15 minute period (Cohn, 1977) with a total 10 hour level of 40 ug per cubic metre in a 10 hour work day.

By these standards the levels allowed in U K are high especially when it is realised that it has been recommended that the permitted level should be less than 50 ug/m^3 (Tsuchiya, 1976).

It is therefore very obvious that there has been a steady fall in the levels of cadmium permitted in working atmospheres and this can be directly related to the growing awareness of the toxic effects of the metal.

The ideal value for T L V would be 0 but for practical purposes it is unlikely this value will be achieved in the working environment.

ENVIRONMENTAL ASPECTS OF CADMIUM.

CHAPTER 5.

ENVIRONMENTAL ASPECTS

General

The involvement of the general population in cadmium poisoning obviously does not arise by direct industrial exposure but by atmospheric pollution or contamination of food by cadmium. Great care has to be taken in the interpretation of atmospheric or environmental levels of cadmium. Studies of the Severn Estuary have shown that the level can be as high as 5 ug/l and this could be interpreted as evidence that we may well live in a cadmium polluted society. It should be remembered however that on the shores of the Severn is the Avonmouth Zinc Refinery which may well add significantly to the cadmium content of the Severn in that area.

Most authorities do not consider cadmium to be a major atmospheric hazard but one author considers that cadmium in the atmosphere does create a possible environmental hazard and even suggests that the metal could be implicated in cancer problems (Godfrain et al, 1977). At present there is little to substantiate this concept of a general cancer link but local effects may be much more significant than has hitherto been realised.

It is quite clear that the greatest pollution of the environment by the metal has occured since the 1930's and this may well be relevant when considering changes in certain disease patterns. One reason

for the rising importance of cadmium has been its growing use in a wide variety of industrial processes. One unnatural source of cadmium poisoning is cigarette inhalation. It is estimated that 1 x 20 pack of cigarettes contains 30 ug cadmium and it has been demonstrated that at the lighted end of a cigarette the temperature exceeds the boiling point of cadmium i.e. 767^{o}C. Smoking has been shown to result in a 10 - 20% increase in the body burden of cadmium (Nandi et al, 1969; Commission European Communities, 1978) and if 10% of the cadmium is absorbed then the rate of accumulation is 0.5 ug/pack per year (Lewis et al, 1972). Smoking is therefore an important factor in the assessment of cadmium intoxication since it can be shown that there are significant differences in blood levels of cadmium between smokers and non smokers (Wilden, 1973) and it can be shown that the 24 hour excretion of cadmium increases with age and with smoking habits (Elinder et al, 1977). The range quoted in 'normal' urine in this particular series was 0.25 - 0.40 ug/vol. It is therefore obvious that smoking, combined with atmospheric pollution in general contributes to whole body cadmium levels. Nevertheless it is important to continually be aware that many industrial uses of cadmium exist and very often such processes may not be obvious to the casual observer. For example cadmium can be found in all sorts of unexpected combinations of

metals and one of these is mercury amalgam (Cotter and Cotter, 1951).

Among the less well recognised industries where cadmium could be a potential hazard are those such as the recovery of scrap metal which possibly could cause environmental pollution by the metal and it should be realised that cadmium is added to the atmosphere as a result of the combustion of coal and oil (Webb,1977).

Cadmium is in common usage in electroplating of steel to prevent corrosion (Kazantzis, 1970) and it has been used as a fungicide and nematocide. More recently it has found a use as a stabilizer in the plastic industry (Webb, 1977).

While industrial poisoning is obviously important to small groups of workers, the vast majority of the population probably acquire cadmium from food (Varma and Katz, 1978). Involvement of man from eating contaminated plants or fish was first realised by Kobayashi who noted that when cadmium pollution of an environment occurred, then man could be secondly involved as a result of consuming food or fish thus contaminated (Kobayashi, 1971). In modern society food may be important as a cadmium source since it can be shown that the addition of sewage sludge to soils increases the cadmium content of herbage (Stover, Sommers and Silviera, 1976).

One of the most important food sources in the world is rice. When unpolished and polished rice are analysed with respect to trace metal content it is

found that there is a reduction in the zinc and copper content in polished rice but no difference with respect to cadmium. Rice from Japan has the highest level of cadmium as compared with other countries whereas Brazil has the lowest cadmium content. It is possible that rice could result in 20 ug/day of cadmium ingestion for a human who consumed this cereal as a basic food source.

If by some industrial process the area water supply becomes polluted with cadmium the amount taken in from food may rise to 600 ug/day. Such levels have been reached in certain areas of Japan - where the population can on average consume in their staple food as much cadmium in one day as the recommended weekly maximum of 400 - 600 ug (FAO/WHO recommended levels). If one then studies the population in Japan and compares this with western civilizations it is possible to show potential cadmium effects manifested by higher cadmium/zinc ratios in blood as compared with equivalent populations in Africa, U S A and Europe - the latter three areas having a low overall consumption of rice. A much greater and prolonged epidemiological assessment is required before firm conclusions can be made about the possible role of cadmium effects on such populations. As discussed in this work kidney cadmium levels are found to be higher in Japan as compared with Sweden and other countries including our own. (Chap. 14).

In the United Kingdom 15 - 30 ug/day would appear to be the average dietary intake and the normal excretion is in the order of 2 ug/day and certainly less than 5 ug/day. It is very unlikely therefore that a situation such as that which produced the classical 'itai-itai' disease in Japan (Kobayashi, 1971) would be likely to occur as a result of food ingestion in the United Kingdom.

Very little work has been undertaken to uncover possible sources of cadmium involvement in food chains and this is surprising when it is realized that lead in milk is considered to be affected by environmental pollution and can be 80 times as high in milk from contaminated as compared to non contaminated areas. Efforts are now being made to extend these observations to food chains in man and an example of their importance is shown by the finding that measurements of lead and cadmium in raw milk confirmed the mean concentration of lead to be 91 ug/Kg and cadmium 6.0 ug/Kg in California (Bruhn and Franke, 1976). Further extensions of such observations may well add weight to arguments for further careful control of environmental pollution by cadmium.

Apart from the general hazards, poisoning can arise in such domestic circumstance as has occurred when subjects were poisoned as a result of making lemonade using tartaric acid or in the making of iced tea where cadmium was shown to be leached from the

metal trays or containers containing the tartaric acid mixture (Frant and Kleeman, 1941). Another potential source in the domestic situation are culinary glazes (Crosby, 1977) but overall in the U K in most food substances cadmium is at the limit of detection.

In the U K the main concentrated food sources of cadmium are to be found in shell-fish, liver and kidney. By contrast in the U S A the main source is from grains of cereals (Commission of European Community, 1978). Again the 'unexpectedness of cadmium' is demonstrated by the finding that when several varieties of tea and coffee are compared then 'instant coffee' contains the highest amount of the metal but no definite pathological process - e.g. hypertension - has been linked with the intake of this beveridge (Horwitz and Vander Linden, 1974).

Recently there has been a great interest in the possible contamination of vegetables grown in the village of Shipham in South West England (Carruthers and Smith, 1979). Examination of the preliminary blood analyses from these individuals living in the village confirm an average of less than 9 Nmol/1 (1ug/L) in non smokers and in smokers the corresponding figure is 18 Nmol/1 (2 ug/L). When compared with the findings in the industrially exposed workers which I have studied in Scotland, then the blood values are quite low. I had the opportunity of examining the Shipham figures and the male with the highest blood level within the group significantly worked in a factory

which is situated within 100 yards of the boundary wall of the Rio Tinto Zinc Smelter - suggesting that he may well have been subjected to an atmospheric pollution and certainly NOT a pollution from contaminated vegetables as judged by his blood level of cadmium.

Water pollution

Although it is easy to measure total world production of cadmium (Table 4) not a great deal is known about the natural geochemical cycle of the metal.

In a study of the vertical distribution of cadmium in the North Atlantic (Eaton, 1976) it was found that there is very little variation in concentration of the metal to a depth of over 400 metres. Surface waters however have the highest values probably due to biological activity and almost certainly these levels are anthropogenic in origin.

In coastal waters there is great concern about possible pollution especially by non ferrous metals in general (Visser, 1976). To give some indication of the problem it has to be realized that approximately 500 tons per annum are produced in sludges from electroplating in the U S A (De Fillipo, 1974) and in the U K the amounts produced in 1972, 1973 and 1974 were respectively 165, 346 and 308 tons of cadmium from smelters.

The sea is a source of food which can be contaminated by sewage. The North Sea illustrates the dangers of possible concentration of metals and other toxic substances. It is only 1% of all ocean volume but produces 5% of the world's fish for human consumption and high levels of cadmium in polluted water were considered to have been a contributing factor in itai itai disease.

It is therefore recommended that as a general

principle heavy metals should be combined in an insoluble form when sea dumping is used as a method of disposal (Gray, 1977). In the Glasgow area many tons of sewage per annum are dumped in the Clyde estuary in addition to effluxes from metal treatment processes.

The effect of cadmium on shellfish has been demonstrated in an experiment in which the addition of as little as 0.1 ppm cadmium caused the death of clams (venerepas decussata) in ten days (Carter, 1976). Similar effects were seen in a variety of other shell fish (Leading Article, Lancet, 1976; Kazantzis, 1973). Fish can be contaminated by trace elements around the outfall of submarine sewage disposal (McDermott et al, 1976). Although it is possible to show chromium intoxication in such situations no evidence of a similar effect of cadmium has been demonstrated.

It is possible in industrial plants to recover cadmium along with other elements such as zinc or cyanide to allow recycling of water for industrial usage (Schrantz, 1976).

There is controversy over the significance of a variety of chemicals in domestic water supply in terms of their possible relationship to chronic diseases (Angino, Wixson and Smith, 1977). In hard water areas carbonate and phosphate in the water result in precipitation of cadmium which then is removed and thus is made unavailable for human intake. There can be large variations in domestic water content of the metal

TABLE 4.

	1972	1973	1974
North America	5271	5294	4773
Latin America	436	435	465
Europe	3986	4375	4559
USSR & Sattelites	3787	3822	4170
Africa	516	438	476
Asia	3608	3748	3601
Australia	794	747	800

Table 4. Total world production of cadmium (tons) 1972 - 1974. (De Fillipo, Minerals Year Book, 1974).

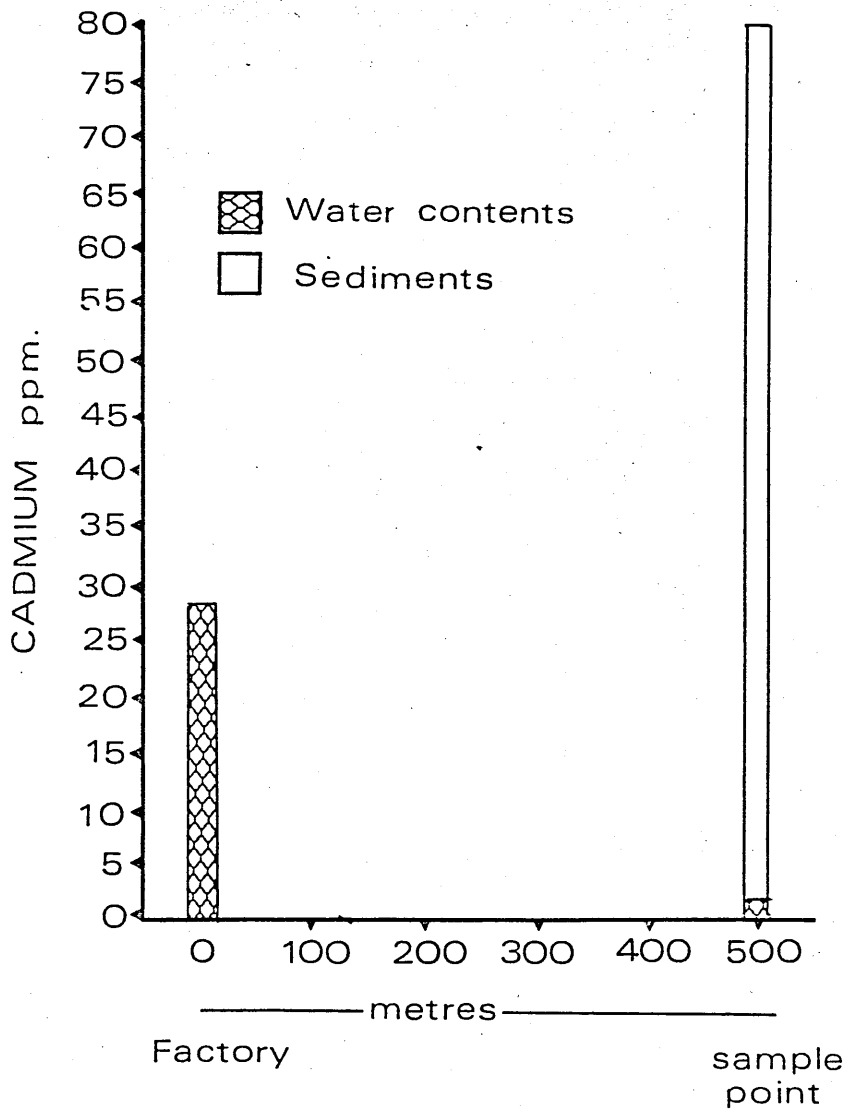

Fig. 8. The effect of an electro plating factory effluent on a local river system as shown by cadmium content of water and sediments.

e.g. in Boston zero per cent of samples had an excess of cadmium as compared with Seattle with 7% showing excess cadmium content. It should be remembered that there can be a high 'pick up rate' in the water distribution process.

One of the most interesting and often quoted correlations is that of the effect of hard and soft water on cardio vascular mortality rates in matched populations (Allwright, Coulson and Netels, 1974). Very little has been done to elucidate the role of cadmium in this context.

There is good evidence from the literature that the presence of a cadmium source in an environment will greatly increase the cadmium content of water in that area. It has to be noted, however, that the content of cadmium in water becomes greatly reduced with distance from the source. Sediments which could become important in biological systems can contain 80 ppm i.e. 20 times as much cadmium at the 500 metre sampling points. (Fig. 8). This is best illustrated by the Japanese experience where itai itai was first recorded and which was attributed to a contamination of the Jintsu by zinc smelting operations (Kitamura, 1977). Although levels of cadmium in water can be increased by the effluent resulting from the extraction of zinc ores as has been found in Japan, it should be remembered that such levels are not found in U K at any work location. Nevertheless a recent study has shown an enhancement of

of upper core sediments in Scotland in Loch Lomond (Farmer and Baxter, 1980). Such enhancement is not due to large deposits of cadmium in the loch but is due to the general activities of man in the area. It should be realized that this particular water is pumped to several small reservoirs used for domestic consumption.

Smelter emissions

There are different acts involved in air pollution legislation, but basically it is recommended that respirable cadmium levels in the atmosphere should not be greater than 0.05 mg/m^3; for dust, soluble in hydrochloric acid, the level recommended should not exceed 0.2 mg per cubic metre.

Cadmium contamination of the atmosphere may be (a) general or (b) local related to a particular work process and therefore confined to a small area usually in high concentration.

Lead smelters cause an increase in cadmium contamination of soils and in the atmosphere. Smelters have been shown to produce cadmium in a particulate size of less than 4.7 um. which is the upper limit of size capable of being inhaled (Dorn, Pierce, Phillips and Chase, 1976). Factors which determine the outfall of cadmium from smelters are aridity, wind velocity, thermal inversions and geographical topography (Rosenblum, Shoutts and Candelaria, 1976).

In an environmental study on a test farm near a lead smelter it was found that 88% cadmium of the metal was in the respirable form.

Apart from lead smelters there is good evidence that zinc works also cause atmospheric pollution by cadmium and it has been shown that large amounts of both elements can accumulate in resistant plants in the outfall from such smelters (Kazmierczakowa, 1975).

Coal fired power stations produce the greatest concentration of respirable cadmium and are obviously more common than lead smelters. In South Wales coals - cadmium is fortunately one of the least abundant elements (Chatterjee and Pooley, 1977).

Urban air has a high deposition of trace metals (Davidson, 1977) and this clearly can occur from a large variety of industrial processes e.g. it is not generally realized that because of its low boiling point cadmium is released during the resmelting of scrap metal (Varma and Katz, 1978). Another good example of local atmospheric pollution important in an environment such as that of the West of Scotland is the contamination produced during the dismantling of old ships (Beton et al, 1966).

Cadmium is however more likely to be significant when local contamination occurs in a work process and it should be realized that the element is involved in many 'unexpected' processes such as the stabilization of plastics.

Since the 'local' type of poisoning is more likely to be severe it should always be remembered that high exposure to dust or fumes can result in acute poisoning and if exposure is low and prolonged chronic poisoning occurs. As recently as 1980 (Lucas et al, 1980) an acute death occurred in a 'local' contamination.

In the local industrial complex the problem of dealing with fumes at atmospheric temperature is

important and continuous extraction with regular testing of the fume extraction plant is essential (Allen, 1977).

Although the general atmospheric levels are clearly important for the individual, it should be realized that one packet of cigarettes contains 30 ug/cadmium and of this 70% passes into tobacco smoke (Lewis et al, 1972) thereby greatly increasing the total intake for the individual who smokes cigarettes.

Interesting work has been undertaken which has analysed different atmospheres with respect to cadmium content. The general consensus is that rural areas have, as would be expected, the least problems but proximity to an industrial source greatly increases atmospheric concentrations of cadmium (Table 5).

TABLE 5.

Site	Cadmium concentration ug/m^3
RURAL AIR	0.0001 - 0.043
URBAN AIR	0.002 - 0.7
CADMIUM EMISSION SOURCE	0.010 - 5.0

Table 5. The effect of a cadmium emission source causing an even greater atmospheric level in an urban as compared to a rural atmosphere.

Soil pollution

It is now extremely difficult to find soil areas which are free from cadmium pollution even to determine the acceptable naturally occurring mean levels (Kreuzer et al, 1976).

Natural cadmium ores contribute little to soils (John, Van Haehoven and Cross, 1975) and therefore soil contamination is most likely to originate from such processes as ore smelting, metal refining and other industrial uses.

Examination of soil distribution in a vertical plane has revealed that cadmium tends to be in the top 5 cm. It is however available to plants and can be influenced by pH e.g. an increased uptake by raddish (raphenus salivush) is seen when the pH is reduced from 7.2 to 5.9 and by potassium which reduces the uptake of cadmium in soy beans (Haghiri, 1976). Fertilizers applied either in chemical or organic form increase the cadmium availability to plants. Sewage sludge (Anderssen, 1977) has been shown to increase the cadmium content of plants grown on the treated soil. (Fig. 9).

Cadmium content of sludge may vary widely e.g. in Michegan 2 - 1000 ug/kg while in England and Wales values of 60 - 1500 ug/kg are recorded (Stover, et al, 1976). Cadmium in sludge is likely to be present as sulphides which are easily oxidized to form exchangeable forms of cadmium as compared to cadmium

carbonate which is less available.

Since phosphate fertilizers contain as much as 28 ug/kg cadmium they become a potential source of basic food contamination with respect to cadmium (Andersson, 1977). Calcium by contrast reduces the cadmium content of humus and upper layer cadmium bio-availability.

In biological terms cadmium content of soils only becomes of significant importance when man manipulates the environment either by heating fossil fuels or by adding fertilizers to increase food production. Igneous rocks, sandstone and limestones contain very little cadmium. (Fig. 10).

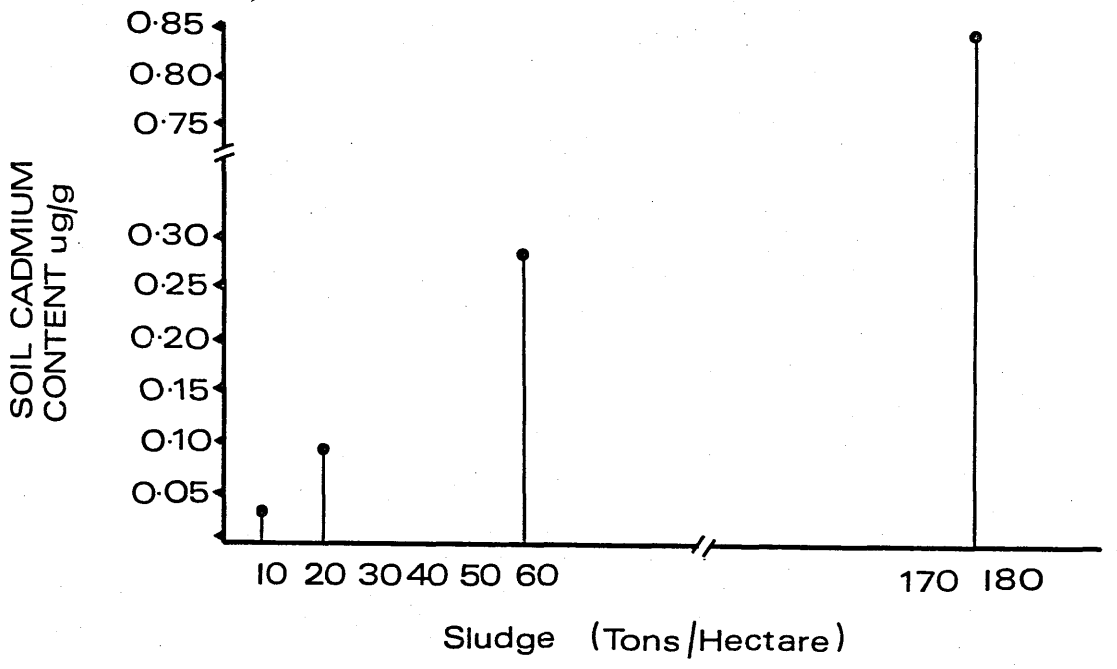

Fig. 9. Effect of adding sewage sludge to soil cadmium content. (Friberg, 1974).

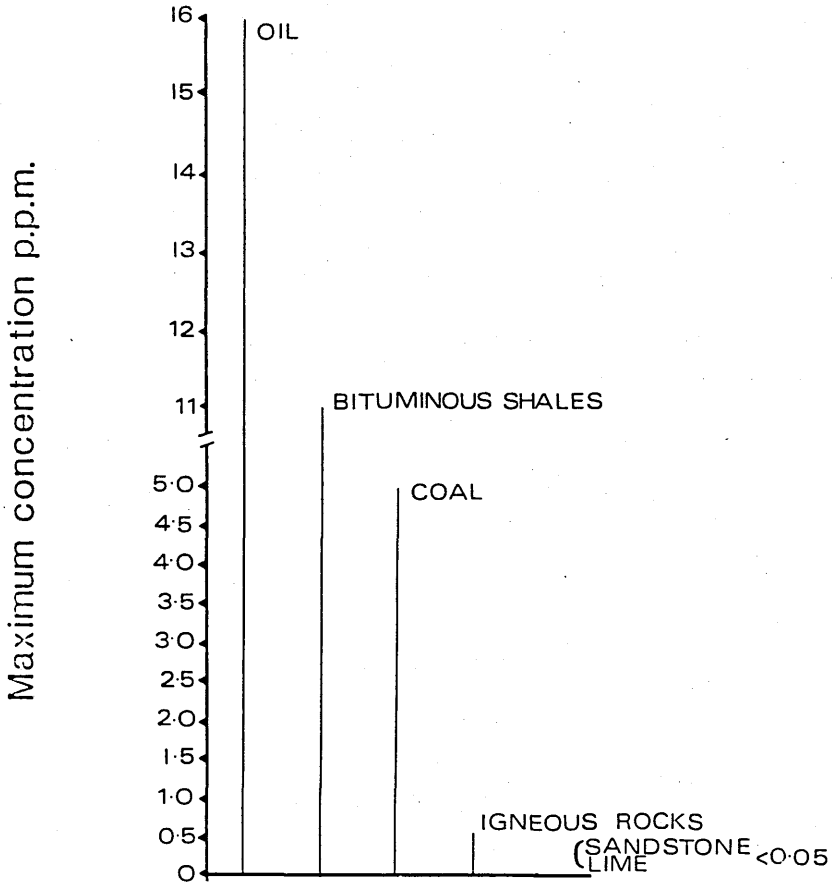

Fig. 10. To show the variation of the concentration of cadmium expressed as parts per million (ppm) in a variety of different geological formations. (Criteria for Cadmium. Commission of the European Communities, 1978).

Plant/Animal contamination

Geographical and geochemical factors are clearly important in determining how plants and animals are likely to be contaminated by substances such as the trace elements.

Examination of food intake figures reveals that there is a wide variation of the wheatflour content of cadmium even within one country. (Fig. 11).

The wide discrepancies probably indicate a marked difference in methods of agriculture. The uptake of cadmium by plants however is not a simple matter as the metal differs from lead and mercury which are simply retained by soils. Cadmium by contrast rises dramatically with the application of fertilizers or by reducing the pH of soil. This is shown by the demonstration that the cadmium uptake of plants can be greatly increased by certain fertilisers (Payer et al, 1976). In one such study in Germany it was shown that of the 4 - 5 ppm cadmium found in plants 50% originated in super phosphate fertilizers. Calcium causes the release of cadmium from clay soils containing kaolinite and illite whereas potassium reduces the release of the metal and consequently the absorption of cadmium by such plants as soy bean (Haghiri, 1976).

Apart from calcium and potassium it has been shown in studies of corn plants that there is a complex interaction between cadmium, lead and boron uptake by corn plants which helps emphasise just how complicated inter metal action and reaction

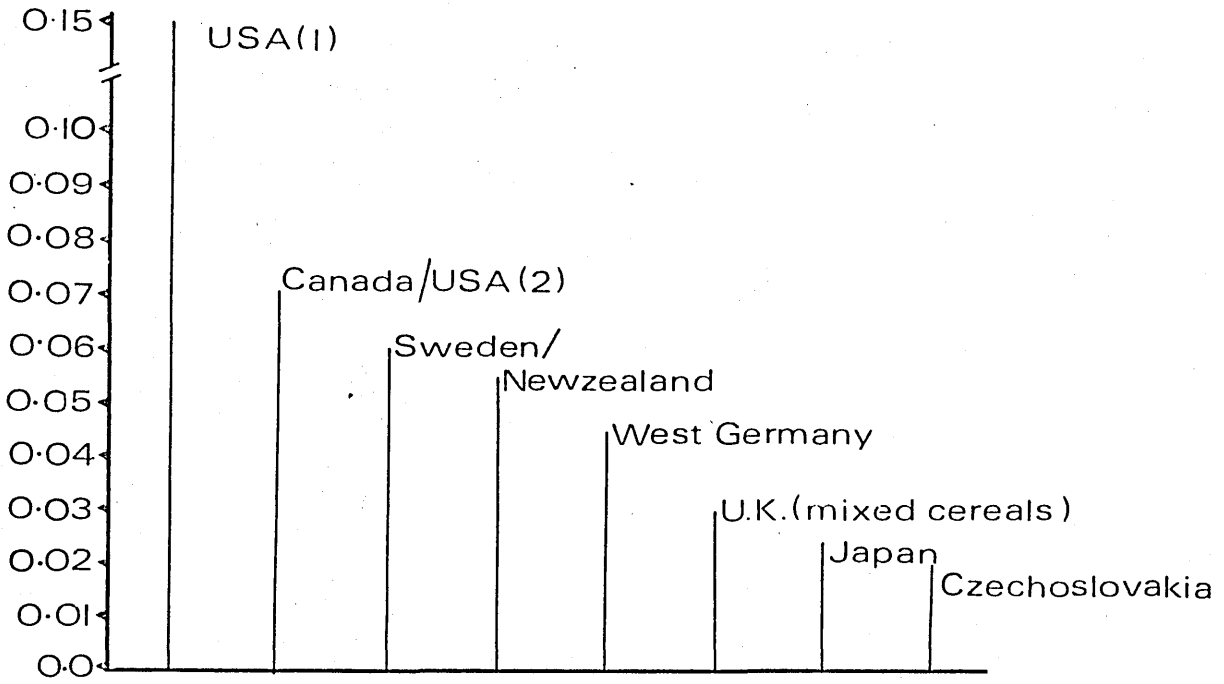

Fig. 11. The variation in cadmium content in different wheats from different countries. 2 areas in the U S A illustrate the variation which can occur. The differences can be accounted for by different agricultural methods.
(Criteria for Cadmium. Commission of the European Communities, 1978).

becomes in biological systems (Walker, Miller and Hassett, 1977).

Plants may be further contaminated by emissions from metal smelters or as has been shown, the cadmium content of trees is higher when they are growing next to motorways (Mahkouska, 1977). Such contamination is unlikely to be of major importance in human beings but when staple food stuffs are implicated then the problem assumes a different proportion. As already stated, rice can be shown to have a high cadmium content in certain areas of the world particularly Japan and unlike zinc and copper there is no reduction of cadmium content in polished as opposed to unpolished rice (Masironi, et al, 1977).

Relatively little work has been undertaken on the geochemical relationships between cadmium and health but it is of interest that cerebro-vascular accidents and hypertension are major problems in Japan, but by contrast are relatively less of a problem in Africa, U S A, and Europe where the rice content of diet is much lower. This field of research clearly must be pursued in view of the suggestion that cadmium/zinc ratios are higher in kidneys of hypertensive subjects.

Since man is the ultimate concern in cadmium contamination it should be realised that apart from plant food intake, he may greatly increase his intake of cadmium orally due to the consumption of meat particularly organ meats such as liver and kidney. It has been shown that cattle, like man,

demonstrate an increasing renal and hepatic content with age but when cattle are reared in non cadmium polluted areas then the cadmium level is found to be below the limit of detection (Kreuzer et al, 1976).

EFFECTS OF CADMIUM ON VARIOUS BIOLOGICAL SYSTEMS.

CHAPTER 6

EFFECTS ON BIOLOGICAL SYSTEMS

LUNGS

In chronic cadmium poisoning lung changes do occur and in such subjects who as a result of cadmium inhalation develop emphysematous lungs, the blood cadmium values are normally higher than in control populations (Leading article, Lancet, 1973).

From experimental animal studies it has been shown that cadmium causes an increased centrilobular emphysema, sub-pleural thickening accompanied by collagen deposition, and plasma cell infiltration (Miller, Murthy and Sorenson, 1974). This helps to emphasise that although lung effects are at present thought to be less important than they were formerly the element does have significant pulmonary effects and these may be fatal (Lane and Campbell, 1954).

From animal work one interesting postulation arises that after recovery from acute lung injury the healed lesion possibly creates a local immune reaction.

When referring to human lung changes it must always be appreciated that smoking is a major factor leading to accumulation of cadmium in tissue (Lewis et al, 1972).

In considering cadmium and smoking it should be realised that when a cigarette is ignited 70% of the cadmium in the vegetable material passes into the smoke.

Early observations clearly indicated a profound effect of cadmium on lungs - on occasions leading to fatalities. More recently however the respiratory system as a site likely to be a major target for cadmium induced pathological changes has been relegated to a less important place relative to the renal system. Chronic cadmium poisoning can however be accompanied by respiratory effects but in assessing such effects a full cognizance of smoking habits is essential.

HYPTERTENSION

Perhaps there is more argument over the relationship of cadmium to blood pressure than any other possible systemic effect of the element (Schroeder and Brattleboro, 1964). The different arguments seem to be based on establishing whether (i) the metal acts directly on blood vessels which it has been shown to do in testes, (ii) whether it causes secondary hypertension by its renal effects or (iii) whether it causes some other effect such as an adrenal action via the renin angiotensin mechanism.

In epidemiological studies it has been shown that there is a correlation between atmospheric cadmium levels and cardio vascular death rates (Carrol, 1966; Schroeder, 1970) and that there is a statistically significant difference in cadmium content of kidneys ($P<0.05$) in hypertensive as compared with non hypertensive subjects (Lener and Bibr, 1971).

If an environmental cause/effect relationship is sought it can be shown that the level of cadmium in domestic water where the latter is 'soft' could be higher when delivered at the tap than in hard water areas thereby incriminating cadmium as a factor in cardiac death rates in soft water areas (Sharrett, 1977). The evidence for such an association, although attractive in theory, is contradictory and since cadmium intake from drinking water is low in humans there

is therefore little evidence to incriminate a significant water source of the element in human hypertension.

In human subjects it would be very interesting if blood cadmium levels correlated with the blood pressure levels but this has not been found to be the case (Holden, 1969).

It has been shown that the mean cadmium/zinc ratios are found to be high in kidneys in hypertensive subjects (McKenzie and Kay, 1973; Schroeder, 1965; Thind and Fischer, 1976), and that there is a high liver and kidney cadmium content in patients who succumb to hypertension (Glauser, Bello and Glauser, 1976). Schroeder has shown a raised cadmium in 'hypertensive kidneys' but not at a statistically significant level (Schroeder, 1965). To explain a possible mechanism of cadmium induced hypertension Schoeder and workers speculate that cadmium may well replace copper or iron in monoaminoxidase which is an inhibitor of pressor agents thereby causing a pressor effect i.e. hypertension.

In the controversy over whether blood or urine cadmium values are more indicative of cadmium poisoning it was found that in a group of workers employed in making copper/cadmium alloys, the blood cadmium level was more relevant as a means of predicting hypertension than the urine values (Piscator, 1976). A further study of the problem (Thind and Fischer, 1976) showed that the mean

cadmium level was higher in hypertensive subjects and consequently the cadmium/zinc ratios were significantly higher. Interestingly these authors pointed out that the reports on 'itai itai' disease - thought to be a cadmium induced condition - do not include hypertension as being one of the principle findings.

It is therefore obvious that the evidence linking cadmium and hypertension in humans is controversial (Voors, Shuman and Gallagher, 1975). The only really consistent finding in a variety of reports is that in hypertensive subjects there is a significant increase in the cadmium/zinc ratio and therefore animal work has been very extensive and important in trying to assess the effect of cadmium on blood pressures. It has been demonstrated that small doses of cadmium can induce hypertension in rats (Schroeder and Vinton, 1962) and in such animals it has been possible to demonstrate elevated circulatory renin activity following cadmium injection (Perry and Erlanger, 1973). It is speculated by these authors that the mechanism involved may result from altered sodium re-absorption in the kidney tubules - a major site of cadmium deposition.

The very small amounts of cadmium (Schroeder,1964) necessary to cause hypertension in rats are shown in experiments such as the one in which hypertension was created in weaning rats by giving a low dosage of cadmium e.g. 1, 2.5 or 5 ppm in drinking water. What is puzzling

however is that higher doses of the metal cause a fall in blood pressure in an animal which is clearly exhibiting the more general effects of the metal (Perry and Erlanger, 1974).

It has also been shown that cadmium in drinking water of rats causes histological changes in arterioles and these are characterized by proliferation of endothelial cells, sub-intimal fibrosis and smooth muscle hypertrophy (Kanisawa and Schroeder, 1969). It is possible if one remembers the mechanism whereby cadmium probably induces its gonadal effects that it could cause hypertension not by a renal or aldosterone mechanism, but by its ability to affect small blood vessel structure. These vascular effects result in a reduced survival rate in male rats. To add further confusion to the possible mechanisms of a hypertensive effect of cadmium it has been shown that in 16 cadmium treated animals 5 developed phaeochromocytomas (Perry, et al, 1967).

Hypertensive changes in animals can be induced by administering the metal by a variety of routes and interestingly it is possible to reverse the effects of cadmium hypertension in animals by the use of zinc chelate - di sodium zinc E D T A (Schroeder and Buckman, 1967).

Although there is considerable debate about the effects of cadmium on blood pressure, it is still considered that it could be very important

in relation to human hypertension (Schroder, 1965). The role and possible mechanisms of cadmium hypertension are still debatable but from epidemiological evidence and from the altered cadmium zinc ratios coupled with the animal work the element clearly is important in hypertension if only by producing hypertension secondary to renal failure.

CALCIUM

The effects of cadmium in calcium metabolism are less dramatic on the short term but to a urologist they are particularly important in chronic cadmium poisoning.

Renal stone formation is a feature of chronic cadmium poisoning and the associated renal tubular acidosis is probably responsible for the hypercalciuria (Kazantzis, et al, 1963) and subsequent skeletal demineralization (Webb, 1977) which occurs in chronic cadmium poisoning.

In animals cadmium can be shown to cause a negative calcium balance (Yuhas, Miya and Schnell, 1978). Cadmium could influence calcium metablism (1) by interference with absorption (2) via parathyroid mechanisms and possibly (3) due to the renal effects.

Calcium is absorbed in the duodeno-jujenal segment of the small bowel by an active carrier energy dependant process and by a passive mechanism in more distal bowel segments.

With increasing age calcium absorption diminishes (Bullamore et al, 1970) which is interesting as it is generally recognised that with increasing age the body burden of cadmium rises.

In the complex equation involving absorption of calcium and cadmium the duodenum has been found

to have a high affinity for cadmium (Ando, et al, 1977) which with the jejunum happens to be the site of maximum calcium absorption (Wills, 1973). In the duodenal mucosa the calcium binding protein has as great an affinity for cadmium as calcium. In animals with a restricted calcium intake there is an increased calcium binding protein (Ca BP) activity in duodenal mucosa and an increased cadmium uptake (Washko and Cousins, 1976; Washko and Cousins, 1977). It is possible to demonstrate that in vivo cadmium is preferentially taken up by CaBP in calcium deficient animals (Washko and Cousins, 1976) although other authors consider cadmium to be a non competitive inhibitor of calcium absorption (Hamilton and Smith, 1977).

Cadmium induced renal histological changes are more pronounced in calcium deficient animals than normal with the proximal tubules being the most severely affected part of the kidney (Takashima, Nishino and Itokawa, 1978).

Cadmium pretreatment of animals is obviously very complex in that not only is there an altered calcium transfer across the duodenal mucosa (Ando et al, 1977) but there is also a reduction in 1:25 vit D_3 activity in these cells (Lorentzon and Larsson, 1977). As an extension of these experiments it has been shown that rats exposed to cadmium have renal mitochondria which have a low 1:25 Vit.D production capability. The significance of implicating

Vit. D in cadmium toxicology rests on the realization that Vit. D has been shown to play a part in mobilisation of bone zinc and cadmium (Worker and Migicousky, 1961).

It should be remembered that there is a link between phosphate and calcium absorption sites in the villi of the small bowel (Wills, 1973) and this may be implicated in the hypophosphataemia of cadmium poisoning. Hypophosphataemia may be the reason why cadmium poisoning can induce feelings of weakness, paraesthesia and such vague symptoms as muscle and joint pains (Leading article, Lancet, 1971) which if sought can be elicited from subjects with cadmium poisoning.

In primary hypophosphataemia it has been noted that such patients have a lowered phosphate transportation and that the tubular defects include glycosuria, amino aciduria, phosphaturia and Vit. D resistent rickets (Leading article, Lancet, 1971); these biochemical abnormalities are also found in chronic cadmium poisoning. The one characteristic of primary hypophosphataemia which is not found is the high urine calcium output of chronic cadmium poisoning. Ultimately osteo malacia may occur in such individuals and it is considered that in the light of our own observations on the biochemical and physical abnormalities in coppersmiths that a syndrome of hypophosphataemia, normocalcaemia with elevated blood and urine cadmium values coupled with renal failure and hypercalciuria is as clear cut as the Fanconi syndrome.

It is against the above background of biochemical abnormality that elevated urine calcium levels become very significant in chronic cadmium poisoning and with the histological changes the kidneys in chronic cadmium poisoning have possible nucleation sites for calcium deposition which helps explain the high prevalence of stone disease in cadmium poisoning.

In general stone formers have a higher mean calcium excretion than non stone formers (Bulusi, et al, 1970) and men have a higher calcium excretion than women whether they are stone formers or not. Stone formers have also been found to excrete less sodium and potassium than normal individuals and by contrast to have a higher output of zinc in urine (King, Mulvaney and Johnson, 1971). Normally these findings have been regarded as being a secondary phenomenon associated with a high urine calcium output, but there are many patients with 'idiopathic hypercalciuria' which many of the defects found in chronic cadmium posioning where the blood or urine cadmium levels have never been estimated. In consequence many 'idiopathic hypercalciuria' subjects may have been missed cases of chronic cadmium poisoning.

There is clearly a complex interaction between cadmium and calcium. In addition cadmium causes alteration in cells which both in the kidneys and gut are involved with Vit. D metabolism. Coupled with these effects cadmium clearly alters phosphate

absorption and excretion.

It has been recognised for some time that the osteomalacia of Renal tubular acidosis is associated with hypercalciuria, hypophosphataemia and increased faecal excretion of calcium (Richards, Chamberlin and Wrong, 1972). Cadmium could well have been the missing factor in many cases of idiopathic hypercalciuria expecially when renal tubular acidosis is present. The search for a cadmium source and the simple measurement of cadmium values or the effects which it causes on renal cells would appear to be a reasonable investigative procedure in renal stone formers. The present author admits that but for the intensive investigation of a group of workers where potential cadmium poisoning was suspected initially then the possible link between cadmium and many of the biochemical abnormalities in the work force could easily have been missed. The lesson to be learned is clearly that when biochemical abnormalities of the type above are found when investigating subjects with calcium abnormalities then the possibility of cadmium being implicated should be constantly borne in mind.

CARCINOMA

In 1775 Sir Percival Pott described the first case of occupationally induced cancer i.e. scrotal cancer. It was subsequently noted that there was an abnormal rise in lung cancer rates in haematitic workers (Leading article, Lancet 1970) and although no single aetiological factor could be identified, it was speculated that radon, silica and silicotuberculosis were implicated.

Despite a considerable interest in possible industrial sources of carcinogens there have been remarkably few proven 'cause and effect' relationships established. The problem is even more intriguing when it is remembered that possibly 80 - 90% of all human cancers are environmental in origin (Leading article, British Medical Journal, 1969). Unexpected carcinogens still occur e.g. in mineral oils (Annotation, Lancet, 1968) but relatively little work has been undertaken to study the effects of the trace elements in carcinogenesis either as single agents or as combined agents.

Perhaps one of the reasons why it is difficult to clearly identify single metal carcinogens is that cancer arising as a result of occupational exposure to any substance may take several years before a 'cause and effect' is clinically established. The issue is further complicated since such cancers can develop after a time lapse without further contact with the carcinogen.

This is well illustrated in asbestosis. A very good example of the 'delayed' effect of a trace metal carcinogen is illustrated by the observation that when a nickel factory was opened in 1902 no particular thought of a cancer link was considered. By 1924 however (Leading article, Lancet 1971) it became apparent that there was an increase in the number of nasopharyngeal and bronchogenic carcinomas among the work force. In this instance it should be realised that a simple cause and effect between nickel and cancer was difficult to identify since several metals including cobalt, selenium, tellurium and a variety of precious metals were involved in the factory processes.

Despite the difficulties of identifying direct cause and effect relationships in cancer, it has been known since 1822 that one trace metal - arsenic - is a causal factor in skin cancer (Gunn, Gould and Anderson, 1967). Other specific examples of single metal exposure and particular tumours are chromium in nasopharyngeal cancer, beryllium in lung cancer. Many metals have produced cancers in animals including chromium, cobalt, copper, lead, mercury, selenium, silver and tin.

Interest in cadmium as a possible factor in carcinogenesis arises because of observations in humans and as a result of animal experiments. There is still considerable speculation as to whether cadmium does or does not cause neoplasia in human beings (Malcolm, 1972; Fishbein, 1976) but high cadmium and

copper body burdens are associated with many types of cancer (Miller, Wylie and McKeown, 1976) as for example in bronchogenic carcinoma where the amount of cadmium is significantly elevated in kidney, liver and blood (Strain et al, 1972; Morgan, 1970; Morgan, Birch and Watkins, 1971).

A significant association has been recorded between renal cancer and exposure to cadmium; in a study of 64 cases a possible synergistic effect of occupational exposure and smoking has been shown (Kolonel, 1976).

One of the major urological interests linking cadmium with cancer stems from the important observations that in a group of alkali battery workers there were 8 deaths in 70 men and of these 5 died of cancer and 3 of these were of cancer of the prostate(Ca prostate) (Potts, 1965).

At least one group thinks that there appears to be a correlation between atmospheric levels of cadmium and cancer of the lung, bronchus, oral cavity, oesophagus and stomach (Hagstrom, Sprague and Lanran, 1967). The same authors noted that Ca of the prostate in urban areas is high but failed to demonstrate excess amounts of heavy metals in the study area.

Some authors agree that there is an increased risk of a Ca prostate in cadmium exposed individuals but this occurs only in situations where there has been a major occupational exposure (Kolonel and Winkelstein, 1977). A study of a group of workers in recent times has

confirmed that in a work force of 268 cadmium-metal battery workers and 94 cadmium-copper alloy workers there is an increased likelihood of respiratory and renal disease with a statistically significant increase in nasopharyngeal cancers. There is also a greater risk of lung, colonic and prostatic cancer but not at a significant level (Kjellstrom, Friberg and Rahnster, 1979).

There is some evidence of an association between cadmium and prostatic cancer as shown by the increased cadmium in cells in carcinoma of the prostate (Habib et al, 1976) but great care has to be taken in interpreting such data since the same findings can be demonstrated in benign prostatic hyperplasia. Clearly this observation requires a great deal more study.

Further interesting observations relating human tissue levels of cadmium to cancer and other diseases show for example that there is a significant variation in tissue levels of cadmium in subjects dying of neoplasia when compared with hypertensive and other diseases (Morgan, 1969).

Despite these tentative observations it must be emphasised that some authors claim that cadmium is unlikely to be a carcinogen in man and the cadmium ion is unlikely to be a factor in general or in particular tumours such as C A of the prostate (Malcolm, 1972).

It should always be remembered that although there are conflicting views about the possible aetiological

role of cadmium in Ca it was only in 1950 that the existence of chronic cadmium poisoning was first recorded (Friberg, 1950). It is possible that time alone will confirm or deny some of the earlier speculations about the role of cadmium as a factor in human cancer and the long biological half life makes it unwise to be dogmatic in assessing its role in cancerogenisis.

If one confines ones interest specifically to prostate then the most important observations are that:-

1 In malignant prostatic disease it has been shown that there is a reduction in zinc in prostatic tissue (Habib et al, 1976) but it is also known that the zinc content falls in chronic prostatitis (Hoare, Delory and Penner, 1956).

2 In occupationally exposed individuals using cadmium in a variety of processes there is an apparently greater risk of men developing Ca prostate.

The search for other possible links between cadmium and Ca has been very limited despite the finding of a high renal cadmium content in patients dying of a variety of tumours (Morgan, 1969).

As with other potential carcinogens, a considerable amount of animal experimentation has been undertaken. As a result much conflicting evidence has become available and this helps emphasise

the complexity of assessing the effects of one single element and its interactions with others. In the experimental animal cadmium causes tissue changes which range from the fine structural effects in lung where the sub pleural elastic layer is thickened (Miller, Murthy and Sorenson, 1974) to the production of tumours in rats at injection sites or at distant sites such as the testis (Gunn, Gould and Anderson, 1967).

Not every cell type responds to cadmium by undergoing neoplastic change and to date it is largely those cells of mesenchymal origin such as subcutaneous tissues, subperiosteal and intra muscular cells which respond by becoming neoplastic (Gunn, Gould and Anderson, 1967). The pleomorphic sarcomas which result from cadmium suggest that the tumours arise from injury of the fibroblasts.

Several theories exist as to why cadmium could cause cancer in animals:-

1 Since the element dissolves slowly in tissue fluids cadmium may cause a mechanical effect on tissues resulting in cancerous change (Heath Webb, 1967).

2 It is possible that cadmium interferes with cellular phosphorylation which is characteristically altered in tumour cell respiration (Morgan, 1970). Cadmium ion could therefore initiate Ca change by altering mitochrondrial oxidation and phosphorylation (Jacobs, et al, 1976).

3 It is very significant that five metal salts including cadmium have been shown to interfere with D N A and R N A synthesis (Hoffman and Niyogi, 1977).

However it should be remembered that cancer induction in animals may be species specific and in mice experimental work suggests that a variety of metals including chromium, lead, cadmium, nickel and titanium do not cause cancerous change (Schroeder, Balassa and Vinton, 1964).

By contrast in rats it is apparent that in vivo cellular changes (Lasnitzki, 1951) including increase in cell division, hyperplasia and squamous metaplasia with increased basal cell growth can be induced by cadmium (Chandler and Timms, 1976). Cadmium also affects stroma which might be important in maintaining cell stability.

It has been shown using radioisotope techniques that cadmium can reduce the content of zinc in certain tissues (Robini, et al, 1961) and the corollary to this observation is that zinc can reduce the carcinogenic effects of cadmium if administered as zinc acetate (Gunn, et al[1], 1961; Ferme and Carpenter, 1967; Gunn, Gould and Anderson, 1964). Apart from zinc, magnesium may help to protect against cadmium induced cancer. Magnesium may be very interesting in this context since in magnesium deficient rats the lymphocytes have an impaired or reduced cellular immunity (Mease, 1974). The story

becomes more complicated when it is realised that cadmium induced tumours still have the capability of producing androgens (Gunn, Gould and Anderson,[2] 1965).

Early studies of the effects of cadmium on the rat testes and prostate suggested that the toxic effects of cadmium could have been caused by its ability to induce zinc displacement from its normal homeostatic pathway (Cotzias, Berg and Selloch, 1961). Further support for this theory arose when it was realised that cadmium induced injury in rats which is characterised by the inability of testes and dorso-lateral prostate to take up zinc (Gunn, Gould and Anderson,[2] 1961). By contrast the ventral lobe is not susceptible to cadmium induced changes and significantly this lobe is not under ICSH control. It has been suggested that the zinc in the dorsolateral lobe of the rat prostate and in the testes is different from that found in other organs in that it has been shown to be under hormonal control. As a result of this type of study it was suggested that zinc has a local protective effect on cadmium induced changes. It is now universally accepted that actual replacement within the cell at sites of zinc metabolism is unlikely to be the mechanism whereby cadmium causes a reduction in cadmium carcinogenesis (Gunn, Gould and Anderson, 1964; Ferme and Carpenter, 1967). The mechanism whereby zinc exerts its protection may be by the induction of metallothionein and not by metalloenzyme displacement (Webb, 1971).

There has been criticism of the many results obtained in animal studies because the metal has been injected subcutaneously or intra muscularly (Cousins et al, 1977). By using injections the metal bypasses the homeostatic mechanisms intrinsic within the G I tract and secondly the concentrations employed are too high and therefore non physiological.

Nevertheless, there is sufficient evidence from all the above studies that cadmium can be carcinogenic when present in high concentrations in tissues. The problem with respect to human cancer is whether the slow but progressive accumulation of cadmium can induce cancer in certain organs.

REPRODUCTION

One of the most important findings among the early experimental work with cadmium was the observation that cadmium induced characteristic and reproducible effects on rat testes. The element causes microscopic changes within a few hours of injection viz:- oedema, haemorrhagic appearances and 'blue' testicle. Microscopically such testes show evidence of necrosis of the semeniferous lining which apparently recovers (Parizek, 1957). If rats subjected to cadmium are observed for 12 - 18 months they characteristically develop Leydig (interstitial)cell tumours. (I.C.T.).

These effects on testicle occur as a result of vascular insufficiency rather than a direct effect on the testicular cells. Within 3 hours post injection there is a reduction in blood flow and angiographic studies support the concept that cadmium induces its effects by acting on fine blood vessels supplying the testes (Niemi and Kormano, 1965; Gunn, Gould and Anderson,[3] 1965). Further evidence to support a vascular effect by cadmium is given by the observation that vascular ligation causes similar effects and in the long term I C T (Gunn, Gould and Anderson,[2] 1965). With respect to the short term effects apparently normal recovery occurs at 14 days (Waites and Setchell, 1966).

It is thought that cadmium induces damage by

causing alterations in the permeability of small blood vessels to glucose (increased after cadmium injection) resulting in an increased glucose concentration in testes (Harkonen and Korman, 1970). After four hours there is a marked fall in testicular glucose content with a corresponding rise in lactic acid concentration.

The vascular injury in testes is a 'cadmium specific' effect on existing endothelial cells (Gunn, Gould and Anderson, 1966). Following an initial cadmium assault on blood vessels regenerated blood vessels do not show the same cadmium response and this would suggest that there is a possible biochemical difference in the two endothelial linings. This intriguing problem is further complicated by the suggestion that there are strain differences in susceptibility to cadmium induced changes (Gunn, Gould and Anderson,[1] 1965) as is evidenced by different animals exhibiting different capabilities in their ability to handle cadmium (Johnson, Sigman and Miller, 1970). This difference between species can be demonstrated by the fact that there is no obvious cadmium damaging effect on avian as opposed to mamalian testes (Johnson and Sigman, 1971) and since cadmium can be shown to attain almost equal ratios in certain cellular sub-fragments in the two species it suggests a probable different enzyme capability. Species variability to cadmium can be confirmed by showing that the metal is capable of causing altered androgen synthesis in Salmonids (Sangalong and O'Halloran, 1972).

Zinc as has been shown reduces the likelihood of cadmium induced I C T tumours (Webb, 1972; Parizek, 1957). Zinc is capable of initiating the production of Cd-MT in liver i.e. the animal is 'primed' to accept and bind cadmium when it is subsequently exposed to the metal and although zinc administration to negate cadmium effects is a very attractive proposition it has to be realised that zinc exerts its effect by inducing the animal to produce Cd-MT and Cd-MT by itself is toxic to tissue other than testes and in particular the kidney (Singh and Nath, 1972; Nordberg, 1971).

One interesting observation is that the lesions induced by cadmium in rat testes resemble those induced by giving the animal a reduced Vit. E intake (Mason, et al, 1964) but it does not appear to be an anti-Vit. E agent (Kar and Das, 1960).

Relatively little work has been undertaken to study the effects of cadmium on reproductive tract in female animals. This is surprising in view of the ten times increase in still-births when cadmium is given to experimental animals (Bryce-Smith, et al, 1977). Cadmium, in female rats, is firmly bound in the liver and kidneys during pregnancy (Webb, 1972). Injected cadmium damages the placenta and foetus but there is evidence that prior injected cadmium is firmly bound in kidneys and is not mobilized to participate in this process.

The reproductive capacity of rats is affected by cadmium in that rats injected with cadmium show a loss of copulatory activity (Madlafousek, Hlinak and Parizek, 1971), for three weeks post injection but 'normality' is restored after two months. Androgen protects against the initial effects but in the higher primates the effect of cadmium on testes is such that it is possible to 'chemically sterilize' monkeys by cadmium injection (Kar, 1961). This work suggests that the element may be of a greater importance in human subfertility especially if it is remembered that smoking causes a reduction in male fecundity and that it is normal to advise men to reduce smoking during treatment for subfertility.

IRON

In a variety of studies of the effects of cadmium on humans it has been regularly reported that anaemia is a feature of the chronic cadmium poisoning. Although there is a fall in haemoglobin levels there does not appear to be any obvious change in bone marrow erythropoiesis. According to some authors (Berlin, Fredericsson and Linge, 1966) this suggests either a change in life span of the erythrocyte or an inhibition of haemoglobin synthesis caused by interference with the transport of iron. Parenteral iron relieves the anaemia.

In studying the haematological effects of cadmium one of the most complex interactions between metals is encountered. Involved in the complex are iron, copper, cadmium and zinc. Examples of this interaction can be seen when cadmium is shown to replace copper and zinc in their active metabolites and furthermore cadmium induces a copper deficiency (Hill, et al, 1963).

In iron deficiency the body burden of cadmium is found to be 7 times greater than normal (Ragan, 1977). Iron deficiency is probably more prevalent in cadmium poisoning than has been formerly recognised and this has been largely overlooked in the clinical management of subjects with chronic cadmium poisoning.

From experimental animal work possible mechanisms for the cadmium induced anaemia can be speculated. It has been shown for instance that when cadmium is found in duodenal mucosa there is a complex cadmium

metallothionein (Sugawara and Sugawara, 1977) along with increased activity of enzymes such as iso-citrate dehydrogenase and glucose phosphate dehydrogenase. Accompanying these enzymatic changes in duodenal mucosa cadmium causes an increase in zinc content and a reduced magnesium and manganese content.

Cadmium is therefore clearly capable of changing the intestinal mucosa in such a manner that it interferes with the absorption of other elements e.g. cadmium has been shown to inhibit copper absorption in rat duodenum (Davies and Campbell, 1977). It has been demonstrated that cadmium acts by inhibition of the binding of copper to a low molecular weight protein in the mucosal cytosol.

It has been shown by auto radiographic techniques that there is a high excretion of cadmium by gastric and colonic mucosa and also significantly in bile (Berlin and Vilberg, 1963). The situation is even further complicated by experiments such as those which have shown that the absence of copper increases the effectiveness of cadmium in reducing the haemoglobin concentration and it also reduced the numbers of red blood cells (Hill et al, 1963). Despite some observations that cadmium does not affect bone marrow there is evidence of a marrow suppression as evidenced by the disappearance of fat cells accompanied by an accelerated haemoglobin synthesis in cadmium poisoning. There is also the possibility that cadmium causes a reduction in the life span of red

blood cells (Prigge, Baumert and Mehle, 1977).

If the renal effects of cadmium are considered then it is possible that the formation of erythropoietin or its precursor in the kidney may be inhibited by cadmium and the anaemia could therefore be secondary to the renal effects of cadmium (Greaves, 1977).

It has been shown in the experimental animal that cadmium can reduce iron absorption (Hamilton and Valberg, 1974) and it is possible that despite the other potential mechanisms whereby cadmium could induce anaemia it is by this effect on iron absorption that cadmium produces anaemia. Cadmium probably forms a cadmium metallothionein in the duodenal mucosa resulting in a blockage of iron absorption.

Protection against cadmium anaemia can be achieved in the Japanese quail (Colorinix coturnix japonica) by giving extra ascorbic acid (Spivey Fox, 1975). Ascorbic acid is known to promote the absorption of iron and this facility of absorption clearly is important in reducing the effects of cadmium but it should be remembered that iron by itself apparently does not prevent cadmium toxicity and is probably inhibited from doing so because of the enteropathy induced by cadmium.

METALLOTHIONEIN

One of the most important realisations about cadmium is that it induces the formation of a complex protein - metallothionein (Cd-MT) - in the liver and it is in this complex that cadmium is transported by blood and lodges in organs such as the kidney. The Cd-MT complex contains zinc and copper and the molecular weight is 6500 (Leber and Miya, 1976). Studies of human Cd-MT confirm that it contains 4.2% cadmium, 2.6% zinc, 0.5% Hg and 0.3% copper (Pulido, Kagi and Vallee, 1966). The Cd-MT probably contains two cadmium binding proteins one of which contains cadmium and zinc and the other zinc only (Leber and Miya, 1976). It has been possible to separate these two forms of Cd-MT by isoelectric focussing (Nordberg et al, 1972). The one which focused at pH 4.5 has zinc but the other - isoelectric peak 3.9 - contains no zinc.

From horses it has been possible to isolate Cd-MT which is a Cadmium/zinc complex (Kagi and Vallee, 1961) in which sulphur is present as cysteine and the molecular weight is 10,000 ± 260. The complex also contains copper (0.1%) and zinc (2.2%).

Cd-MT has been shown to contain 4 proteins and of these 3 are cadmium binders and one is a zinc binder (Schroeder and Nason, 1974). The cysteine and sulphlydil groups appear to be the sites for cadmium binding (Schroeder and Nason, 1974).

The equine renal cortical Cd-MT contains 2.9% cadmium and 0.6% zinc per gram dry weight. The cadmium content is significantly higher in Cd-MT than in any known metallo enzyme (Kagi and Vallee, 1960).

Cadmium is bound to metallothionein in the gut and may be absorbed in this state (Valberg et al, 1977). When the mucosa is exposed to cadmium then broadening of the villi and pseudo stratification of the epithelium, accompanied by swelling of the mitochondria, can be demonstrated. However less than 5% of mucosal cadmium enters the blood stream (Valberg et al, 1977). If desquamation of the gut occurs this may help to give some protection against the metal. Large doses of Cd-MT are capable of causing necrosis of the mucosal cells. In the Japanese quail it is possible to demonstrate inflammatory cell infiltration in the gut mucosa following cadmium exposure and it has been shown that cadmium competes with calcium at binding sites for calcium in the mucosa (Hamilton and Smith, 1977).

Cd-MT can be induced by repeated injections of non toxic doses of cadmium. It is of a low molecular weight and is filtered by the glomerulus and re-absorbed in the proximal convoluted tubule (Webb and Etienne, 1977). After injection of Cd-MT it can be shown that 90% of the complex is recoverable from the renal cortex (Foulkes, 1978). A further important aspect of giving an animal small

doses of cadmium (Cherian, 1977) is that such pre-exposure to cadmium results in liver cells being able to produce Cd-MT very rapidly (Daniel, Webb and Cempel, 1977). On any subsequent exposure cadmium bound to MT is ten times more toxic than cadmium which is present in an unbound state (Webb and Etienne, 1977).

Some interesting paradoxes occur with respect of Cd-MT e.g. by itself it can cause nephropathy (Cherian, Goyer and Dalaquerriere-Richardson, 1976) as is demonstrated by degenerative changes occurring in glomeruli (Itokawa, et al, 1974) and yet the renal excretion of cadmium does not appear to involve Cd-MT (Nomiyama and Foulkes, 1977).

In complete contradiction to the ability of Cd-MT to cause renal damage it would appear that Cd-MT protects against cadmium induced testicular necrosis. Not all animals exhibit the same response to cadmium even in their own life cycles e.g. younger animals show less accumulation of the metal suggesting that they have some protective mechanism (Jugo, 1977).

It is interesting to speculate how Cd-MT affects cells. It is considered that the toxicity is probably due to the ligands to which cadmium is firmly bound affecting enzymes and cell membranes (Jugo, 1977) and it is possible in animals to reduce cadmium related mortality by giving mixed ligand chelates (Schubert and Derr, 1978).

From the above experimental studies it is now realised that zinc protection against the effects of cadmium is not related to metallo enzyme substitution but due to the formation of metallothionein which is Cd-MT (Webb, 1971).

EFFECT OF CADMIUM ON KIDNEY.

CHAPTER 7.

THE EFFECTS OF CADMIUM ON KIDNEY

Early in the studies of chronic cadmium poisoning it was realised by Friberg that renal lesions would eventually be seen to be more important than pulmonary changes (Bonnell, 1955).

It is interesting that when the cadmium content of renal cortex is compared between specimens from the 19th and 20th centuries the figures are 15.1 ug/g and 57.1 ug/g dry weight respectively showing that in the present era there has been a much greater exposure to cadmium than when the metal was first introduced (Elinder, 1977). This coincides with the great increase in use of the metal in the present century.

In studies of modern general populations it has been shown that in Japanese subjects there is a rise in renal cortical cadmium with age (Tschuya, Seki and Sugita, 1976). The highest levels are present in men between 30 - 40 years. Similar results were obtained from an analysis of 292 autopsies in Sweden (Elinder et al, 1976). Other workers have confirmed that in different populations renal cadmium is higher in white males and cigarette smokers (Morgan, 1976; Hammer et al, 1973). From an autopsy study it was realised that cancer patients had higher and more variable kidney cadmium levels than non cancer subjects (Hammer et al, 1973) but the full significance of this finding is not clear

in the context of the overall cancer causing potential of cadmium. Apart from lodging in kidneys it has long been recognised that cadmium causes kidney damage as is shown in an epidemiological survey of a group of workers where a confirmed death rate from nephritis of 15.0 (per 100) compared with the expected rate of 5.3. This occurred in a group of coppersmiths and careful analysis suggests that this incidence represents an undiagnosed cadmium poisoning of long standing (Davies, 1972), but it should be remembered that in acute deaths from cadmium, renal necrosis is an important feature (Beton et al, 1966). It is very surprising that very few deaths from renal failure have been attributed to chronic cadmium poisoning but this is probably related to the fact that it may be several years after exposure before chronic cadmium poisoning becomes evident and therefore the cause of the renal failure may not be fully appreciated (Hansen, Kjellstrom and Vesterberg, 1977).

The distribution of cadmium in the kidney reveals a greater concentration in the cortex as compared to the medulla (Hansen, et al, 1977). This is not uniform throughout life and there is a relative reduction in the amount of cadmium in the cortex of kidney with age (Kjellstrom, 1971). Similar differences exist between those who are industrially exposed and between smokers and non smokers. Two interesting studies on the level of cadmium in renal cortex have confirmed firstly that mongols have a

higher renal cadmium content than expected,accompanied by a higher than normal zinc content (Gross, Yeager and Middendorf, 1976). The second of these observations confirms a higher level in kidneys in plumbers emphasising that those who are involved in occupations where metals are used are at greater risk of accumulating the metal than non metal workers (Gross, et al, 1976).

Further interest and verification of the above has been demonstrated by the modern technique of measuring cadmium content of kidney by in vivo neutron activation analyses. Such studies have revealed that in subjects who have been occupationally exposed especially when there is impaired renal function then there is a greater concentration of cadmium in the renal cortex (Roels et al, 1979).

One of the interesting features of renal accumulation of cadmium is that it becomes reduced after the age of 50 (Webb, 1972). It is important to realise that the biological half life has been calculated to be 30 years indicating that the bulk of ingested cadmium is excreted very slowly. This allows the metal to damage the kidneys over a prolonged period of time.

Apart from occupational exposure the effects of cadmium can be influenced by dietary intake and by the rate of excretion of the metal. Excretion occurs in two phases viz: (1) a rapid excretion of 10% ingested cadmium and (2) a slow excretion (90%).

This must obviously be a factor in the greater levels found in older subjects.

Histological effects

Cadmium causes two main effects on the kidney. Firstly it causes structural damage in tubules and in the glomeruli. Secondly it causes a wide variety of biochemical effects which result from interference with normal function.

Very few studies of the effects of cadmium in human kidneys have been undertaken and this is hardly surprising since the changes produced could be related to a number of different factors. It is obvious that when dealing with a known nephrotoxin every step should be taken to avoid exposing human subjects to the substance. Therefore to understand the histological effects produced by cadmium it is necessary to revert to the animal model. The range of renal damage may extend from mild tubular changes to gross glomerular damage. Ultimately if chronic cadmium exposure continues then nephrolithiasis will occur (Friberg, 1959) and the main theme of this work is to demonstrate the importance of cadmium in the context of stone disease.

It is very difficult to obtain accurate figures relating cortical cadmium levels to histological changes but in an effort to quantitate the significant levels of cadmium in cortex the W H O task force group suggest 200 ug/g wet weight as the critical concentration (Nomiyama, 1977; Elinder, Piscator and Linnman, 1977) but the figure could easily be an

over estimate of the amount of cadmium necessary to cause renal damage.

Until recently most attention has been directed towards the tubular effects of cadmium and it is because of this emphasis that the glomerular effects have been largely overlooked. Early work suggested that there was no major histological differences in animals given the metal for only 6 as compared with 12 months. It is interesting from such early work that glomerular changes were actually noted and in 1960 Bonnell postulated these changes could be of a secondary type. He also recorded a case of fibro hyaline change in human glomeruli in a cadmium exposed individual. That glomerular damage can occur is important in the assessment of proteinuria occuring in chronic cadmium poisoning.

Several workers have now recorded and have confirmed that changes do occur in glomeruli and in the glomerular endothelial cells when animals are exposed to trace levels of cadmium. e.g. there is evidence that following exposure to the metal then after 29 weeks there is definite evidence of glomerular capsule thickening and ultimately hyalinization and fibrosis of the basement membrane of the glomeruli (Axelsson and Piscator, 1966; Seth et al, 1976) with deposition of a non specific stained material (Kanisawa and Schroeder, 1969).

Further evidence of glomerular damage is

demonstrated using autoradiographic techniques where it can be shown that there is very obvious cadmium deposition in the Bowman's capsule in the kidneys of experimental animals (Friberg, 1952). The glomerular vasculature also is affected in that the arterioles show proliferation of basal cells and medial cell thickening.

In a study of chronic exposure to cadmium the ultra structural changes in rabbits have been studied over periods of between two weeks and seven months and both tubular and glomerular lesions can be clearly observed (Castano, 1971). Early in the process there was increased rough endoplasmic reticulum in the glomerulus and tonofibrils. It is suggested that cadmium does not cause immediate or direct changes in the glomerulus. In these experiments clear spaces occurred in cells and since immunoglobulins are glutaraldehyde soluble they may well be represented by clear spaces (Itokawa et al, 1974) suggesting that cadmium glomerular changes may represent an immune reaction.

In these experimental studies amyloid deposition in glomeruli has been demonstrated (Castano and Vigliani, 1972; Baum and Worthen, 1967) and it is suggested that such a finding could be relevant in human amyloidosis although there is no evidence that this hypothesis has been properly studied (Castano, 1971).

The long biological half life of cadmium could be important for another reason namely that chronic

exposure is associated with an increased $Beta_2$ galactosidase excretion suggesting damage to the urinary tract lining epithelium (Kazantzis, 1979). In chronic cadmium poisoning this could be important as a mechanism which could induce changes in the transitional cell epithelium at a lower level in the urinary tract. To date no correlation has been recorded between cadmium and the induction of transitional cell carcinomas.

Interestingly it has been found that metallothionein induces greater renal damage than cadmium chloride (Nordberg, Goyer and Nordberg, 1975). Metallothionein protects testis from cadmium but paradoxically does not appear to offer a similar protection to kidney cells (Cherian et al, 1976). Cadmium metallothionein induces vacuolation of renal cells with swelling of mitochondrial granules.

Apart from the immediate effects of cadmium on cells it is important to realize that there is selective accumulation of cadmium in rat kidney (Gunn and Gould, 1957). The young rat cortex which has fewer nephrons than the adult concentrates less cadmium than adult renal cortex. It is obvious that the histological effects can easily become progressive and if an immune response is occurring then the process, once initiated, may well be self perpetuating.

Biochemical effects

The biochemical effects are well recognised and some of these are used (i) in making the diagnosis of cadmium poisoning, (ii) as a means of differentiating the condition from other renal disease and (iii) can potentially be used to follow the progress of the condition.

In a series of experiments using subcutaneously injected cadmium chlorate it was possible to demonstrate that creatinine clearance was reduced but not significantly, glycosuria significantly increased and alkaline phosphatase activity in the cortex reduced to a highly significant degree (Axellson and Piscator, 1966).

In rats it has been shown that cadmium decreases sodium excretion,(Foulkes et al, 1974; Lener and Musil, 1971) and along with these changes in sodium excretion which are similar to those caused by aldosterone, proximal tubular reabsorption of calcium is altered. These effects of cadmium on sodium handling by the proximal tubules could result from altered sodium transport, changes in energy supply or alterations in membrane permeability (Vander, 1962). The overall result is that cadmium has been shown to increase sodium reabsorption in the proximal tubule (Vander, 1962).

The greatest debate in recent years has centred on the type of proteinuria induced in cadmium poisoning viz: is it of a large molecular weight type

i.e. glomerular proteinuria or is it tubular proteinuria.

As a practical tool in epidemiological work the outcome of this debate is very important. This has been well illustrated by studies of proteinuria in Japanese populations. In 'itai itai' disease there is a 100% to 300% increase in $Beta_2$ microglobulin in the urine but when using B_2 microglobulin in epidemiological work it should be noted that there is a pH effect in that $Beta_2$ is less stable at pH<5.6 (Shiroishi, et al, 1977). In one study it has been observed that there is a 50 - 100% daily variation in $Beta_2$ output over a ten day period (Kjellstrom, Evrin and Rahnster, 1977). From these observations variability of protein excretion can clearly be seen to be an important consideration which an investigator must be very aware of in assessing possible cases of chronic cadmium poisoning (Keckwick, 1955).

In a study in 1955 of men exposed to cadmium the prevalence of proteinuria was found to be 25% as compared with 5% in a control group (Smith, Kench and Lane, 1955). The urine cadmium was 0.580 ug/l as opposed to 0.20 ug/l in controls which raises the important question of the level of renal cortical cadmium required to cause proteinuria. It is estimated that if cadmium reaches 200 ug/g in kidneys then proteinuria will occur but the proteinuria induced by cadmium is not necessarily related to a single exposure to cadmium in that low dosage over a prolonged

time may result in high levels of proteinuria. The reason for this effect is firstly the long biological half life and secondly relates to the slow excretion of the metal. It is possible to alter the prevalence of proteinuria in an exposed work force despite the long biological half life by improving environmental control (Tsuchiya, 1976).

There is evidence from animal work that the proteinuria may be hormone dependant or dependant to some extent on hormone activity in that cadmium administration is associated with a reduced testosterone activity (Nordberg, 1975; King, Clark and Faeder, 1976) but hormonal influence on the cortical accumulation of cadmium has not been demonstrated despite the ability of the renal cortex to selectively accumulate the metal. The controlling mechanism of cadmium accumulation is not known.

Apart from the ability of cadmium to cause changes in sodium and calcium absorption in the proximal tubules the metal causes a number of different biochemical effects on the kidneys. One of these is renal tubular acidosis which is probably more common than previously realized (Seedat, 1972).

Cadmium causes significant changes in calcium excretion which is very relevant in that individuals exposed to the metal will develop renal stone disease. In parallel with the changes in calcium excretion cadmium causes increased urine excretion of phosphate. It should be remembered that the symptoms of

phosphaturia with hypophosphataemia include myopathy and osteomalacia with anorexia, muscle weakness and bone tenderness (Leading article, Lancet, 1978) and these symptoms can be found in chronic cadmium poisoning. The observer should therefore be aware of their potential significance when dealing with unexplained phosphate abnormalities. Since glycosuria also occurs in cadmium poisoning it should be remembered that in 'phosphate diabetes' there is characteristically a hypophosphataemia and hyperphosphaturia.

Glycosuria like tubular proteinuria and amino aciduria increases with increasing cadmium in the urine (Nogawa et al, 1977). In subjects with the highest $Beta_2$ excretion there is usually glycosuria accompanied by glomerular type proteinuria (Shiroishi et al, 1977).

Among the rather specialized biochemical abnormalities caused by cadmium damage to tubules, amino aciduria is not considered to be a good indicator of cadmium poisoning (Schroeder, 1967).

In cadmium exposed animals a variety of other biochemical effects occur in cadmium poisoning such as a significant increase in renal zinc and decrease in copper and less so manganese (Seth et al, 1976). This observation helps emphasise the complicated inter-relationship between trace elements. There is evidence from

animal experiments that some of the effects of cadmium on kidney can be prevented by other elements such as zinc or selenium (Mason and Young, 1964) but as yet these elements have not been shown to be of any therapeutic value in the treatment of chronic cadmium poisoning nor has ethanyl calcium disodium (di 2EDTA) (Friberg, 1959) which has been shown to be of some protective and even therapeutic value in experimental models (Schroeder, 1967).

One other biochemical 'curiosity' arises from the reduction which cadmium causes in alkaline phosphatase activity (Axellson, Dahlgren and Piscator, 1968). This is very interesting since zinc which is the metal of this metallo enzyme accumulates in cortex as a result of cadmium accumulation in CdMT. The full significance of this altered enzyme activity is not understood. Other enzyme abnormalities probably exist (Castano and Vigliani, 1972) but these have been little studied.

ESTABLISHMENT OF STONE PREVALENCE.

CHAPTER 8.

ESTABLISHMENT OF STONE PREVALENCE

During 1975 it was decided to establish the prevalence of stone disease in a community in the West Central belt of Scotland - namely the new town of Cumbernauld. Most references to stone disease in any community are in terms of "incidence" derived from studies of hospital admissions for the disease. Normally such "incidences" are expressed as number of treated cases per 1000 or for 10,000 inpatients. In order to establish the true prevalence of a condition it is necessary to investigate either the total population or to examine a random sampleof that population.

METHOD

All persons who rent a house in Cumbernauld are registered by the Development Corporation, and this independent organization provided a random sample of the population (7000). Each individual on the random sample was invited to complete a questionnaire and to come to the health centre for completion of data, height and weight checks, and a plain abdominal radiograph. All x-rays were reviewed separately by two consultants and where a disagreement existed, a third consultant acted as arbiter. A midstream specimen of urine was obtained and submitted to culture by a dip slide technique. The specimens were incubated for 24 hours, and the bacterial content recorded as significant or otherwise. The remaining urine was tested for haematuria, glycosuria, proteinuria, and bile.

Blood plasma from each person was analysed for calcium, phosphate, protein, alkaline phosphatase and urate concentrations.

RESULTS

The random sample included 3398 individuals (1650 men and 1748 women) who completed the initial evaluation. However, 1 man and 106 women were not examined by x-ray. In addition to the random sample 205 male and 458 female unsolicited volunteers completed the initial evaluation. Twenty-one volunteer women were not examined by x-ray.

Over 90% of subjects were born in Scotland. Information from the Development Corporation statistics confirms that just over 90% of the town population originates within the Strathclyde region (91.0% of survey).

Age Group Studied

Persons less than 20 years old were deliberately excluded as far as possible because of our unwillingness to x-ray people in the younger age groups. There are, however, certain householders who are less than 20, and seven such subjects were examined (Table 6). Comparison of the age distribution shows that the survey sample tends to follow the pattern for the new town, which does not follow the Scottish population in general. This reflects the general bias of the population towards the younger age groups in new towns. The reduced number in the older age groups is explained

TABLE 6.

Age group	Random		Volunteer		Cumbernauld (% population)	Scotland (% population)
	No.	%	No.	%		
10-19	7	0.2	1	0.2	20.6	12.6
20-30	691	20.3	93	14.2	17.3	27.4
30-39	1054	31.0	231	34.9	16.4	22.9
40-49	839	24.7	202	30.6	12.4	23.5
50-59	487	14.3	90	13.6	7.8	22.8
60-69	218	6.4	37	5.6	4.8	18.7
70+	81	2.4	3	0.5	2.5	15.8

Table 6. Age groups of population attending survey compared with the distribution of the same age groups in the populations of Cumbernauld and in the general population of Scotland.

by the fact that the survey was undertaken in the evenings, which meant that older people were less likely to attend, especially in winter.

X-ray findings

Plain abdominal film. Failure to x-ray female subjects usually resulted from the fact that they were beyond ten days from the start of menstruation or were pregnant. Strenuous efforts were made to reduce this number, but many had changed address or refused to return after the initial attendance.

Intravenous pyelography. When it was agreed by all three consultants that a shadow in the renal area could possibly be a calcified renal stone, the individual was invited to undergo intravenous pyelography with oblique films where necessary to ascertain whether or not a stone was present. As a result 118 cases of stone disease were proven, giving a prevalence of those x-rayed of 3.58% (3.47% of the total random survey) (Table 7). It is interesting to note that there is no obvious difference between men (60) and women (58) in the survey with respect to stone prevalence. In the volunteer group the prevalence in both men and women followed the same pattern but at a rate of 1% less than the random survey.

In addition to the stone cases in the survey other renal pathology was uncovered as a result of the plain abdominal x-ray. These included two parathyroid tumors in conjunction with abnormal biochemistry, two cases of latent tuberculosis, one case of renal carcinoma, and one

TABLE 7.

	Random		Volunteers	
	Male	Female	Male	Female
Right kidney	19	23	1	3
Left kidney	34	32	5	7
Bilateral	7	3	1	-
Total	60	58	7	10
% stones total sample	3.47%		2.5%	
% stones subjects x-rayed	3.58%		2.6%	

Table 7. Positive stones confirmed by intravenous pyelography in a random as compared with a volunteer population in Cumbernauld New Town.

calcified renal cyst.

DISCUSSION

In previous epidemiological studies, incidence of upper urinary tract stone disease is usually defined as the number of such cases seen in a hospital relative to the toal number of admissions to the hospital (Barker and Doonan, 1978). The results of these studies give a wide variation of incidence and make it impossible to speculate about associations between stone disease and other conditions such as coronary heart disorders (Ljunghall and Hedstrand, 1976) or to pick out at-risk groups in the population, such as occurs in certain occupations (Scott et al, 1976; Blacklock, 1965; Larsen and Phillips, 1962).

When the incidence of stone disease is taken from the hospital statistics (Boyce, Garvey and Strawcutter, 1956), it is clearly dependent upon a number of variable factors such as the availability and quality of radiological services, the aggression and pursuit of the diagnosis by the hospital staff, and the awareness and reference of patients from general practitioners to the hospital. Prevalence can only be properly defined by specifically screening a population.

Despite the fact that a considerable amount of time and effort have been spent on clinical problems associated with stone disease such as urinary tract infection (Chinn et al, 1976) or calcium metabolism (Arcila et al, 1972), relatively little work has been done to confirm the prevalence of the disease in

different populations. This is surprising since it would help to confirm or deny statements such as "the incidence is rising" and would also help to allow positive study of specialized groups (Scott, et al, 1976) that are at risk in a population. Such an approach would help orient new research to uncover scarcely recognized etiologic factors that could be relevant in the pathophysiology of a disease affecting a socioeconomic group of major importance in any community.

It has therefore been possible from the present study to establish the true prevalence of stone disease in a community in the West Central belt of Scotland. By establishing such a figure it then becomes possible to compare any special group against the general population stone pattern. Statistics derived from hospital treated subjects refer to a very special group in any community. (Andersen, 1968).

STUDY OF COPPERSMITHS EXPOSED TO CADMIUM.

CHAPTER 9.

Investigation of a workforce to assess the effects of cadmium exposure.

In 1975 I was asked to investigate a group of workers who had been chronically exposed to cadmium fume over a period of at least ten years.

The fume had arisen from the use of brazing rods which contained 20% cadmium. (Fig. 12). This is a common industrial practice since the metal reduces costs by replacing silver in the rods and it allows metal solder to flow more easily. This is the eutectic property of the solder.

The process in the factory under study involved the soldering of small copper tubes on to engine housings which form the compressor units of refrigeration plants (Fig. 13). The process is a 'production line' type and thousands of operations were completed each year. (Fig. 14).

Measurements of the cadmium in the atmosphere confirmed that the threshold limit values had reached as high as four times the then acceptable upper limit ($0.05\ mg/m^3$). It should be noted that cadmium is a Prescribed Substance under the appropriate Industrial Acts (1955) and any levels in excess of T L V values merits the cessation of the process involved.

Due to alterations in the factory layout the coppersmiths had undertaken a variety of brazing procedures at several different points in the factory.

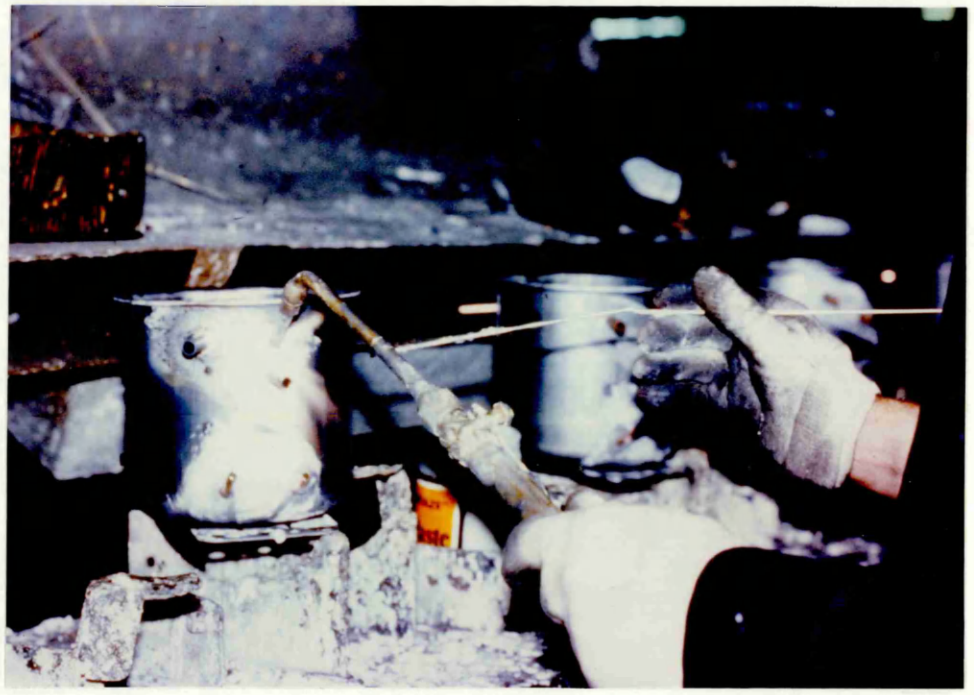

Fig. 12 The brazing process showing the rod containing 20% cadmium. The general area of the work bench is heavily contaminated with cadmium.

Fig. 13 Finished product - a compressor unit for a domestic refrigerator showing at the top two small copper tubes which have been brazed on to the engine housing. The actual braze is hidden by paint.

Fig. 14 This illustrates the production line system showing copper tubes brazed on to the metal lids of the compressors. The workman is not wearing a protective mask.

This meant that the factory dust must contain cadmium by virtue of the process and the air circulation within the factory.

There was no record within the previous five years of any attempts being made by the management to clean the factory roof - an important point as will be seen later. Some of the roof dust (Fig. 15) was obtained and analysed. The cadmium content was found to be 1.45 mg/g of dust.

Background cadmium levels

Initially it was difficult to get accurate estimations of the cadmium levels in the factory but with the realization by the Management that a problem existed then regular sampling of air and dust was undertaken at different points in the factory. Examination of the Fig. 16 reveals that in October 1975 the levels were certainly above the T L V (0.05 mg/m^3).

In December 1975 the Management instituted a programme of roof cleaning which involved removing parts of the roof and general cleaning of the area above the brazing point. This is shown by a rise in the general atmospheric levels.

When the cleaning process was completed the cadmium levels in the atmosphere rapidly returned to barely measurable levels and with the withdrawal of the cadmium containing rods the measurements of atmospheric levels showed that cadmium

Fig. 15 Sample of the dust from the factory roof. This material contained 1.45 mg/g cadmium.

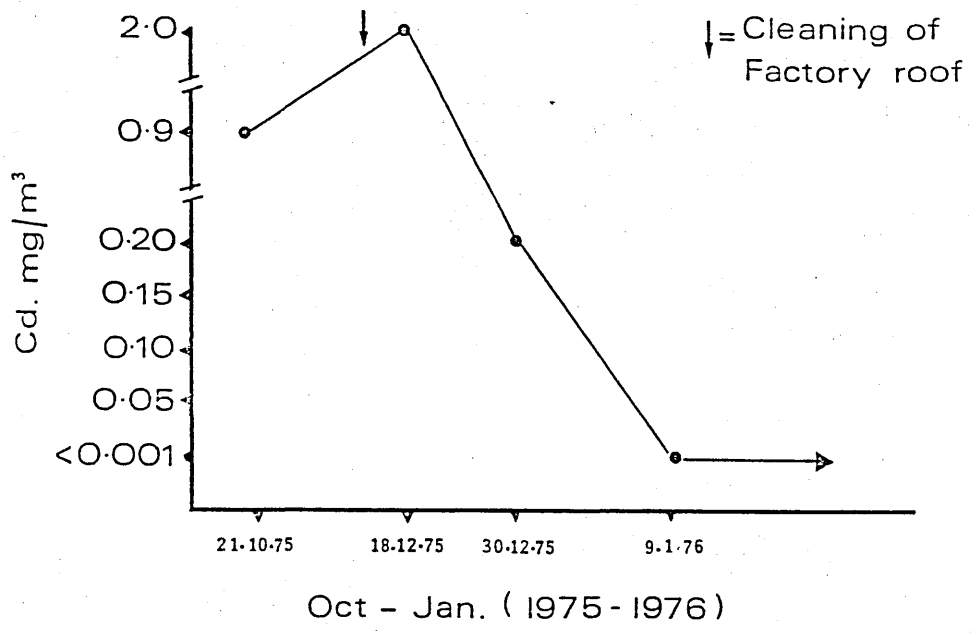

Fig. 16 Atmospheric levels of cadmium measured before and after the cessation of brazing operations. The cleaning of the factory roof is indicated.

remained at a level of less than 0.001 mg/cubic metre of air.

For reasons which I cannot explain the Management had supplied a variety of workers with personalized monitors and from 4 sets of results (Fig. 17) it can be seen that with the cessation of the use of the dangerous rods in late October 1975 the level of cadmium recorded by these devices dropped dramatically but rose again in mid/late December corresponding with the factory cleaning programme. Further results exist for personal monitor levels following the discarding of the rods but unfortunately the data available does not allow an accurate date to be appended to the results. But in all the measurements the values are uniformly less than 0.002 mg/cubic metre.

When asked to investigate the possibility of chronic cadmium poisoning I consulted the available statutory data and this revealed that in 1975 the regulations seemed to indicate that exposure to cadmium, the demonstration of emphysema and the presence of proteinuria, constituted the necessary criteria used to establish chronic cadmium poisoning.

Initial Groups Studied

Group I (27 coppersmiths) were invited in the first instance to attend as out patients for medical examination. The average time spent on the process which involved the use of a cadmium containing solder by these workers was 17.8 years.

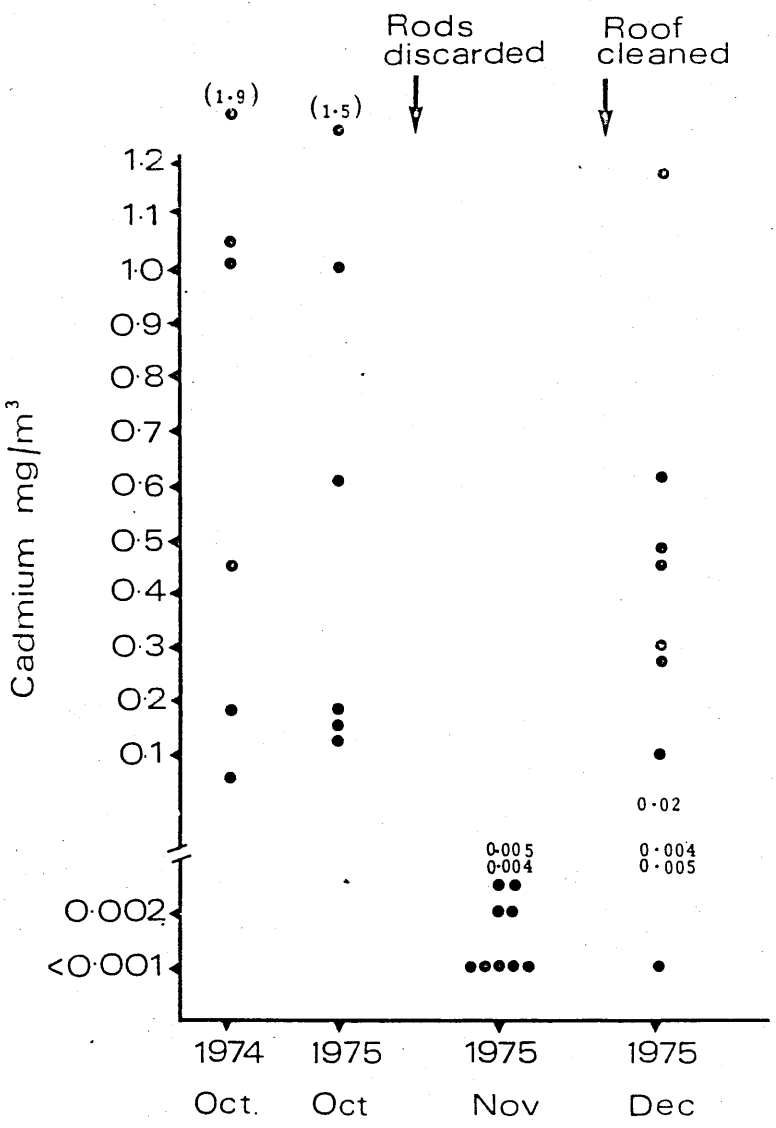

Fig. 17 The levels of cadmium found on individual samplers on the same subjects monitored between 1974 and 1975.

Control Group (Group II) A section of the work force (19 men) who worked in close proximity to the coppersmiths were subjected to exactly the same investigation as Group I. These men were sheet metal workers who were not involved in the brazing process. The average time spent in the same industrial premises was 17.9 years.

Method

Each individual was interviewed and a record made of their social, medical and industrial history. The blood pressure was recorded in the recumbent position and an X-ray of the chest (full plate) and of the abdomen was taken. A vitalograph record was made by two separate observers and the average of the two observations was taken for each individual.

Biochemical estimations

Each subject had blood removed without compression and the following estimations were made:- urea: creatinine: sodium: potassium: chloride: CO_2 content: bilirubin: alkaline and acid phosphatase: alanine and aspartate amino transferase (ALT and AspT): inorganic phosphate: total proteins: calcium and urate. All of these measurements were undertaken in the routine laboratory, Department of Biochemistry, Royal Infirmary, Glasgow. The trace elements measured in blood were cadmium, copper, zinc, magnesium and lead. The trace element measurements were undertaken in the trace element laboratory in the same hospital, using atomic absorption spectrophotometry. A 24 hour sample of

urine was collected and analysed for calcium, cadmium, creatinine and urinary proteins. Where the latter were elevated a quantitative measurement was undertaken. Urine zinc and copper were also measured.

The blood and urine cadmium values were also measured by an atomic fluorescence technique. This technique was developed and proved in the University of Strathclyde and urine and blood from non industrially exposed individuals were used to establish reference values. The results from the blood and urine biochemical investigations were compared to the reference values of the Royal Infirmary Biochemistry Laboratory. The blood cadmium values were compared with 98 randomly selected patient samples coming to the laboratory for routine analyses. Urine cadmium results were compared to values obtained from 42 student volunteers. The level of contamination by atmospheric cadmium was shown to be minimal at the site where the coppersmiths were initially examined.

To check that there was no obvious local contamination at the hospital site where blood was withdrawn all of the standard procedures, needles and syringes were used to make a mock aspiration of deionized water at the exact point in the clinic where the blood was withdrawn from the individual subjects. When checked by this method cadmium could not be detected in the water after it had been passed through the system.

Results.

In the first instance any result which was out-with the normal range for the laboratory was recorded as an abnormality.

There did not appear to be any direct co-relation between length of time of exposure and the overall number of abnormalities found in any one individual.

Using the same criteria there was no obvious relationship between the blood cadmium values and 'total abnormalities' and equally with respect to urine cadmium values and all abnormalities. However if the blood cadmium values were arranged in units of 5 (ug/l) then evidence of a relationship between cadmium levels and 'abnormalities' becomes more obvious. A similar factor emerges for urine abnormalities (Fig. 18).

Since cadmium intoxication is associated with the development of proteinuria it could be expected that a possible relationship would exist between blood cadmium levels and the total amount of protein in the urine. In eleven subjects significant proteinuria (>120 mg/24 hours) was noted but there was no obvious relationship to the blood levels of cadmium (Fig. 19).

A similar observation can be made when urine cadmium levels are measured against the total protein measured in urine (urine cadmium in ug/vol). (Fig. 20).

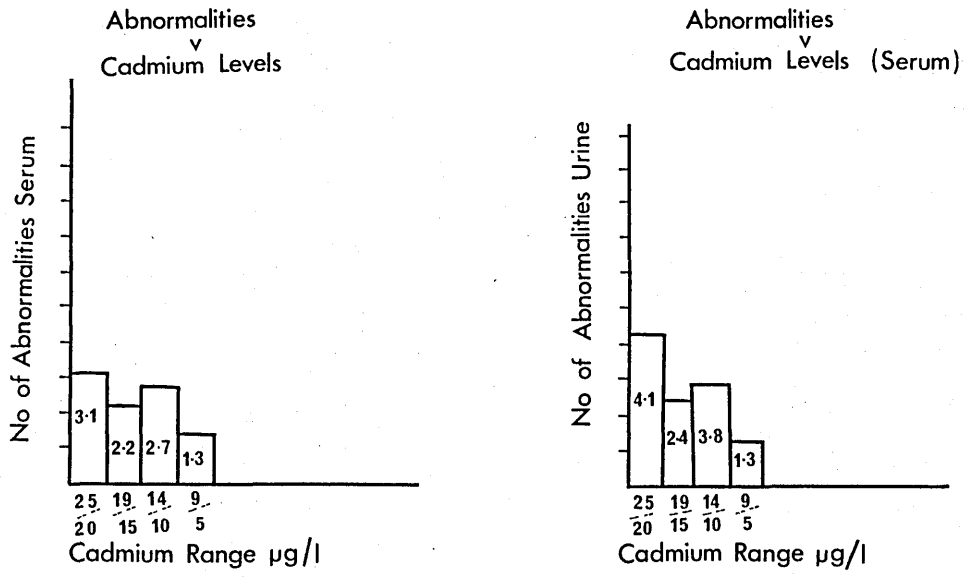

Fig. 18. Abnormalities in serum and urine grouped in units of 5. Any abnormal result outwith the 'normal' range was included.

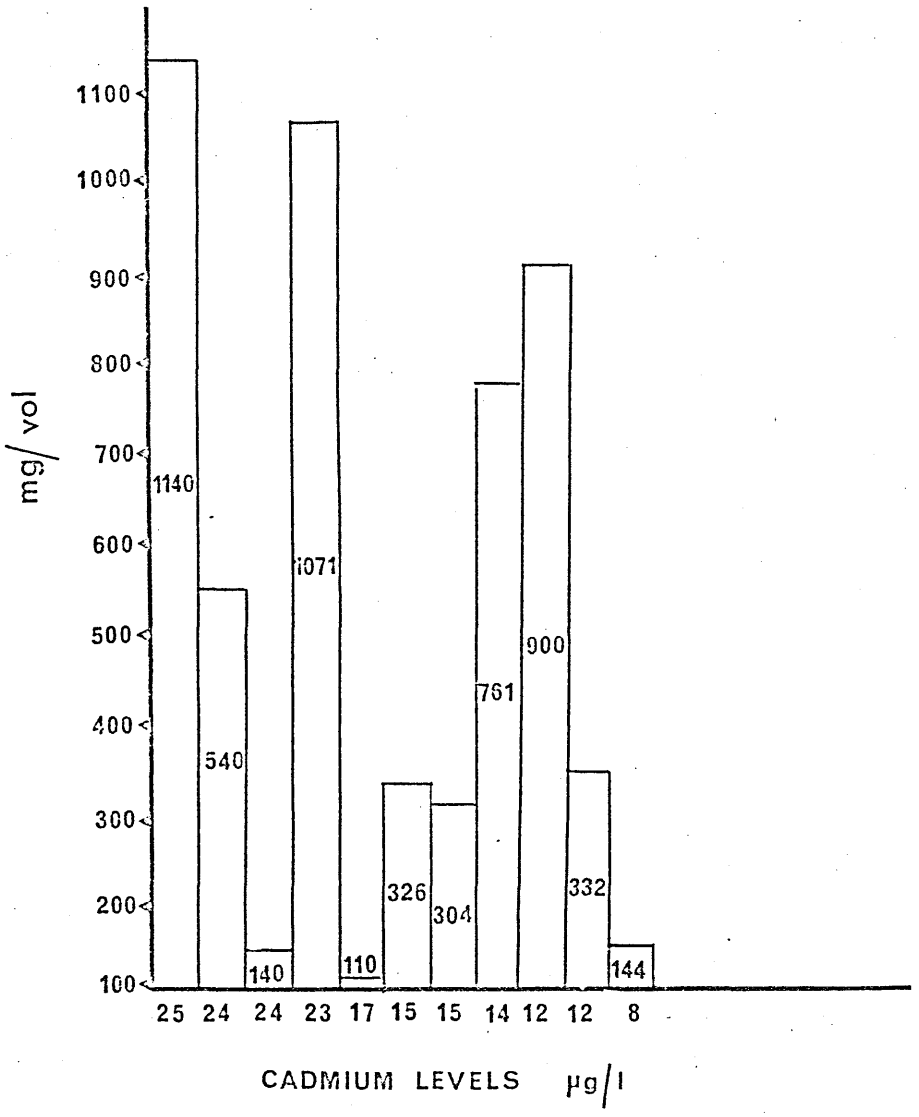

Fig. 19 Blood cadmium levels related to total protein excreted in urine. The protein measured is total protein and does not indicate low molecular weight protein output.

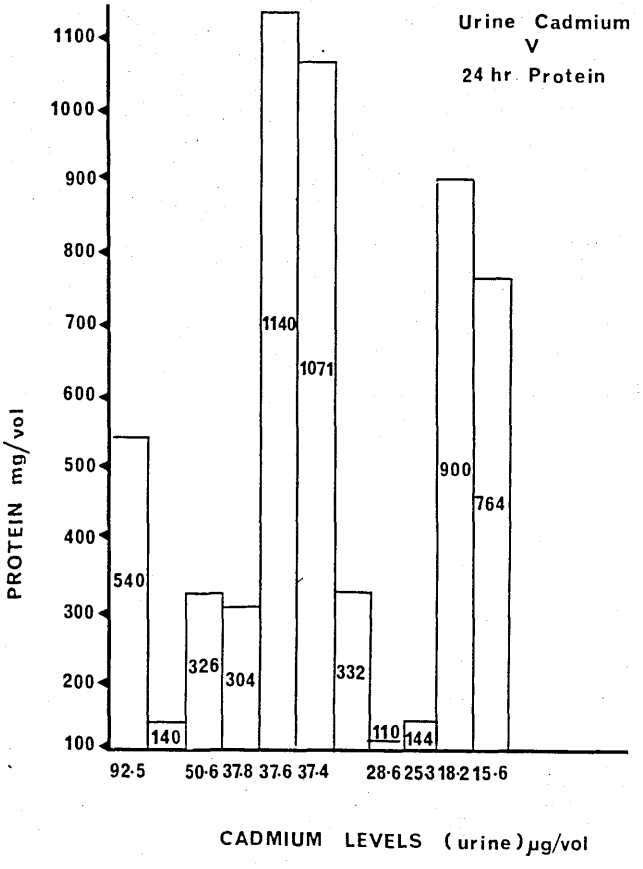

Fig. 20. Urine cadmium values related to proteinuria. In 2 subjects the urine cadmium result was not measured along with the estimation of protein.

Examination of those within the group with abnormal X-rays followed by intravenous pyelography and where appropriate examination of recent hospital records of two subjects confirmed that 18.5% of the group had evidence of urinary tract stone disease. This compared with a prevalence of 5.4% in the sheet metal workers and 3.5% in 3398 random subjects in the population study (Fig. 21). (Chap. 8).

As well as there being no immediate or obvious relationship between the blood levels of cadmium and other measurements such as protein in the urine no obvious correlation could be made between the blood cadmium and urine calcium levels (Fig. 22).

The first major insight into the potential problems of the group was found by examination of the trace element abnormalities in blood and urine (Table 8).

The most obvious finding was that 24 of 27 subjects had blood cadmium values greater than 8 ug/l which at that time was regarded as being the upper limit of normal by the laboratory and that 26 of 27 had higher than normal urine cadmium values. In addition 20 of 26 estimated urine zinc values were elevated and 22 of 26 subjects had hypercalciuria.

The problems of the group were highlighted when a comparison is made between the coppersmiths (Group I) and the control group of sheet metal workers

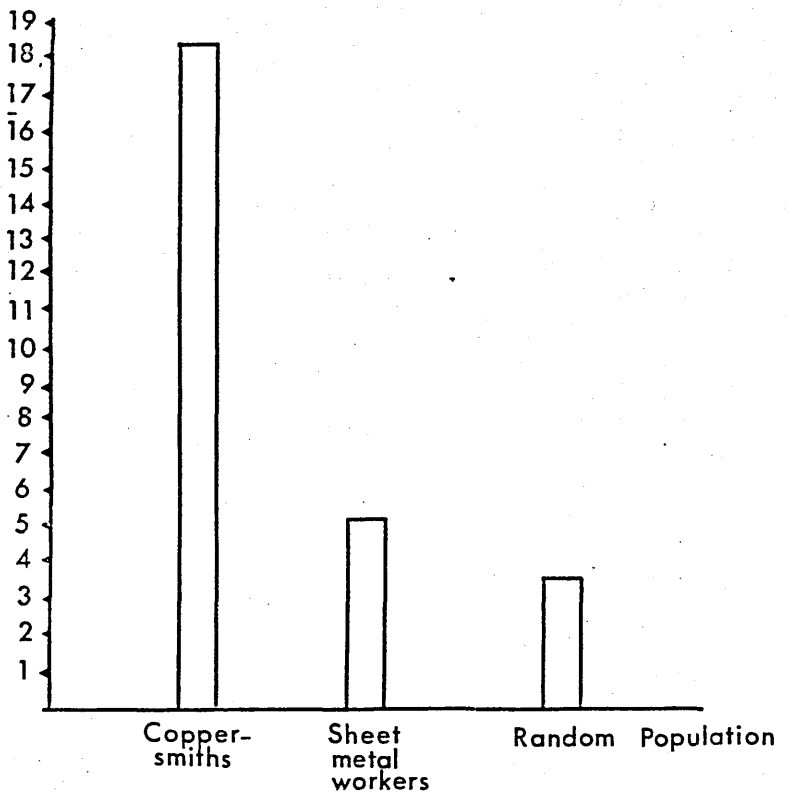

Fig. 21 Initial prevalence of stone disease in coppersmiths. The rate of 18.5% in the coppersmiths compared with 5.4% in the control group and 3.5% in the random population.

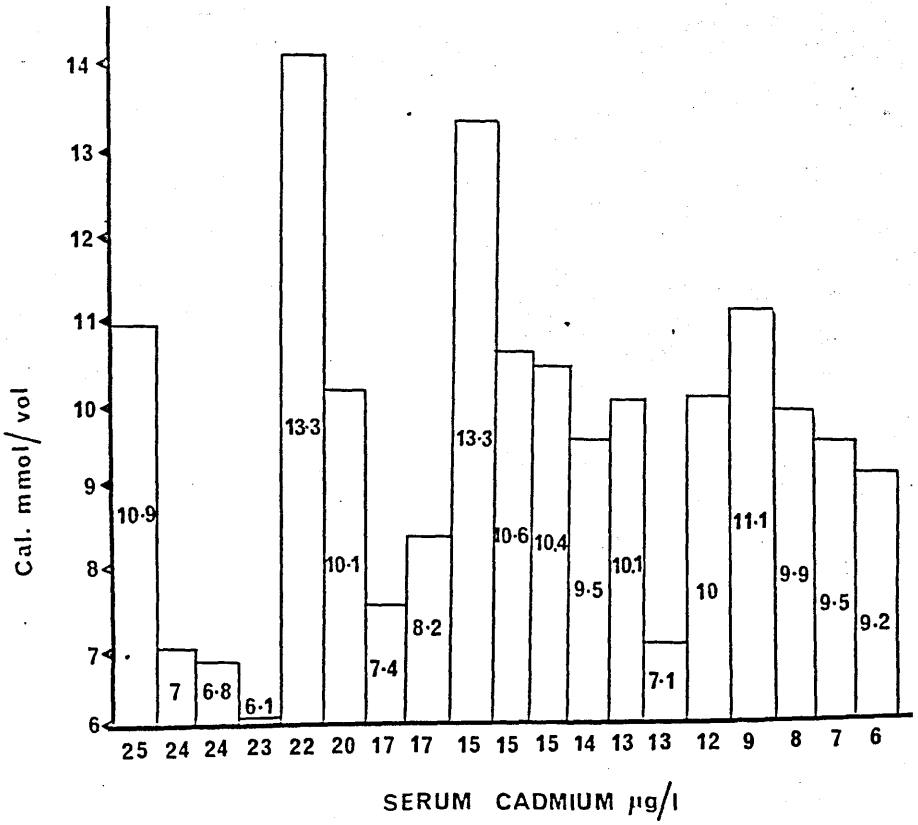

Fig. 22 The wide variation of urine calcium output as compared with the blood cadmium values on initial investigation of the 27 coppersmiths.

TABLE 8

Serum	Normal Range	Normal	Elevated	Low	No.
Magnesium	0.7-1.0 m mol/L	26	-	-	26
Copper	15-25 u mol/L	24	-	2	26
Zinc	14-18.4 mol/L	-	24	-	27
Cadmium	0-8.0 ug/L	3	24	-	27
Urine					
Calcium	3.0-6.0 m mol/vol	3	22	1	26
Magnesium	2.3-10-7 m mol/vol	22	-	4	26
Zinc	4.6-10.6 u mol/vol	6	20	-	26
Copper	0.8 u mol/vol	7	19	-	26
Cadmium	4 ug/vol	-	27	-	27

Table 8.

Initial results in 27 coppersmiths. Both the serum and urine results indicate that as a whole the group were displaying a pattern of serum results which were abnormal with respect to cadmium - zinc and urine results which were abnormal with respect to cadmium, calcium, zinc and copper.

i.e. those subjects in Group II.

In terms of 'overall' abnormalities the two groups quite clearly present a different picture (Fig. 23) suggesting that the coppersmiths were a rather unique group of individuals.

Of particular interest was the difference between the two factory study groups in respect of the urinary calcium output and the percentage with significant proteinuria (Fig. 24).

A direct comparison was made between Groups I and II and a reference population of students with respect to blood and urine cadmium levels.

Between group comparisons (Gp I v Gp II) showed that of all the parameters measured the creatinine and inorganic phosphate values were significantly different and that both Group I and Group II subjects were significantly different from the reference population with respect to blood and urine cadmium values (Table 9).

Having established that the Group I subjects were on the whole different from Group II subjects and had a potential cadmium problem it was obvious that an outpatient type investigation could be criticised on several accounts. In the first instance contamination of samples by clothing or from hair could possibly influence results in the Group I subjects. The problem of diet and patient preparation was then considered to be a major possible source of error. Therefore in the months of April and May coppersmiths were admitted to the

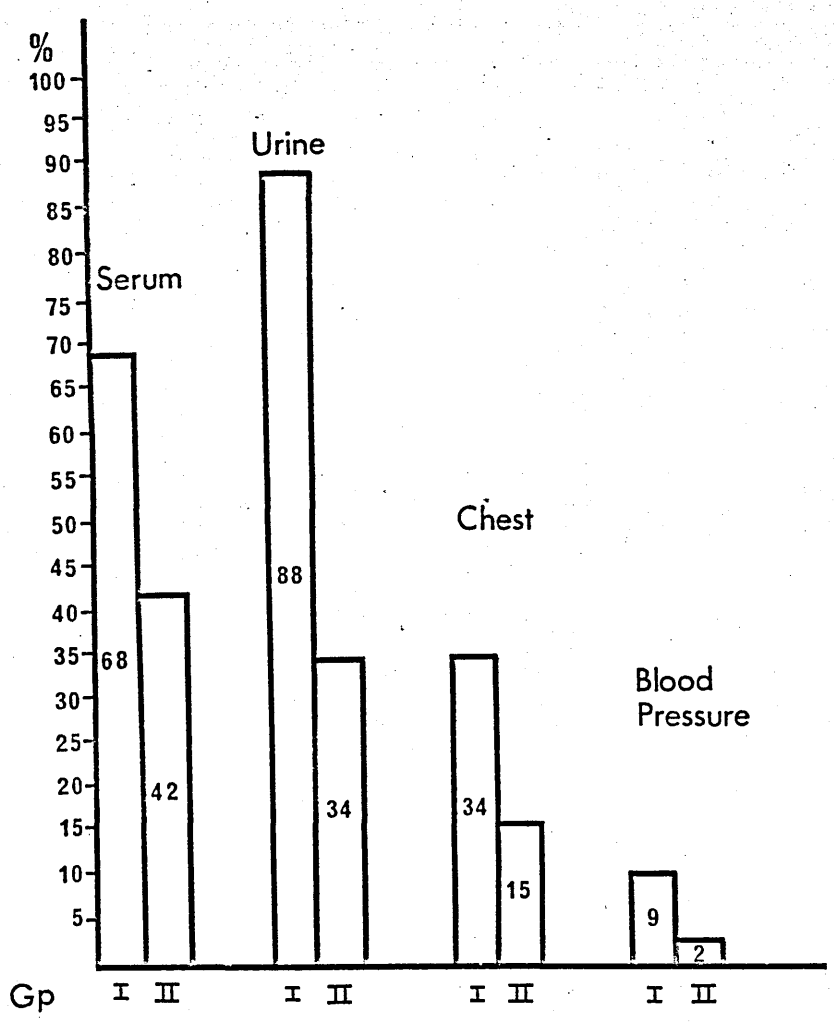

Fig. 23 Preliminary examination. Comparison of Coppersmiths (Group I) and the Sheet Metal Workers (Group II) showing that overall the coppersmiths were twice as likely to have an abnormality of a serum/urine biochemical parameter or an abnormality of respiratory function or blood pressure.

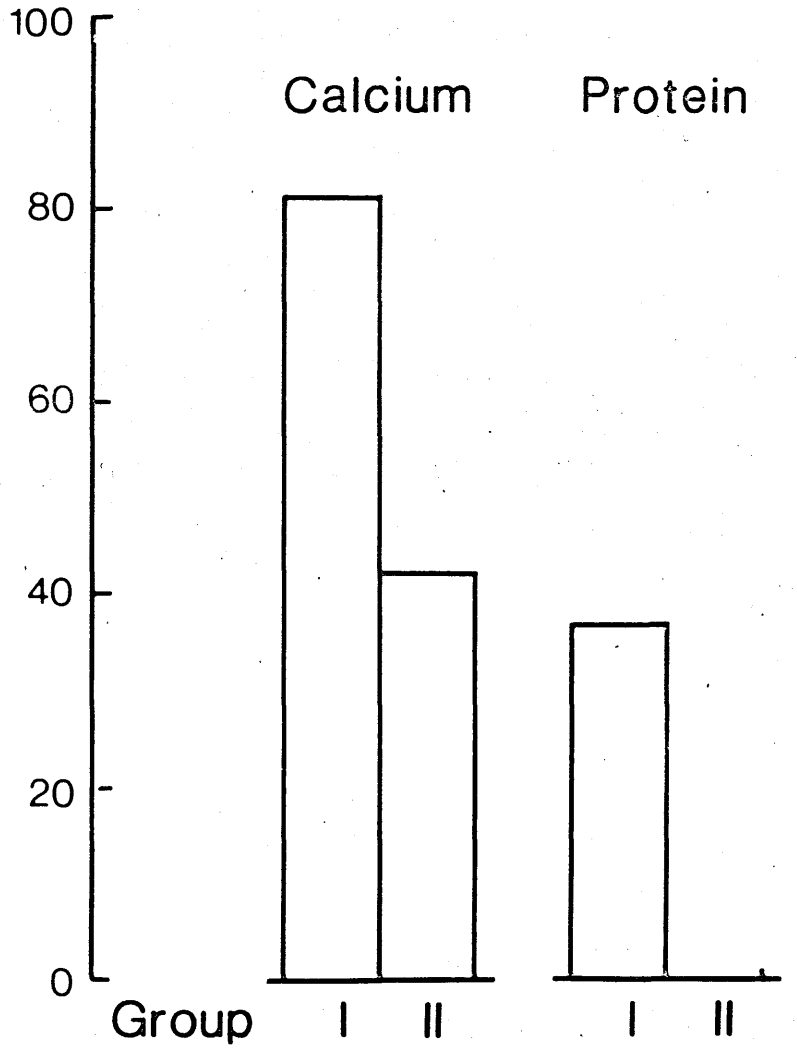

Fig. 24. Abnormal urine calcium and protein excretion in Coppersmiths (Gp. I) and in Sheet Metal Workers (Gp. II).

TABLE 9

	Gp.	No	Mean	
Creatinine	I	27	117.7 ± 29.7 u mol/l	p<0.05
	II	19	102.7 ± 14.7 "	
Phosphate	I	27	0.78 ± 0.18 mmol/l	p<0.05
Inorganic	II	19	0.93 ± 0.36 "	
Blood cadmium	I	27	15.8 ± 5.4 ug/l	p<0.05
	II	19	14.5 ± 7.2 "	p<0.05
Ref values		98	4.0 ± 1.0 "	
Urine cadmium	I	26	37.1 ± 19.2 "	p<0.05
	II	15	51.2 ± 18.0 "	p<0.05
Ref values		42	10.5 ± 4.2 "	

Table 9.

Comparison of different biochemical parameters between 3 groups - Coppersmiths (Gp I) and Sheet Metal Workers (Gp II) V non-exposed reference population. Those parameters indicating a statistically significant difference are enumerated in the table.

ward side room in pairs to allow intensive inpatient investigation.

During this period they were confined to the ward area and underwent the following regime:-

1 Diet - standard ward diet.

2 Twice daily baths with hair washing and nail clipping and scrubbing.

3 Daily blood cadmium levels were estimated resulting in the mean of four samples being available.

4 Urine phosphate and blood calcium and phosphate parameters were measured in a fasting state.

5 Bone densitometry was undertaken.

6 24 hour urine samples were collected under supervision.

7 Blood pressure was measured twice daily in a resting state.

8 Acid load test, estimates of glycosuria and the presence or otherwise of anosmia was established.

24 coppersmiths agreed to take part in this exercise. In the first instance the results are presented as variations of normal laboratory ranges. In each of the following figures the number of possible results is given in the top line of figures, those with normal results are recorded and variations are given as being elevated above normal or less than the normally accepted range for the laboratory.

Liver function tests Since liver is a normal 'target' organ for cadmium the alkaline phosphatase and transaminase (SGOT and SGPT) were measured. A bromsulphthalein test was undertaken in 4 out of 22 of the subjects (Fig. 25). Examination of these tests did not reveal any evidence of excessive liver damage in the group.

Urea and electrolytes As a crude measurement of overall kidney function these parameters along with the creatinine values do not suggest the possibility of renal damage (Fig. 26) to be a major problem in the group.

Cadmium/trace element measurements (blood) The finding of an 18.5% prevalence of stone disease clearly merited further detailed studies of the general calcium status of the individuals.

In only one subject was there any deviation from normal with respect to blood calcium values. However, as had been noted in the initial investigation the serum inorganic phosphate was again found to be reduced in 10 of 24 subjects. This is particularly of interest since while being investigated in the ward the phosphate measurements were undertaken while the subject was in a fasting state and the effects of diet were therefore eliminated (Fig. 27). All subjects were found to have elevated blood cadmium values and normal serum magnesium levels. Despite the fact that the men have an apparently normal diet and are actually working with copper 8 were found to

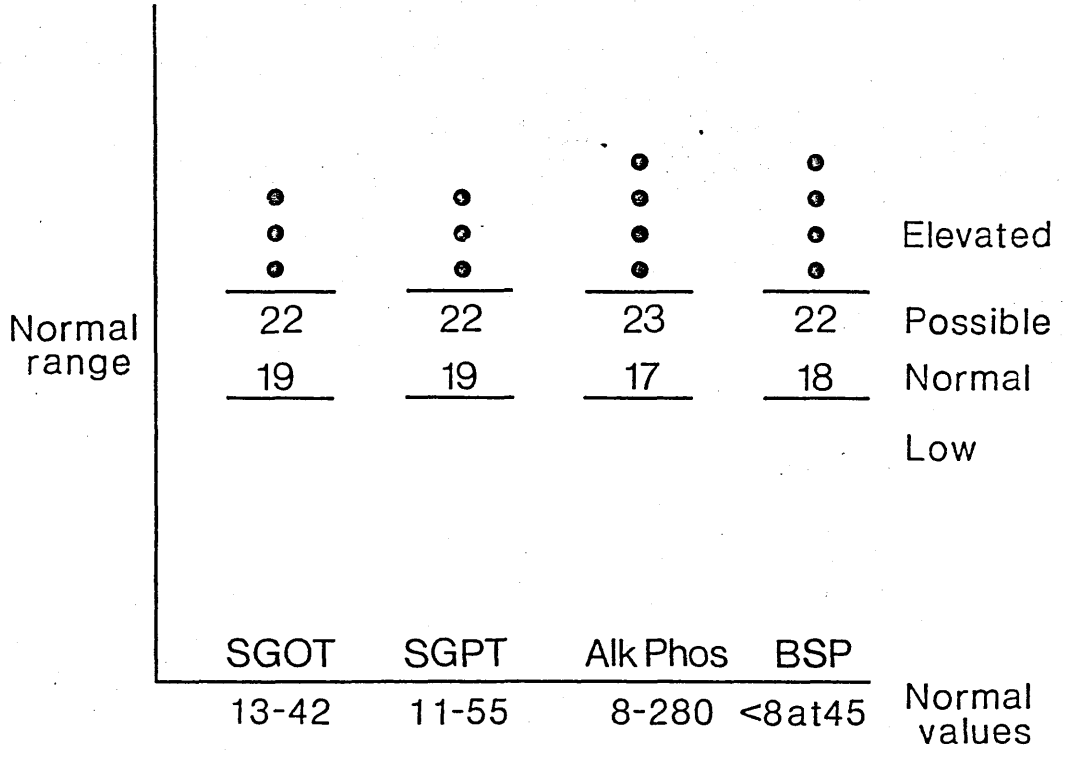

Fig. 25 To show the possible subjects with abnormal liver function tests including bromsulphthalein absorption abnormalities (BSP). The 'possible' number of results is the top line of the figure and the bottom line of figures represents those within the normal range.

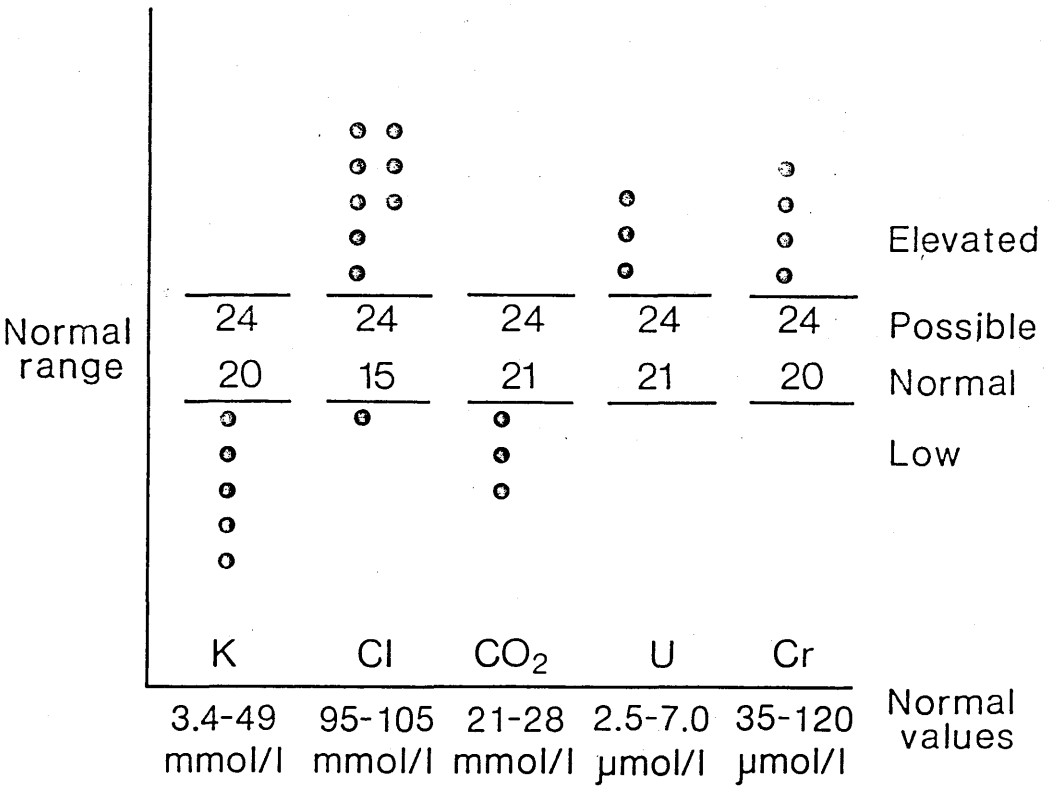

Fig. 26 Biochemical examination of blood in 24 coppersmiths showing those with abnormalities of electrolytes, urea and creatinine.

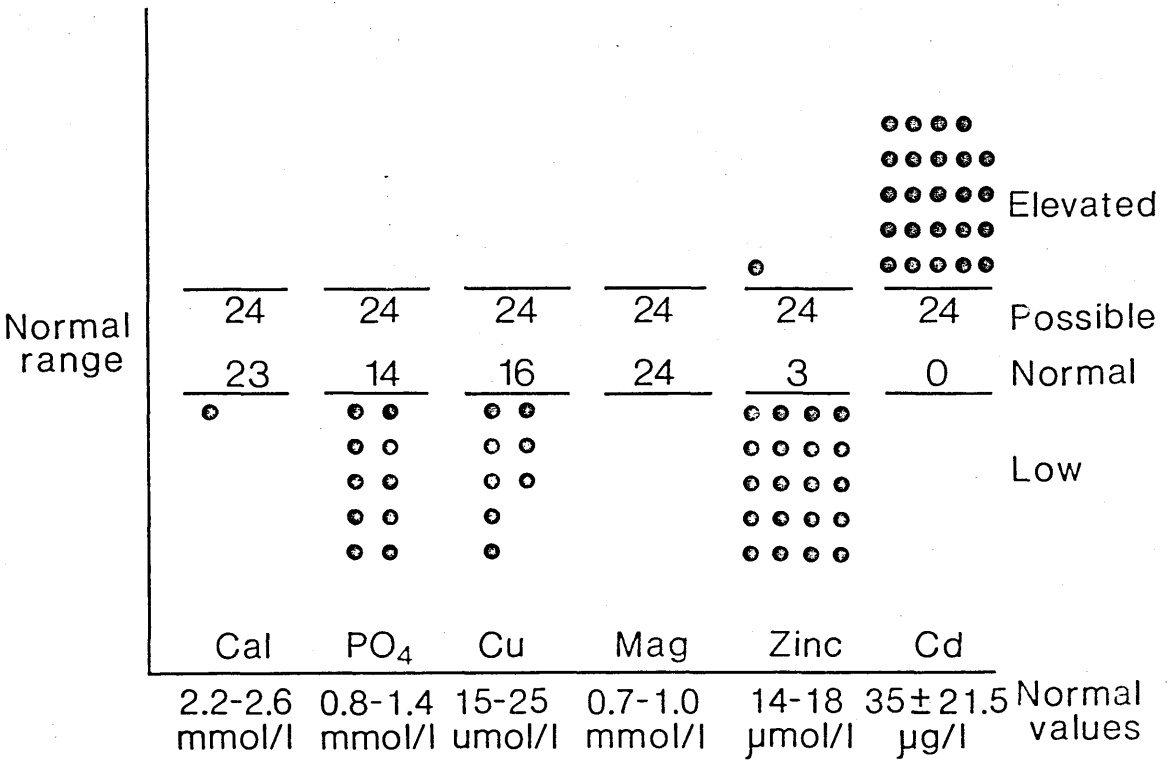

Fig. 27 Biochemical examination of blood calcium, phosphate and trace element measurements in 24 coppersmiths. The cadmium values are the mean of 4 consecutive daily examinations.

be below the normal range with respect to serum copper values. In addition 20 of the 24 subjects were below normal with respect to serum zinc values.

Urine analyses In the 22 subjects where results were available 9 subjects were found to have proteinuria (large molecular weight) in significant amounts and 10 subjects were found to have a reduced creatinine clearance (Fig. 28).

Fifteen of 24 subjects were found to have evidence of tubular acidosis. Renal tubular acidosis was measured using a standard ammonium chloride loading test and this confirms the significance of the serum abnormalities already referred to above.

Urine abnormalities Renal tubular excretion of phosphate was found to be impaired in 9 of 16 subjects while 19 had evidence of excessive urine calcium excretion. The estimation of urine phosphate excretion and reabsorption was by measuring the Tubular Maximum reabsorption of phosphate ($TmPO_4$).

On the last day of the tests all 24 subjects were found to have excessive amounts of cadmium in their urine (range 24.3 - 116.8 ugs/24 hours). (These figures for urine cadmium levels are exceptionally high. In discussion with the biochemists they suggested that the methodology employed to measure urine cadmium values was probably inaccurate at that time and resulted in a proportion of 'false high' results).

In addition to excess cadmium excretion 24 were found to be excreting excess amounts of copper and 20

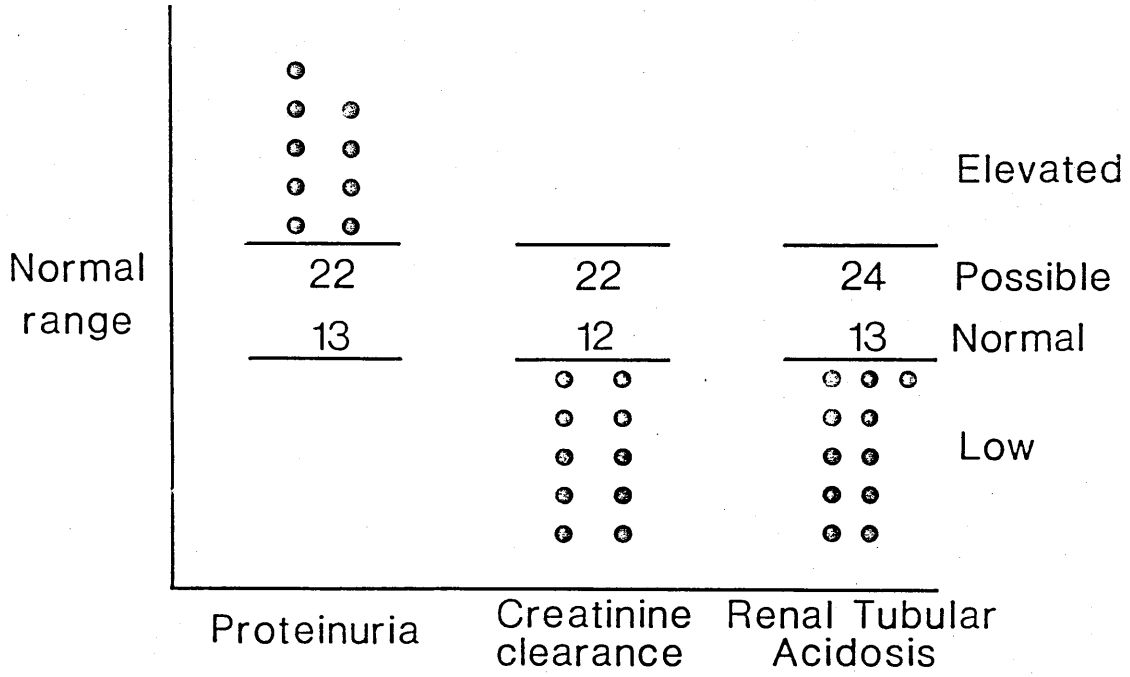

Fig. 28 Urine analysis on inpatient studies indicating the presence of proteinuria reduced creatinine clearance and evidence of tubular damage as indicated by renal tubular acidosis.

have evidence of hyperzincuria (Fig. 29).

Glycosuria Further evidence of impaired tubular/ glomerular function is shown by the finding of 6 subjects with glycosuria all of whom had a normal glucose tolerance test.

Haematological abnormalities This aspect of cadmium poisoning is rarely referred to in the literature but is alluded to in most reported series of cadmium poisoning. Six subjects out of 19 were found to have haemoglobin values of less than 14g % and 10 subjects had serum iron values of less than 16 ug/l which is the mean value found in a random study of 'normal' population. Further investigation of this aspect confirmed that there is a significant correlation between the serum iron and copper results in the group (Fig. 30).

Anosmia Six subjects were found to have complete anosmia and 4 had partial anosmia, in 22 subjects tested i.e. just under 50% of subjects have an impairment of their sense of smell.

Bone densitometry This test failed to reveal any abnormality in any one individual within the group.

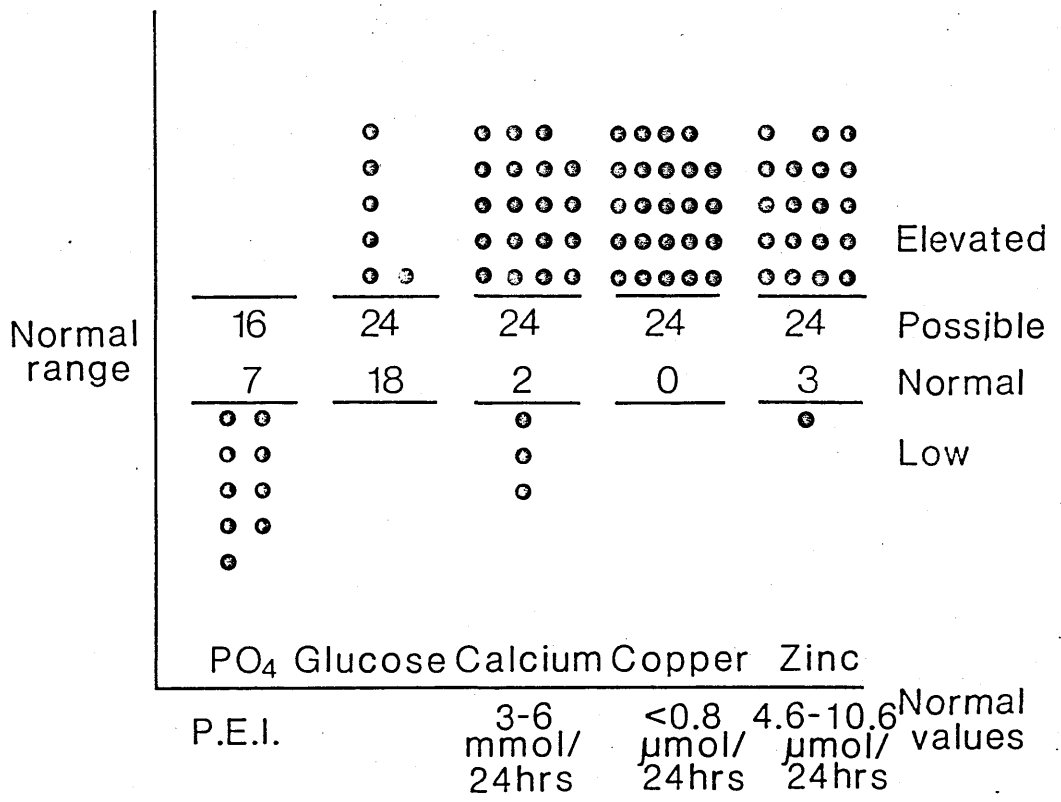

Fig. 29 Measurement of urine biochemical parameters in coppersmiths.

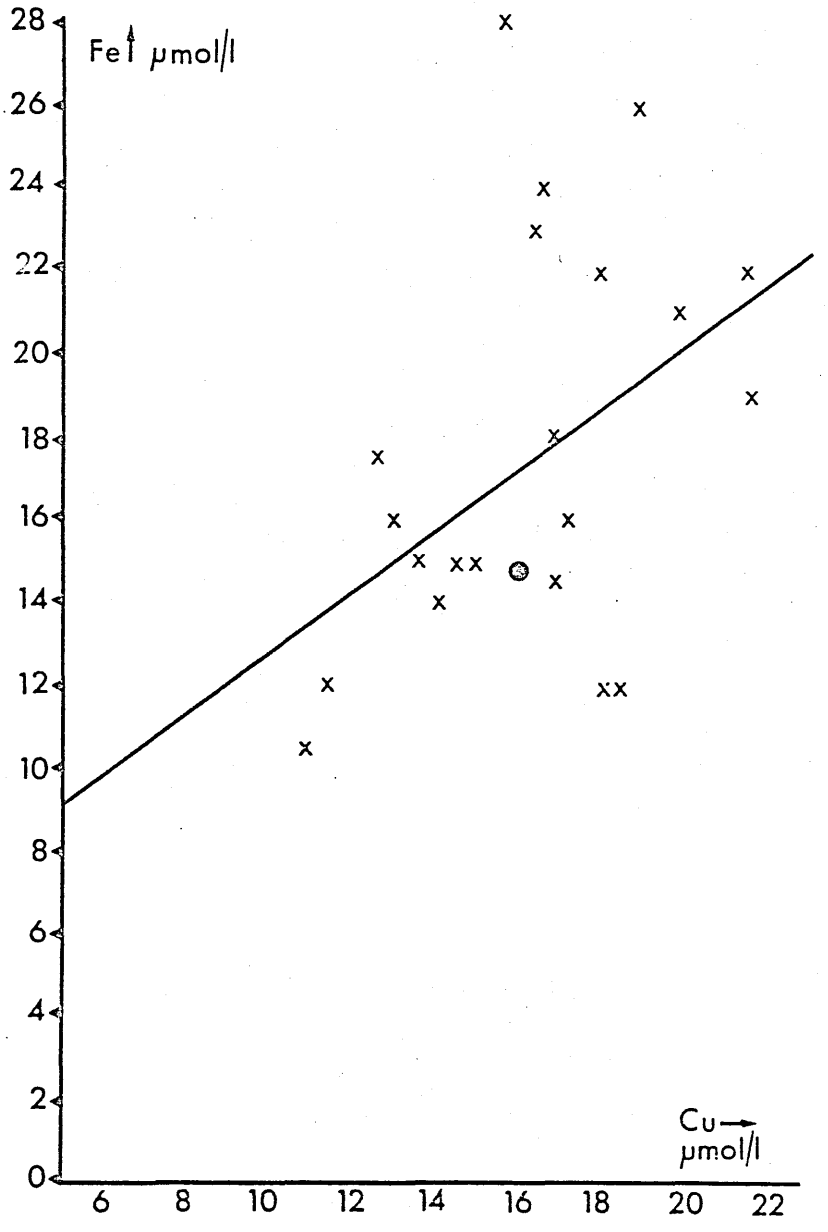

Fig. 30 To show the correlation between the serum iron and copper values in coppersmiths.

COMPARISON OF DIFFERENT GROUPS EXPOSED TO CADMIUM.

CHAPTER 10

Comparison of different groups exposed to cadmium.

At the time of the initial investigation of the coppersmiths it was decided to investigate a group of sheet metal workers who worked in close proximity to the coppersmiths but who were not directly involved in the brazing process.

Subsequently a further group from the parent factory and from a branch factory which was physically separated from the main building by 200 yards were examined. This latter group consisted of a mixed group of workers who were involved in a variety of different assembly line duties and metal working machinery.

Since the factory was situated on an industrial estate the local interest among the general work force allied to the fact that the factory medical officer had committments in a totally different company,made it possible to add a fourth group of workers to the comparative study of the coppersmith group. These workers from a completely different company had been principally involved in a cadmium plating process and to a limited extent in cadmium brazing. It was therefore possible to compare results from 5 different groups, viz:-

TABLE 10.

GROUP	BLOOD CADMIUM	
	MEAN	MEDIAN
I	15.9	15.0
II	14.4	12.5
III	11.8	10.2
IV	7.9	8.0
V	16.4	16.4

Significant differences (Mann Whitney)

1 v 3	($p<0.05$)	3 v 5	($p<0.05$)
1 v 4	($p<0.001$)	4 v 5	($p<0.001$)
2 v 4	($p<0.01$)		

Table 10 Blood cadmium values (mean and median values). The comparison of the median values is by a Mann Whitney test confirming that the coppersmiths and sheet metal workers had blood cadmium levels significantly different from the two control groups.

Group I - Coppersmiths (27) as outpatients

Group II - Sheet metal workers (19)

Group III - Mixed group (14) from parent and subsidiary factory

Group IV - Mixed group (23) from a completely separate factory using a cadmium plating process

Group V - Coppersmiths (24) as inpatient group

Statistical analyses of group results

Each of the above groups of workers were examined as outpatients. The exception to this was the group of coppersmiths who were admitted for supervision and assessment to the ward (Gp. V subjects).

The help of a statistician was necessary to analyse the results obtained from each group. It was obvious that the 'distribution' of values for each parameter measured was asymetrical and a Mann Whitney test was employed by the statistician thereby allowing comparison of median values to be undertaken, in addition to the determination of the mean values.

Blood cadmium values

This has been found to be significantly different in Group I, II and V subjects as compared with those in Group III and IV. (Fig. 31).

Examination of Table 10 confirms that, in those workers who were involved or who worked in close proximity to the brazing process (Gps. I & II) the

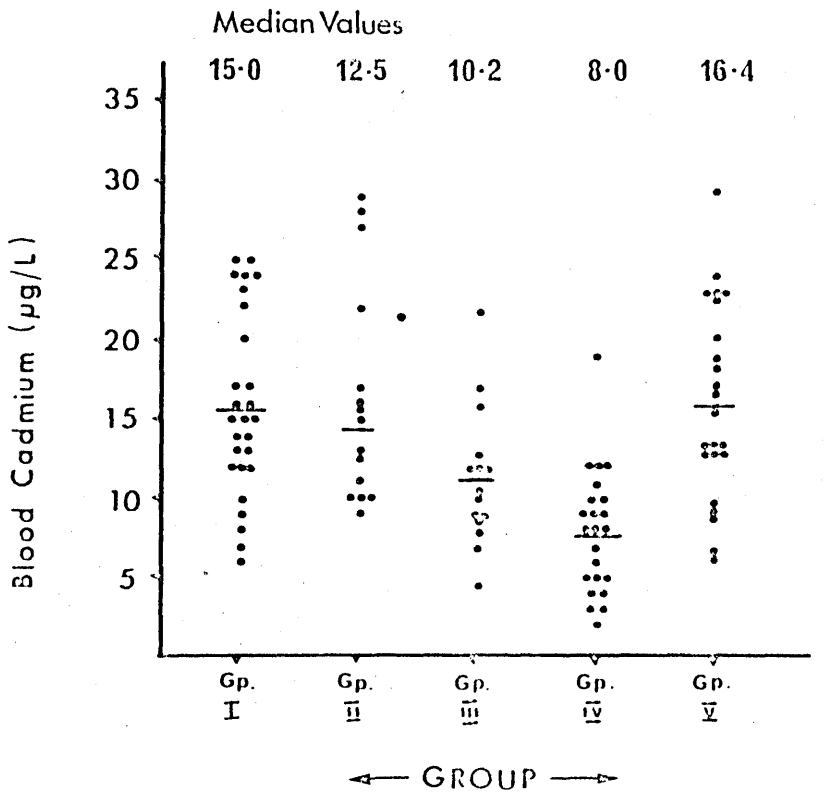

Fig. 31. Initial blood cadmium values in subjects in Groups I - V showing range and median values of each group.

blood cadmium values were significantly higher when compared with the other two groups.

The finding of a significant difference between Group II and Group IV individuals emphasises the extent of pollution within the vicinity of the brazing process. The latter group,involved in a cadmium plating process,were clearly less contaminated with the metal than the coppersmiths and the sheet metal workers.

The significant differences between Group III subjects and the coppersmiths emphasises the dangers of having been involved in the brazing process. It should however be emphasised that the individuals in Gp. III were not found to have blood cadmium values which were statistically significantly different from Gp. II workers. This clearly indicates a spectrum of severity of contamination. All groups had mean blood cadmium values at least 3 times greater than the mean values found in a non exposed population as shown in a study by the laboratory of 231 non exposed individuals where blood cadmium values were measured over an age range of 20 - 80 years. The mean blood cadmium value did not in any single age group exceed 2 ug/L (Cunningham, 1980).

Proteinuria

Once again the coppersmiths are quite different from the other 3 groups in that 42% of the group had large mol. wt. proteinuria in significant quantities.

(Fig. 32) on the initial investigation and 42% had the abnormality on inpatient investigation.

Biochemical findings relevant to stone formation

Serum calcium

Comparison of all five groups confirms most subjects had serum calcium values which fell within the normal accepted range (2.2 - 2.6 mmol/L) as used in the laboratory. The three high values found on initial screening were normal on repeat examination. (Fig. 33).

Serum inorganic phosphate

The mean value of this parameter has been found to be highly significantly different ($p<0.001$) in Group V subjects i.e. fasting coppersmiths when compared with Groups II, III and IV. (Fig. 34).

Urine calcium

The initial finding that 81.4% of the coppersmiths had hypercalciuria was confirmed in inpatient investigation and within this group approximately twice as many subjects had this abnormality as compared with any other group (Fig. 32).

This parameter was naturally of considerable interest especially since the coppersmiths have been found to have such a high prevalence of stone disease.

From the group comparisons (Table 11) it can be seen that from both the outpatient and inpatient

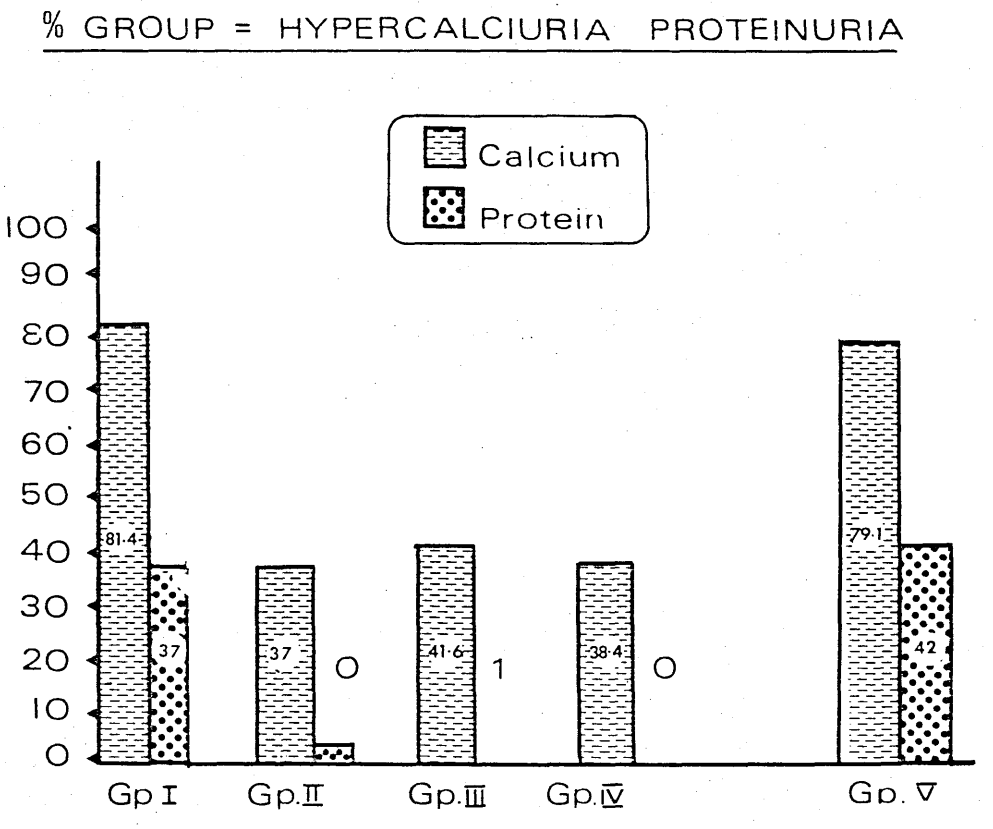

Fig. 32 Urine calcium and proteinuria Gps. I - V. The absence of significant large molecular weight proteinuria is confirmed in Gps. II, III and IV.

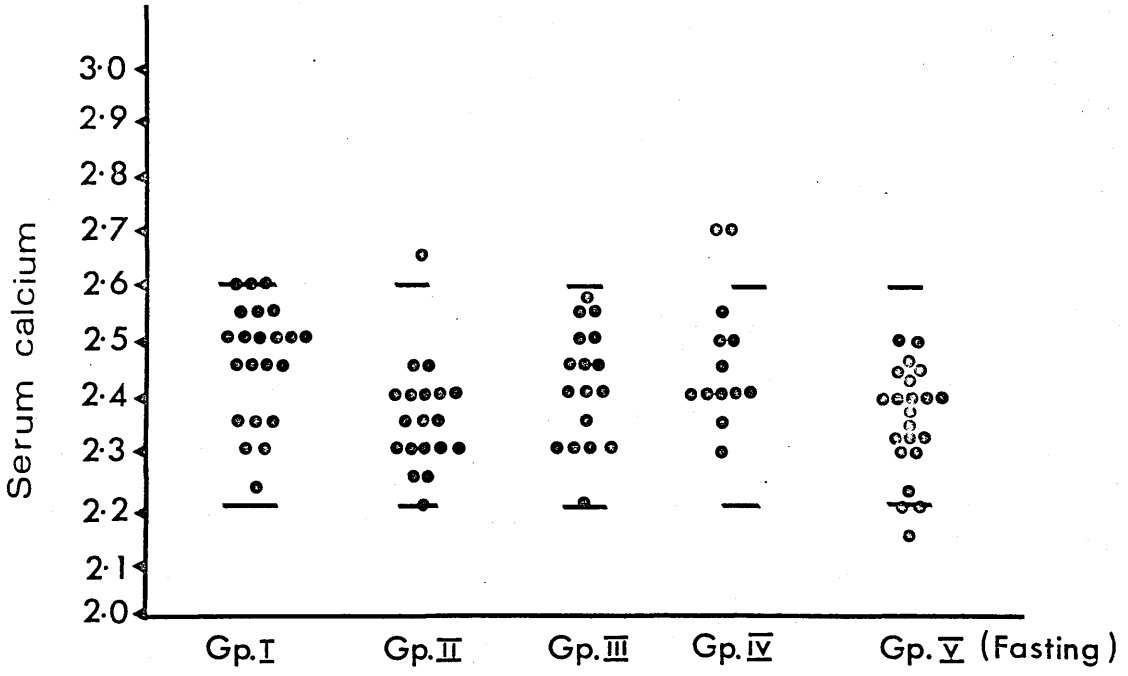

Fig. 33 Serum calcium values (m mol/litre)

Groups I - V.

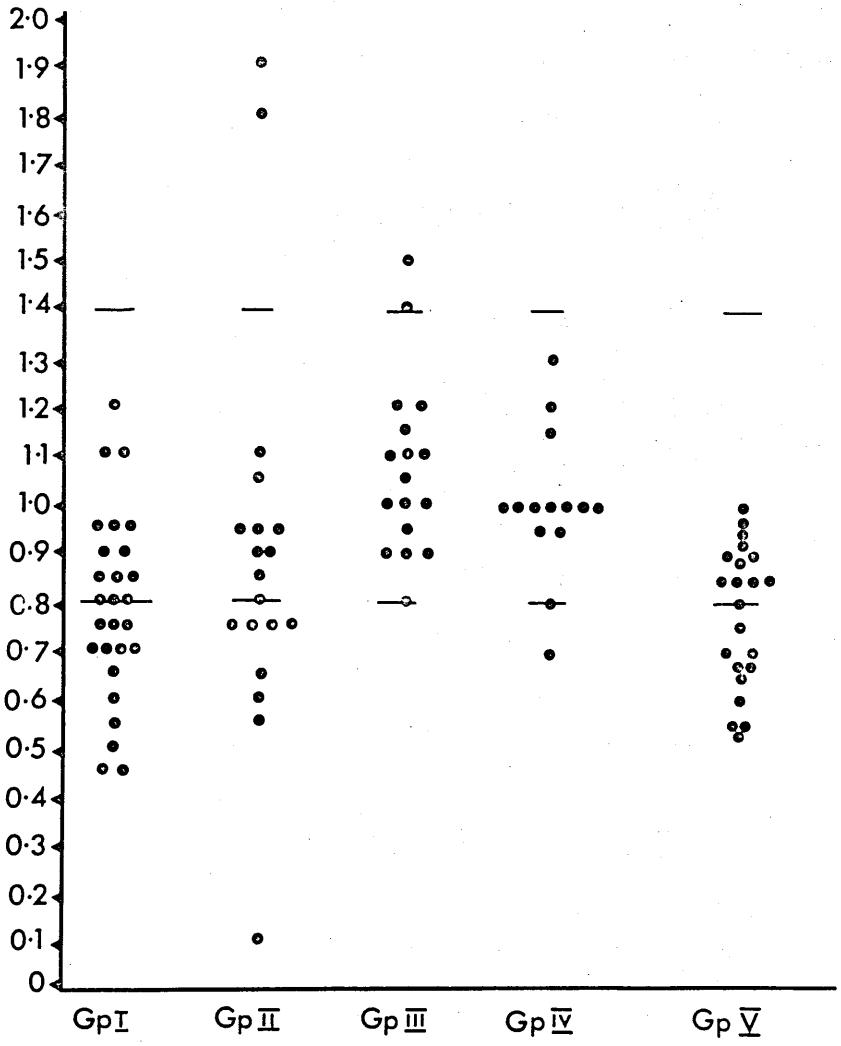

Fig. 34 Serum inorganic phosphate values m mol/L Gps. I - V. The Gp. V subjects have highly signivicantly lower values ($p<0.001$).

studies, the coppersmiths clearly have been excreting calcium in the urine in much higher quantities than the two least exposed groups of workers (Gp. III & Gp. IV).

TABLE 11

GROUP	URINE CALCIUM (m mol/vol)	
	MEAN	MEDIAN
I	9.1	9.5
II	8.2	7.1
III	5.7	5.0
IV	5.3	4.9
V	7.8	8.3

Significant differences (Mann Whitney)

1 v 3	($p<0.01$)	4 v 5	($p<0.01$)
1 v 4	($p<0.001$)		

Table 11. Comparisons of mean and median urine calcium output values in 5 groups. Comparison of the median values confirm significant differences between the coppersmiths and the least exposed workers in Gps. III and IV.

Renal function

Serum urea

As a measure of overall renal function this parameter did not reveal any significant differences between the groups. (Table 12).

Serum creatinine

This particular measurement (Table 13) proved to be interesting when comparisons between the 5 groups were made.

Examination of median values confirmed statistically significant differences which indicate that the coppersmiths as a group showed a greater tendency to have reduction in overall renal function.

Urine sodium

This parameter was assessed because of the known renal tubular effect of cadmium.

Since urine sodium excretion is normally a markedly variable phenomenon great care has to be taken in interpreting the results for this ion. Interestingly on inpatient measurements the coppersmiths values reached statistically significance when compared with Gp. III subjects but not with Gp. IV subjects. Gp. III subjects from examination of serum urea, creatinine and urine sodium excretion would appear to have the most efficient overall renal function indicating a possible lesser degree of renal damage. (Table 14).

Other trace metals

Serum copper

Since the group under study worked with

TABLE 12

GROUP	SERUM UREA (mmol/l)	
	MEAN	MEDIAN
I	5.7	5.6
II	5.6	5.5
III	5.0	4.7
IV	6.2	6.2
V	5.5	5.2

Significant differences (Mann Whitney test)

NIL

Table 12 Comparison of median values of serum urea between all groups confirming the lack of any significant differences.

TABLE 13

GROUP	SERUM CREATININE (mmol/l)	
	MEAN	MEDIAN
I	117.7	117.0
II	102.7	100.0
III	87.2	90.0
IV	103.1	103.0
V	109.2	99.0

Significant differences (Mann Whitney test)

1 v 2	($p<0.05$)	3 v 4	($p<0.05$)
1 v 3	($p<0.001$)	3 v 5	($p<0.05$)
2 v 3	($p<0.05$)		

Table 13 Comparison of serum creatinine values between the 5 groups. No particular group had a mean value which was a particularly abnormally elevated with respect to the normal accepted ranges but the coppersmiths had a less efficient renal handling of creatinine than any other group including the sheet metal workers (Gp. II).

TABLE 14

GROUP	URINE SODIUM (m mol/vol)	
	MEAN	MEDIAN
I	191.3	178.5
II	225.1	223.0
III	159.5	148.0
IV	163.7	157.0
V	199.4	198.0

Significant differences (Mann Whitney test)

2 v 3 ($p<0.05$)

3 v 5 ($p<0.05$)

Table 14 Comparison of urine sodium excretion between Groups I - V showing that both the coppersmiths (Gp. V) and sheet metal workers (Gp. II) excrete significantly more sodium than Gp. III workers.

copper as well as cadmium it was considered to be essential to measure this particular parameter.

In only 2 comparisons could a significant difference be found. Surprisingly the Gp. III individuals had higher median as well as mean serum copper values when compared with the coppersmiths. This was found both on outpatient and inpatient measurements and in the latter instance the values reached statistical significance. (Table 15).

Serum Zinc

The close association of cadmium and zinc in cadmium metallothionein (Cd-Mt) indicated that this trace metal should be measured in the assessment of any study of cadmium toxicity.

Examination of the initial zinc values strongly suggested that this particular measurement would prove to be of great value in the assessment of work populations who had been intensively exposed to cadmium. However, when the coppersmiths (Gp. V) were examined as inpatients there was a statistically highly significant difference between the zinc values obtained at that time as compared with the initial zinc measurements (Table 16).

Urine Copper

As with the measurements of blood copper it was decided to examine the groups to establish whether or not the 'occupational' aspect of handling copper would be reflected in any measureable differences

TABLE 15

GROUP	SERUM COPPER (u mol/L)	
	MEAN	MEDIAN
I	17.8	17.9
II	15.7	15.5
III	19.2	18.3
IV	16.9	16.5
V	16.3	16.4

Significant differences (Mann Whitney)

1 v 2 ($p<0.05$)

3 v 5 ($p<0.05$)

Table 15 Serum copper values showing that the least exposed workers (Gp. III) have significantly higher values than the coppersmiths in the fasting state (Gp. V).

TABLE 16

GROUP	SERUM ZINC (u mol/L)	
	MEAN	MEDIAN
I	15.0	15.1
II	13.4	13.8
III	11.9	11.2
IV	12.0	12.0
V	12.2	11.7

Significant differences (Mann Whitney)

1 v 2	($p<0.05$)	1 v 4	($p<0.001$)
1 v 3	($p<0.001$)	1 v 5	($p<0.001$)

Table 16 Serum zinc values in all 5 groups showing that the initial values found in coppersmiths were significantly different from every other group including those found on inpatient examination of coppersmiths.

between the five groups.

It was interesting to note that when removed from the work situation and measured under hospital conditions the urine copper values in the coppersmiths reached their highest values and were highly significantly different even from the initial measurements in the groups. (Table 17).

Urine Zinc

As in the examination of blood zinc values and because of the association between cadmium and zinc it was considered necessary to measure this parameter.

The coppersmiths were found to be, as a group, significantly different from Gp. III subjects but surprisingly showed no statistically significant difference when compared with the group of workers from the separate factory. (Table 18).

TABLE 17

GROUP	URINE COPPER (u mol/vol)	
	MEAN	MEDIAN
I	2.6	1.3
II	2.2	1.5
III	1.7	1.7
IV	1.0	1.0
V	8.3	6.1

Significant differences (Mann Whitney test)

1 v 4	($p<0.05$)	2 v 5	($p<0.001$)
1 v 5	($p<0.001$)	3 v 4	($p<0.01$)
2 v 4	($p<0.001$)	3 v 5	($p<0.001$)
2 v 4	($p<0.001$)	4 v 5	($p<0.001$)

Table 17 Urine copper values in 5 groups of workers confirming that when removed from the work situation the coppersmiths (Gp. V) excreted an amount of copper which was signficantly greater than in the work situation as shown by a comparison of median values (Mann Whitney test).

TABLE 18

GROUP	URINE ZINC (u mol/vol)	
	MEAN	MEDIAN
I	22.1	14.7
II	14.3	11.9
III	8.6	7.2
IV	12.3	12.1
V	13.5	14.0

Significant differences (Mann Whitney)

1 v 3	($p<0.05$)	3 v 4	($p<0.05$)
2 v 3	($p<0.05$)	3 v 5	($p<0.01$)

Table 18 Comparison of urine zinc excretion values in 5 groups of workers confirming that in the least exposed workers (Gp. III) the median value of zinc excretion was significantly different from every other group (Mann Whitney test).

Discussion

When it is suspected that a population has been submitted to chronic cadmium poisoning the present emphasis is to measure the blood cadmium and the excretion of low molecular weight protein in the urine (Bernard et al, 1979; Nomiyama et al, 1977; Kitamura, 1979; Kjellstrom, Shiroishi and Evrin, 1977). The above practice has resulted from a variety of studies of groups of individuals who have been chronically exposed to cadmium in industrial situations (Cooper, 1977; Kjellstrom, et al, 1979). Such studies have alluded to other different biochemical parameters which could be expected to be abnormal in cadmium poisoning. An appreciation of such biochemical abnormalities can be of considerable importance when assessing an individual subject.

When measuring blood cadmium it has to be appreciated that an elevated blood cadmium will indicate exposure to the trace element but there is considerable debate as to whether blood or urine cadmium levels are measures of the total body burden of cadmium (Lauwerys, Buchet and Roels, 1976). Until recently it has been generally accepted that blood cadmium values can be interpreted as evidence of recent exposure and are likely to be elevated only in the short term (Welinder, et al, 1977).

In order to find supplementary evidence of the biochemical effects of exposure to cadmium the present study at the outset was designed to cover as many different biochemical parameters as possible. Specific attention was paid to other associated trace metals and also to search for effects which could result from the known effects of the trace metal on the renal tubule (Bernard, et al, 1978; Nomiyama et al, 1977; Kazantzis et al, 1963; Lauwerys et al, 1974).

Many biochemical parameters other than the blood levels and the level of B_2 microglobulin excretion have been extensively studied but I am not aware of between group comparisons having been made as in the present work. The logic of looking at other trace metals is that there is a very complicated interaction between different metals such as exists between cadmium and zinc (Pulido, et al, 1966; Kagi and Vallee, 1961). Even the form in which such metals are presented to the gastro intestinal mucosa can determine whether or not they act with or competitively inhibit the absorption of other metals (Hamilton and Valberg, 1974; Washko and Cousins, 1977).

Cadmium is known to affect the absorption of other metals such as copper and iron. In addition it can, after it has entered the biological system, affect the intrinsic metabolic pathways of these two elements

(Petering, Choudhury and Stemmer, 1979).
The reactions and effects of interactions of cadmium can be affected by the dietary status of animals and it is now beginning to be realized that other influences such as Vit. D can influence cadmium and its relationships to elements such as calcium (Thawley et al, 1977).

The metabolism of two elements in particular have long been recognised to be affected by cadmium viz. zinc and calcium. These two elements are of particular interest to urologists because both when excreted excessively are known to be associated with stone formation. The other major interest to urologists is that in the experimental animal the zinc status of an animal can determine whether or not cadmium will induce testicular atrophy (Bremner and Campbell, 1978).

The physico-chemical similarities between cadmium and zinc are well recognised and in kidney substance zinc concentration increases with cadmium accumulation (Elinder and Piscator, 1978). This latter phenomenon is now recognised to be due to the binding of zinc within cadmium protein complexes such as cadmium metallothionein (Cd-Mt) within kidney cells.

Recent work indicates a similar finding with copper within cadmium protein complexes in kidney cells (Zelazowski and Szymanska, 1980).

In a discussion of cadmium induced hypercalciuria, Kazantzis (Kazantzis, 1979) commented that although proteinuria may be the first manifestation of damage to the kidney by cadmium, it is the effects resulting from prolonged hypercalciuria which are more likely to be of clinical significance to the individual. This clearly demands a prolonged and careful long term supervision of patients when chronic cadmium poisoning is suspected since the excess excretion of calcium in urine, if prolonged, results ultimately in the development of osteomalacia (Blainey et al, 1980; Kazantzis, 1979).

In a search of the literature for parameters of a biochemical nature which would be easily measured and which could be expected to be rendered abnormal by cadmium it was noted that cadmium has long been recognised to have an effect on sodium absorption by the renal tubule (Vander, 1962). It is recognised that interpretation of this particular parameter is difficult since it varies considerably in normal subjects but it was considered that if there were any gross effects on sodium excretion resulting from cadmium exposure, then these could be discovered or appreciated by between group analysis.

The present aspect of this study was therefore directed to the examination of a variety of different biochemical parameters which could be affected by cadmium in order to determine whether or not this

could be useful in assessing patients with potential chronic cadmium poisoning. These parameters could be measured in any hospital laboratory where atomic absorption facilities are available. By comparing different groups of workers with a clearly different level of exposure to the trace element it was hoped that any major differences would be obvious and could then be indicated in any screening or follow up programme. Some indication of the effects of chronic exposure can be determined by comparing Gp. V subjects against all other groups. Although the Gp. V subjects are the same as Gp. I, they were assessed approximately 9 months after the initial investigations and the results obtained were from inpatient studies thereby eliminating any factors such as variations in diet or possible added contamination arising from contamination from nail or hair residues of trace metals.

From these studies it can be seen that

(1) The serum creatinine level gives an indication that in terms of renal function then the coppersmiths although not uniformly showing evidence of renal failure, had less efficient renal function than the control groups. Blood urea is not of any great value in this context.

(2) Although serum zinc values were initially very high (Gp. I results) these rapidly returned to non significant levels on suspension of the cadmium brazing process.

(3) Serum copper levels are unlikely to be of major value but since the Gp. III individuals had statistically significantly higher values than Gp. V subjects it could reasonably be deduced that cadmium has reduced the absorption of copper in those who have the greatest exposure to the latter metal. This is an important finding in the interpretation and management of cadmium induced anaemia.

(4) Measurements of urine sodium excretion is of no major interest in these subjects in practical terms.

(5) Urine copper measurements indicate that when removed from the environment where cadmium intoxication was occurring the urine values for this parameter rose quite dramatically and reached a high level of significance. Taken with the serum findings it is possible to speculate a temporary blocking effect on copper absorption.

(6) Urine zinc is considered to be of value in view of its association with stone disease and the statistically significant differences between those who have been severely as compared to those who have been mildly exposed makes this metal of interest.

(7) Urine calcium. The coppersmiths both in the outpatient and inpatient survey were found to

excrete significantly higher calcium in urine when compared with the least severely exposed individuals.

These findings are summarized in Table 19 and relate only to those parameters analysed in the 5 groups under study. The table is based on the comparison of initial and later measurements in the coppersmiths (Gp. I and Gp. V) which were undertaken at an interval of 9 months. All of these measurements have been assessed on an annual basis in the coppersmiths over a period of 7 years (Chap. 11) and cognizance of these latter findings is taken into account in the formation of the summary table. Proteinuria is excluded from these discussions since it has been so well discussed by other authors.

TABLE 19.

Blood	Immediate	Long Term
Cadmium	High	High
Zinc	High	Low
Copper	High	Low
Urea	Nil	Moderate
Creatinine	Moderate	High
Serum inorganic phosphate	High	Low
Urine		
Calcium	High	High
Sodium	Nil	Moderate
Copper	Low	High
Zinc	Moderate/High	Moderate/High

Table 19. Suggested value of readily available biochemical measurements other than proeinuria in the immediate and long term assessment of a work force suspected of having been exposed to cadmium.

PROSPECTIVE STUDY OF COPPERSMITHS
1975 - 1981.

CHAPTER 11.

Prospective study of Coppersmiths 1975 - 1981.

Because of its nephrotoxic effects urologists should be aware of cadmium and of its importance in renal stone formation (Kajantzis, 1970; Kjellstrom, 1977). The present prospective study was designed to assess the development of stone disease in the coppersmiths who had been chronically exposed to cadmium and who had been investigated initially in 1975.

MATERIAL AND METHODS

The twenty-seven coppersmiths were examined initially in August 1975 and their various biochemical parameters were measured and recorded early in October of that particular year. The group have undergone the same investigations in October or within two months of October in every year since 1975. These men had blood removed to allow estimations of the serum electrolytes, creatinine, calcium, serum inorganic phosphate and blood cadmium levels. In addition the serum zinc and copper values were measured. A twenty-four hour urine was collected and the calcium, cadmium, copper and zinc contents were estimated along with the large molecular weight protein content. From 1978 onwards it became possible to measure the low molecular weight protein B_2 microglobulin in urine by a radio immunoassay technique. At the same time each year

a chest x-ray and plain abdominal film were undertaken. The x-ray films reported were made by two individuals working separately and where a calcified lesion was found in either the right or left renal areas it was proven or excluded as a renal stone by plain tomography and intravenous pyelography. Blood cadmium was measured by an atomic fluorescence technique (Fell, Ottoway and Hussein, 1977). Urine cadmium levels were measured from 1975 but in that particular year and in 1976 the methodology was unsatisfactory and results were therefore discarded for these two years. A population which was not known to have been exposed to industrial cadmium pollution was used to establish a normal distribution pattern of the various biochemical parameters measured in the study (Cunningham, 1980). All other biochemical estimations were completed in the routine laboratory, Department of Biochemistry, Royal Infirmary,Glasgow.

RESULTS

ANNUAL FOLLOW-UP OF GROUP 1 SUBJECTS

Blood Cadmium

Because of the relatively small numbers involved it was decided on advice from the statisticians that a group paired analysis (Wilcoxon Rank Paired Test) should be undertaken to assess the significance or otherwise of these results. As can be seen (Table 20), only in 1977 and in 1979 did the serum cadmium levels become significantly lower than the results in 1975. This finding is extremely important as

it indicates a very high degree of pollution in these men and indicates that due to the very high level of exposure the blood cadmium levels after six years were not significantly different from the initial blood cadmium levels.

Proteinuria

The coppersmiths had estimations undertaken of the large molecular weight protein in urine each year and it can be seen that the percentage of the group having significant large molecular weight proteinuria in 1981 as compared with 1975 has more than doubled (Fig. 35). The low molecular weight proteinuria in the group has, since it has been measured in 1978, been regularly in excess of 70% in all subjects where this has been measured (Fig. 36).

Urine Zinc Values

Because of the association between cadmium and zinc this has been regularly monitored and although initially the group showed a tendency to have hyperzincuria the mean urinary zinc has fallen throughout the study and is now within the normal range (Fig. 37).

Urine Calcium Values

These have been shown to be consistently greater than the upper limit of normal usually accepted in our laboratory, namely 6 mmol/volume despite attempts to reduce the calcium out-put using Bendrofluazide (Fig. 38).

TABLE 20

YEAR	NO	$\bar{X}$	YEAR	$\bar{X}$	SIGNIFICANCE
1975	23	15.17	1976	16.2	NS
1975	22	16.09	1977	10.6	$p<0.01$
1975	25	15.88	1978	16.6	NS
1975	26	15.84	1979	12.31	$p<0.05$
1975	25	15.92	1980	15.54	NS
1975	19	14.78	1981	13.81	NS

Table 20. Paired analysis blood cadmium values 1975 - 1981.

The blood cadmium values have been compared using a Wilcoxon Rank Paired Test and show that in only 2 years (1977 and 1979) did the blood cadmium reach a level which was significantly lower than in 1975. This indicates that the blood cadmium does not become significantly less over the period of this study.

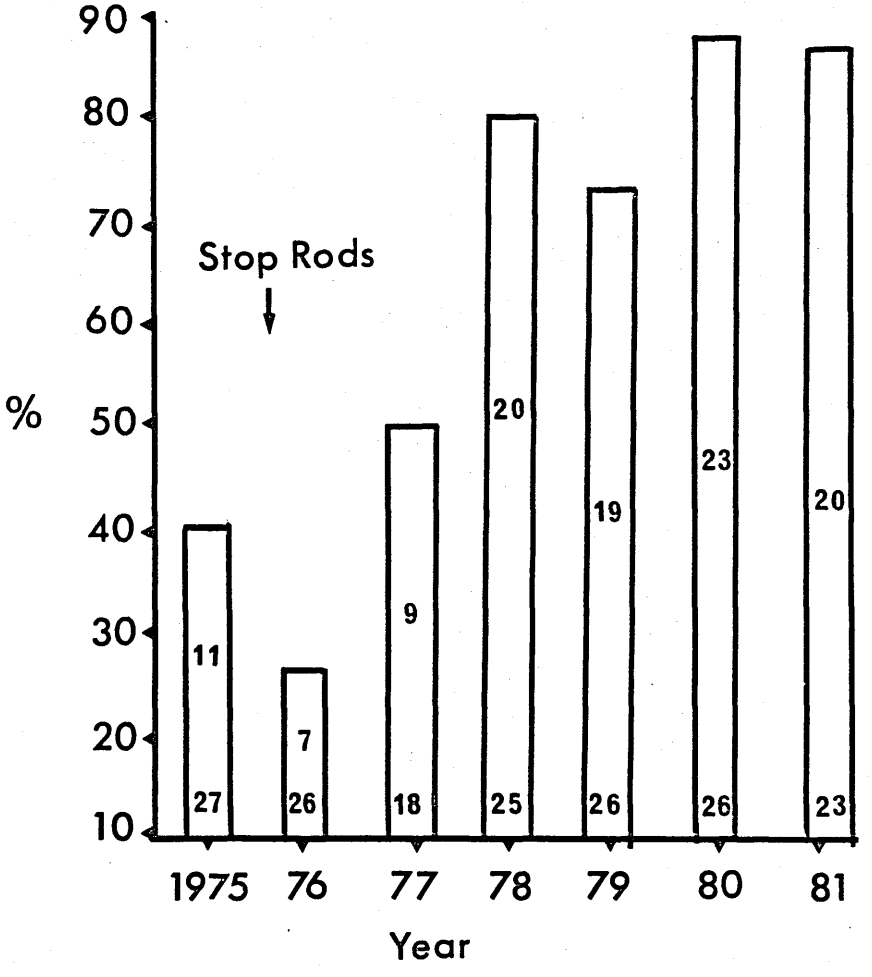

Fig. 35. The development of high mol mass proteinuria in the coppersmiths over a 7 year period.

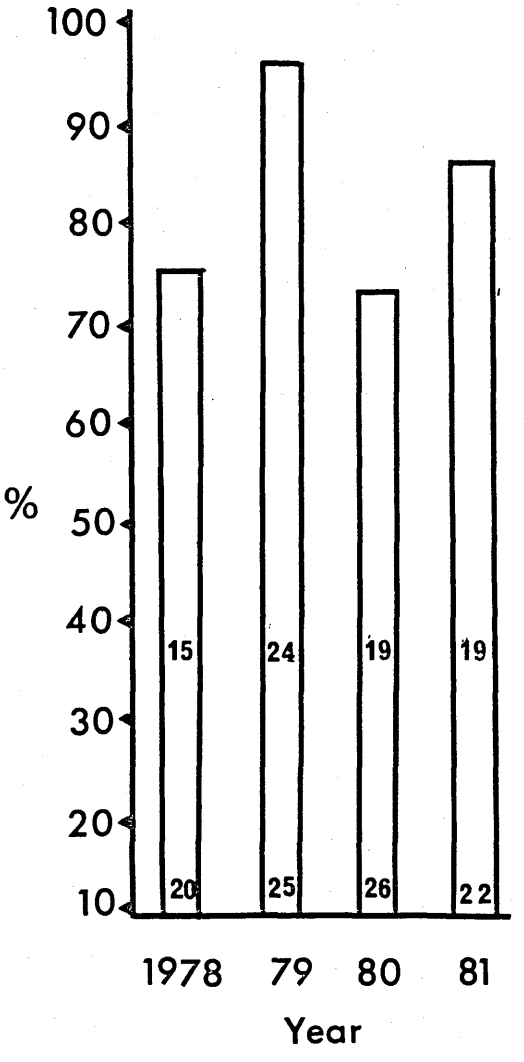

Fig. 36. The development of low mol mass proteinuria in the coppersmiths over a 4 year period.

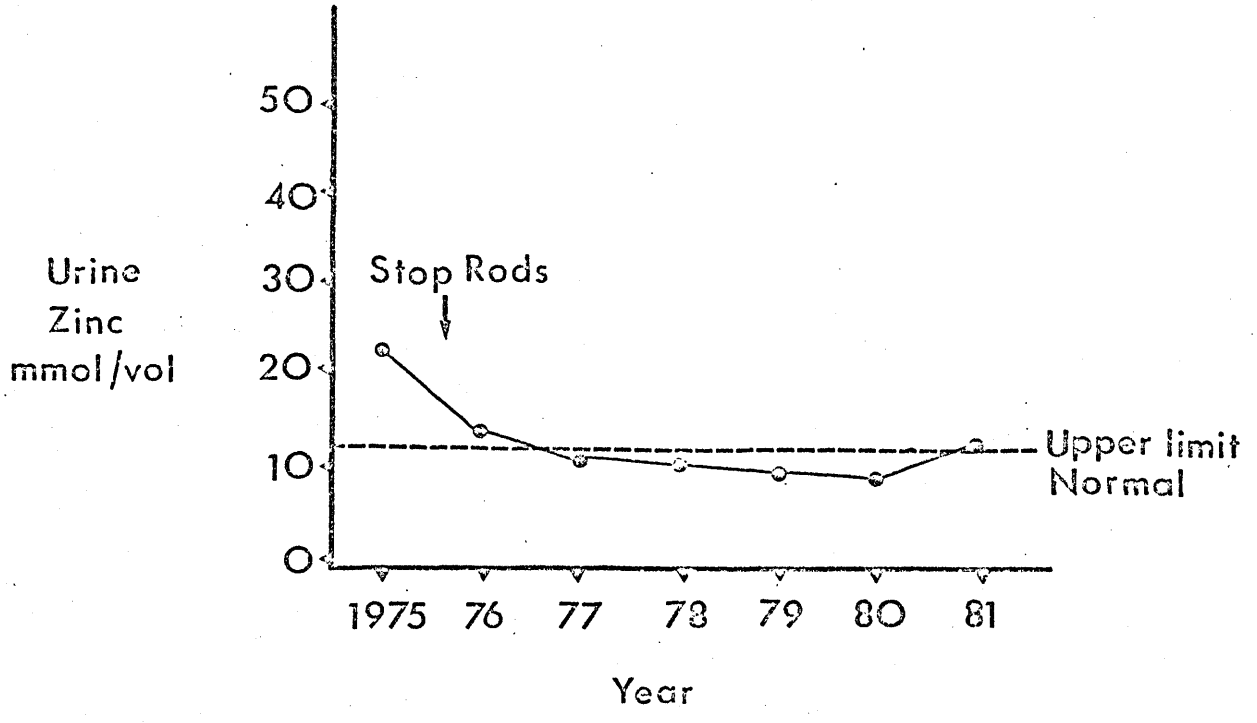

Fig. 37 The mean urine zinc values before and after cessation of the cadmium rods.

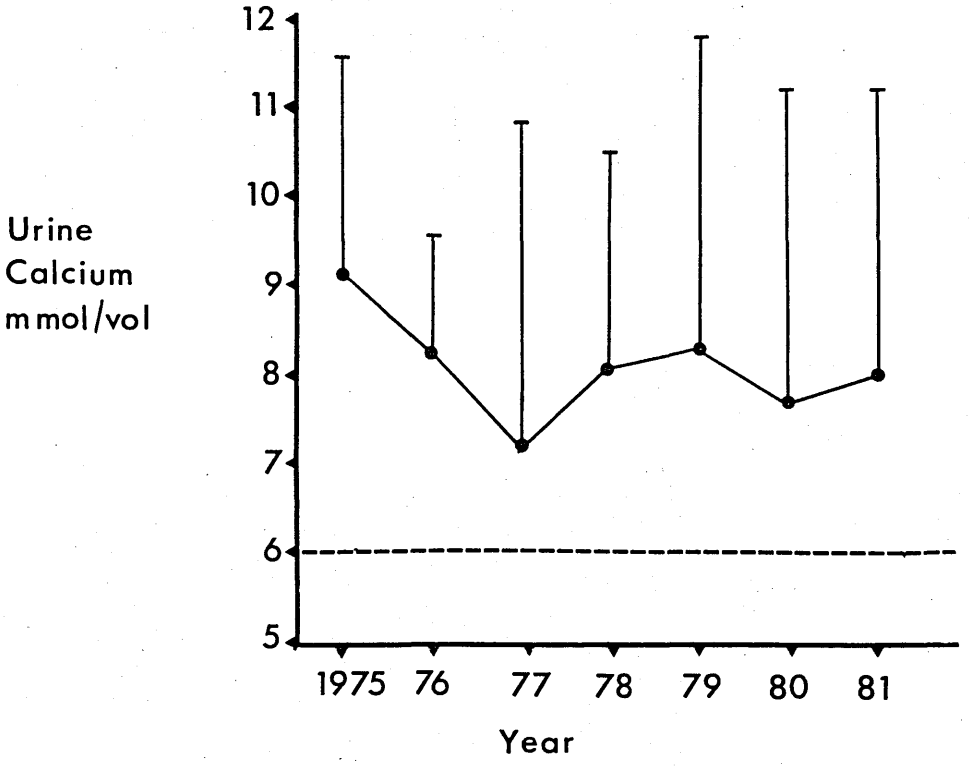

Fig. 38. The excretion of calcium per 24 hours (mean values ± 1 S.D). Bendrofluazide 5 mg/day was given with sodium bicarbonate 3 gm/day in an attempt to reduce the calcium loss.

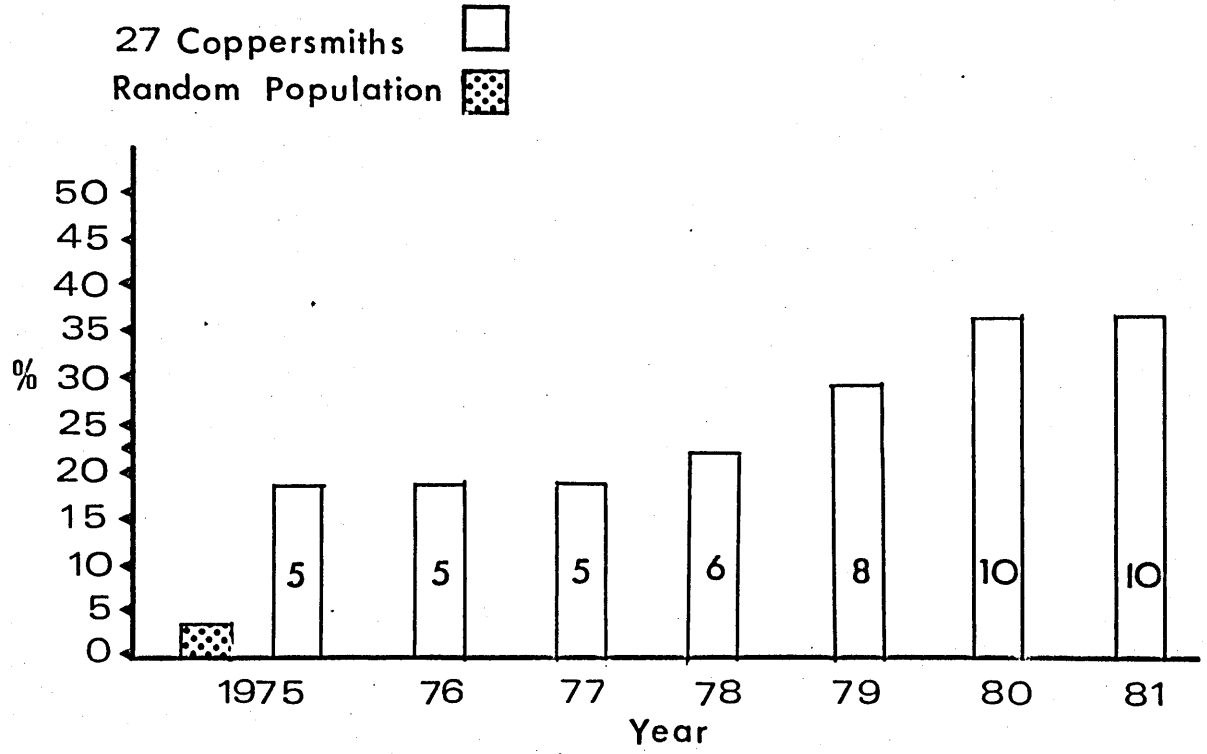

Fig. 39. Stone disease within the group over a 7 year period. In 1975 the prevalence of stone disease was 18.5% as compared with a random population percentage figure of 3.5%. By 1981 the value had reached 37%.

STONE DISEASE

The coppersmiths underwent an annual X-ray. The presence of calcified shadow in the area of either kidney was investigated by further X-rays, i.e. plain tomography and intravenous pyelogram. As can be seen (Fig. 39) in 1980 and 1981 the incidence of stone disease was just under 37% as compared with the prevalence in a random population survey of 3.5% in this area.

The men underwent further X-rays in October 1982 and at that time another man had developed a stone so that by 1982 the incidence of stone disease had reached 40.7% within the group.

DISCUSSION

Cadmium is generally regarded as being a very toxic metal but it is surprising that the presence of the metal as a significant air pollutant is often missed (Buell, 1975). It is always possible that when other metals such as copper are used in an industrial process (Moreton, 1977) then the toxic effects of cadmium can easily be overlooked. This is probably best illustrated by the fact that following the realisation that chronic cadmium poisoning was a distinct clinical entity (Friberg, 1950) it was tewenty-six years later before the first recorded case of chronic cadmium poisoning was recorded in Australia (Meerkin, Clarke and Oliphant, 1976).

In order to make the diagnosis of chronic cadmium poisoning it is necessary to have proof of exposure to the metal and then to be able to demonstrate the presence of excessive cadmium in blood along with certain abnormal biochemical parameters which result from cadmium exposure. At the present time most emphasis has been placed on the demonstration of elevated blood cadmium levels and excess excretion of certain urinary proteins. There has been a considerable debate as to the significance of blood cadmium values. It is not unusual to find statements to the effect that blood cadmium values are a representation of recent cadmium exposure (Lauwerys, Buchet and Roels, 1976). Blood cadmium is considered to be related to the level rather than the duration of exposure (Welinder, et al, 1977).

The present study has shown that on cessation of the use of cadmium it was possible to continue to measure very high levels of cadmium in the serum of individuals six years after the initial measurements had been made. It was not possible to demonstrate a statistically significant fall in cadmium values after six years although in two years during the study the levels did become significantly lower. One possible interpretation of this finding is that in these particular individuals, after an initial clearing of cadmium from the blood the vast tissue reserves of cadmium are generally being mobilised and transported in the blood stream prior

to excretion.

Cadmium effects on the kidneys are particularly important as they cause the kidney to undergo certain histological changes resulting in the occurrence of low molecular weight tubular type proteinuria (Kjellstrom, et al, 1977). Since the earliest description of chronic cadmium poisoning (Friberg, 1950) many authorities have regarded low molecular weight tubular proteinuria as the hallmark of chronic cadmium poisoning (Adams, Harrison and Scott, 1966), whereas other workers regard larger molecular weight proteinuria indicating glomelular damage to be equally important. It is clearly adviseable to measure both large and low molecular weight proteins in urine when investigating chronic cadmium poisoning (Itokawa, et al, 1974; Bernard et al, 1976; Hansen et al, 1977). As in other studies the present work shows that there has been a progressive increase in the numbers of patients who have been excreting excessive protein in their urine both of a large and a low molecular weight type.

For a urologist the significance of cadmium rests upon its renal toxic effects not only in terms of biochemical changes, but more particularly because the metal can be a factor in the production of renal stone disease. Cadmium has been known to produce renal damage (Axellsson and Piscator, 1966) but it has only recently been realised that the damage may be due less to the cadmium and more to the complex

metallothionein which is produced by the liver in response to the presence of cadmium. It is in this complex that the metal is transported to and lodged in the kidneys. The thionein itself without the metal is clearly capable of producing renal toxic effects (Cherian et al, 1976). In the first report on the subject (Friberg, 1950) the presence of stone disease was found in seven of fifty-eight subjects (12.1%) and in Adam's series (Adam et al, 1966) it was noted that 20% of the individuals had stone disease on initial investigation. Speculation about this high stone prevalence resulted in the theory that cadmium caused an excess excretion of a variety of different salts (Friberg, 1959) but it is clear that from work already published by our group (Aughey and Scott, 1977) that the kidney response to cadmium results in the deposition of calcific focci in the basement membranes of the renal tubule. These calcific focci combined with the cell damage and collagen deposition probably are the initiating factors causing stone formation. I am not aware of any particular prospective study designed to assess the development or otherwise of urinary tract stone disease in chronic cadmium poisoning.

Where exposure levels are high and where blood levels of cadmium are found to be excessively high, then it is considered from the evidence presented that apart from undergoing a variety of biochemical tests to ascertain whether or not there is renal damage, a plain abdominal film should be undertaken in the

assessment of the individual patient. When indicated, this should be supplemented with an intravenous pyelogram. The comparison of the results between different groups and the prospective study has helped us to determine which biochemical parameters are likely to be of value in assessing individual subjects.

The blood and urine cadmium values along with the low molecular weight protein and large molecular weight protein values should be estimated. As already recorded serum inorganic phosphate should be measured (Scott et al, 1981). Estimations of serum copper and zinc values are of considerable interest but the interpretation of these results is still unclear in terms of the assessment of chronic cadmium poisoning. It is clearly necessary to make an initial assessment of the urine calcium output.

Due to the widespread use of this non-essential toxic metal in industry it clearly is of importance to those found to have unexplained proteinuria, "idiopathic hypercalcuria" or non-metabolic stone disease to be alert to the possibility of an 'occupational factor' such as cadmium, causing the stone problem in an individual patient.

STUDIES OF DIFFERENT WORK GROUPS
in 1981 - 1982.

CHAPTER 12

Studies of different work groups.

In 1975 advice was given to the management of the factory in which the coppersmiths were working to stop using the cadmium containing rods. This advice was immediately accepted and the men involved in the brazing process were reviewed annually.

The blood cadmium values in the coppersmiths were monitored annually and as can be seen (Fig. 40) the blood cadmium levels have consistently been greater than 10 ug/L. Between 1980 and 1982 the mean blood cadmium levels have fallen and this is the longest period of time over which such a sustained fall has been observed (Table 21).

Because of a general interest by the workers who clearly discussed the investigations with other men from different factories, it was possible to investigate subjects who had been involved in a variety of different cadmium processes. As far as can be ascertained most were involved in some type of brazing procedure but in one factory a cadmium plating process was employed.

A 'league table' was drawn up of the different factory groups which were investigated in 1981 and 1982 on the basis of the mean blood cadmium levels (Fig. 41). By doing so it was possible to compare the results obtained in the coppersmiths in 1981 - 1982 against the different factory groups. When the blood cadmium values for the different factories were assembled then there is a progressive rise from workers who had values equivalent to non exposed populations (Cunningham, 1980)

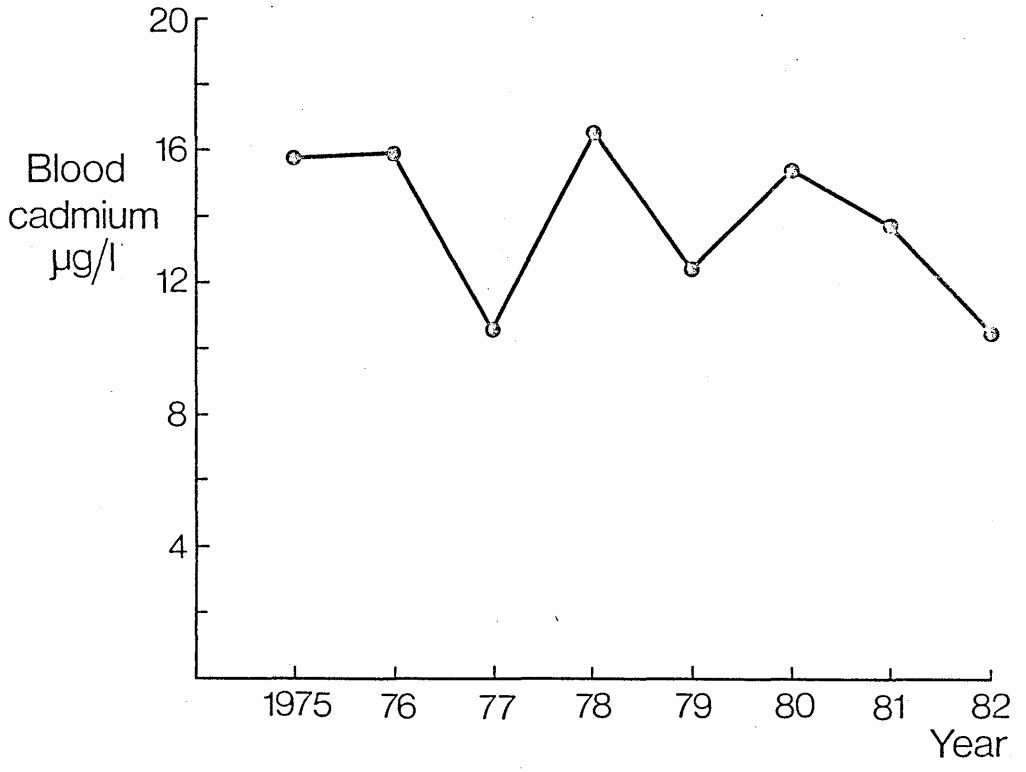

Fig. 40. Mean blood cadmium values in coppersmiths from 1975 - 1982.

TABLE 21.

YEAR	NO	$\bar{x}$ BLOOD CADMIUM	± S.D.
1975	27	15.8	5.4
1976	24	15.9	5.9
1977	23	10.56	4.4
1978	24	16.6	6.8
1979	26	12.3	6.1
1980	25	15.5	11.3
1981	19	13.8	6.6
1982	23	10.5	4.3

Table 21 Mean blood cadmium (1975 - 1982).
This table demonstrates the mean blood cadmium values in the coppersmiths between 1975 and 1982 and confirms that after 7 years the values were still in excess of 10 ug/L.

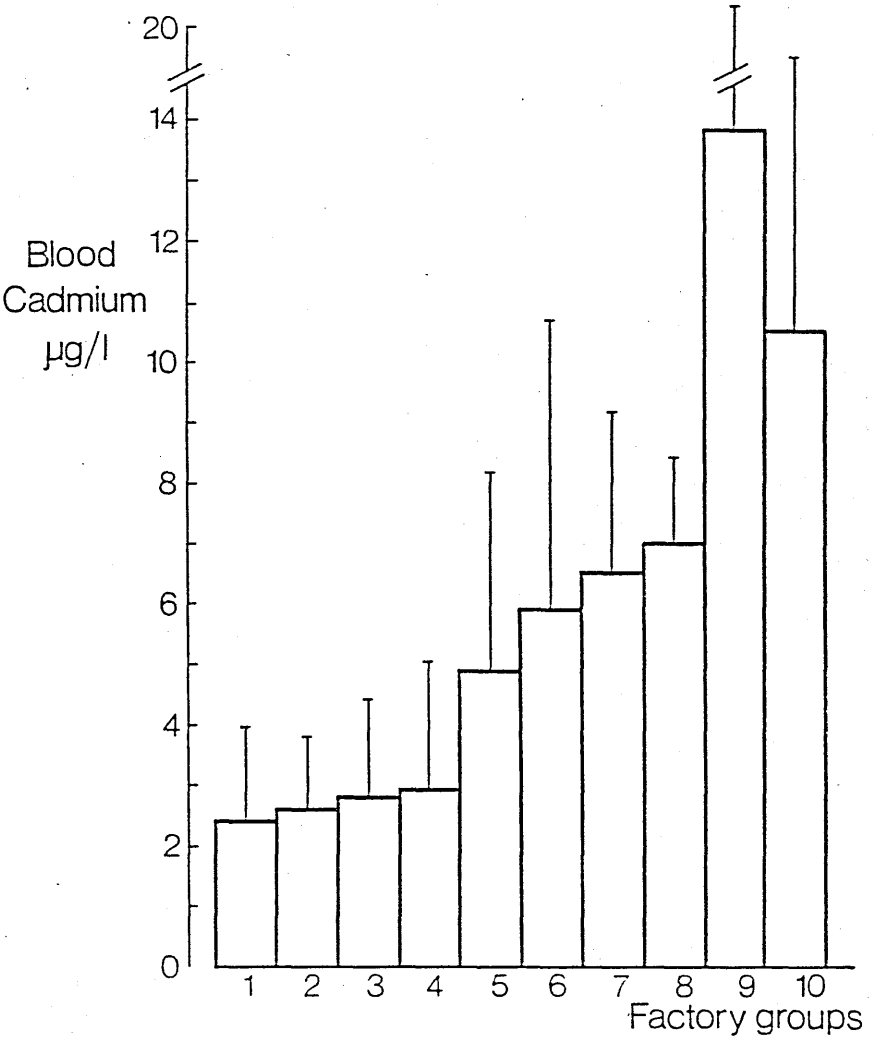

Fig. 41. Mean blood cadmium values for different factory groups. Groups 7 - 10 were employed in the Prestcold Factory.

at one end of the scale to the coppersmiths at the other end (Fig. 41). Using the blood cadmium values it was necessary to reassign the workers of certain individual groups.

Group 3 subjects (Table 22) consisted of a group of 6 men who belonged to the original Group IV (Chap. 10, page 120). These men on original screening had been found to have had elevated urine calcium values and it was decided to try to minimize their likelihood of forming stones by administering bendrofluazide 5 mg/day with potassium 600 mg. t d s. This therapy was given on a continuing basis under the supervision of the factory nurse.

It was also possible in 1981 - 82 to examine some of the general workers from the parent factory (Group 7 Table 22) and 5 of the original sheet metal control group (Group 8, Table 22). With respect to the Group 3 and 8 workers some indication of the pattern of change in the mean blood cadmium values was possible since some members of each of these groups had been reviewed annually (Tables 23 and 24). In addition to having some insight into the pattern of blood cadmium levels in these groups it was possible to confirm the variable proteinuria in both of these groups (Tables 25 and 26). In Group 3 subjects (Table 25) proteinuria, both large and low molecular weight has been variable although two subjects have constantly shown a variable degree of significant proteinuria (large molecular weight).

TABLE 22.

GROUP	FACTORY	NO	$\bar{x}$ BLOOD CADMIUM	S.D.
1	U I E (Shipbuilders)	20	2.4	1.6
2	British Leyland	5	2.6	1.2
3	Rolls Royce	4	2.8	1.6
4	Craig Nicol	34	2.9	2.1
5	Barr & Stroud	6	4.9	3.3
6	Kelvin Diesels	5	5.9	4.8
7	Prestcold (misc.)	14	6.5	2.7
8	Group 2 Sheet metal workers	5	7.0	1.9
9	Coppersmiths (1981)	19	13.8	6.6
10	Coppersmiths (1982)	23	10.5	4.3

Table 22 Comparison of cadmium values - 1981/82.
The cadmium processes were mainly brazing procedures. The lowest values were obtained in men involved in ship building where ventilation would be less of a problem. Groups 7 - 8 and 9 were those employed in a variety of occupations in one particular factory.

The mean urine calcium in Group 3 subjects has only within the past two years fallen to a level slightly greater than the upper limit of normal and interestingly this has paralleled a 50% reduction in the blood cadmium values (Table 23).

Examination of the blood cadmium values in the sheet metal workers (Table 24) has shown that, like the coppersmiths, this group, who were the original group chosen specifically to allow comparison with the coppersmiths, have had a mean blood cadmium value of less than 8 ug/L in only 4 of 7 years and even in 1981 had values which were three times greater than the mean value found in a control population of non exposed individuals (Cunningham 1980). Proteinuria has not become a major problem within the group but obviously in the future could become very important because of the generally high cadmium levels (Table 26).

When the results from the different factory groups were examined in 1980 - 1981 then only Groups 1, 2, 3 and 4 had mean blood cadmium values of less than 4 ug/L. The mean cadmium value in the Group 6 subjects ($\bar{x}$ 5.9 ug/L) is interesting because by taking a careful industrial history I discovered that one of these subjects had previously been employed as a coppersmith in the same factory as the coppersmiths and indeed had spent most of his working life in the latter factory. If the results of this individual are omitted from Group 6 then it changes the pattern of "severity" of contamination as

TABLE 23.

YEAR	NO	$\bar{x}$ BLOOD CADMIUM	S.D.
1976	6	5.8	1.5
1977	6	5.3	1.1
1978	6	3.7	0.4
1979	not evaluated		
1980	6	2.6	1.3
1981	4	2.2	1.2

Table 23 Blood cadmium values (ug/L) Group 3 (formally Group IV).

This table demonstrates that after initial estimations of blood cadmium values it took at least 3 years before the values approached the levels in a non exposed random population.

TABLE 24.

YEAR	NO	$\bar{x}$ BLOOD CADMIUM ug/L	± I.S.D.
1975	19	14.5	7.0
1976	13	7.3	5.7
1977	14	10.8	5.8
1978	13	6.1	5.0
1979	9	6.1	5.5
1980	2	9.45	0.05
1981	5	7.0	1.9

Table 24 Blood cadmium values - Group 8 (formally Group II) subjects.

This group were the original control group and it can be seen that it was 4 years after initial estimations before the blood cadmium values reached values equivalent to the values found in the random control population.

TABLE 25.

YEAR	NO	SIGNIFICANT PROTEINURIA	
		Large mol. weight	Low mol. weight
1976	6	0	-
1977	6	0	-
1978	6	2	1
1979	6	4	1
1980	6	1	0
1981	4	2	0

Table 25 Proteinuria - Group 3 subjects (formally Group IV).

The variability of proteinuria in these subjects is demonstrated. Significant proteinuria (B_2 microglobulinuria) appeared to be variable.

TABLE 26.

YEAR	NO. POSSIBLE	SIGNIFICANT LARGE MOL. WT.	LOW MOL. WT. (B_2)
1975	19	0	-
1976	4	1	-
1977	13	1	-
1978	11	4	3
1979	9	4	2
1980	3	3	1
1981	4	1	1

Table 26 Group 8 (formally Group II) subjects - proteinuria (significant).

Proteinuria within this group is variable both with respect to large and low molecular weight proteinuria.

judged by mean blood cadmium levels (Fig. 42).

From these figures we can see that there is an ascending scale with respect to mean blood cadmium values and that the Prestcold workers in whatever group (Groups 7, 8, 9 and 10) clearly have suffered the greatest level of contamination from exposure to cadmium. Groups 9 and 10 give the mean blood cadmium values for the coppersmiths in 1981 and 1982 (Fig. 42).

Since urine cadmium (Table 27) can be an indication of previous loading with cadmium there is clearly an ascending progression of these values which has tended to parallel the blood cadmium values (Fig. 43). The exception to this is Group 6 which is probably falsely high because of the one individual already alluded to in respect of blood cadmium values. If, as with the blood cadmium values, the one individual is removed from the group the mean urine cadmium value for Group 6 becomes 4.5 ug/vol. which is very much in keeping with progression seen in the blood cadmium levels (Fig. 44).

The values obtained for blood and urine cadmium in the various factory workers almost exactly parallel each other which is logical in that these parameters give an indication of the level of general contamination within the factory complex whatever the main process.

Urine calcium in all of the subjects (Table 28) in Groups 1 - 7 generally fell within the normal range of 3 - 6 mmol/vol. The exception is Group 3 subjects who had been specially selected because they had

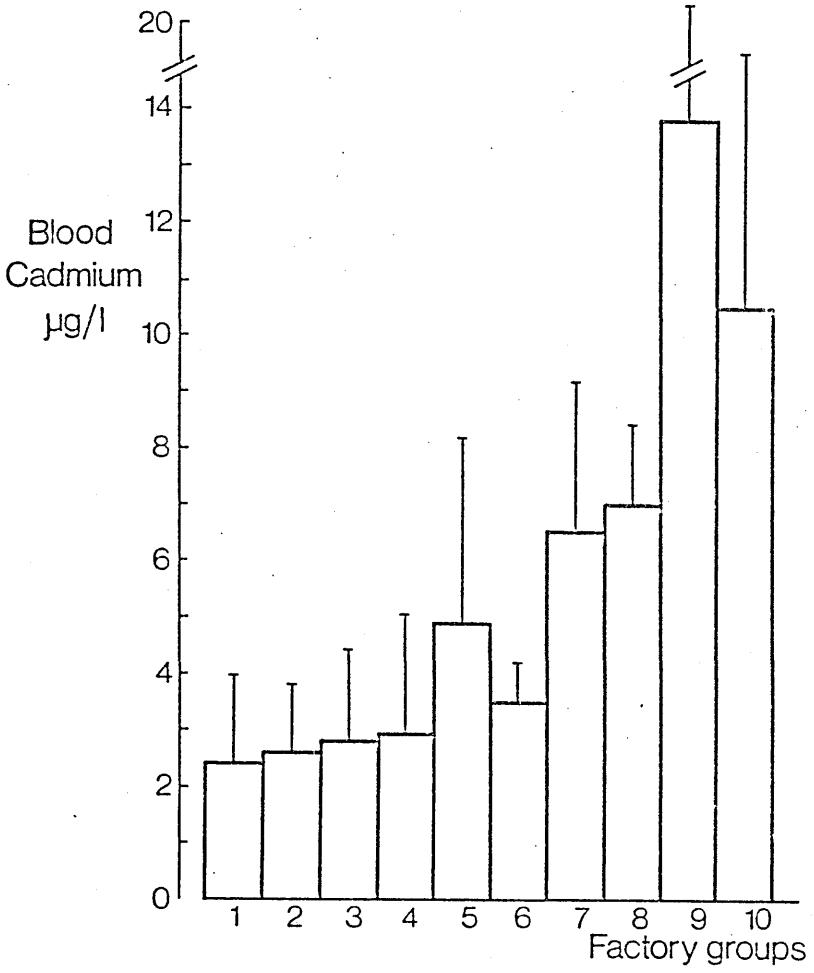

Fig. 42. Mean cadmium values in different factory groups showing the effect of correlating industrial history with cadmium exposure with special reference to Group 6 individuals.

TABLE 27.

GROUP	FACTORY	NO	$\bar{x}$ URINE CADMIUM	S.D.
1	U I E (Shipbuilders)	18	2.3	2.6
2	British Leyland	5	1.3	0.5
3	Rolls Royce	4	2.2	1.2
4	Craig Nicol	33	1.9	1.9
5	Barr & Stroud	5	3.1	1.1
6	Kelvin Diesels	5	10.2	11.1
7	Prestcold (misc.)	12	6.04	2.1
8	Group 2 Sheet metal workers	5	7.0	1.9
9	Coppersmiths (1981)	22	23.5	19.6
10	Coppersmiths (1982)	22	15.7	6.3

Table 27 Urine cadmium in different factory groups. This parameter reveals that the overall pattern is apparently different from that obtained when blood cadmium values are tabulated.

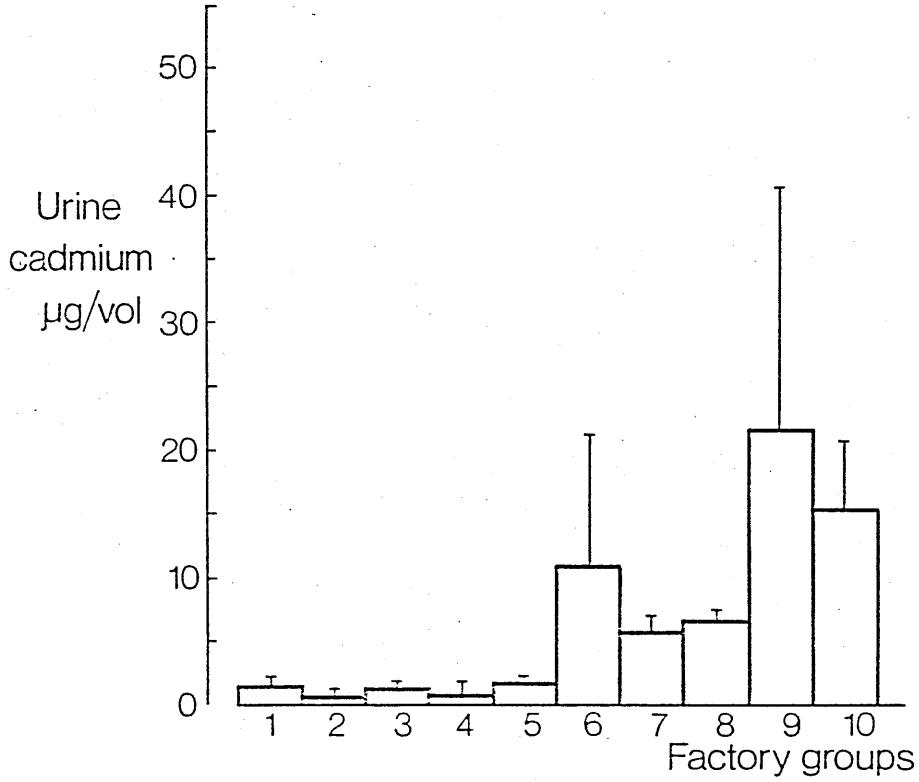

Fig. 43. Urine cadmium values in different factory groups confirming the highest excretion rates in coppersmiths (Groups 9 & 10).

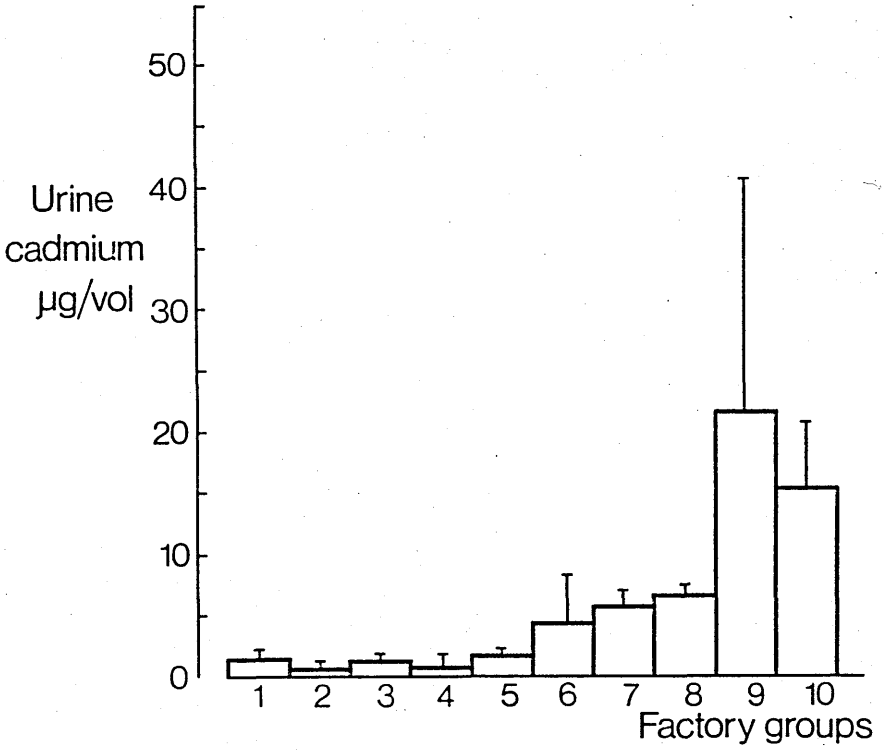

Fig. 44. Urine cadmium excretion in different factory groups showing the effect of correlating values with industrial history with special reference to Group 6 individuals.

TABLE 28.

GROUP	FACTORY	NO	$\bar{x}$	S.D.
1	U I E (Shipbuilders)	18	4.9	3.3
2	British Leyland	5	3.4	1.5
3	Rolls Royce	4	6.9	1.8
4	Craig Nicol	34	4.2	2.0
5	Barr & Stroud	5	4.0	0.3
6	Kelvin Diesels	5	3.7	1.9
7	Prestcold (misc.)	13	5.3	2.4
8	Group 2 Sheet metal workers	4	7.15	3.9
9	Coppersmiths (1981)	22	8.02	3.2
10	Coppersmiths (1982)	20	8.20	3.3

Table 28 Urine calcium.

The table illustrates that with the exception of Group 3 individuals who were specifically followed because of high urine calcium values, that the urine calcium excretion again gives an indication of the severity of cadmium exposure as seen from examination of blood and urine cadmium values.

elevated urine calcium values of more than 6 mmol/vol. The finding of very obvious hypercalciuria in the Group 8, 9 and 10 subjects helps to emphasize the importance of measuring urine calcium in the assessment of the effects of cadmium in exposed workers (Fig. 45).

Proteinuria

Many authors consider that measuring low molecular weight proteinuria (B_2 microglobulin). (Fig. 46) is the significant parameter to be used as an indication of chronic cadmium poisoning.

With respect to the percent of each 2 groups with both large and low molecular weight protein the coppersmiths are quite unique and as has already been shown over the years 1978 to 1982 have been increasing the percentage of the group with low molecular weight protein. Latterly this has meant that over 90% of these men have significant low molecular weight proteinuria (Table 29).

Apart from the large proportion of the coppersmith group with low molecular weight proteinuria indicating the severity of contamination within these subjects, there is a similar indication of a major problem as shown by those with significant large molecular weight proteinuria (Fig. 47).

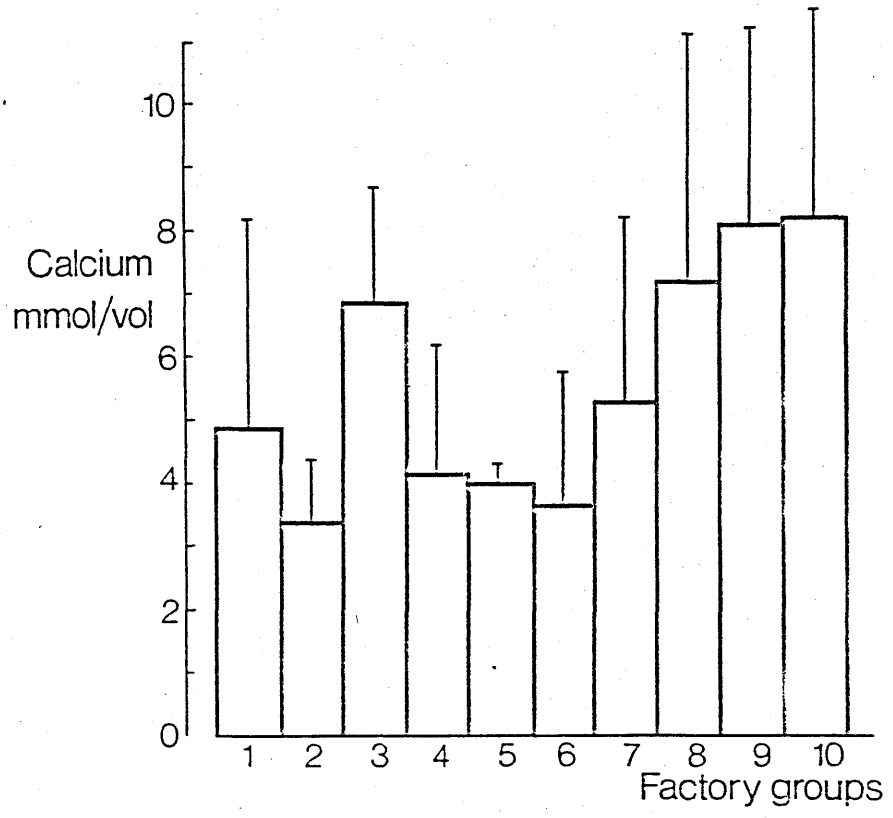

Fig. 45. Urine calcium excretion in different factory groups. Group 3 were being followed up from 1975 specifically because the subjects had hypercalciuria.

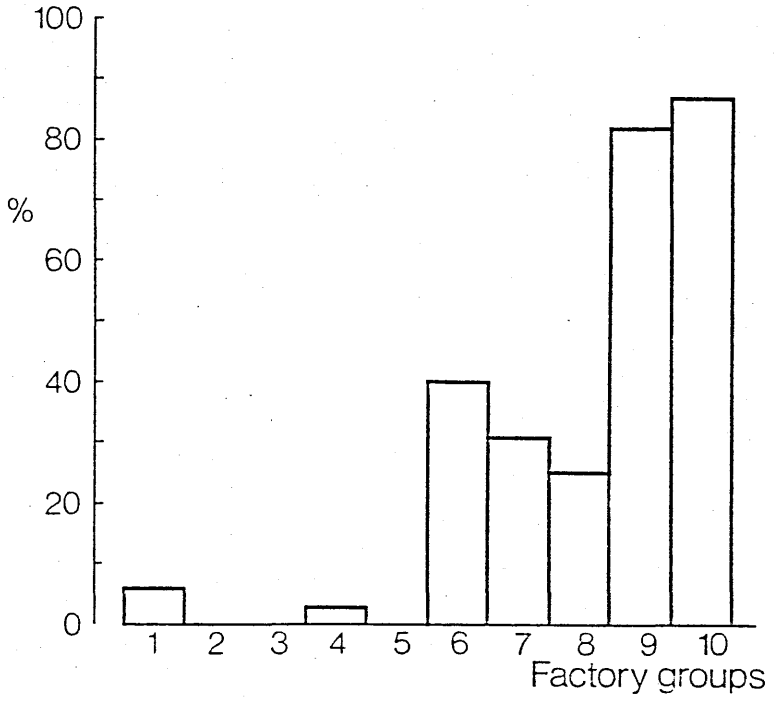

Fig. 46. Proteinuria - (low mol. wt.) - significant. Excretion of significant amounts of B_2 microglobulin in different factory groups. Group 6 is abnormally high because of 1 individual.

TABLE 29.

GROUP	FACTORY	NO	LARGE MOL. WT.	%	LOW MOL. WT. (B_2 MICROGLOBULIN)	%
1	U I E (Shipbuilders)	17	3	17.6	1	5.8
2	British Leyland	5	1	20.0	0	0
3	Rolls Royce	4	2	50.0	0	0
4	Craig Nicol	34	7	20.5	1	2.9
5	Barr & Stroud	6	0	0	0	0
6	Kelvin Diesels	5	2	40.0	2	40
7	Prestcold (misc.)	13	3	23.0	4	30.7
8	Group 2 Sheet metal workers	4	1	25.0	1	25.0
9	Coppersmiths (1981)	22	20	90.0	18	81.8
10	Coppersmiths (1982)	22	16	72.7	19	86.3

Table 29. Comparison of proteinuria within factory groups. Comparison of 10 different groups showing the % within each group with a significant proteinuria both of a large and low molecular weight type. The coppersmiths duly showing a pattern clearly indicating the severity of the problem within that particular group.

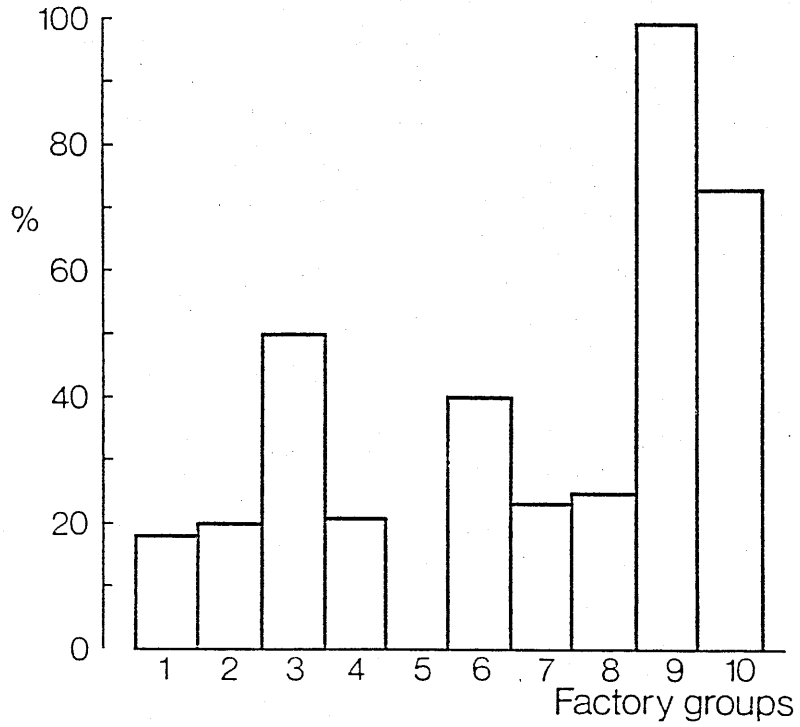

Fig. 47. Proteinuria - (large mol. wt.) - significant. Excretion of significant amounts of large mol. wt. protein in different factory groups.

DISCUSSION

Apart from monitoring the coppersmiths on an annual basis (Chap. 11) it was possible to examine several of the members of other groups who were initially examined in 1975 and 1976. Some members of at least 3 of these groups were available for examination during 1981 and 1982 and although the numbers were small and variable, it is considered that they do give some indication as to what happens to parameters such as blood and urine cadmium values once the men and the management become aware of a problem and make some effort to reduce the contamination of the atmosphere. Two groups are particularly interesting in this context namely the group who were followed because at initial investigation they had persistent hypercalciuria and the group of sheet metal workers who had initially been used as a control group. The latter were particularly difficult to follow up because on the closure of the factory in 1978 these men in their search for employment, became widely scattered and despite great efforts to monitor them on an annual basis similar to the coppersmiths, it was found that many had either left the area or failed to comply with requests to attend for examination. The pattern of changes in blood cadmium in the group, however, is very similar to that found in the hypercalciuria group and reveals that it takes at least 3 years before a fall in blood cadmium occurred which would indicate a reduction in circulating cadmium.

Examination of the group with high urine calcium values who have been very carefully supervised while receiving therapy which is known to reduce urine calcium levels (Nassim, 1965; Jorgensen, 1972 and Coe, 1977) confirms that in the presence of a cadmium problem it is very difficult to reduce the excretion of urine calcium. This fact is of particular importance since it was this group of workers who along with the coppersmiths were evaluated with respect to total body calcium values by in vivo neutron activation analyses. As already shown and published (Scott, et al, 1980) (Fig. 48) the effect of the hypercalciuria is,when related to duration of employment and therefore cadmium exposure, reflected in a significant fall in total body calcium.

The other factory groups examined are of interest because on inspection of some of the premises it was found that the use of cadmium was minimal although in one factory the T L V values were found to have been exceeded. In those workers who tended to work in surroundings which were less well enclosed i.e. in shipbuilding, the levels of blood cadmium were the lowest found in any one group.

Overall, the blood cadmium values if taken on a group basis and arranged in an ascending scale, give a very good indication of the pattern of abnormalities likely to be found in other measured parameters.

Great care has to be taken in determining the industrial history of the individuals as can be shown

by the fact that with the small numbers examined in Group 6 one individual who had spent most of his life working as a coppersmith in the Prestcold factory caused the overall results for that group to be falsely high. By comparing the different factory groups in 1981 and 1982 the severity of the persistent contamination within the coppersmith group is confirmed and shows that blood cadmium levels give a very good indication of which individuals are most likely to have abnormalities of a significant nature including proteinuria and hypercalciuria. The significance of the latter is of particular importance since it may be very difficult to reduce a persistent loss of calcium even with recognised therapy and long term this may result in depletion of skeletal calcium. This has been demonstrated in the present study by the reduction of whole body calcium related to duration of employment.

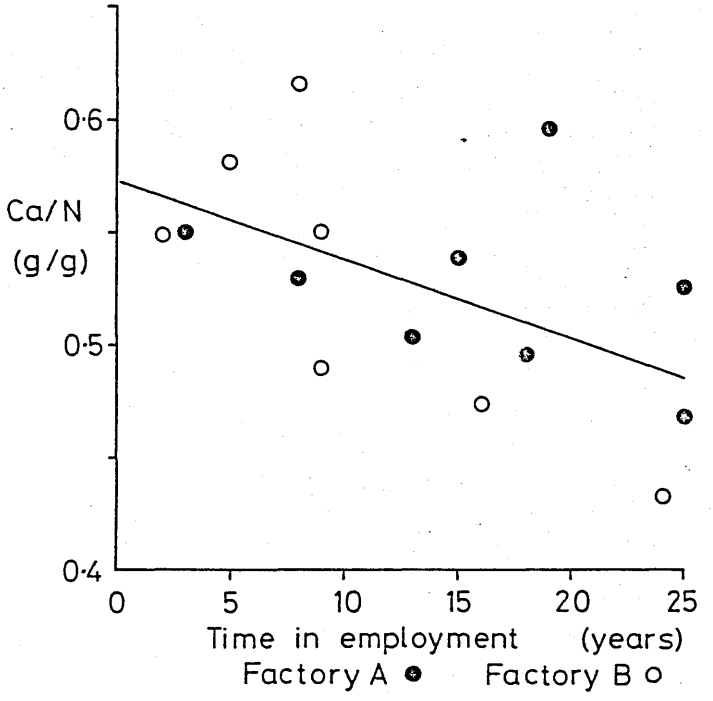

Fig. 48. Whole body calcium in workers exposed to cadmium confirming that there is a significant correlation between a reduced calcium and duration of employment.

STUDY OF GENERAL WORKERS IN FACTORY WITH CADMIUM POLLUTION PROBLEM.

CHAPTER 13.

Study of general workers in factory.

When the initial investigation of the coppersmiths in the Prestcold factory was undertaken it was realised that the cadmium fume could escape into the general atmosphere and hence contaminate other workers. Subsequent enquiry into previous work practices confirmed that brazing had, at different times, been undertaken in a variety of sites within the factory. In order to assess the effects of cadmium on the general workforce in the factory an opportunity was given to all the workforce to volunteer to be screened.

The general workforce was approximately 700 - 800 but as in all large factories a number of men changed employment during the study. The study took place in 1977 - 1978.

METHOD

A form was circulated (Appendix I) to all members of staff and when completed forms were returned to the medical centre. The questionnaire form was devised to cover such details as the duration of employment, smoking habits, marital status and in particular enquiry was made with respect to previous renal or pulmonary problems.

The completness of the form was assured as far as possible and blood was then withdrawn to estimate blood cadmium, zinc, iron and copper along with the serum inorganic phosphate and haemoglobin value. The biochemical

estimations undertaken were done in the same laboratory and by the same methods as the coppersmiths.

RESULTS

Four hundred and three individuals attended the survey and of the remaining workforce 29 completed forms but failed to attend the medical centre for reasons which included awkwardness of shift working. Every effort was made to accommodate as many individuals as possible.

Respiratory symptomatology

As would be expected smokers gave answers suggesting more respiratory problems (Table 30) both in male and female subjects.

Previous renal problems

The same question was asked of the general workforce as had been asked at the Cumbernauld Health Survey with respect to previous renal disease (Table 31). In the answers to every question the smokers had a much greater problem apparently than the non smokers as judged by their responses. This aspect of smoking and upper urinary tract problems has received very little attention in the literature. But what the survey did highlight was that the subjects studied in the factory scan had a greater chance of having had a stone problem than that found in the normal population (Table 32). The figures obtained in the general population survey show that a positive history of stone disease was 1.1% as compared with 3.4% in the factory workforce. To give further support to the argument that the

TABLE 30.

	MALE		FEMALE	
	SMOKERS	N/SMOKERS	SMOKERS	N/SMOKERS
BRONCHITIS	25	5	4	1
PNEUMONIA/PLEURISY	22	10	1	0
HAEMOPTYSIS/OTHER	12	4	3	0
BRONCHITIS + PNEUMONIA PLEURISY	11	1	2	0
BRONCHITIS + HAEMOPTYSIS	3	0	0	0
PNEUMONIA/PLEURISY/ HAEMOPTYSIS	2	1	0	0
MULTIPLE CHEST PROBLEMS	7	3	0	0

TABLE 30. Factory scan. The response to questions concerning a history of previous or existing respiratory problems showing the increased number with a response in both male and female smokers.

TABLE 31

CONDITION/SYMPTOM	MALE				FEMALE			
	SMOKERS		N/SMOKERS		SMOKERS		N/SMOKERS	
	No.	%	No.	%	No.	%	No.	%
KIDNEY DISEASE	25	(6.7)	5	(1.3)	1	(3.1)	-	-
COLIC	7	(1.8)	5	(1.3)	1	(3.1)	-	-
PASSED GRAVEL OR STONE	8	(2.1)	3	(0.8)	-	-	-	-
HAEMATURIA	16	(4.3)	4	(1.0)	2	(6.2)	-	-
NOCTURIA	19	(5.1)	4	(1.0)	2	(6.2)	-	-
I.V.P.	26	(7.0)	7	(1.8)	5	(15.0)	1	(3.1)
RENAL BIOPSY	1	(0.2)	-	-	-	-	-	-

TABLE 31. Previous history of Renal lithiasis and current urinary symptomatology.

It is shown in this table that in those who smoked (male and female) there was a much higher percentage with previous urinary symptomatology.

workforce were different from the general population is the finding that almost twice as many in the factory gave a positive history of having passed a stone or gravel as compared with the findings in the general population (Table 32).

This apparently higher than normal prevalence of previous stone disease becomes much more important when it is remembered that at the initial study the coppersmiths who were the most actively involved with the cadmium rods had a prevalence of stone disease in the order of 18.5% and even the sheet metal workers who acted as an initial control group were found to have a prevalence of stone disease greater than the normal population. Perhaps if the general workers had been individually x-rayed then the prevalence of stone disease would be much higher because asymptomatic stones would have been diagnosed. It was however not practical or possible to undertake this exercise within the time available.

As an extra check on the overall picture the 29 workers who did not attend the survey but who had completed the questionnaire were analysed separately. This group (Table 33) again showed that the smokers had a higher chance of having had previous renal disease. The group also were more likely to have passed gravel than in the general population and once again proved to have twice as many subjects with a positive history of stone disease. The stone formers were all male subjects.

Blood cadmium values

In the analyses of the blood cadmium results the subjects

TABLE 32.

SYMPTOM	FACTORY WORKERS SCAN	RANDOM POPULATION
STONE DISEASE	3.4%	1.1%
COLIC	3.2%	3.1%
PASSAGE OF STONES/GRAVEL	2.7%	1.4%

Table 32. This table indicates that as judged by previous history those who worked in the Prestcold factory were twice as likely to have passed a stone as those subjects in the random population survey. A previous history of stone disease was 3 times more likely in the factory workers as compared with the random population.

were divided into 4 groups - male smokers and non smokers and similarly female smokers and non smokers.

A total of 372 blood cadmium values were available after the initial screening. In both males and females (Tables 34, 35) smokers tended to have higher blood cadmium values than non smokers which is the normal distribution in any 'normal' population. However as can be seen from the Tables and illustrated in Fig. 49, 50 the population studied was not normal. The finding of mean blood cadmium values which were higher in non smokers helps to emphasise that the workers had already been exposed to an abnormal situation and the high ambient atmospheric cadmium levels had clearly reversed the normal patterns of blood cadmium levels.

In all of the male age groups (Table 34) the mean blood cadmium was greater than 8 ug/L in those who smoked and greater than 5 ug/L in non smokers. These figures compare with a mean blood cadmium of less than 2 ug/L in a non exposed random population. The female workers showed similar mean blood cadmium values which were well above the random reference population values (Table 35).

A further indication of the abnormal circumstances within the general workforce can be discovered when the mean blood cadmium values (Tables 36, 37) are related to the duration of employment. As can be seen in Fig. 51 the duration of employment alters the expected pattern of higher mean cadmium levels in smokers as compared with non smokers. After 10 years of employment the non smokers had higher mean blood cadmium values than the smokers.

Table 33.

PREVIOUS HISTORY	SMOKERS		N/SMOKERS		RANDOM POPULATION
	No.	%	No.	%	
STONE DISEASE	2	(2.1)	1	(1.07)	1.1%
COLIC	3	(3.2)	1	(1.07)	3.1%
PASSAGE OF STONE/GRAVEL	-	-	2	(2.1)	1.4%

Table 33. Factory Scan. Non attenders - results of questionnaire.

This table again emphasises the effect of smoking habits on the finding of a previous history of urinary tract stone disease. Smokers are twice as likely to have a history of stone disease as non smokers.

Table 34.

AGE YEARS	SMOKERS			NON SMOKERS		
	No.	$\bar{x}$	S.D.	No.	$\bar{x}$	S.D.
20 - 29	27	8.6	4.2	21	5.72	3.9
30 - 39	44	8.76	3.3	24	9.10	4.93
40 - 49	84	10.40	4.6	32	7.10	4.20
50 - 59	78	8.30	3.9	16	7.90	3.9
60+	12	9.4	3.5	4	12.45	2.5

Table 34. Blood cadmium levels v. age (males).
The mean blood cadmium values v age in the male factory workers showing the comparison between smokers and non smokers and the age distribution of blood cadmium.

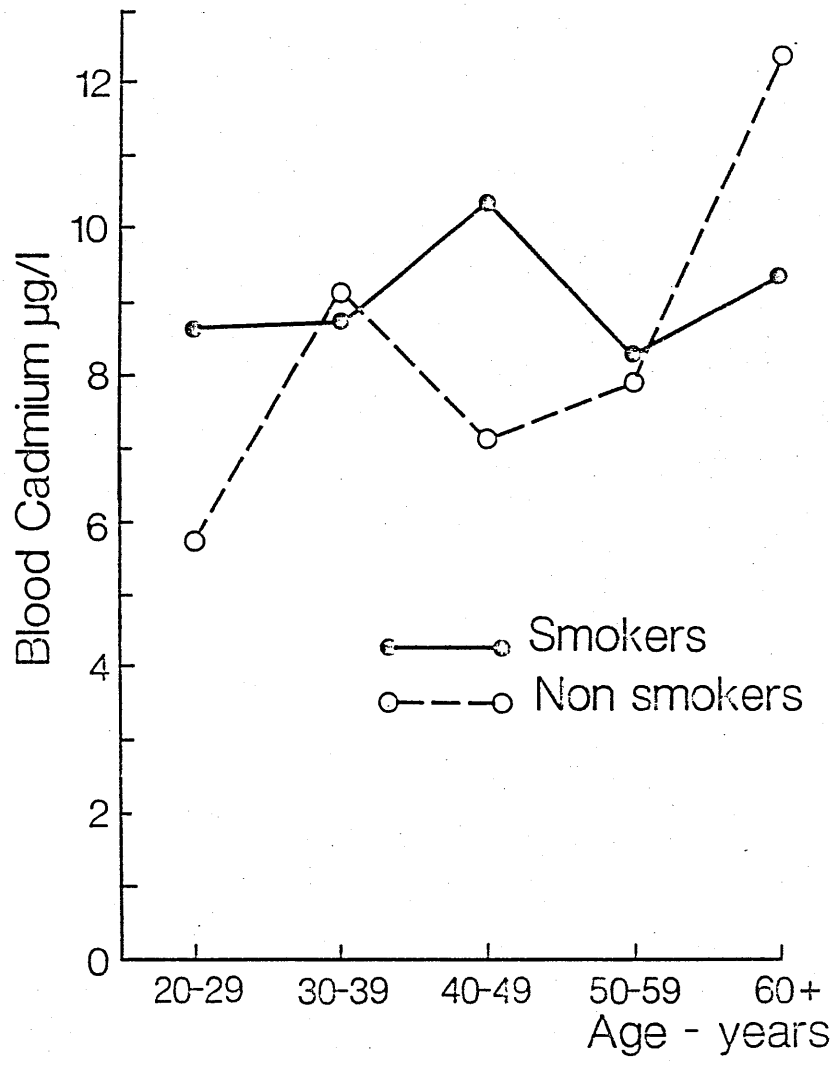

Fig. 49. The effect of smoking on mean blood cadmium related to age - male subjects.

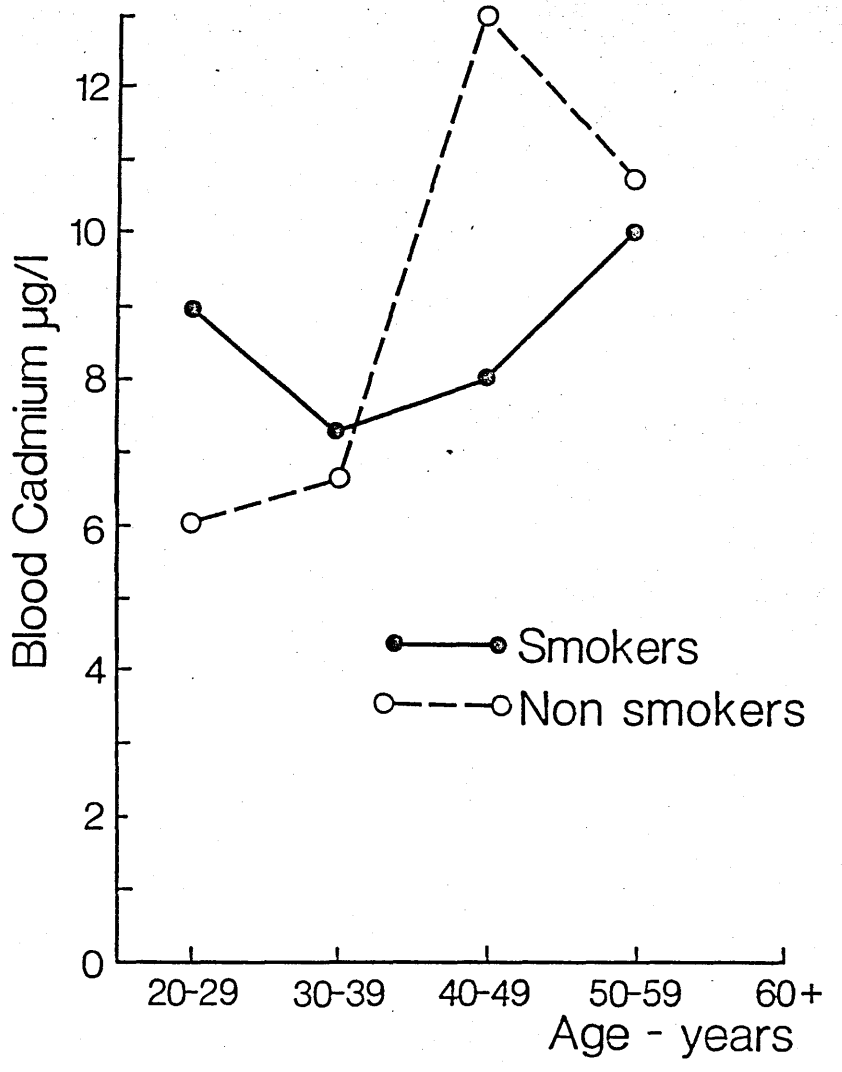

Fig. 50. The effect of smoking on mean blood cadmium related to age - female subjects.

Table 35.

AGE	SMOKERS No.	$\bar{x}$	S.D.	NON SMOKERS No.	$\bar{x}$	S.D.
20 - 29	4	8.95	1.4	1	6.0	
30 - 39	9	7.20	5.6	3	6.6	4.4
40 - 49	4	8.0	2.7	2	13.0	1.0
50 - 59	1	10.0	-	6	10.7	3.7

Table 35. Blood cadmium levels v. age (females).
The mean blood cadmium values v. age in the female factory workers showing the comparison between smokers and non smokers and the age distribution of blood cadmium.

Table 36.

YEARS	No.	$\bar{x}$	S D
0 - 5	26	7.7	5.1
6 - 10	19	5.7	2.7
11 - 15	25	8.0	5.5
16 - 20	7	9.4	2.4
21 - 25	6	12.7	7.2
26 - 30	3	7.0	2.3
30 +	3	8.5	4.6

Table 36. Male non smokers. Mean blood cadmium v duration of employment.
The highest values are obtained in those employed for 21 - 25 years. Short periods of employment can result in values equivalent to personnel employed for more than 25 years.

Table 37.

YEARS.	No.	$\bar{x}$	S D
0 - 5	56	9.0	4.3
6 - 10	36	8.2	4.4
11 - 15	66	7.8	3.5
16 - 20	24	10.1	6.1
21 - 25	7	11.7	4.2
25 - 30	19	10.5	5.3
30 +	14	8.8	3.6

Table 37. Male Smokers. Mean blood cadmium v. duration of employment.

The mean blood cadmium values vary with duration of employment and reach a peak value at between 21 and 25 years service. Short duration of employment can result in values which are not statistically different from those obtained in persons employed for a much greater duration of time.

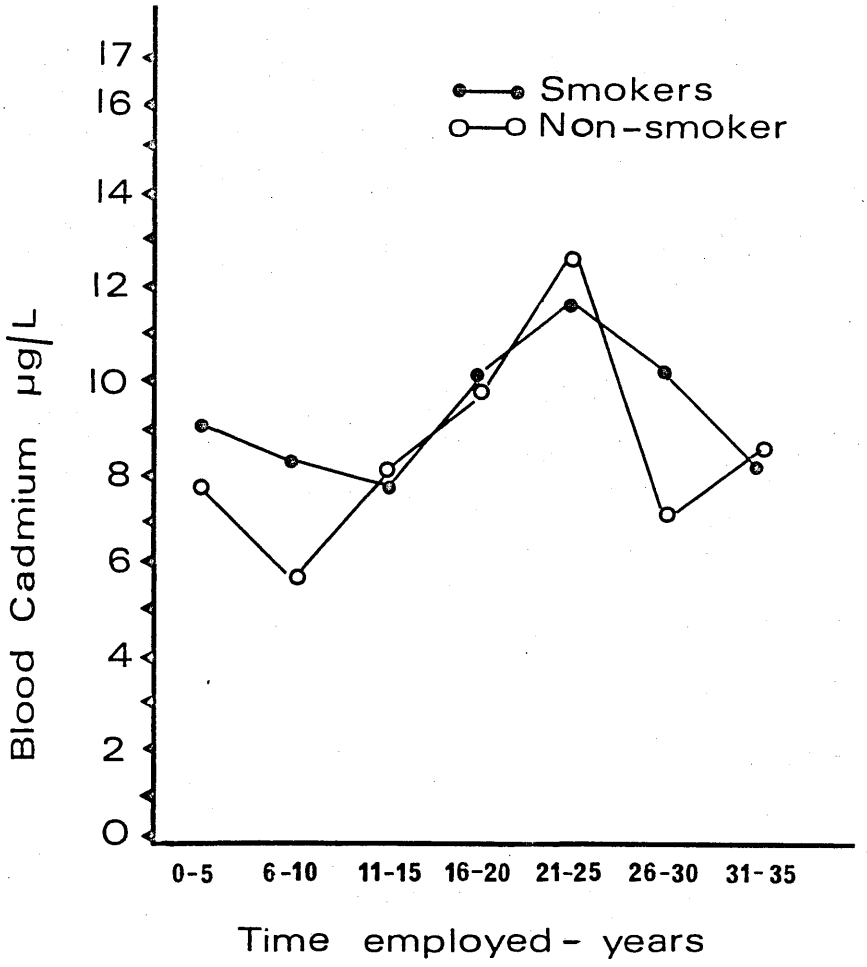

Fig. 51. General factory workers - (male). Mean blood cadmium levels related to smoking habits and duration of employment.

From the findings of blood cadmium values related to age and time of employment it is clear that all normal patterns had been destroyed in this factory.

Other Parameters

From the experience with the coppersmiths it was decided to measure a variety of different parameters which were likely to be affected by cadmium. As can be seen in both the male and female subjects (Tables 38, 39) there were no obvious significant differences for any of the parameters of interest.

Serum inorganic phosphate

This particular measurement proved to be very useful as a means of predicting which of the coppersmiths either had calculus disease or subsequently developed stone disease during the period of study (Fig. 52). When compared with the mean serum inorganic phosphate values in a random population there was no obvious difference between the values found in both male (Fig. 53) and female subjects (Fig. 54) in the factory scan and the random population. However, in 30 subjects with serum inorganic phosphate values of less than 1 mmol/L the prevalence of stone disease was 13.1% (4 of 30 subjects) Fig. 55. Although the serum inorganic phosphate was not found to be substantially significantly different from the normal population values, the higher prevalence of stone disease associated with low serum inorganic phosphate values is emphasised in cadmium exposed workers.

TABLE 38.

BLOOD PARAMETER	AGE C20		20 - 29		30 - 39		40 - 49		50 - 59		60+	
	S	N/S	S	N/S	S	N/S	S	N/S	S	N/S	S	N/S
HAEMOGLOBIN	14.6		15.3	14.8	15.5	14.8	14.9	14.5	14.4	14.42	14.1	13.4
IRON	25.0		19.3	21.3	20.5	19.1	19.2	17.6	18.7	13.9	14.4	21.75
INORG. PHOSPHATE	1.35		1.3	1.2	1.3	1.2	1.3	1.2	1.2	1.08	1.37	1.1
COPPER	15.85		17.4	1.57	16.7	15.5	18.2	16.1	17.4	17.1	21.2	16.59
ZINC	14.5		12.8	12.8	13.7	12.3	14.2	13.2	13.4	12.3	12.7	13.3
CADMIUM	6.15		8.6	5.71	8.6	9.1	10.4	7.1	8.3	7.9	9.4	12.45

TABLE 38. Factory Scan. Male Subjects.

The different parameters measured in the initial factory scan in male subjects showing the results in smokers (S) and non smokers (N/S). The results are the mean values found in each age group. Apart from the high cadmium values no particular parameter is grossly abnormal.

TABLE 39.

BLOOD PARAMETER	AGE	20 - 29		30 - 39		40 - 49		50 - 59	
		S	N/S	S	N/S	S	N/S	S	N/S
HAEMOGLOBIN		17.5	13.2	13.3	13.0	13.8	13.8	14.1	14
IRON		19.5	11	20.8	18.0	19.1	13.7	13.5	21
IRORG. PHOSPHATE		0.9	1.40	1.2	1.0	1.2	1.2	1.2	0.85
COPPER		19.2	46.0	19.0	18.3	19.7	20.2	20.6	18.3
ZINC		11.6	14.7	14.6	16.1	12.6	16.8	14.8	17.3
CADMIUM		8.95	6.0	7.2	6.6	8.0	13.0	10.0	10.7

Table 39. Factory Scan. Female subjects.

The different parameters measured in the initial factory scan in female subjects showing a comparison between smokers (S) and non smokers (N/S). The blood cadmium values are the only measurements consistently abnormal in all age groups.

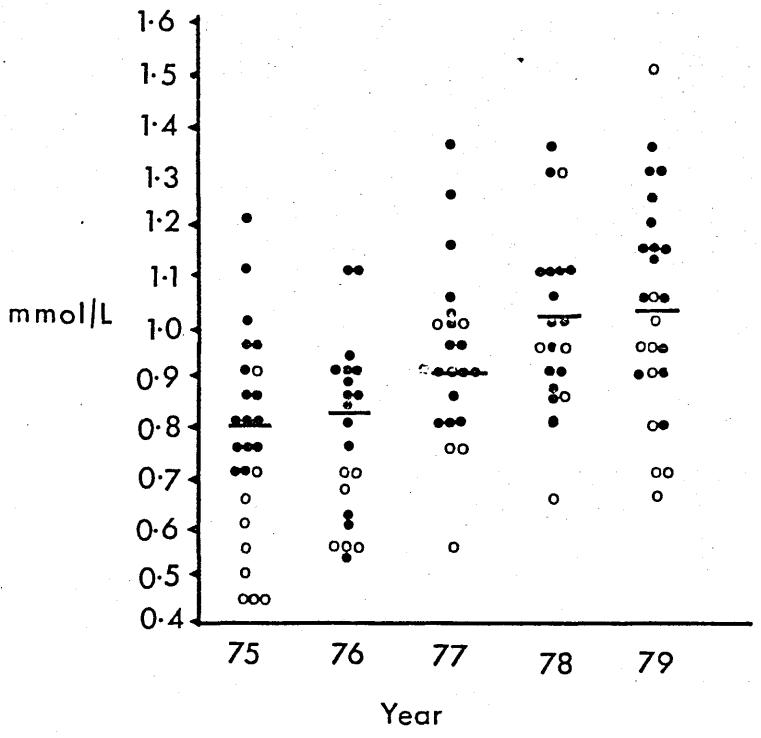

Fig. 52. The annual values of serum inorganic phosphate values in coppersmiths. In 1975 those represented by a clear circle either had a stone or developed a stone over the period shown in this figure.

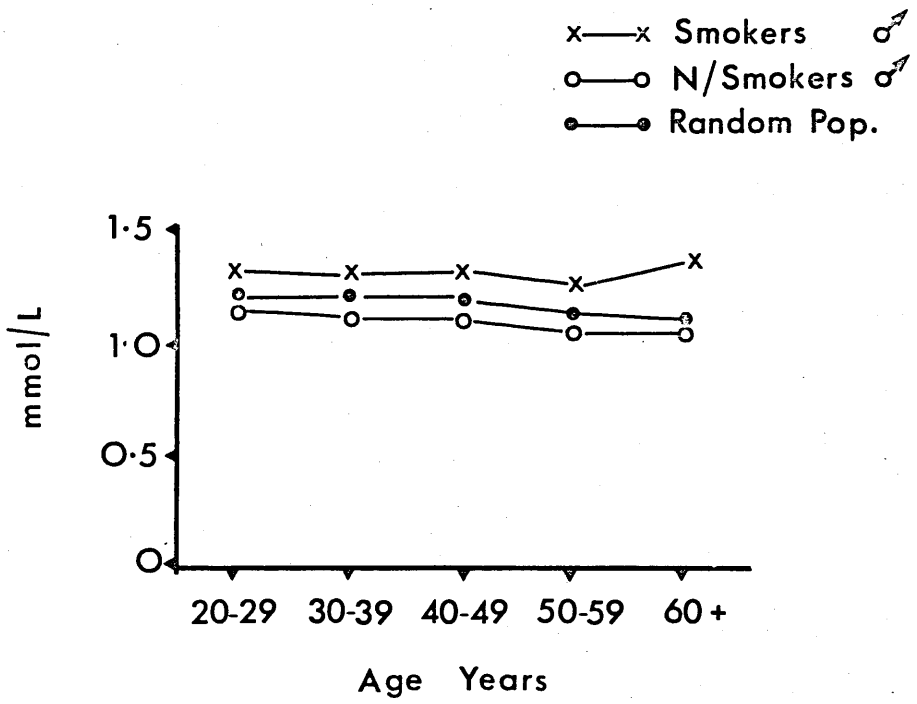

Fig. 53. Mean serum inorganic phosphate in male workers (smokers and non smokers) V the random population.

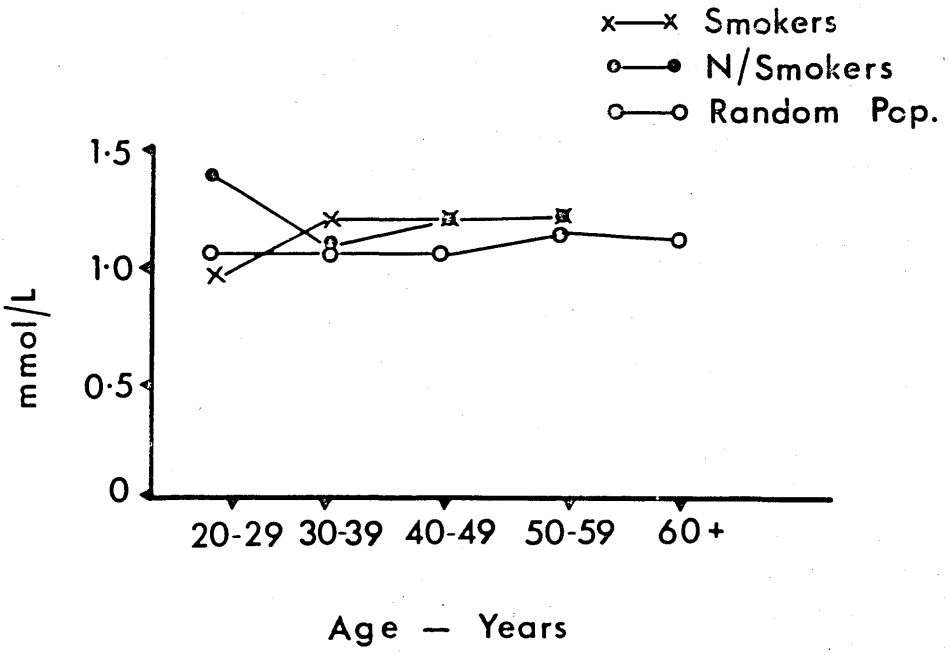

Fig. 54. Mean serum inorganic phosphate in female workers (smokers and non smokers) V the random population.

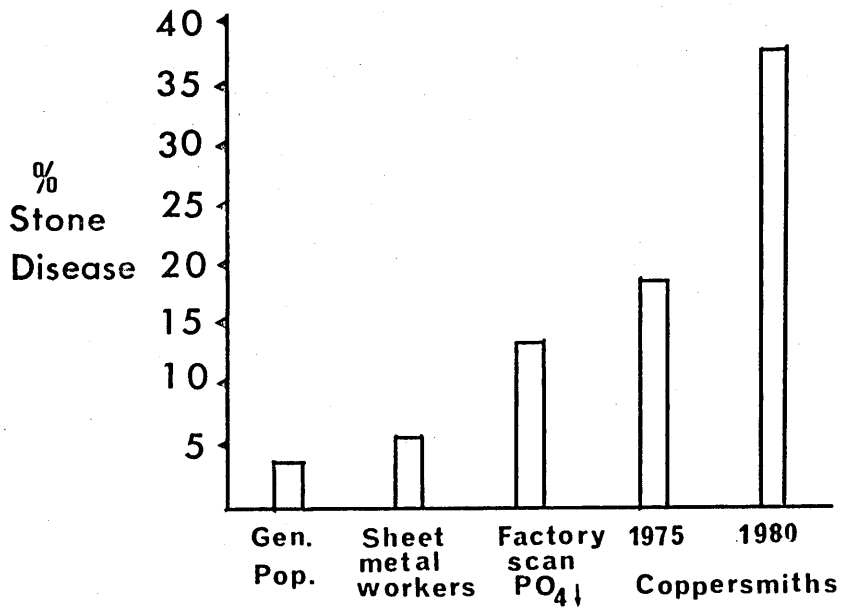

Fig. 55. The prevalence of stone disease in the general population compared with cadmium exposed workers.

Repeat blood cadmium values

It is considered by some authorities that the blood cadmium is an indicator of recent exposure. When a high blood cadmium value was found every effort was made to repeat the measurement - usually within 3 weeks of the initial sample being checked. As can be seen in male subjects when the mean values are compared then at every age group except that over 60 years of age the mean values had fallen but were still very much higher than the random non exposed population (Fig. 56).

Proteinuria

Urines from subjects in the factory scan were treated by the same labstix analyses as in the general population survey. This revealed that 10.66% of the factory subjects gave a positive reaction as compared with 3.6% of the random population survey.

Particular occupation related to cadmium levels

Apart from the groups of coppersmiths already studied there were other coppersmiths who were not examined as part of the special groups of workers. Obviously since the factory worked a shift system and since all men in the initial studies were not necessarily interested to participate then 7 other coppersmiths were still available for study. As can be seen (Table 40) of the general factory scan the highest mean blood cadmium levels were found in these highly specialised workers. The only group among male workers who approximated to the non exposed population were the apprentice engineers. Of

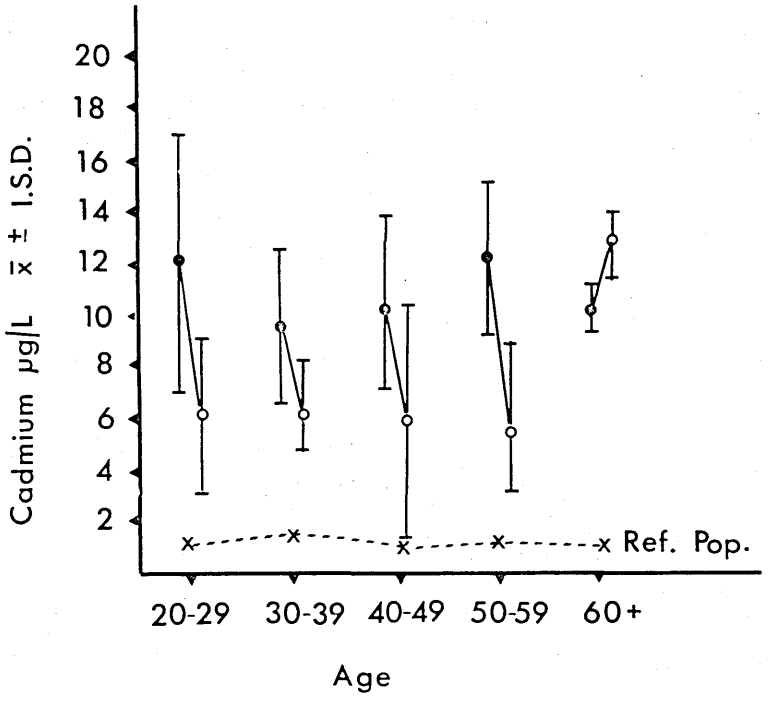

Fig. 56. The effect of repeating initial blood cadmium values in the general factory workers. The mean values fell in all age groups except those over 60 years of age.

TABLE 40.

	No.	$\bar{x}$	S D
COPPERSMITHS	7	11.4	4.3
SHEET METAL WRKS.	5	11.3	2.8
FOREMAN	8	11.3	4.8
PACKERS	6	11.2	2.0
TURNERS	3	10.0	2.8
STOREMAN	6	9.9	6.0
TOOL MAKERS	38	9.16	4.5
FITTERS	13	9.1	7.9
INSPECTORS	12	9.0	4.8
WKS. STUDY ENGINEER	3	9.0	4.3
ASSEMBLERS	80	8.8	4.5
BUYER	2	8.6	4.3
MAIL OPERATORS	95	8.7	4.5
MANAGERS	5	8.6	4.4
LABOURERS	18	8.5	3.7
WELDERS	4	8.2	6.2
ENGINEERS	20	6.5	3.9
SEMI SKILLED	9	7.0	4.9
ELECTRICIANS	4	5.9	1.06
DRIVERS	4	5.4	1.7
APPRENTICE ENGINEERS	5	3.0	2.6

TABLE 40. The main occupational groups of men working in the factory are shown. This emphasizes that those most involved in 'hot metal' work or who worked in close proximity to the brazing pots had the highest mean blood cadmium values.

the 21 different types of occupations studied 16 groups had, among the men, mean blood cadmium values greater than 8 ug/L which figure had been taken as the working upper limit of normality. With respect to female subjects 5 of the 10 different occupational groups had values greater than 8 ug/L mean blood cadmium values (Table 41). One of the most interesting groups in this context were the typists. On enquiry with the management it was discovered that the bulk of these individuals worked in the same office or area of the main building. For several years. The extraction unit duct had passed through the office in which these girls had been working. Since they were nowhere near the brazing process it is suggested that a faulty duct caused them to become contaminated. Similarly, the receptionist and telephonist worked in the same area of the building as the typists.

TABLE 41.

	No.	$\bar{x}$ ug/L	S D
RECEPTIONIST	1	14	-
VIEWERS	4	12.3	1.7
TELEPHONIST	1	11.0	-
S/HAND TYPIST	1	11.0	-
CLERKESS	16	9.8	3.9
MACH. OPERATORS	8	7.4	2.2
INSPECTORS	1	6.2	-
ASSEMBLER	1	5.6	-
COMPT. OPERATOR	4	4.7	5.4
T WIRE	1	2.0	-

Table 41. Factory Scan. Occupation v $\bar{x}$ Blood Cadmium (Females). The mean blood cadmium values (ug/L) in female employees within the factory. The finding of the highest values in women who were in front section of the building is related to previous routes of exhaust ventilation through that part of the building.

Discussion

There are several reports in the literature of the examination of small groups of workers involved in a variety of different cadmium processes. These reports have ranged from examination of work forces suspected of having become contaminated to supervision of groups known to be at risk (Scott et al, 1981; Stewart and Hughes, 1981) and usually are directed towards estimations of the proteinuria found in the work force (Adams, Harrison and Scott, 1969; Bernard, et al, 1979; Bonnell, 1955). The present examination of 403 individuals was designed in order to devise and evaluate a simple questionnaire type of record along with a biochemical profile of the individuals concerned. The aim was to achieve these ends in as short a time as possible. Unfortunately just as the results were being evaluated the factory was closed because of economic reasons. This meant that further assessment of some of the findings was abruptly terminated.

An example of the interesting possibilities of such an approach is now given. By general agreement between workers representatives and management, the first 100 results of blood cadmium measurements were analysed for the individual in terms of the actual site within the factory where he or she performed the bulk of his or her daily tasks. It was possible to specify 3 particular sites remote from the main brazing areas where the blood cadmium values were consistently higher than 10 ug/L. The management confirmed that at these sites there had been brazing procedures carried out over several years

and on inspection of these particular sites there were large overhead air vents which were covered in dust. It is clear that the workers in these areas would continue to be contaminated by dust particles which would explain the high levels found in workers in these particular locations. A similar reason related to changes in factory layout gives the explanation as to why females working in offices along the east side of the building had unexpectedly high blood cadmium levels. There was clear evidence that the ventilation ducts from the brazing areas had originally passed through this area of the factory.

From the previous medical histories obtained in the questionnaire it is clear that stone disease in the general work force was a greater problem than that found in the general population study of this particular problem.

Apart from the obvious difference to be expected between smokers and non smokers there is no immediate comparable group available which would allow specific comments to be made about the respiratory problems with the factory workers.

Analyses of the blood biochemical parameters confirmed that apart from the blood cadmium and serum inorganic phosphate values no great value could be attached to the other measurements such as the serum zinc or copper values.

The blood cadmium values clearly indicate that the level of contamination within the factory was very general

and resulted in mean blood cadmium levels in all age groups which were at least twice as high as the control subjects. The level of contamination also upset the expected differences related to smoking habits (Wilden, 1973) and to duration of employment. The repeat blood cadmium values also confirmed the high values of the general work force.

The serum inorganic phosphate values although not significantly reduced below those found in the normal population did where these were estimated indicate for this cadmium exposed group of workers the likelihood that the individual had had a previous positive history of stone disease. This interesting fact coupled with the severe effects on calcium metabolism caused by cadmium would suggest that in the monitoring of cadmium exposed workers the serum inorganic phosphate is worthy of estimation as part of a factory screening programme.

As a general rule the haemoglobin should be checked (Tsuchiya, 1976) but in the present study there were no obvious overall reductions in this parameter as judged by the mean haemoglobin values obtained in both the male and female subjects who were reviewed.

If the blood cadmium is recognised as being an indication of whole body burden as well as giving insight into recent exposure then it is clear that the majority of workers in the Prestcold factory did have a problem related to chronic cadmium exposure.

STUDIES OF CADMIUM IN POST MORTEM KIDNEYS.

CHAPTER 14

RENAL CADMIUM

It has become possible in fairly recent times to be able to measure the cadmium content in individual organs such as the liver and kidney by in vivo neutron activation analyses thereby making it possible to assess the effects of cadmium exposure on work forces (Chettle et al, 1979; Cummins et al, 1980).

There is,however, still a necessity to assess the cadmium content of organs such as the kidney by chemical measurements and to correlate such measureable cadmium with the cause of death. It is possible by such relatively simple methods to be able to study much larger numbers of specimens and also to separate the cortical and medullary cadmium levels. It is also possible with good baseline data to be able to compare the cadmium content between different areas of one country and also between countries.

The present work was undertaken in order to establish the renal cadmium content in the West of Scotland and to establish a baseline against which other areas of the U.K. could be measured.

METHOD

At post mortems undertaken in Glasgow Royal Infirmary the lower pole of the left kidney was removed and stored in a plastic bag at $-20^{\circ}C$. When sufficient numbers of specimens were obtained they were delivered to one technician for analyses. The cortex and medulla were

separated using plastic instruments and the zinc and cadmium contents of the specimens were measured in the trace metal laboratory at the Royal Infirmary. In addition the calcium content was measured. All measurements were expressed as ug/gram of renal substance both dry and wet weight measurements. Samples were stained and prepared for light microscopy after staining with haemotoxylin eosin and by a Masson stain.

Physio-pathological data.

The age and sex of the subjects was carefully recorded and a careful search was made to discover the cause of death along with the smoking habits of the individual. The post mortem reports were carefully studied and categorised into 7 main groups according to which disease was most likely to have been present during the patients life, i.e. when exposure to cadmium could have been relevant to any disease process such as respiratory disorders. If a subject had died from septicaemia following a surgical procedure but had good evidence of having had chronic emphysema then the death, for purposes of assessment in terms of exposure to cadmium, would be classified as pulmonary. A number of diseases such as rheumatoid arthritis were classified as miscellaneous conditions provided it was clear that the disease process had been present for some time during the patient's life. What this means is that chronic disease processes more likely to be affected by cadmium were being assessed as compared with acute causes of death. Thus 7 broad categories of disease were established.

Results

The results are expressed with respect to the wet weight of cadmium in renal cortex and medulla. When the first 300 kidneys had been analysed it was possible to have paired analyses for all 3 elements in 290 samples. The other 10 samples are accounted for by 5 control specimens and 5 in which results for all 3 elements were not available (Table 42).

It was found that there were highly significant differences ($p<0.001$) for all 3 elements when cortical values were compared with medullary values.

Cadmium content v. disease category

When the cortical cadmium values were analysed for each of the 7 disease categories (Table 43) then no obvious significant differences could be found when 'normal distribution' analyses techniques were applied in the analyses of the results. In both male and female subjects the distribution of cadmium tends, as would be expected to be asymetrical (Fig. 58). Because of this obvious analytical problem all results were analysed using a Mann Whitney test. This confirmed that there was a significant difference of both medullary cadmium and zinc values in those deaths classified as pulmonary or cancer when compared with the values obtained in the miscellaneous group (Table 44).

There is a significant difference of zinc content when the pulmonary death subjects are compared with the miscellaneous group.

Effect of age on cadmium content.

It is usually stated that with increasing age the cadmium content of kidneys rises from a zero value at birth to reach a maxum value at age 50. In the series the highest median values were found in the age group 31 - 40 (Fig. 58). This phenomenon is probably a feature of the small numbers in this group (Table 45). Examination of the data of the 9 subjects in the group confirmed that they did not appear to be grossly different from the general series although interestingly 2 of the subjectshad hepatic disease (Table 46). Apart from this slight variation from other reported series, the general trend in our study is for the maximum levels to be found around the age of 50.

After the age of 50 there is a fall in cortical cadmium but the medullary cadmium only really starts to fall after age 60 (Fig. 59). Statistical analysis was applied (Mann Whitney test) to ascertain whether or not there is any obvious variation between age groups. The greatest differences are found when subjects over the age of 81 are compared with those in younger age bands (Table 47). With respect to cadmium and zinc the greatest differences are found between those subjects who are more than 50 years when compared with those over 81 years of age. With calcium there is the same pattern of very highly significant differences a decade earlier i.e. over 40 years.

TABLE 42.

	Both sexes		Males		Females	
	No.	$\bar{x}$	No.	$\bar{x}$	No.	$\bar{x}$
Cadmium (cortex)	293	17.93	155	17.87	135	18.14
Cadmium (medulla)	290	11.51	153	11.38	135	11.79
Zinc (cortex)	293	37.68	155	35.40	135	39.35
Zinc (medulla)	290	29.81	153	28.13	135	31.75
Calcium (cortex)	293	189.20	155	210.42	135	163.05
Calcium (medulla)	290	222.88	153	247.31	135	195.67

(Cortex v medulla $p < 0.001$ for all 3 elements)

Table 42. This table confirms the values of cadmium (wet weight) in both sexes and shows that like zinc the higher levels are found in the renal cortex ($p<0.001$) as compared with the medulla. The reverse occurs with respect to calcium.

TABLE 43.

Disease Category	BOTH SEXES		MALES		FEMALES	
	No.	$\bar{x}$ Cd.	No.	$\bar{x}$ Cd.	No.	$\bar{x}$ Cd.
Pulmonary	34	20.05	22	19.22	12	21.56
Cancer	108	17.95	56	16.73	52	19.27
Ischaemic heart disease	45	16.10	30	17.13	15	14.06
Hepatic disease	23	21.60	12	25.70	11	17.12
Renal disease	6	15.28	1	11.00	5	16.14
Cerebro vascular accident	30	19.27	17	14.09	13	25.00
Miscellaneous	44	16.05	17	19.03	27	14.18

Table 43. The 7 disease categories are shown together with the mean cadmium values (ug/g wet weight). There is no significant difference demonstrated for any one disease category when normal distribution statistical analyses techniques are applied.

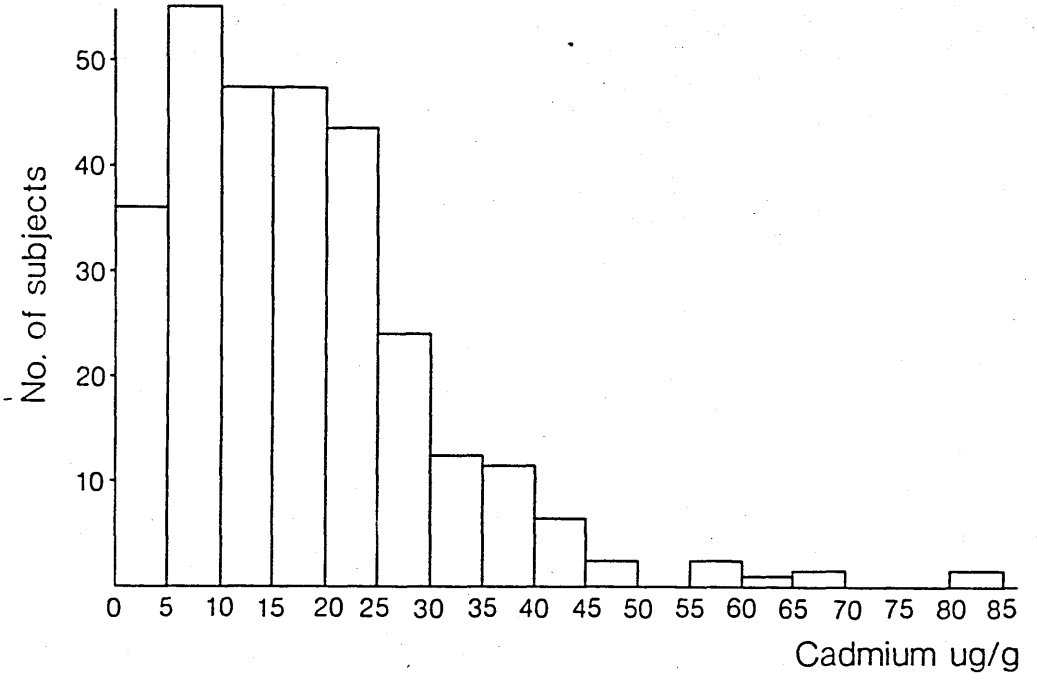

Fig. 57. The asymetrical distribution of renal cortical cadmium in both sexes (293 subjects) - all disease categories.

TABLE 44.

ELEMENT	SITE	SIGNIFICANT DIFFERENCES (DISEASE)
CADMIUM	MEDULLA	PULMONARY v MISCELLANEOUS
		CANCER V MISCELLANEOUS
ZINC	MEDULLA	PULMONARY v MISCELLANEOUS

Table. 44. The analyses of cadmium values using a Mann Whitney test confirms that only in the renal medulla were there any significant differences with respect to pulmonary and cancer subjects when compared with those where the pathological condition was described as miscellaneous.

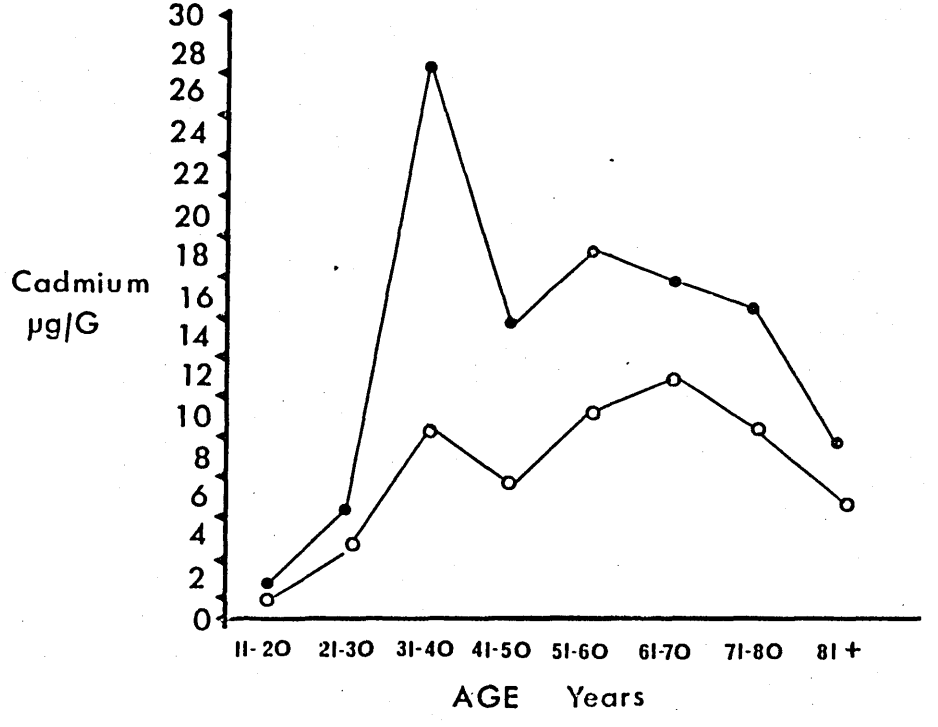

Fig. 58. The distribution of median values of renal cortical cadmium (ug/G wet weight).

TABLE 45.

AGE GROUP	NO.	CORTEX		No.	MEDULLA	
		MEDIAN	MEAN		MEDIAN	MEAN
11 - 20	3	1.50	1.53	3	1.00	1.13
21 - 20	2	5.55	5.55	2	3.50	3.60
31 - 40	9	27.59	26.30	9	9.40	21.33
41 - 50	27	14.60	16.65	26	6.75	9.14
51 - 60	56	18.30	20.43	56	10.35	14.33
61 - 70	86	16.95	20.32	85	12.00	13.09
71 - 80	79	15.50	16.77	79	9.50	9.94
81+	28	8.95	10.75	28	5.85	6.90

Table 45. The age distribution of renal cortical and medullary cadmium. Apart from the peculiar rise in the age group 31-40 years there is a progressive rise from birth to age 50. Thereafter the cortical and subsequently the medullary levels start to fall.

TABLE 46.

Renal cortical/medullary cadmium subjects aged 31 - 40.

SEX	AGE	DISEASE	CADMIUM ug/G	
			CORTEX	MEDULLA
Male	31	Marfans syndrome	23.6	5.2
Male	36	Cirrhosis	45.0	70.0
Male	40	Ischaemic heart disease	27.5	11.0
Female	32	Peritonitis	3.6	3.0
Female	33	Partial hepatectomy	3.4	2.5
Female	33	Renal failure	9.2	9.2
Female	35	C A Cervix	19.1	9.4
Female	39	Broncho pneumonia	40.8	38.7
Female	40	Emphysema	59.5	43.4

Table 46. The values (ug/G wet weight) of the renal and medullary cadmium values found in subjects aged 31-40. All 3 of the male subjects had values above the median of the total series and interestingly the 2 female subjects with the highest values died from respiratory causes.

TABLE 47.

ELEMENT	SITE	AGE BAND	SIGNIFICANCE
Cadmium	Cortex	51 - 60	***
		61 - 70	***
		71 - 80	**
"	Medulla	51 - 60	**
		61 - 70	**
Zinc	Cortex	51 - 60	***
		61 - 70	**
		71 - 80	*
"	Medulla	51 - 60	**
		61 - 70	**
Calcium	Cortex	41 - 50	**
		51 - 60	***
		61 - 70	***
"	Medulla	41 - 50	**
		51 - 60	***
		61 - 70	***

Difference			
	***	very highly significant	($p<0.001$)
	**	highly significant	($p<0.01$)
	*	significant	($p<0.1$)

Table 47. In this table the median values found of all 3 elements for each age band have been compared with the median values obtained in age group 81 and over. The age band 51-60 proved to be the one where there was a highly significant difference with respect to cortical cadmium and zinc.

TABLE 48.

ELEMENT	SITE	DAILY CIGARETTE CONSUMPTION		
		Less than 10	10-25	25+
Cadmium	Cortex	-	***	*
Cadmium	Medulla	-	***	**
Zinc	Medulla	*	-	-

*	significant	(p<0.1)
**	highly significant	(p<0.01)
***	very highly significant	(p<0.001)

Table 48. This table confirms that when smokers are compared with non smokers then highly significant differences are found in cortical and medullary cadmium levels in those who smoked 10-25 cigarettes per day. The heavier smokers do not appear to have such a significant difference.

Table 49.

DISEASE	TOTAL	MISSING INFORMATION	SMOKERS		NON SMOKERS	
	No.	No.	No.	$\bar{x}$	No.	$\bar{x}$
Pulmonary	34	7	17	19.80	10	18.20
Ischaemic heart disease	45	15	19	19.80	11	12.60
Ca lung	30	8	16	17.60	6	15.60
Ca gastro intestinal tract	42	12	13	20.70	17	19.50

$\bar{x}$ = median value

Table 49. 4 main groups of common conditions have been analyzed (Mann Whitney test) and confirm that in those subjects who died from ischaemic heart disease statistically significant differences have been obtained between smokers and non smokers with respect to renal cortical cadmium values ($p<0.05$).

Smoking habits.

Renal cortical cadmium is known to be affected by smoking and as far as possible efforts were made to determine the smoking habits of the individual subjects. In 195 subjects sufficient information was available to allow a correlation between cadmium content and smoking habits to be assessed. When non smokers are compared with those who smoke any cigarettes in excess of 25 per day, then the cadmium and zinc contents become statistically significantly different (Table 48). Non smokers have significantly less cadmium than smokers but surprisingly it was in those subjects who smoked between 10 - 25 cigarettes where the greatest differences were found. It is recognized that most persons will regularly underestimate their total daily consumption of cigarettes. No differences with respect to calcium could be found in any group comparison.

Having ascertained the smoking habits of the individuals it was possible to group these individuals into 4 main disease categories (Table 49). By sub classifying those subjects dying from carcinoma of lung and gastro intestinal cancers it was possible to consider 4 groups of at least 30 subjects. Comparison of median values confirmed that there is a significant difference ($p<0.05$) (Mann Whitney test) between the group of smokers dying from ischaemic heart disease as compared with the non smokers dying from similar causes with respect to cortical cadmium content.

Comparison with other centres

3 other major series have been completed in studies similar to the present (Table 50). The most major difference is in the Japanese series where the overall mean cadmium is 57.99 ug/g tissue.

DISCUSSION

At birth human beings do not have a measurable cadmium content in kidneys but with increasing age the cadmium content in the body in general and the kidney in particular steadily increases.

Like other metals (Baker et al, 1977) it is possible that the intake of cadmium can be affected because the individual lives in close proximity to a major production site. However, very few people live in such a unique environment and cadmium intake from dietary intake is much more likely to account for the general levels found in population groups. In most countries something in the order of 25 - 75 ug/day are absorbed from food sources (Friberg et al, 1974).

Man can increase the amount of potential cadmium in the diet by manipulating the environment. For example, by adding fertilizers including sewage sludge to soil, then the cadmium uptake by plants can be greatly enhanced (Anderssen, 1977). Atmospheric pollution is another potential source of human contamination by cadmium. Some authors have shown a positive correlation between atmospheric cadmium levels and death rates from hypertension (Carroll, 1966) but such observations

TABLE 50.

STUDY	YEAR	NO	AGE	CADMIUM CORTEX
Elinder et al	1976	292	50	22.00 ug/g
Miller et al	1976	91	6/12-93	16.80 ug/g
Tsuchiya et al	1976	160	40-49	203.8 ug/g
Present	1981	155	(males)	17.87 ug/g
		135	(females)	18.14 ug/g

Table 50. The values obtained in the present series compare with other western series. The Japanese values are confined to 1 age band and suggest a major difference from the series from Western countries.

thus far have not been substantiated.

By whatever route cadmium enters the body it eventually is concentrated in the kidney. From studies of such accumulations of cadmium it has been shown in the experimental animal that there is a positive correlation between renal cadmium levels and the development of hypertension in such animals (Schroeder and Battleboro, 1964). If such a relationship is proven, it could prove to have very important implications with respect to hypertension in humans especially among smokers. It is recognised that renal cadmium values are higher in men than in women and that smokers have higher cadmium levels than non smokers (Hammer et al, 1973) and that cigarette smoking probably contributes 0.1 to 0.2 ug of cadmium per cigarette (Ostergaard, 1977).

Various attempts have been made to correlate the cause of death to the renal content of cadmium. One of the most interesting aspects has been attempts to relate cadmium contents to cancer in general and to specific tumours in particular. It has been recorded that there is a significantly higher renal content of cadmium in the kidney of those dying from bronchogenic carcinoma (Morgan, 1970) and similarly in renal cancer (Kolonel, 1976).

Care has to be taken in the interpretation of cadmium content and disease however, as it has been shown that in neoplasia there can be a wide variation in tissue cadmium levels (Morgan, 1969).

There has been relatively little informed study of this problem and good information is therefore lacking

(Fishbein, 1976). By contrast there is now a greater awareness of the effects of industrial exposure and possible carcinogenic effects (Kjellstrom, et al, 1979).

The present study has enabled the level of cadmium in kidney to be established in a sample of 300 post mortem kidneys obtained from 1 unit in the West of Scotland. Apart from this basic and necessary data it has been emphasised that there are significant differences between the cortex and medulla with respect to cadmium, zinc and calcium contents. In the case of calcium this is an inverse relationship.

When compared with other studies, the values found in this area are similar to those found in other western countries such as Sweden (Elinder, et al, 1976) and Australia (Miller, et al, 1976). In subjects from all three of these countries the cadmium levels are not more than half as much as the levels found in Japanese studies (Tsuchiya, et al, 1976). What is of interest however is that in 1 age band - 40 - 49 - in the Japanese series the levels found are at the "critical concentration" values (Kjellstrom, 1979).

The present study has confirmed that smoking can be a very important factor in adding to the renal concentration of cadmium.

Of particular interest in the context of cadmium content is the finding of statistically significantly higher levels in those dying from pulmonary or neoplastic causes of death as compared with those in the miscellaneous group. In an area with a recognised high death rate from coronary heart disease the observation of significant

differences between smokers and non smokers clearly merits further study and consideration.

STUDIES OF RENAL CADMIUM IN VARIOUS U.K. CENTRES AND IN 2 COPPERSMITHS.

CHAPTER 15

Renal cadmium in post mortem kidneys and in 2 coppersmiths.

Having obtained the results of the analyses of renal cortical cadmium in 300 subjects the study was extended and in addition to results obtained from local samples, various samples in U K were analysed in the same laboratory using the same techniques and analytical methods. The collection of the data has allowed sufficient numbers to be collected as to give a very meaningful statistical analysis of 500 samples from the local specimens.

Method and statistical analyses.

All specimens were the lower pole of the left kidney and these samples were stored at -20°C before rapid transportation in the frozen state to the one laboratory. Kidney digests were prepared and the samples were analysed by atomic absorption spectrometry for all 3 elements.

Statistical analyses.

This was done by submitting all the data to a computer and analyses was undertaken using a Kruskal-Wallis test. Thereafter where a further analyses was undertaken, a Mann Whitney test was performed.

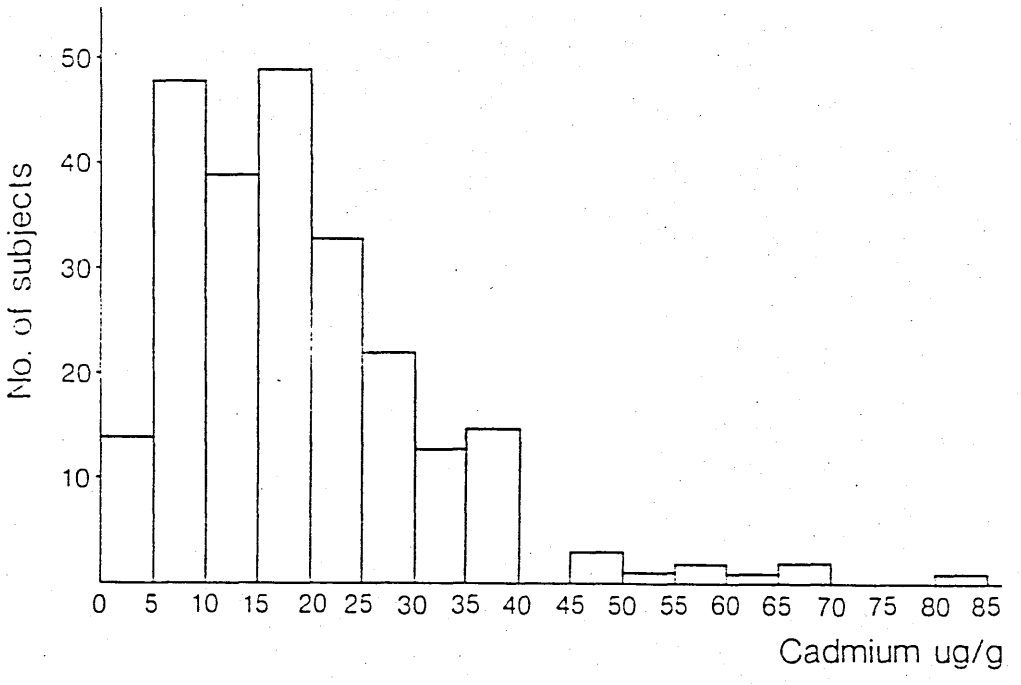

Fig. 59. Renal cortical cadmium (ug/g wet weight) in 244 male subjects - all disease categories.

TABLE 51.

		MALES (244)	FEMALES (228)
CORTEX	MEAN	19.3 ug/g	18.9 ug/g
	MEDIAN	16.9 ug/g	15.0 ug/g
		(242) ug/g	(230) ug/g
MEDULLA	MEAN	11.4 ug/g	10.2 ug/g
	MEDIAN	9.0 ug/g	8.0 ug/g
	MALES v FEMALES	Not significant	
	CORTEX v MEDULLA	p<0.001 (Mann Whitney)	

TABLE 51 CORTICAL v MEDULLARY CADMIUM

ug/g WET WEIGHT

Comparison of the median values (Mann Whitney test) confirms that there is a very highly significant difference between cortical and medullary cadmium values as expressed in ug/g wet weight in 472 subjects.

RESULTS

Frequency distribution of 500 samples.

In all categories including cortical and medullary cadmium values in both males and females there was a very clear 'skew' with respect to results obtained for each parameter. The results for male subjects are shown in (Fig. 59) where 244 values are presented.

Comparison of cortical and medullary cadmium.

It is possible to demonstrate as already shown that there is a highly significant difference between the cortical and medullary cadmium values (Table 51) but that there is no significant difference between the male and female subjects.

The numbers in each group were of sufficient size to allow meaningful statistical analyses except in each of the decades less than 40 years. It was therefore necessary to combine all subjects of less than 40 years into one large group (Fig. 60).

Using a comparison of median values and by taking the 95% limits in each group (Kruskal Wallis test) it is possible to demonstrate that the peak values for cortical cadmium were in the age group 50 - 59 and also with medullary cadmium. (Table 52).

With respect to cortical cadmium the value falls after 59 years but the medullary value remains at the peak level until after 69 years of age (Fig. 61).

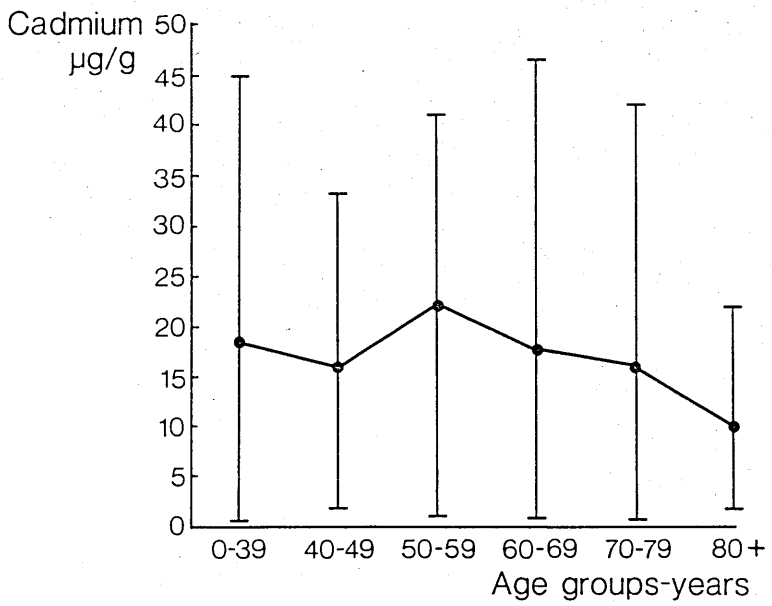

Fig. 60 Renal cortical cadmium values ug/g wet weight. All subjects of less than 40 years are grouped together.
Median values V age 95% range Kruskal Wallis $p<0.001$.

TABLE 52.

AGE	CORTEX NO.	CORTEX MEAN	CORTEX MEDIAN	MEDULLA NO.	MEDULLA MEAN	MEDULLA MEDIAN
40-	10	19.13	16.00	10	13.11	6.50
40 - 49	32	17.70	16.00	31	9.77	9.00
50 - 59	67	22.54	22.10	67	12.20	10.40
60 - 69	121	21.11	17.50	123	12.63	10.40
70 - 79	164	19.04	16.45	164	10.42	8.45
80+	69	12.33	10.00	68	6.96	5.40

KRUSKAL WALLIS $p<0.001$

TABLE 52 CADMIUM v AGE

463 values

The mean and median values of cadmium in renal cortex (ug/g wet weight) to show that comparison of median values confirms that there are highly significant differences between cortex and medulla at all ages.

TABLE 53.

SMOKING PATTERN	CORTEX NO.	CORTEX MEAN	CORTEX MEDIAN	MEDULLA NO.	MEDULLA MEAN	MEDULLA MEDIAN
Not known	89	18.12	16.00	89	11.04	9.00
10 cigs/day	21	15.59	13.60	21	8.22	7.60
10-20 "	40	25.51	19.75	40	13.99	9.00
20-40 "	82	22.08	19.70	80	12.76	11.70
40 "	23	23.28	22.10	23	12.66	9.20
Pipe	15	14.80	12.00	15	7.38	7.00
Cigars	4	11.98	12.10	4	6.13	4.25
Stopped 10 years	8	20.95	18.30	8	8.84	9.50
Non smoker	88	13.84	10.85	90	8.26	5.05
KRUSKAL WALLIS		$p<0.001$				

TABLE 52. CADMIUM v SMOKING HABITS

370 values

The cortical cadmium values in 370 subjects where the smoking habits were known. The highest values are found in those who smoked more than 40 cigarettes per day. The act of stopping smoking for 10 years does not cause a significant fall in renal cortical cadmium.

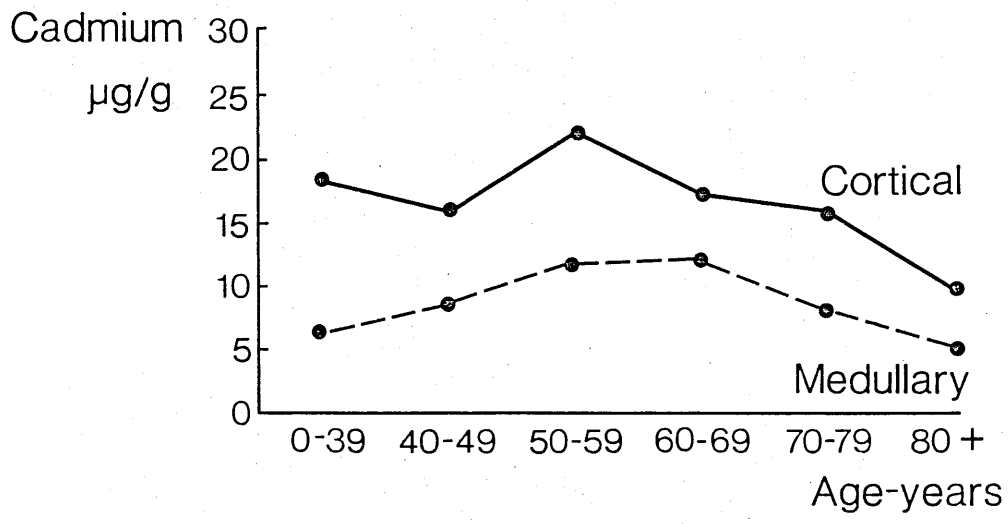

Fig. 61. Renal cortical V medullary cadmium (ug/g wet weight). Median values V age.

That smoking is an important factor in the accummulation of cadmium is well recognised. Examination of the cortical cadmium values confirm that those who smoked the greater number of cigarettes per day had the highest median values with respect to the cortical cadmium levels (Table 53). The group who were classified as being 'not known' were subjects who on admission to hospital were clearly so ill that information regarding smoking habits could not be obtained or would have been simply of academic interest? Of the 500 subjects under review there were 130 subjects in whom it was clear that no effort had been made to obtain the relevant information or if it had, then it had not been recorded.

Apart from the obvious upwards progression in values in cigarette smokers it is interesting that the pipe and cigar smokers are not materially different from the non smokers. In those subjects who had given up smoking more than 10 years prior to death the values of cortical cadmium were almost as great as those who smoked more than 10 cigarettes per day. This accords with the recognised long biological half life of cadmium (Fig. 62).

The low values obtained in pipe and cigar smokers may reflect a lack of inhalation of the tobacco smoke. The pattern of the medullary cadmium content is very similar to the cortical levels when smoking habits are compared with cadmium levels. The major differences are that the heaviest cigarette smokers have a lower

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TABLE 54.

DISEASE		CORTEX NO.	CORTEX MEAN	CORTEX MEDIAN	MEDULLA NO.	MEDULLA MEAN	MEDULLA MEDIAN
1	Pulmonary	49	20.97	15.60	50	10.73	10.00
2	Cancer	166	20.26	18.00	165	11.96	9.50
3	Ishaemic heart disease	104	18.27	15.40	130	10.00	7.00
4	Hepatic	29	20.79	17.50	29	11.39	10.00
5	Renal	9	19.63	11.00	9	6.90	7.20
6	Cerebro vascular accident	41	19.65	15.00	42	12.70	9.00
7	Miscellaneous	71	16.25	12.00	71	8.44	5.10
KRUSKAL WALLIS		$p<0.05$					

TABLE 54. When all subjects who died from a form of cancer are compared it was found that using the 95% limits around the median (Kruskal Wallis test) there is a significant difference within this category of disease.

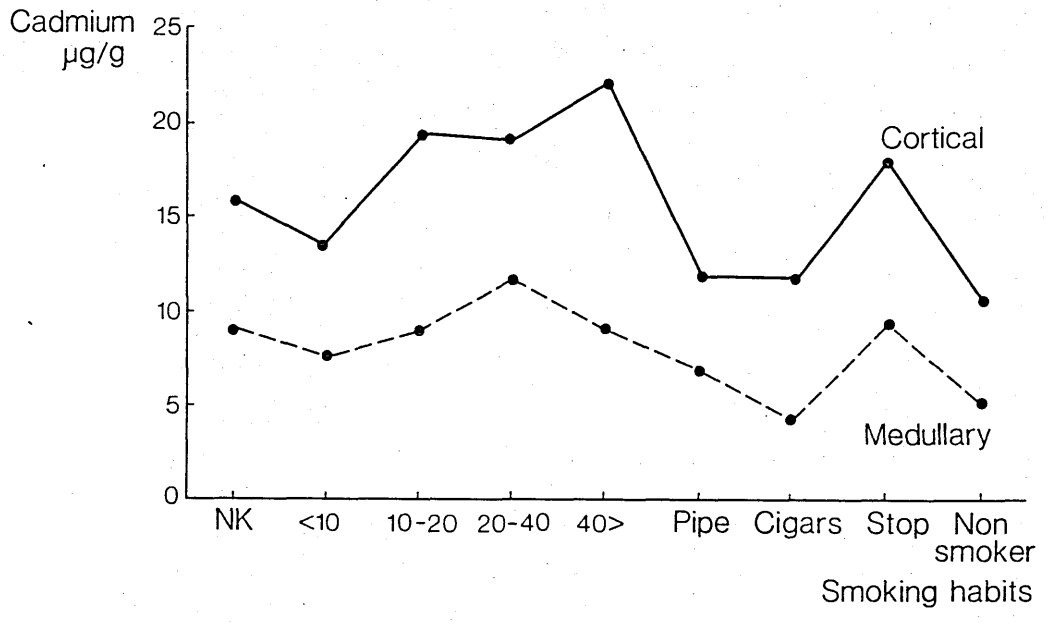

Fig. 62. Renal cortical cadmium (ug/g wet weight)
Median values V smoking habits.
In subjects N.K. (not known) it was
impossible to obtain good information
on admission of the subject to hospital.

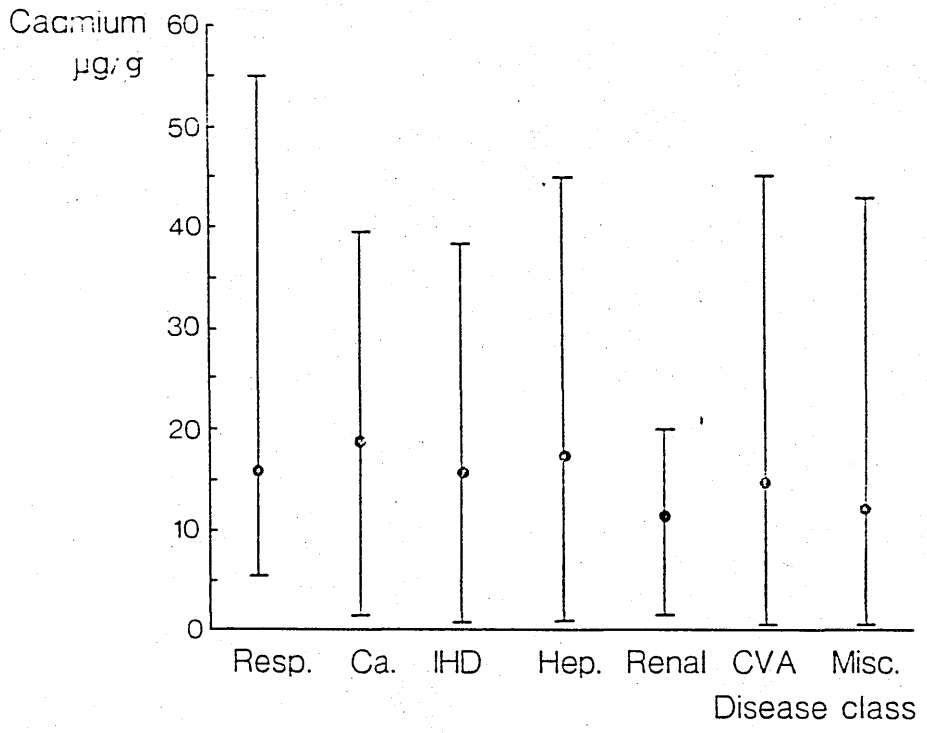

Fig. 63. Cortical cadmium values related to disease category confirming the significantly higher values in those subjects who died from any variety of cancer.
Renal cortical cadmium (ug/g wet weight)
Median values V Disease.
95% Kruskal Wallis $p<0.05$.

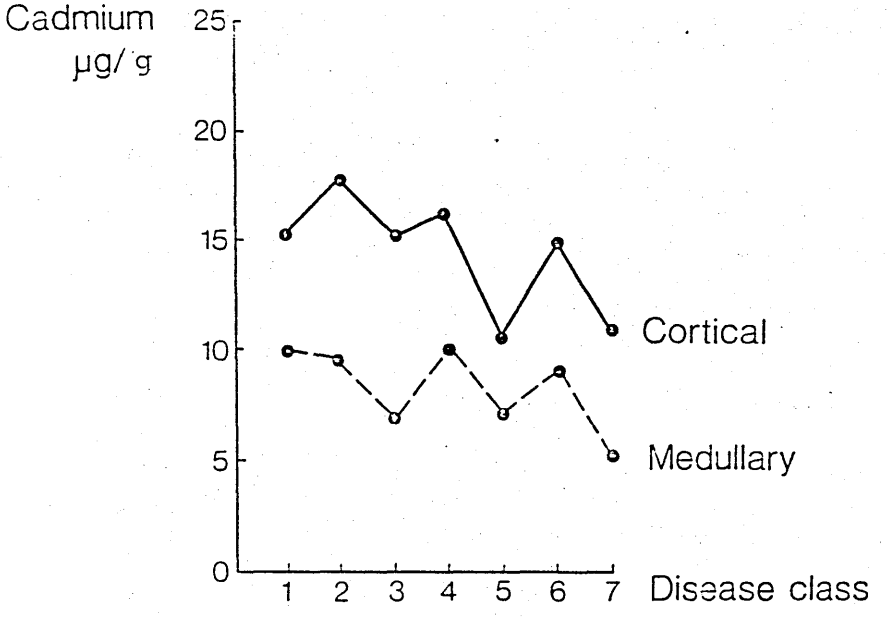

Fig. 64. Cortical and medullary cadmium values in different disease categories. Those who died from hepatic causes had the highest medullary cadmium content. Renal cortical cadmium (ug/g wet weight) Median values V Disease.

Samples from other centres in U.K.

Along with the samples obtained locally it was possible to collect kidney samples from several different centres in the United Kingdom. The lower pole of the left kidney was obtained and stored at $-4^{\circ}C$ as in the case of the local samples. When a sufficient number had been accumulated the specimens were transported to our laboratory where they underwent an analysis similar to the local specimens (Table 55).

The results confirm that Bristol has the highest mean cortical cadmium values. This could be explained on the basis of the heavy industrialization of that particular city but what is particularly significant about Bristol is that it has a zinc smelter in the area. The obvious conclusion to be drawn is that the atmosphere in Bristol probably is slightly more contaminated than the other areas. It is also interesting that Sheffield with a high industrial capacity for steel making is the only other city with a mean cortical cadmium value of greater than 20 ug/g wet weight. By contrast Cardiff which lies westwards of Bristol has been found to have the lowest values and Aberdeen which until recent times was much less industrialized than any of the other cities, has a lower value than Glasgow.

TABLE 55.

CITY	No. of samples	Mean Cortical cadmium (ug/g wet weight)
Glasgow males	244	19.3
Glasgow females	228	18.9
Bristol	19	24.84
Sheffield	27	21.92
Belfast	50	19.8
Aberdeen	31	17.9
Cardiff	21	16.5

Table 55. Mean cortical cadmium (ug/g wet weight) in 6 different centres in U.K. This confirms that Bristol has the highest values with Cardiff which is the area having the lowest values. The results indicate that the Avonmouth Smelter could be of significance. It is considered that because of the low numbers from centres other than Glasgow that statistical analysis would be misleading.

During the time that the renal cadmium measurements were being established it became possible to measure the cadmium zinc and calcium contents in kidney specimens obtained from 2 coppersmiths.

These 2 coppersmiths were included in the group of 27 coppersmiths studied in the initial factory scan. They had been followed on an annual basis as part of the group and although the second subject because of chronic ill health did not attend regularly, it is possible to correlate the biochemical findings with the kidney samples. Because of the annual review and a knowledge of the cadmium and other parameters measured the results in these two subjects are of considerable interest.

Kidney samples.

In subject No. 1 the man developed a secondary tumour deposit in his nasal sinuses. Biopsy confirmed this to be a secondary deposit from a renal adeno carcinoma. An intravenous pyelogram was undertaken and a left renal tumour was diagnosed. A left nephrectomy was carried out and the tumour tissue and the 'normal' renal substance analysed in exactly the same method as the other samples which were analysed to obtain the values already quoted.

In subject No. 2 a post mortem study was undertaken following the demise of the patient from a bronchial carcinoma. To all intents the kidneys

appeared to be normal.

Results of analyses.

Blood and urine cadmium values.

In both subjects the blood cadmium values never reached the mean values obtained in non-exposed random subjects and the urine cadmium values were always greater than 4 ug/vol, which is regarded as the upper limit of normal in non-exposed individuals (Cunningham, 1981). Prior to 1977 urine cadmium values were considered to be invalid for technical reasons (Table 56).

Proteinuria.

In subject No. 1 there is a fairly constant increase in the total urine excretion of large molecular weight proteinuria and from 1978 onwards an abnormally high rate of excretion of B_2 microglobulin in the urine per 24 hours. The results in 1981 are not in keeping with the general pattern but it was in that period that the subject underwent major surgery. The second subject did not excrete such large amounts of protein but the B_2/creatinine ratio (B_2/Ccr) was elevated (more than 14/1in 3 of 4 years).

Examination of other measurements in these two individuals showed that subject No. 1 had hypercalciuria in 4 of 8 measurements (50%) as compared with 1 of 5 (20%) of measurements of urine calcium in subject No. 2. There were no other major differences between the two individuals.

Renal cadmium content.

In the total series the mean cadmium for 244 men was 19.3 ug/g (Table 56). Both of the coppersmiths exceeded this figure by a substantial amount (Table 56). Interestingly the 'abnormal' kidney substance within the tumour tissue the cadmium levels were very low (3 ug/g).

What is very interesting about these results is that the individual (Subject No. 2) with the lower blood and urine cadmium values and a less obvious proteinuria had the highest renal cortical and medullary levels of cadmium. It is possible that because of a general poorer health record he was not so active at work as compared with subject No. 1. As a result he probably absorbed a greater amount of fumes because he would tend to be longer in at the brazing process. What cannot be explained however is why he should with a higher serum cadmium be found to have fewer biochemical stigmata of chronic cadmium poisoning. Cadmium in biological systems is clearly still a major enigma.

TABLE 56.

	CORTEX	MEDULLA
Subject No. 1		
Kidney	147	55
Tumour	3	-
Tumour	3	-
Subject No. 2		
Kidney	236	188

TABLE 56 The cadmium content of cortex and medulla in the kidneys of 2 coppersmiths. The content of the tumour tissue was obtained in 2 separate samples of the tumour.

Discussion.

This further extension of the study of renal cadmium content has confirmed that the values obtained in West Central Scotland do not differ in any way from those found in other western countries. The general pattern of renal cortical cadmium reveals, as other workers have already shown, that the content of cadmium is related to two main factors namely age and smoking habits.

It is clear that from birth there is a steady accumulation of cadmium until middle age and thereafter a decline in cortical cadmium content. This raises an interesting problem as to whether the fall occurs as a result of previous exposure in industrial activities several decades previously or whether there is a loss of kidney substance. It is also possible that there is an increased urinary excretion of cadmium but why this should be is not at all clear. There are some obvious advantages in being a pipe or cigar smoker as compared with a heavy cigarette smoker since the levels found in these smokers were similar to those found in non smokers. This suggests that pipe and cigar smokers do not inhale the tobacco fume. It is also clear that those who give up smoking still continue to have high levels which would be expected in view of the long biological half life of the metal.

The finding of significantly higher levels in subjects dying from cancer could be very significant

but clearly merits further consideration and research especially in view of the very high levels found in the two coppersmiths.

In these two latter subjects it has been possible to have some indication of the major biochemical abnormalities over a period of years prior to the actual measurement of the renal cortical cadmium content. It is interesting that values found in these men are the highest found in all the kidney measurements and it is also very significant that one of these men had a renal tumour.

With respect to the various values found from different centres in U.K. it is important to realize that it is the mean values which are being compared. Since there is an asymetrical distribution of cadmium in these subjects it would be very unwise to draw any specific conclusion about such results. Indeed no attempt has been made to apply a statistical analyses at this stage for these very reasons. Nevertheless, in view of the advantage of being able to measure cadmium in one centre the fact that the city which has the largest zinc ore smelter has subjects with the highest values indicates that there is probably a significant atmospheric pollution of individuals in that area.

CONCLUSION.

APPENDICES.

REFERENCES.

CHAPTER 16

CONCLUSION

Chronic cadmium poisoning has only been recognised as a distinct clinical entity since 1950. Following the initial discovery of the element most authorities concentrated their efforts on diagnosing acute cadmium poisoning and since such patients were liable to develop acute pulmonary distress most emphasis in the early studies of chronic cadmium poisoning were concentrated upon the development of emphysema as a result of chronic exposure to cadmium. Emphysema is a common condition and can occur from a variety of different causes not least of which is the effect of long term cigarette smoking. As well as causing emphysema early workers recorded the finding of proteinuria in chronic cadmium poisoning and this prompted a considerable amount of experimental and epidemiological work designed to ascertain the type and quality of proteinuria in chronic cadmium poisoning in a variety of different general and industrial environments.

The major conclusions of these studies is that cadmium exerts its major toxic effects on kidneys rather than lungs and that both large and low molecular weight proteinuria can occur as a result of cadmium nephrotoxicity. There are a number of studies which have been directed to ascertaining at what critical renal cortical level of cadmium does proteinuria occur in the clinical evaluation of the subject. The general opinion at present would seem

to indicate that at levels of 200 ug/g wet weight, then significant proteinuria does occur in chronic cadmium poisoning.

Apart from the debate about the types of proteinuria in chronic cadmium poisoning it has to be realized that there is a variability and delay in the occurrence of significant proteinuria in chronic cadmium poisoning. There is even debate as to whether or not the presence of proteinuria does represent an effect of cadmium which is in any way significant for the individual subject. Since the proteinuria occurs as a result of tubular and glomerular damage and since the biological half life of cadmium is at least 20 years and since it is a little over 30 years since the condition of chronic cadmium poisoning was first described, it would be unwise to dismiss the presence of proteinuria as a simple casual finding in cadmium poisoning. The presence of proteinuria since it occurs as a result of renal cellular damage must be accorded a position of considerable significance and should be regarded along with other measurements as an indicator of considerable importance.

There is no doubt that if any one of the individual subjects in the clinical part of this study had been examined on their own it would have been very easy to miss the possibility of cadmium exposure and its effects. Indeed one such individual had been regularly examined by me for several years before an explanation of his recurrent stone problem was revealed. However added weight and certainty of diagnosis was given by studying

the results of this particular individual as part of a group of subjects who had been heavily exposed to cadmium while at work. It was possible to gauge to what extent this group has been affected and to have some indication of their whole body burden of cadmium by (a) comparing them with other groups from within their own factory as well as other cadmium process workers and (b) from the prospective study of the changes which have or have not occurred in certain biological parameters of chronic cadmium poisoning. It is clear that proteinuria is important in this context but the blood and urine cadmium levels have clearly isolated the 27 coppersmiths as a group with the most severe exposure to the metal. It is not difficult to understand why this should be since the men were clearly inhaling cadmium fumes without protection.

Although there is no obvious scientific reason why some workers should be apparently more severely affected than others some insight was obtained which could explain the differences in contamination levels by careful enquiry into the working practices of the various members of the group. One participant classified his co-workers according to whether or not they 'brazed' or 'burned' the cadmium rods. He also was able to indicate which workers were 'quick' or who tended to 'hang over the job'. It was interesting that the quick workers and those who brazed rather than burned the metal were those who had the lowest blood cadmium levels.

By combining the experience in the Prestcold factory with the post mortem studies of the levels of cadmium found in renal substance it has been possible to demonstrate in 2 coppersmiths that the level of cortical cadmium found in the renal substance is well in excess of the normal levels to be expected in this area.

Since in vivo neutron activation analyses of the individual coppersmiths to establish kidney cadmium levels was not undertaken, it is important to have been able to measure actual levels in renal substance in two individuals. One of these subjects developed an adenocarcinoma of the kidney and underwent a nephrectomy, the other succumbed to a bronchial carcinoma. In both cases the values obtained from the renal cortical cadmium levels were the highest found in any subjects and helped to confirm the accummulation of cadmium in the kidney in exposed individuals. It is intriguing to realise that there is one author who has already noted significantly higher levels of cadmium in kidneys affected by a primary adenocarcinoma. Clearly cadmium is an element widely used in industry which is important in terms of its nephrotoxicity. Despite the preponderance of literature in recent times which has concentrated on the type of proteinuria caused by cadmium, it is the effects of the metal on calcium metabolism combined with its cellular damage which results in renal stone formation which is of greatest importance to urologists. The long term effects of

the calcium loss can result in skeletal damage and hence before assigning a patient to the diagnosis of "idiopathic hypercalciuria" it is essential to ascertain whether or not he or she has been exposed to heavy metal poisoning and in particular cadmium in an industrial process.

In order to try to minimize the likelihood of an individual developing stone disease it has been the policy within the confines of the various groups studied to attempt to reduce urinary calcium excretion. It has been difficult to achieve this effect by the use of a thiazide diuretic combined with an alkalizing agent namely sodium bicarbonate.

Apart from the desire to minimize the chances of stone formation it has also been realized from in vivo neutron activation analyses of two of the study groups of workers that the continuing loss of calcium is leading to an overall reduction in total body calcium which ultimately could result in bone changes such as osteomalacia (Fig. 48). This has already been recorded in itai itai disease and in a few isolated instances in other factory studies.

In order to study cadmium effects on kidneys it was realized that it was important to establish the levels of cadmium in kidneys in the general population. In general terms it has been shown that the mean cadmium levels in the west central belt of Scotland are similar to those found in other parts of the United

Kingdom. This particular part of the study has however revealed some interesting facts related to the statistically higher levels found in subjects dying from ischaemic heart disease and even more intriguingly the significally higher levels in those dying from cancer.

It would appear therefore that as far as the urologist is concerned cadmium can be a very important factor in causing renal stone disease. The stones produced by cadmium are not different from other stones i.e. they tend to be calcium oxalate/phosphate stones. An awareness that a reasonably common industrial pollutant can cause stones is of importance. Apart from causing stones by renal cellular damage cadmium can cause a variety of different biochemical abnormalities such as a reduced serum inorganic phosphate or an elevated urine calcium. It has therefore to be considered as a cause for such biochemical abnormalities. If a cadmium source can be identified in an industrial situation then removal of the individual or of the source has obvious benefits. Failure to recognise cadmium poisoning will ultimately result in a persistent loss of calcium with the long term possibility of depletion of skeletal calcium.

From studies of general post mortems it is clear that industrial pollution is of major significance in raising kidney cadmium levels. The general population are more likely to have a rise in renal cadmium from smoking. What may prove

to be very significant is that the metal has an important role to play in cancer either by its overall effect on renal biochemistry or as a cellular poison with a much wider effect on cells than has hitherto been realized. With its long biological half life and the complete failure to demonstrate an essential biological role for the metal, it clearly merits the title of non-essential toxic trace element. It may well be that by taking a careful individual history in all stone cases, urologists may well uncover hitherto undiagnosed individuals who suffer from chronic cadmium poisoning.

APPENDIX I.

CADMIUM SURVEY

PART I

NAME _____
(Surname)

_____
(first names)

ADDRESS _____

_____

DATE OF INTERVIEW _____(day) _____(month) _____(year)

DATE OF BIRTH _____(day) _____(month) _____(year)

SEX MALE/FEMALE

CIVIL STATUS SINGLE/MARRIED/WIDOWED

OCCUPATION _____

RACE _____

PART II - RENAL QUESTIONNAIRE

	YES	NO
1 Have you ever had kidney trouble	_____	_____
2 Have you ever been treated for:-		
Renal colic	_____	_____
Ureteric colic	_____	_____
Kidney stones	_____	_____
Gravel in the urine	_____	_____
3 Have you ever had blood in the urine?	_____	_____
4 Have you ever been treated for high blood pressure?	_____	_____
5 Do you regularly get up at night to pass urine?	_____	_____
6 Have you ever had your kidneys X-rayed?	_____	_____

If so, where? _____

when? _____

7 Are you married	_____	_____

If so, for how long? _____

8 Do you have a family?	_____	_____

If so, indicate age and sex

_____

_____

_____

_____

PART III - RESPIRATORY QUESTIONNAIRE

COUGH	YES	NO
1 Do you usually cough first thing in the morning (on getting up*) in the winter? Count a cough with first smoke or on first going out of doors. Exclude clearing throat or a single cough.	_____	_____
2 Do you usually cough during the day - or at night - in the winter? Ignore an occasional cough.	_____	_____
If 'NO' on both questions 1 and 2, go to question 4. If 'YES' to either question 1 or 2 -		
3 Do you cough like this on most days (or nights*) for as much as three months each year?	_____	_____
PLEGHM		
4 Do you usually bring up any phlegm from your chest first thing in the morning (on getting up*) in the winter? Count phlegm with the first smoke or on first going out of doors. Exclude phlegm from the nose. Count swallowed phlegm.	_____	_____
5 Do you usually bring up any phlegm from your chest during the day - or at night - in the winter?	_____	_____
If 'NO' to both question 4 and 5 go to question 7a. If 'YES' to either question 4 or 5 -		
6 Do you bring up phlegm like this on most days (or nights*) for as much as three months each year?	_____	_____
7a In the past three years have you had a period of(increased) cough and phlegm lasting for three weeks or more?	_____	_____
If 'NO' to question 7a, go to question 8. If 'YES' to question 7a -		

		YES	NO
7b/c	Have you had more than one such period?	_____	_____
8	Have you ever coughed up blood?	_____	_____
	If 'NO' to question 8, go to question 9. If 'YES' to question 8 -		
8a	Was this in the past year?	_____	_____

BREATHLESSNESS

9a	Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?	_____	_____
	If 'YES' to question 9a -		
9b	Do you get short of breath walking with other people of your own age on level ground?	_____	_____
	If 'YES' to question 9b -		
9c	Do you have to stop for breath when walking at your own pace on level ground?	_____	_____

NASAL CATARRH

10	Do you usually have a stuffy nose or catarrh at the back of your nose in the winter?	_____	_____
11	Do you have this in the summer?	_____	_____
	If 'YES' to question 10 or 11 -		
12	Do you have this on most days for as much as three months each year?	_____	_____

HAVE YOU EVER HAD:-

13	An injury or operation affecting your chest?	_____	_____
14	Heart trouble?	_____	_____
15	Bronchitis?	_____	_____
16	Pneumonia?	_____	_____

		YES	NO
17	Pleurisy?	_____	_____
18	Pulmonary tuberculosis?	_____	_____
19	Bronchial asthma?	_____	_____
20	Emphysema?	_____	_____
21	Bronchiectasis?	_____	_____
22	Other chest trouble?	_____	_____

TOBACCO SMOKING

23a	Do you smoke? (Record 'YES' if regular smoker up to one month ago).	_____	_____
	Do you inhale the smoke?	_____	_____
	Would you say you inhale the smoke: Slightly (S), moderately (M), deeply (D)?	S M D	
	How old were you when you started smoking regularly?	_____	
	How many manufactured cigarettes do you usually smoke per day? (per working day)	_____	
	(at weekends)	_____	
	How much tobacco (oz/g) do you usually smoke per week in hand-rolled cigarettes?	_____	
	How much pipe tobacco (oz/g) do you usually smoke per week?	_____	
	How many cigars do you usually smoke per week - specify (L) large, (S) small?	_____	
23b	Have you ever smoked as much as one cigarette a day (or one ounce of tobacco a month) for as long as a year?	_____	_____
	How old were you when you started smoking regularly?	_____	
	How old were you when you last gave up smoking?	_____	

	YES	NO
How many manufactured cigarettes per day were you smoking before you gave up? (per working day)	_____	
(at weekends)	_____	
How much tobacco (oz/g) per week were you smoking in hand-rolled cigarettes before you gave up?	_____	
How much pipe tobacco (oz/g)per week were you smoking before you gave up?	_____	
How many cigars per week were you smoking before you gave up - specify (L) large, (S) small?	_____	

APPENDIX II.

PUBLICATIONS ARISING FROM WORK IN THIS THESIS.

Scott, R., Paterson, P.J., Mills, E.A., McKirdy, A., Fell, G.S., Ottoway, J.M., Hussain, F.E.R., Fitzgerald-Finch, O.P., Yates, A.S., Lamont, A. & Roxburgh, S. (1976) Chemical and biochemical abnormalities in coppersmiths exposed to cadmium. Lancet. 396 - 398.

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