

EMPHYSEMA AND PROTEINURIA IN MEN CASTING COPPER-CADMIUM ALLOYS

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Diseases of occupational origin occur as acute or chronic illnesses. The former are usually dramatic and the connexion between symptoms and occupation is obvious. An insidious illness developing over many years and due to long exposure to small quantities of a poisonous substance may long go unrecognized as being of occupational origin.

Since all the recorded cases of chronic cadmium poisoning had occurred among men employed in the alkaline accumulator industry, it was decided to investigate other industries where cadmium is used. This paper describes five cases of chronic cadmium poisoning and reports the results of an investigation of men employed at two factories in England where an alloy of copper and cadmium is manufactured.

Because cadmium increases the wear and durability of copper without reducing significantly its electrical conductivity the alloy is used to replace pure copper for certain purposes. These include post-office telephone wires, high-tension electrical conductor cables, and overhead contact wire for electrically powered omnibuses and trains.

Review of the Literature

Cadmium and its salts have been known to be acutely toxic substances since 1858. The first cases of acute cadmium poisoning were recorded by Sovet in 1858 (quoted by Prodan, 1932) following the inhalation of fine particles of cadmium carbonate which had been used as a silver polish. Numerous reports of acute cadmium poisoning have been published since that time (Frant and Kleeman, 1941; Huck, 1947).

Stephens (1920) first drew attention to the fact that cadmium might cause chronic ill health. He described the case of a man who had been exposed to small quantities of cadmium in the atmosphere of a zinc spelter works. The symptoms were recurrent bronchitis, loss of weight, and weakness, and the man had been receiving compensation for some time for suspected lead poisoning. At necropsy he

was found to have chronic interstitial nephritis and hypertrophy of the heart muscle. The liver was found to contain 0.91 grain of cadmium per pound weight and 0.77 grain of zinc per pound, despite the fact that calamine the zinc ore contained only 0.5 to 1.5% of cadmium and 35 to 40% of zinc. Stephens suggested that the symptoms were due to cadmium and stated that he had seen six similar cases over a period of eight years. Chronic illness due to cadmium was not mentioned in the medical literature again until Manciola (1940) described chronic rhinitis and pharyngitis in men plating metals with cadmium by an electrolytic process. Manciola's patients complained of dryness and irritation of the pharynx, a burning sensation in the nose with epistaxis, and were found to have ulcers in the cartilaginous parts of the nose and in the nasopharynx.

In 1942 Nicaud, Lafitte, and Gros investigated a group of workers in an alkaline accumulator factory in France. No details are given about the number of people employed in the factory or the number of people taking part in the investigation. They describe impairment of general health with marked loss of weight, an iron-deficiency anaemia, and severe osteoporosis with pseudo-fractures of the long bones such as are seen in osteomalacia or rickets. They state that chronic bronchitis and emphysema were occasionally seen in their patients but they were of the opinion that the exposure to cadmium was in no way connected with the condition of the lungs. The skeletal changes were cured by administration of calcium and vitamin D, suggesting that nutritional deficiencies, perhaps connected with the Second World War, may have played some part in their production.

Barthélemy and Moline (1946) and Princi (1947) found that men who had been exposed to cadmium for two or more years developed a golden-yellow ring at the alveolar margin of the teeth. Apart from this discoloration of the teeth, Princi found no

evidence of chronic ill health among a group of 20 men who had worked as cadmium smelters for six months to 22 years. The average concentration of cadmium in the atmosphere was found to be as high as 31.30 mg. per cu. m. and the men were found to be excreting between 11 and 125 μ g. of cadmium per litre of urine. Princi concluded that exposure to cadmium in these conditions did not cause chronic ill health. Hardy and Skinner (1947) investigated a group of five men who had been exposed to cadmium fume for from four to eight years. These men complained of chronic cough and gastro-intestinal symptoms. Although no definite conclusion could be drawn from such a small group, it was suggested that these symptoms were due to cadmium and that further investigation was necessary to confirm this opinion.

In 1946 frequent complaints of tiredness and shortness of breath among men employed in an alkaline accumulator factory in Sweden led to an investigation by Friberg (1948, 1950). The men made small briquettes of cadmium and iron which compose the negative electrode of the accumulator. During manufacture finely divided cadmium oxide dust passed into the working atmosphere and settled on the floor, machines, and benches and on the clothes, hands, and faces of the workers. Of 58 men investigated, 43 had done this work for more than nine years and complained of symptoms. In order of frequency these were dyspnoea, excessive tiredness, impairment of the sense of smell, cough, and a sensation of dryness of the mouth. On examination the abnormal findings were emphysema for the group as a whole compared with a control group, proteinuria in 35 of the 43, impairment of renal function in nine cases, a raised E.S.R. in 31, and anosmia in 14. The average haemoglobin value in this group was lower than normal. Fifteen men who had worked in the same factory for less than four years were free from symptoms and no abnormality was detected on examination.

The urinary protein could not be demonstrated unequivocally by the boiling test, but a positive result was obtained by testing with trichloroacetic acid. Esbach's picric acid test was carried out on 15 cases in which proteinuria had been demonstrated by testing with trichloroacetic acid. The Esbach test was negative in 12 cases but an opalescence was observed in seven. The protein was precipitated with full saturation of the urine with ammonium sulphate but not with 50% saturation. The electrophoretic mobility was lower than ordinary albumin at the protein concentration studied, and corresponded more closely to that of alpha-globulin. Electrophoretic analysis was also carried out on

five cases after concentrating the urinary protein and this showed three or four components, the largest of which was similar to the protein mentioned above. Examination by ultracentrifuge indicated that the molecular weight of this protein was about 20,000 to 30,000.

Administration of cadmium dust to rabbits by inhalation for two to three hours daily for seven and nine months resulted in the appearance of proteinuria in the majority of the animals. This protein had similar characteristics to the protein found in the urine of the workmen. All the rabbits developed emphysema, and inflammatory foci were found in the kidneys of the majority. In a later paper Friberg (1952) describes animal experiments using radioactive cadmium. It was found that only small amounts of cadmium were excreted in the urine until the proteinuria appeared. There was then a striking increase in the quantity of cadmium excreted, and the concentration of cadmium in the urine was found to bear a direct relationship to the amount of protein in the urine. Friberg suggests that cadmium excreted in the urine is bound to the protein.

Baader (1951) investigated a group of 11 workers in an alkaline accumulator factory in Germany. Eight of these, seven men and one woman, were found to have emphysema, proteinuria, and loss of weight. Baader considers that a watery discharge from the nose, which he calls "cadmium snuffles", is an important early sign. He gives a detailed description of a young man aged 39 in whom this was the first symptom. Eight years later he was so disabled by dyspnoea that he was forced to give up work and he died after three years. Necropsy showed severe emphysema, fatty infiltration of the liver, and toxic nephrosis. The renal lesion is not described in detail, but it is important to note that a protein was excreted in the urine which gave similar reactions to that described by Friberg. Although the man had not been working with cadmium for four years before death, there were large deposits of cadmium in the liver and kidneys.

Friberg and Nyström (1952) report the results of re-examination of the men exposed to cadmium for more than nine years in the alkaline accumulator industry in Sweden. There had been no further exposure to cadmium. Five of these 43 men had died. In two cases death was due to emphysema. Two others had died of coronary thrombosis; severe renal damage attributed to cadmium was found at necropsy. One man died from acute pancreatitis; the lungs were found to be emphysematous.

In nine of the remaining 38 men there was evidence to suggest that the disease had progressed.

Increased dyspnoea was complained of by five, proteinuria had developed in four, and in three there was deterioration of renal function assessed by testing the maximum specific gravity of the urine. The symptoms and signs in 25 men were unchanged, whereas in four other men there was a distinct improvement in the performance of tests of respiratory function.

In Friberg's opinion the prognosis for men suffering from emphysema was favourable provided they were removed from exposure to cadmium before the symptoms became severe. Considering that four new cases of proteinuria had occurred and the renal function tests in three men showed greater impairment, Friberg suggests that the renal lesion may eventually become a more important cause of disability than emphysema in many of his cases.

Two fatal cases of emphysema in men casting copper-cadmium alloys were reported by Lane and Campbell (1954). The emphysema developed rapidly over a period of two years without preceding chronic bronchitis or asthma. In one case the diagnosis was confirmed at necropsy. There was widespread emphysema affecting both lungs. In many places the lung substance had been reduced to a coarse spongework but a narrow zone of lung 0.5 to 2 cm. wide under the pleura had been spared. There were therefore no emphysematous bullae on the surface of the lungs. There was little evidence of chronic bronchitis. The cadmium content of the lung was 277 $\mu\text{g.}/100\text{ g.}$ of tissue, of the kidney 233 $\mu\text{g.}/100\text{ g.}$, and of the liver 25 $\mu\text{g.}/100\text{ g.}$

Manufacture of Copper-Cadmium Alloys

The two factories at which the investigations were made will be referred to as factory A and factory B. Both factories produce alloys of copper containing 0.5 to 1% of cadmium. The details of the process and the types of furnace used in the two factories differ but the method is the same in principle. A master alloy containing up to 50% cadmium is manufactured at both factories by a process which will be described, and known amounts of this alloy are added to molten copper.

Process at Factory A.—The master alloy is made in a coke-fired pit-fire furnace and contains 33½% cadmium. Pure cadmium is placed in a crucible which is lowered into the pit fire. When the cadmium is molten, pure copper in the form of copper wire is added. Exhaust ventilation through a flue at the upper half of the pit removes the cadmium fume. As the metals in the crucible become molten they are stirred by the furnace-man to ensure thorough mixing. When the mixing is completed a cover is placed over the crucible before it is removed from the furnace. The molten metal is poured into moulds under exhaust ventilation.

At one time the low-percentage cadmium alloys were produced in this type of furnace. Copper was placed in the crucible and lowered into the pit fire; when the

copper was molten the master alloy was added and the mix stirred. Since the stirring was performed manually and there was no exhaust ventilation over the pit the men were exposed to a high concentration of cadmium fume.

The pit-fire furnace is now used only for the manufacture of the master alloy. The present method of manufacture of the low-percentage alloys is by means of an electrically heated, mechanically controlled furnace called a rocker resistor furnace situated in the same workshop. This furnace is barrel shaped and balanced at each end on rockers (Fig. 1). It is heated by a carbon electrode which passes through the centre of the furnace. Bars of pure copper are introduced into the furnace through a door on the long side. The door is closed and the tap-hole is plugged with fireclay. The copper melts in approximately 50 minutes, and at this stage a known amount of the master alloy is added through the door, which is quickly closed. The total charge is 4 cwt. The furnace is rocked to and fro in its long axis by mechanical means to ensure thorough mixing. Since the boiling point of cadmium is 767° C., and the temperature of the molten copper in the furnace is 1000 to 1100° C., a large amount of finely divided cadmium oxide fume is produced each time cadmium is added to molten copper. This can be seen as a dark yellow cloud similar in appearance to nitrous fumes.

Process in Factory B.—The master alloy is manufactured in an oil-fired pit-fire furnace (Fig. 2) and contains 50% cadmium. The process is different from that in factory A in that the copper is placed in the crucible first and when it becomes molten pure cadmium is introduced. Clouds of cadmium fume are produced, and there are no ventilation hoods to remove the fume from the atmosphere. The mix is stirred manually during and after addition of the cadmium and it is then poured into moulds. The workmen wear cotton-wool pads over the nose and mouth.

The low-percentage copper-cadmium alloy is produced in oil-fired tilting furnaces (Fig. 3) in a different workshop. The furnace stands upright and consists of an outer shell lined by fire brick. A crucible containing the copper is placed inside this shell and a space of 2 to 3 in. remains between the crucible and the furnace wall to allow the flames of the burning oil to heat the crucible. When the copper becomes molten the master alloy is added, the mixture is stirred manually, and the alloy is poured into moulds. Hoods with powerful exhaust ventilation are placed over these furnaces by the workmen during casting operations.

The working conditions in both factories are likely to have been very much worse during the Second World War when the black-out interfered with ventilation.

Method of Investigation

In each of the factories there was a small group of men who were working on the manufacture of copper-cadmium at the time of the investigation or who had done so at some time in the past. There was also a larger group of men in each factory who worked in the vicinity of the copper-cadmium furnaces. Control

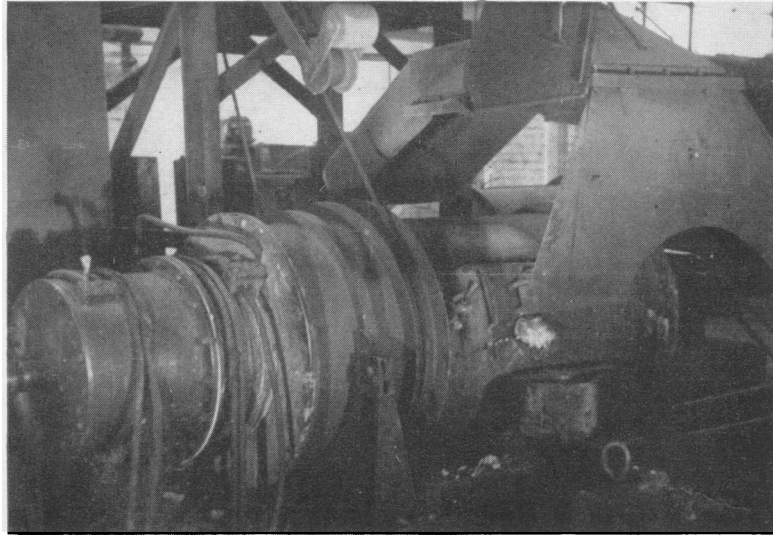


FIG. 1.—Rocker furnace in factory A.



FIG. 2.—Oil-fired pit-fire furnace in factory B.



FIG. 3.—Oil-fired tilting furnace in factory B.

groups of men of comparable ages who did similar work but had never at any time been exposed to cadmium were examined at each factory.

The men were asked to volunteer to take part in the survey. Each man was interviewed and a clinical examination made. The occupational history, the past medical history, and the family history were obtained, and specific inquiry was made about suggestive symptoms such as a watery discharge from the nose, loss of sense of smell, yellow discoloration of the teeth, shortness of breath, abdominal pain, and episodes of metal fume fever. At the clinical examination the height, weight, and blood pressure of each man were recorded. Blood was taken by venepuncture for estimation of the haemoglobin concentration, erythrocyte sedimentation rate (Wintrobe), haematocrit, and the plasma proteins. Each man was asked to provide an early morning specimen of urine and 24-hour specimens were obtained from as many of the workmen as possible. They were asked to collect the specimens away from the factory and preferably at week-ends. The early morning specimens of urine were tested for protein, blood, and sugar. In testing for the protein, an equal volume of 25% trichloroacetic acid was added to the urine in a test-tube and allowed to stand for 10 to 15 minutes. The urine was tested with 3% sulphosalicylic acid in a similar way. The heat test for protein and Esbach's test were done on all urines which gave a positive reaction with trichloroacetic and sulphosalicylic acids. The urine was tested for sugar by Benedict's test and for blood by the benzidine test. The cadmium content of the 24-hour specimens of urine was estimated.

The respiratory function was tested in all the men who attended for examination by measuring the vital capacity, the maximum ventilatory capacity at controlled rates of breathing, and the expiratory fast vital capacity. These are tests of the ventilatory capacity of the lungs. From the data obtained by measuring the vital capacity and maximum ventilatory capacities, the swept fractions at given respiratory rates were calculated. These tests and the detailed results are described separately (Kazantzis, 1955). In order to assess the significance of these tests, the results obtained from the study of control groups at each factory are considered as normal for the population investigated. The outer limits of normal represent the mean plus or minus twice the standard deviation for each of the control groups.

All men taking part in the investigation were asked to attend for chest radiographs. At factory A four radiographs of the chest were taken in each case. These were postero-anterior views in deep inspiration and deep expiration, and corresponding left lateral views following the recommendation of Knott and Christie (1951). In fact it was found that the opinion of the radiologist, based on seeing only postero-anterior views, was not influenced by the appearances in the lateral views (Simon, 1953). It was decided therefore to omit taking lateral chest radiographs of the men examined at factory B.

The cadmium content of the working atmosphere was estimated at both factories. The methods employed and

the results obtained are discussed in detail by King (1955).

In factory A brass, bronze and copper-cadmium alloys are manufactured in the same workshop. Although only 14 men were casting copper-cadmium, 38 others were engaged in the manufacture of brass and bronze. They had worked in the casting shop for from two to 25 years. Since the workshop was comparatively small (150 ft. by 75 ft.) it was considered that all these men were at risk and they have therefore been included in the exposed group (Group 1A). In addition, six men had worked in this workshop in the past, three manufacturing copper-cadmium and three on the brass furnaces. They have also been included. The total number in Group 1A is therefore 58 men (Table 1). Seven other men working

TABLE 1
ANALYSIS INTO AGE GROUPS OF MEN EXPOSED TO
CADMIUM AND CONTROLS

| Age in Years | Factory A | | Factory B | |
|--------------|--------------------|--------------------|--------------------|--------------------|
| | Exposed Group (1A) | Control Group (CA) | Exposed Group (1B) | Control Group (CB) |
| 25 | — | 1 | 1 | 4 |
| 25-34 | 4 | 3 | 11 | 10 |
| 35-44 | 13 | 12 | 15 | 16 |
| 45-54 | 21 | 25 | 9 | 9 |
| 55-64 | 17 | 18 | 5 | 4 |
| 65+ | 3 | 1 | 1 | 1 |
| Total | 58 | 60 | 42 | 44 |

as brass founders in the alloy casting shop refused to take part in the investigation. Early morning specimens of urine were obtained from these men, however, and all were found to be normal. Four men who had worked casting the copper-cadmium alloy were absent from work owing to sickness. They have not been included in Group 1A but they have been investigated in hospital and their case histories are recorded.

The control group was made up of 60 men in the same age distribution who volunteered for examination (Group CA, Table 1). They had all worked in different departments of the same factory, but they had never at any time been exposed to cadmium.

At factory B the low-percentage copper-cadmium alloy was manufactured at one end of a large workshop (440 ft. by 180 ft.). There were 15 men employed at the time of the investigation. Four men manufactured the master alloy in a separate department in another part of the works. There were therefore 19 men employed casting copper-cadmium. They had worked with cadmium for from three to 27 years. A further 23 men had been engaged in the manufacture of the alloy for periods varying from 18 months to 28 years, but at the time of the survey were employed in other departments of the factory. These men were included in the exposed group (Group 1B, Table 1) making a total of 42. The control group was made up of 44 men in the same age distribution who had worked in either the brass or the iron foundry for up to 30 years but who had never been exposed to cadmium (Group CB, Table 1).

One hundred and eighty-seven men worked in other sections of the main workshop refining pure copper and

TABLE 2
SUMMARY OF CLINICAL DETAILS OF MEN WITH SIGNS OF CADMIUM POISONING IN FACTORY A

| Case No. | Age | Exposure | Symptoms | Clinical Findings | B.P. (mm. Hg) | Hb (g.-%) | E.S.R. (Wintrobe mm./hr.) | Urine | | V.C. (l.) | Respiratory Function Tests | | | | Chest Radiograph | Diagnosis | |
|------------------------------------------------------|-----|----------------|----------------------------------------------|---------------------------------------------------------------|---------------|-------------|---------------------------|------------------------|-----------------------------------|-----------|----------------------------|------------------------|------------------------|------------------|------------------|---------------------------|-------------|
| | | | | | | | | Early Morning Specimen | Cd in 24-hr. Specimen (μ g.) | | S.F. ₃₀ (%) | S.F. ₅₀ (%) | S.F. ₇₀ (%) | M.V.C. (l./min.) | | | T.C. (sec.) |
| A5 | 58 | 18 yr. 1935-53 | Dyspnoea 2 yr., cough, loss of weight | Emphysema, liver palpable 2 finger-breadths, soreness of nose | 160/110 | 95 14.1 | 9 | Proteinuria | 42 | 2.78 | 46.2 | 31.9 | 25.6 | 50 | 2.08 | Emphysema and proteinuria | |
| A6 | 60 | 18 yr. 1935-53 | Dyspnoea 4 yr., cough 4 yr. | Emphysema, chronic bronchitis, cyanosis | 150/100 | 90 13.3 | 20 | Normal | No specimen received | 3.70 | 65.3 | — | — | — | 0.73 | Emphysema | |
| A7 | 56 | 32 yr. 1921-53 | Dyspnoea on exertion, no cough | Liver palpable | 150/90 | 85 12.6 | 9 | Proteinuria | 104 | 3.92 | 78.9 | 69.1 | 58.9 | 162 | 0.78 | Proteinuria | |
| A8 | 55 | 20 yr. 1923-43 | Dyspnoea on exertion 4 yr., occasional cough | Emphysema | 130/90 | 105 15.5 | 10 | Proteinuria | 58 | 4.75 | 47.9 | 35.4 | 31.0 | 103 | 1.21 | Emphysema and proteinuria | |
| A9 | 56 | 31 yr. 1920-51 | Dyspnoea on exertion | No abnormal clinical signs | — | — | — | Proteinuria | 63 | — | — | — | — | — | — | Proteinuria | |
| A10 | 42 | 17 yr. 1936-53 | Dyspnoea on exertion 3 yr. | Emphysema, cyanosis | 140/90 | 100 14.8 | 11 | Proteinuria weakly +ve | 57 | 5.5 | 51.2 | 38.6 | 30.8 | 119 | 1.11 | Emphysema and proteinuria | |
| A11 | 65 | 40 yr. | Dyspnoea 10 yr., cough and sputum 10 yr. | Emphysema, chronic bronchitis, benign hypertension | 210/110 | 100 14.8 | 16 | Proteinuria | Cd present but not measurable | 1.71 | 69.2 | 53.4 | 34.9 | 42 | 0.87 | Proteinuria | |
| A12 | 54 | 10 yr. 1935-45 | Dyspnoea 10 yr., cough 10 yr. | Emphysema, chronic bronchitis | 150/100 | 100 14.8 | 5 | Proteinuria | No Cd | 2.39 | 37.6 | 30.7 | 27.3 | 45 | 3.13 | Emphysema and proteinuria | |
| A13 | 61 | 8 yr. | Cough 10 yr., dyspnoea 5 yr. | Emphysema, chronic bronchitis | 170/90 | 95 14.1 | 16 | Normal | No Cd | 3.61 | 49.8 | 36.3 | 25.2 | 64 | 1.47 | Emphysema | |
| Limits of normal obtained by examination of Group CA | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | 54 | 44 | 34 | 74 | 0.91 | | |

V.C. = Vital capacity.
S.F.₃₀ = Swept fraction at 30 respirations per minute.
S.F.₅₀ = Swept fraction at 50 respirations per minute.
S.F.₇₀ = Swept fraction at 70 respirations per minute.
M.V.C. = Maximum ventilatory capacity.
T.C. = Time constant of the expiratory fast vital capacity.

TABLE 3
SUMMARY OF CLINICAL DETAILS OF MEN WITH SIGNS OF CADMIUM POISONING IN FACTORY B

| Case No. | Age | Exposure | Symptoms | Clinical Findings | B.P. (mm. Hg) | Hb (g.%) | E.S.R. (Westergren mm./hr.) | Urine | | Respiratory Function Tests | | | | | | Chest Radiograph | Diagnosis | |
|----------|-----|----------------|-----------------------------------------------|------------------------------------------------------------------------------------------------|---------------|------------|-----------------------------|------------------------|-----------------------------|----------------------------|------------------------|------------------------|------------------|-------------|-------------|------------------|-----------|------------------------|
| | | | | | | | | Early Morning Specimen | Cd in 24-hr. Specimen (µg.) | V.C. (l.) | S.F. ₃₀ (%) | S.F. ₇₀ (%) | M.V.C. (l./min.) | T.C. (sec.) | F.R.A. (l.) | | | T.L.V. (l.) |
| B2 | 49 | 27 yr. 1926-53 | None | None abnormal | 130/80 | 98 14.5 | 2 | Protein +ve | 64 | 5.1 | 33 | 117 | 1.33 | 4.2 | 7.3 | 39.7 | Emphysema | Emphysema, proteinuria |
| B3 | 44 | 9 yr. 1942-51 | Dyspnoea 5 yr., cough, loss of weight | Emphysema, bronchospasm | 150/90 | 90 13.3 | 15 | Protein +ve | 1,240 | 3.89 | 17 | 47 | 3.02 | 5.0 | 7.4 | 43.2 | Normal | Emphysema, proteinuria |
| B4 | 58 | 22 yr. 1931-53 | Dyspnoea 3 yr., cough 2 yr., loss of weight | Emphysema, bronchospasm | 150/90 | 84 12.4 | 15 | Protein +ve | 69 | 2.5 | 27 | 53 | 1.38 | 3.9 | 6.0 | 58.3 | Emphysema | Emphysema, proteinuria |
| B5 | 59 | 17 yr. 1930-47 | Severe dyspnoea 6 mth., onset 5 yr., no cough | Emphysema | 140/80 | 92 13.6 | 15 | Protein +ve | 37 | 3.4 | 37 | 95 | 1.50 | 4.4 | 7.7 | 55.1 | Emphysema | Emphysema, proteinuria |
| B6 | 50 | 7 yr. 1945-52 | Dyspnoea 1 yr., cough 6 mth., loss of weight | Emphysema, bronchospasm, cyanosis, liver palpable 3 fingerbreadths and spleen 2 fingerbreadths | 130/70 | — | 3 | Normal | 24 | 2.3 | 31 | 31 | 1.50 | 5.2 | 7.0 | 67.1 | Emphysema | Emphysema |
| B7 | 41 | 13 yr. 1940-53 | None | Normal | 116/70 | 90 13.3 | 9 | Protein +ve | 160 | 3.9 | 50 | 131 | 0.48 | 4.0 | 7.0 | 44.3 | Normal | Proteinuria |
| B8 | 40 | 17 yr. 1936-53 | Slight dyspnoea on exertion | Normal | 180/120 | — | 4 | Protein +ve | 124 | 5.3 | 51 | 189 | 0.47 | 2.8 | 7.1 | 35.2 | Normal | Proteinuria |
| B9 | 65 | 28 yr. 1922-50 | None | Normal | 150/90 | 98 14.5 | 5 | Protein +ve | 46 | 3.2 | 52 | 110 | 0.59 | 3.0 | 5.7 | 43.8 | Normal | Proteinuria |
| B10 | 45 | 7 yr. 1946-53 | None | Normal | 116/70 | 96 14.2 | 10 | Protein +ve | 375 | 5.1 | 65 | 145 | 0.82 | 4.5 | 8.1 | 39.5 | Normal | Proteinuria |

Limits of normal obtained by examination of Group CB

V.C. = Vital capacity.
 S.F.₃₀ = Swept fraction at 30 respirations per minute.
 S.F.₇₀ = Swept fraction at 70 respirations per minute.
 M.V.C. = Maximum ventilatory capacity.
 T.C. = Time constant of the expiratory fast vital capacity.
 F.R.A. = Functional residual air.
 T.L.V. = Total lung volume.
 R.A./T.L.V. = Residual air/Total lung volume.

casting arsenical copper, bronze and silver bronze, or sorting, inspecting, and cutting the ingots and bars which were cast in the workshop. Of these 187 men, 130 had been employed for more than 12 months and 21 others had at some time in the past been employed in this workshop but at the time of the survey were working in other departments of the factory.

It was estimated that the exposure to cadmium of these 151 men was less than that of men doing similar work in factory A because of the different lay-out in the two factories and the much larger workshop at factory B. They were therefore considered as a separate group in whom the extent of exposure to cadmium was difficult or impossible to assess. Since it was obvious, however, that all were at risk of absorbing some cadmium fume, they were examined. There were no cases in this group in whom the findings were consistent with the diagnosis of chronic cadmium poisoning, and the results of investigation of this group will not be discussed.

Results

In the two factories 100 men who had been exposed to cadmium fume were examined. Of these, nine had emphysema and proteinuria, three had emphysema without proteinuria, and seven had proteinuria without emphysema (Tables 2 and 3). In addition four men at factory A had been forced to give up work because of disabling shortness of breath. They were admitted to hospital for investigation and their case histories are reported separately together with that of one man from factory B who though seriously disabled was still at work at the time of the survey (Table 7). One of the four men from factory A has since died and the necropsy findings are described.

In this investigation independent assessments of the respiratory system were made by clinical and radiological examination and by respiratory function tests. The clinical diagnosis of emphysema was made only when there was a definite history of dyspnoea on effort in a man who had on examination poor chest movement with hyper-resonance on percussion and reduction in the areas of liver and cardiac dullness. The presence or absence of bronchospasm was noted. Heart disease and other lung disease were excluded as far as this is possible by clinical examination alone. The diagnosis of emphysema by clinical examination and radiography is notoriously difficult and there is much disagreement about the specificity of various tests of respiratory function. For the purpose of this investigation the diagnosis of emphysema was made by clinical or radiological examination supported by evidence of impairment of respiratory function assessed as a result of tests referred to above: unless two of these criteria have been satisfied a diagnosis of emphysema has not been made in any man taking part in the survey.

The demonstration of protein in the urine by testing with trichloroacetic or sulphosalicylic acids is an objective test which can be confirmed by testing repeated specimens of urine. This type of proteinuria has been taken to indicate absorption of toxic amounts of cadmium and to support the diagnosis of chronic cadmium poisoning.

Factory A.—Nine of the 58 men in Group 1A were considered to be abnormal. Four had emphysema and proteinuria (Table 2). Two had emphysema without proteinuria. Three had proteinuria alone. Case A11 had clinical evidence of emphysema only, respiratory function tests and chest radiographs were normal: for the purpose of this investigation he is not considered as a case of emphysema. Six of these men had worked on the copper-cadmium furnaces for a minimum of 17 years. The other three cases (A11, A12, and A13) had worked in the vicinity of these furnaces for 40, 10, and eight years respectively (Table 4).

TABLE 4
EXPOSURE TO CADMIUM IN YEARS

| Years of Exposure | Factory A (Group 1A) | Factory B (Group 1B) |
|-------------------|----------------------|----------------------|
| 5 | 4 | 18 |
| 5-9 | 4 (1)* | 11 (3)* |
| 10-14 | 12 | 7 (2)* |
| 15-19 | 12 (3)* | 2 (2)* |
| 20+ | 26 (5)* | 4 (3)* |

*Numbers of men affected.

One man out of the 60 in Group CA had proteinuria. The protein gave the normal reactions of urinary protein to heat and picric acid and the man was found to have hypertension. No cadmium was found in a 24-hour specimen of urine. There were no cases of emphysema in this group. Chronic bronchitis was diagnosed on clinical examination in four men but respiratory function tests and x-ray examination of the chest were normal. In five other men localized areas of emphysema were diagnosed by the radiologist but these men were free of symptoms and the respiratory function tests were normal.

The results of the respiratory function tests are discussed in full by Kazantzis (1955). It was found that there was a significant difference in the performance of the tests between the exposed and control groups (Groups 1A and CA).

The vital capacities (V.C.) and the maximum ventilatory capacities (M.V.C.) are similar in the two groups, but the mean swept fractions at 30, 50 and 70 respirations per minute are significantly lower in Group 1A than in Group CA. The same significant difference is found between these groups for the mean time constant of the expiratory fast vital capacity curve ($p < 0.01$).

TABLE 5
RESULTS OF BLOOD EXAMINATION

| Group | Total | Haemoglobin (%) | | | Haematocrit (c.mm.) | | | Erythrocyte Sedimentation Rate (Wintrobe, mm./hr.) | | |
|-------|-------|-----------------|-------|--------|---------------------|-------|-------|----------------------------------------------------|-------|-------|
| | | Mean | S.D. | Range | Mean | S.D. | Range | Mean | S.D. | Range |
| 1A | 58 | 98 | ±8.0 | 80-115 | 43.6 | ±2.99 | 37-50 | 9 | ±6.64 | 1-39 |
| CA | 60 | 101 | ±5.56 | 90-115 | 45 | ±2.87 | 41-54 | 6.2 | ±5.89 | 1-25 |
| 1B | 42 | 90.6 | ±8.05 | 74-104 | 44.9 | ±3.34 | 38-55 | 7.2 | ±5.16 | 1-21 |
| CB | 44 | 95.4 | ±4.31 | 86-106 | 45.1 | ±2.97 | 35-50 | 6 | ±4.11 | 2-23 |

The mean and standard deviations of the blood examinations are summarized in Table 5. There was no significant difference in the plasma protein levels.

Eight of the men from Group 1A who had worked on the copper-cadmium furnaces had noticed soreness of the nasal mucous membrane accompanied by a thin watery discharge from the nose, but this ceased shortly after leaving work at the end of the day. None admitted to an impairment of the sense of smell. Because the dental hygiene of these men was so poor it was quite impossible to discover whether the characteristic yellow discoloration of the teeth ascribed to cadmium was present or not.

Seventeen men in Group 1A had worked on the copper-cadmium furnaces and 10 had suffered from metal fume fever while working with cadmium. The majority of the men in Group 1A had experienced similar symptoms at some time following the inhalation of zinc fume during brass casting.

The results of the analysis of the 24-hour specimens of urine are summarized in Table 6. A sample of 200 ml. of urine was wet ashed by boiling with a mixture of concentrated sulphuric and nitric acids. A polarograph was used to measure the quantity of cadmium present.

TABLE 6
CADMIUM EXCRETION IN 24-HOUR SPECIMENS OF URINE

| Group | 24-Hour Specimens Received | Cadmium | No Cadmium Found | Greater than 30 µg. per Day |
|-------|----------------------------|---------|------------------|-----------------------------|
| 1A | 44 | 30 | 14 | 15 |
| CA | 49 | 7 | 42 | 1 |
| 1B | 39 | 32 | 7 | 26 |
| CB | 40 | 6 | 34 | 2 |

Twenty-four hour specimens were obtained from 44 of the 58 men in Group 1A. Thirty of these men were excreting cadmium in the urine and 15 of these were excreting more than 30 µg. in 24 hours. Forty-nine of the 60 men in Group CA provided 24-hour specimens. Seven of these men were excreting cadmium in the urine but only one was excreting more than 30 µg. in 24 hours (Table 6).

Factory B.—Ten of the 42 men in Group 1B were considered to be abnormal. Five had emphysema and proteinuria (see Table 3 and Case B1 in Table 7), four had proteinuria alone, and one had emphysema without proteinuria. Case B2 did not complain of symptoms but a diagnosis of emphysema was made on chest radiographs and abnormal respiratory function tests. All 10 men had been exposed to cadmium for over five years (Table 4).

Proteinuria was not demonstrated in any of the 44 men in Group CB. Two men were considered to have x-ray changes characteristic of emphysema. Although both were symptom-free, one showed impaired respiratory function.

The results of the respiratory function tests are discussed in detail by Kazantzis (1955). It was found that there was no significant difference between the vital capacities, the maximum ventilatory capacities and the mean swept fractions of the men in the exposed and control groups (Groups 1B and CB). The mean time constant for the expiratory fast vital capacity curve of the men in Group 1B was, however, significantly different from that of the men in Group CB ($0.025 > p > 0.01$). When the men in Group 1B who had been exposed to cadmium for more than ten years were compared with Group CB, the difference between the mean time constant for the expiratory fast vital capacity curves shows a higher level of significance ($p < 0.01$).

The results of estimating the total lung volume and its subdivisions are discussed by Buxton (1955). Thirty-seven men from Group 1B were examined. The men with more than 10 years' exposure showed a significant increase in the mean value of the residual air expressed as a percentage of the total lung volume ($p < 0.005$). None of the control group (Group CB) were abnormal. There was no significant difference in the mean value for the total lung volume nor in the efficiency of intrapulmonary mixing between Groups 1B and CB.

As in factory A there were differences in the mean haemoglobin, erythrocyte sedimentation rates, and haematocrit readings in the two groups. The results are given in Table 5, but since these differences

are slight and are the result of single observations, no conclusions can be drawn from them. The plasma protein levels were in close approximation.

Specific inquiries failed to reveal evidence of loss of sense of smell, yellow discoloration of the teeth, or abdominal pains, and none had experienced the symptoms of metal fume fever.

The results of the analysis of the 24-hour specimens of urine are summarized in Table 6. Twenty-four hour specimens were obtained from 39 of the 42 men in Group 1B. Thirty-two of these men were excreting cadmium in the urine and 26 of these were excreting more than 30 μg . in 24 hours. Forty men out of the 44 in Group CB provided 24-hour specimens. Six of these men were excreting cadmium in the urine but only two were excreting more than 30 μg . in the 24 hours. The output of cadmium in the urine from the men in Group 1B was found to be greater than that of the men in Group 1A.

Discussion

Cadmium oxide in the form of dust or fume is extremely toxic. Inhalation of high concentrations gives rise to acute chemical pneumonitis. Stephens (1920), Manciola (1940), and Hardy and Skinner (1947) suggested that the presence of small amounts of cadmium in the working atmosphere might give rise to chronic poisoning. Friberg (1950), as the result of an investigation of men exposed to cadmium dust in the manufacture of alkaline accumulators in Sweden, described a chronic illness characterized by emphysema and the excretion of a protein of low molecular weight in the urine. Baader (1951) described a similar syndrome in men manufacturing this type of accumulator in Germany.

The results of the present investigation provide further evidence that repeated exposure to cadmium fume does cause chronic ill health. The illness is characterized by progressive shortness of breath and by the excretion in the urine of a protein complex of low molecular weight. Death occurs as the result of pulmonary heart disease or renal failure. In such cases where the occupational history reveals that the patient has been at risk of absorbing cadmium fume or dust the diagnosis of chronic cadmium poisoning is justified.

Tests of the ventilatory capacity of the lungs which were carried out at both factories showed that there was a definite impairment of respiratory function in the groups of men exposed to cadmium when compared with control groups from the same factories.

The clinical examination and chest radiographs of the men who complained of shortness of breath suggested that the disability was due to emphysema.

The development of the symptoms and the course of the disease in these cases are unlike the chronic hypertrophic emphysema which follows long-standing chronic bronchitis or bronchial asthma, where cough precedes by many years the onset of dyspnoea on exertion. In only a few of the cases found in this investigation was a history of chronic cough obtained. Dyspnoea usually developed gradually over a period of months or years with the development of a cough in the later stages. In some cases cough and dyspnoea followed immediately after a severe upper respiratory tract infection. Whitfield (1952) reviewed the aetiological factors in 103 cases of emphysema and found that 69 gave a history of long-standing chronic bronchitis or bronchial asthma. Only four cases occurred in his series in which the emphysema had developed without a history of preceding pulmonary symptoms.

In studying the men in Group 1B who had been exposed to cadmium for more than 10 years. Buxton found that the volume of the residual air and the residual air expressed as a percentage of the total lung volume were both significantly increased. This is often found in emphysema. When, however, the mean value for the total lung volume of this group was compared with that of the control group (Group CB) it was found to be unaltered and the range was not increased. Furthermore, the mixing coefficients were within normal limits. These results suggest that there are certain differences between the emphysema which develops in men exposed to cadmium fume and the chronic hypertrophic emphysema which follows long-standing chronic bronchitis. In the latter the intrapulmonary mixing coefficient is low and the total lung volume is increased.

Lane and Campbell (1954) describe the necropsy findings in a man who worked on the copper-cadmium furnaces at factory B. In their case not only were there no emphysematous bullae at the periphery of the lungs but there was a narrow zone of normal lung tissue under the pleura and chronic bronchitis was neither widespread nor severe. Thus, the mode of onset, the results of respiratory function tests, and the findings at necropsy in one case support the view that the emphysema which develops in men who have been exposed to cadmium fume is different from the chronic hypertrophic emphysema which follows upon chronic bronchitis. Chronic bronchitis, however, may develop as a complication in men whose lungs have already been damaged by the repeated inhalation of cadmium.

Knowledge of the pathological process and the morbid anatomy of chronic cadmium poisoning

will be fully understood only when more cases have been studied at necropsy.

Friberg (1950) found that the majority of men who had been exposed to cadmium oxide dust in the alkaline accumulator industry for more than eight years excreted a protein in the urine which did not give the usual reactions of urinary protein or Bence-Jones protein. Electrophoretic analysis and examination with the ultracentrifuge suggested that this protein was a globulin and that the molecular weight was in the region of 20,000 to 30,000.

In the present investigation 19 men were found to have proteinuria which gave reactions to routine clinical laboratory tests similar to those of the protein described by Friberg. The boiling test for protein was unreliable; in some cases it was negative and in others a slight cloudiness only was apparent. It was found that non-specific protein precipitants such as 25% trichloroacetic acid and 3% sulphosalicylic acid gave positive reactions when the boiling test was negative or doubtful. Esbach's picric acid reagent produced a general cloudiness on standing but the protein did not settle in the tube so that quantitative determinations by this method were unreliable. Kekwick (1955) describes the results of physico-chemical examination of the serum and of the protein excreted in the urine of four men chosen at random from these 19 cases. The electrophoretic analyses of the sera showed that the proportion of gamma globulin was abnormally high in two cases and that the alpha globulin proportion was slightly above the normal value in all four cases (Kekwick, Table). There did not appear to be a uniformly consistent deviation from the normal which could be attributed unequivocally to cadmium poisoning. Except for one case the electrophoretic pattern of the urinary proteins was similar to those shown in Fig. 1A (Kekwick), where there appears to be a large number of ill-defined components covering a mobility range similar to that of the serum proteins. In Case A3 (Fig. 1B, Kekwick), four relatively well defined components were present but the total protein content of the urine was much higher than in the other cases. In the ultracentrifuge the urinary proteins sedimented as a single component in all four cases. The sedimentation constants correspond with a molecular weight in the range 20,000 to 30,000. Further work is necessary to determine the nature of this protein and to establish whether it is excreted in some form linked to cadmium.

Baader (1952), reporting the case of a man who died as the result of chronic cadmium poisoning, describes the kidney lesion as a toxic nephrosis. In the fatal case reported in this paper (Case A1), the

man died as the result of chronic renal failure. He was under observation for 18 months before death and tests confirmed that the proteinuria was quite unlike that usually associated with chronic glomerulonephritis. The electrophoretic pattern of the protein was non-specific but it was found to have a low molecular weight (Kekwick). On microscopic examination of the kidneys Professor Dorothy Russell was of the opinion that the changes were indistinguishable from the nephritis *repens* of Bright's disease. Further evidence that cadmium causes renal damage is provided by Friberg and Nyström (1952) who re-examined the workmen in the alkaline accumulator industry after five years.

There was no evidence to suggest that these men had any impaired sense of smell, but this may be due to the fact that they were exposed to cadmium oxide fume whereas men who were found to have this complaint in the alkaline accumulator industry were exposed to cadmium oxide dust.

The importance of the presence of cadmium in the urine, except as a confirmation of absorption, is difficult to assess. The quantity of cadmium excreted does not appear to bear any relationship to the severity of poisoning. Workmen exposed to cadmium excreted between 0 and 800 $\mu\text{g.}$ of cadmium per day. Forty-one were excreting more than 30 $\mu\text{g.}$ daily. It was of interest that men who had ceased to work with cadmium for as long as 10 years were still excreting measurable quantities of cadmium in the urine.

All 19 men showing symptoms or signs of chronic cadmium poisoning in this investigation had been exposed to cadmium for more than five years and 13 had been exposed for more than 15 years. Of six men in Group 1B who had worked on the copper-cadmium furnaces for more than 15 years, five were affected (Table 4). All the cases of chronic cadmium poisoning described by Friberg (1950) had more than eight years' exposure to cadmium oxide dust.

The maximum allowable concentration of cadmium in the working atmosphere has been set at 100 $\mu\text{g.}$ per cu. m. (American Conference of Governmental Industrial Hygienists, 1954). In this investigation the average concentration of cadmium in the atmosphere of the workshop over 12-hour periods did not exceed 270 $\mu\text{g.}$ per cu. m. in either factory, but for periods of 15 to 20 minutes every hour during casting the concentration was much higher (King, 1955). These findings are unlikely to be a true reflexion of the working conditions at the time when the majority of the men affected started work. To comply with black-out regulations during the Second World War all windows and doors had to

be closed and covered at night, and the natural ventilation of the workshops was consequently reduced. The average concentration of cadmium in the atmosphere is likely to have been much greater than that found in this investigation. Because there was no evidence in the medical literature to suggest that cadmium could produce chronic ill health, few precautions were taken to remove cadmium from the atmosphere during the war years and in the immediate post-war period. All the men who were affected had worked for at least seven years. Since 1948 conditions have been greatly improved and precautionary measures have been introduced in each factory.

Summary

The results are reported of an investigation of men employed at two factories in England where alloys of copper and cadmium are manufactured.

Five cases of chronic cadmium poisoning including the necropsy findings in one fatal case are described. The findings in a further 18 cases are summarized.

Chronic cadmium poisoning is characterized by (a) the development of emphysema, in which there is some evidence to suggest that the emphysema is not the same as chronic hypertrophic emphysema which follows chronic bronchitis or bronchial asthma; (b) renal disease which is accompanied by the excretion in the urine of a protein with a molecular weight of 20,000 to 30,000. The urinary protein does not give the same reactions to routine clinical laboratory tests as the proteinuria which occurs in glomerulonephritis, cardiovascular-renal disease, or Bence-Jones protein.

Emphysema and proteinuria may both be present or may occur separately in a particular case.

In the fatal case death was due to chronic renal failure.

Twenty-four hour specimens of urine were obtained from 83 men exposed to cadmium.

Cadmium was present in 62 cases and 41 of these were excreting more than 30 μg . per day.

The cadmium concentration of the working atmosphere was estimated under the present working conditions and the significance of these findings in relation to conditions of work in time of war are discussed.

I am indebted to the management of the two factories concerned, particularly the medical and personnel departments without whose wholehearted cooperation the investigation could never have been made.

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APPENDIX I

Case Histories

Case No. A1 (L.H. Record No. 12133/53).—This was a man aged 54 years suffering from chronic renal failure without hypertension and a moderate degree of emphysema. On repeated examination of the urine, the only protein demonstrated was one of low molecular weight which differed from the proteins usually found in the urine in chronic renal disease (Kekwick, Fig. 1). He served in the Armed Forces until 1920 and from 1920 to 1952 he had worked casting an alloy of copper and cadmium. He had also cast brass and bronze during this time. He had always worked on the pit-fire furnace

and for the greater part of this time was responsible for casting the "master alloy" containing 33% cadmium with copper. He had not worked since November, 1952.

He was admitted to the North Staffordshire Royal Infirmary in March, 1953, and transferred to the London Hospital in April, 1953, for further investigation. He was readmitted in uraemic coma on May 20, 1954, and died on May 22.

He was perfectly well until 1948 when he began to get attacks of unproductive cough. These attacks persisted until he stopped work in November, 1952. For 18 months before admission to hospital he had been short

TABLE 7
SUMMARY OF CLINICAL DETAILS OF MEN SERIOUSLY DISABLED BY CADMIUM POISONING

| Case | Date | Hb (g. %) | E.S.R. (Westergren mm./hr.) | Renal Function Tests | | Urine | | Respiratory Function Tests | | | | | Chest Radiograph | Other Data |
|------|----------|-------------|-----------------------------|-----------------------|----------------------------------------------------------|-----------------------------|----------------------|----------------------------|------------------------|------------------------|------------------|-------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | | | | B. Urea (mg./100 ml.) | Urea Concentration Test (maximum urine urea mg./100 ml.) | Mid-stream Specimen | Cd in 24 Hours (μg.) | V.C. (l.) | S.F. ₃₀ (%) | S.F. ₇₀ (%) | M.V.C. (l./min.) | T.C. (sec.) | | |
| A1 | 8. 4.53 | 41 6.1 | 80 | 144 | 900 | Proteinuria | 30-40 | — | — | — | — | — | Normal | Liver function tests normal, normoblastic bone marrow, plasma proteins, see Table 1, Kekwick Died on 22.5.54 |
| | 9.11.53 | 30 | 25 | 141 | — | " | — | 2.83 | 58 | 43 | 74 | 0.79 | Emphysema | |
| A2 | 20. 5.54 | 26 | — | 454 | — | " | — | — | — | — | — | — | — | Liver function tests normal, plasma proteins, 6.45. (albumin 3.22 g. per 100 ml., globulin 3.23 g. per 100 ml.), urea clearance test, 62% 1 hr. P.S.P. excretion, 33.5% 1 hr. |
| | 3. 2.53 | 111 16.5 | 50 | 39 | 1800 | " | 290-980 | 2.46 | 42 | 24 | 42 | 2.39 | Emphysema | |
| A3 | 26.10.53 | 94 | 34 | 42 | 2500 | Proteinuria 0.55 g./100 ml. | 46 | 2.45 | 30 | 17 | 31 | 2.45 | Emphysema | 8.4.52. The results of cardiac catheterization were compatible with emphysema |
| A4 | 18. 3.52 | 104 | 3 | — | — | No protein | 112 | — | — | — | — | — | Emphysema | |
| | 6. 8.53 | 110 | 3 | 38 | 2400 | No protein | — | 2.08 | 30 | 17 | 25 | 4.0 | Emphysema | |
| B1 | 25. 3.54 | 103 | 2 | 45 | 1920 | Proteinuria | 59 | 2.8 | 31 | 17 | 32 | 3.27 | Emphysema | The mixing efficiency, pulmonary diffusing capacity (carbon monoxide technique), and intra - oesophageal pressure studies were carried out at St. Bartholomew's Hospital, London. It was concluded that the disability was due to a moderate degree of emphysema associated with bronchospasm |

of breath on exertion. This was accompanied by a dull, aching pain in the left upper chest which was relieved by resting. There was no past history of haematuria or renal disease.

On examination in April, 1953, there was pallor of the skin and mucous membranes but no obvious loss of weight. There was a pronounced uraemic odour in the breath. He was not dyspnoeic at rest. There was no clinical evidence of cardiac enlargement, but a soft systolic murmur was audible in all areas. The blood pressure was 165/85 mm. Hg on admission to hospital but later fell to and remained at 130/60 mm. Hg. The chest was barrel-shaped and there was increased resonance on percussion with diminution in the area of liver dullness. The breath sounds were vesicular and there were no adventitious sounds. There was no abnormality on examination of the abdomen and the central nervous system.

He was treated with a low-protein diet and unrestricted fluids, but on discharge from hospital his condition was unchanged.

He was readmitted to hospital on November 9, 1953, owing to increasing pallor, shortness of breath, and oedema.

There were purpuric spots scattered over the chest and legs with marked oedema of the legs and back.

He was treated by rest in bed, digitalis folia gr. 1 twice daily, abundant fluids by mouth, and a low-protein diet. He was cautiously transfused with the packed cells of 14 pints of blood over six weeks with marked improvement. On discharge from hospital, haemoglobin was 96% and the blood urea was 165 mg./100 ml.

He was readmitted on May 20, 1954. He had become increasingly drowsy and breathless on exertion for several weeks. On examination he was very pale and almost comatose. There were purpuric haemorrhages of the buccal mucous membranes. There was a pericardial friction rub and the blood pressure was 140/100 mm. Hg.

Haemoglobin was 26% (3.8 g.%) and the blood urea was 454 mg. per 100 ml.

The results of laboratory and other investigations are summarized in Table 7.

Necropsy Findings.—The lungs were oedematous and there was a moderate, diffuse emphysema, with occasional bullae measuring up to 2 by 1 cm. There was a small area, 6 by 3 cm., of focal bronchiectasis in the inferior and posteromedial aspect of the left lung.

There was a sero-fibrinous pericarditis, the pericardial sac containing about 30 ml. of free fluid. The left ventricle was hypertrophied and slightly dilated, and there was slight general atheroma with a few flecks in the main pulmonary arteries.

There was considerable reduction in the size of the kidneys, which weighed only 99 g. The subcapsular surfaces were smooth and grey. The renal cortex was narrow and had an indistinct pattern but contained a few small cysts measuring up to 0.3 cm. in diameter.

The liver was pale and oedematous, weighing 1,829 g. It showed a strong iron reaction as did the otherwise normal spleen. There was mucous catarrh of the stomach and intestines. The endocrine glands and brain were normal.

There was osteoporosis of the sternum, ribs, femora, right radius and ulna, and thinning of the vault of the skull. The sternum and ribs were easily cut with a knife. The sternal marrow was partly adipose and there were islands of bright pink marrow in the upper 8 cm. of the shaft of the right femur. The corticalis of the femur was white and dense.

CADMIUM IN TISSUES

| Tissue | Wet Weight (g.) | Cd in Sample (mg.) | Cd/100 g. Tissue (mg.) |
|-------------------------|-----------------|--------------------|------------------------|
| Muscle | 50 | 0.560 | 1.120 |
| Lung | 125 | 2.53 | 2.024 |
| Kidney | 20 | 1.23 | 6.15 |
| Liver | 75 | 24.76 | 33.01 |
| Spleen | 50 | 1.94 | 3.88 |
| Small intestine | 150 | 1.15 | 0.764 |
| Rib | 40 | 0.290 | 0.725 |
| Long bone | 30 | 0.150 | 0.50 |

Both lobes of the left lung and the lower lobe of the right lung showed great but uneven emphysema. The subpleural zone was not spared. There was moderate anthracosis, and occasional dust-macrophages occupied alveolar spaces. There was no fibrosis and no inflammatory interstitial infiltration apart from a few foci of lymphocytes which were usually adjacent to arteries. In the less emphysematous parts there was extensive oedematous exudate in the alveolar spaces with early stages of purulent bronchopneumonia. The bronchioles elsewhere showed mucous catarrh only. No structural changes were present in the arteries and arterioles.

The pericardium, in sections from both ventricles, bore a few superficial deposits of fibrin. There was oedema of the epicardium which was sparsely infiltrated with polymorphonuclear leucocytes and round cells. This infiltration extended into the adjacent intermuscular septa. The muscle fibres of the right ventricle were slightly hypertrophied, and in the left ventricle this change was more pronounced. In the latter a few small foci of fibrosis were found in the deeper parts of the myocardium. The associated blood-vessels were normal.

The cortex of the kidneys was uniformly reduced in depth and was diffusely affected by interstitial fibrosis.

Many of the glomeruli had undergone ischaemic atrophy in association with fatty-hyaline degeneration of the smaller arterioles. Residual glomeruli frequently appeared unchanged, but some showed degenerative changes in the tuft best demonstrated by the presence of focal sudanophil deposits in the lobules. In such glomeruli there were sometimes adhesions between the tuft and Bowman's capsule. This degenerative change was evidently of a progressive character because a good many glomeruli could be identified in advanced stages of non-ischaemic atrophy, that is, a shrinkage with complete loss of cells in the tuft without the hyaline collagenous thickening of Bowman's capsule that characterizes ischaemic atrophy.

The tubules were often grossly atrophied, containing hyaline casts. Other tubules were dilated, containing brightly eosinophil granular casts mingled with leucocytes, or aggregates of leucocytes alone. In such tubules the epithelium was flattened and the distinctive features of the proximal and distal parts of the nephron were lost. Casts were very conspicuous in the collecting tubules of the medulla. The density of the collagen fibres in the interstitial tissue was variable. Where this was least dense the tissue was more cellular and contained spindle fibroblasts. There was a good deal of lymphocytic infiltration, especially beneath the capsule and near the junction of cortex and medulla. No sudanophil material was present either in the tubules or interstitial tissue.

In addition to fatty-hyaline changes in the arterioles, the larger arteries showed moderate hypertrophy.

Sections from the sternum, a rib, and the right femur showed advanced osteoporosis. The marrow in all was partly adipose; haemopoiesis appeared normal.

No structural changes were present in the liver. The Kupffer cells contained free iron-pigment. Only slight fatty change affected the parenchyma and this was of irregular distribution.

The pulp of the spleen was congested and considerable amounts of free iron-pigment occupied groups of macrophages.

The pituitary, parathyroids, adrenal, and thyroid were normal, apart from discrete colloidal adenomata in the last-mentioned.

In the testis there was diffuse atrophy of the seminiferous tubules without inflammatory infiltration. In a few foci atrophy was complete.

No abnormality was found in sections of the hypothalamus, basal ganglia, and cerebellum.

Case No. A2 (L.H. Record No. 3919/53).—A man aged 52 years suffered from severe emphysema with slight impairment of renal function. The characteristic protein was present in the urine. He had worked all his life in the non-ferrous metal industry but from 1937 to 1950 he had been casting an alloy of copper and cadmium, the first three years on the pit-fire furnace and the latter 10 years on the rocker resistor furnace. He was admitted to the London Hospital in February, 1953.

He was quite well until 1945. Dyspnoea developed at this time and by 1949 he was unable to do his usual job. There was no wheezing and no seasonal variation of the dyspnoea. He developed a persistent cough in

1949 producing 2 to 3 oz. sputum daily. In 1950 he was given a light job in another department in the factory and since 1951 he has been unable to work at all. He had lost 2 to 3 st. in weight since 1948, appetite was poor, and he complained of slight epigastric pain.

On examination in February, 1953, there was obvious muscle wasting and he was short of breath on the slightest exertion. The cardiovascular system was normal with a blood pressure of 115/75 mm. Hg. The chest was barrel-shaped and chest movements were much diminished. There was increased resonance on percussion of the chest and cardiac and liver dullness could not be elicited. Heart sounds were distant, the breath sounds were vesicular, and scattered rhonchi were audible over both lungs. The spleen was palpable two fingerbreadths below the left costal margin and the liver edge was just palpable below the right costal margin. There was no abnormality of the nervous system.

The results of laboratory and other investigations are summarized in Table 7.

Case No. A3 (L.H. Record No. 38128/53).—A man aged 58 years suffered from severe emphysema. The characteristic protein was present in the urine. Except for service in the army in 1914–18 he had always worked in the same factory, and from 1935 to 1946 had been casting alloys of copper and cadmium. He had been employed on the rocker resistor furnace during the whole of this time. In 1946 he was forced to take a light job and since that time he has been unable to resume his former occupation.

He was admitted to the London Hospital in October, 1953. He was quite well until 1943 when he developed cough and dyspnoea. The cough has persisted and the dyspnoea has gradually become more severe. At the present time he can walk only 20 to 30 yards. During the past four years he has complained of a sensation of tightness in the left upper chest which is relieved by rest. Since 1940 he has noticed a clear, watery discharge from the nose which is unrelated to upper respiratory tract infection. He has lost almost 2 st. in weight since 1946.

On examination in October, 1953, there was evidence of marked loss of weight, and he was short of breath on slight exertion. There was cyanosis of the lips. The heart was not enlarged clinically, pulse was regular at 90 beats per minute, and the blood pressure was 130/75 mm. Hg. The chest was barrel shaped with increased resonance on percussion and diminution of cardiac and liver dullness. Breath sounds were present over both lungs, with many high-pitched expiratory rhonchi and basal crepitations.

The results of laboratory and other investigations are summarized in Table 7.

Case No. A4 (L.H. Record No. 25498/53).—A man aged 49 years suffered from severe emphysema. He had always worked at the same factory except for four years in the Potteries where he had been employed grinding clay in a water mill. From 1935 to 1947 he was casting

copper alloys : bronze and brass only from 1935 to 1939 but from 1939 to 1947 he had been employed on the pit-fire furnace casting the copper-cadmium master alloy. Because of his symptoms he changed to a light job in 1947 and has been unable to work since 1950. He was admitted to the Queen Elizabeth Hospital, Birmingham, in March, 1952, and to the London Hospital in August, 1953.

He suffered from a cough from 1942 but there was no disability until 1947, when he noticed that he was getting short of breath on exertion. The dyspnoea became steadily more severe and at present he is able to walk only 25 to 30 yards on level ground. There has been marked loss of weight, amounting to 3 st. in six years. He has suffered from nasal catarrh with a clear mucous discharge since 1940, and he complains of right subcostal pain aggravated by exercise since 1947.

On examination in March, 1952, he was thin, orthopnoeic, and the lips were cyanosed. The cardiovascular system was normal with a blood pressure of 140/90 mm. Hg. The cardiac apex was not palpable and the heart sounds were faint. The chest was barrel shaped with gross diminution of movement on respiration. The expansion of the chest was $\frac{1}{2}$ in. There was increased resonance on percussion of the chest, and cardiac and liver dullness were absent. The breath sounds were audible in both lungs with generalized, high-pitched expiratory rhonchi. Neither the liver nor the spleen was palpable and palpation of the abdomen showed no abnormality. There was no oedema of the ankles.

The results of laboratory and other investigations are summarized in Table 7.

Case No. B1 (L.H. Record No. 9954/54).—This man aged 52 years was suffering from emphysema with slight impairment of renal function. The characteristic protein was present in the urine. He had worked from 1930 to 1940 casting alloys of copper and cadmium in a pit furnace.

He was admitted to the London Hospital in March, 1954.

He first noticed dyspnoea on exertion in 1939. He changed his job in 1940 on the advice of his doctor and since this time has worked in another department of the factory. Since 1951 he has become increasingly dyspnoeic on exertion and he has lost 2½ st. in weight. He has complained of epigastric pain, relieved by alkaline powders, since 1950.

On examination in March, 1954, there was evidence of marked loss of weight and he was dyspnoeic at rest. There was no cyanosis, finger clubbing, or pallor. The cardiovascular system was normal and the blood pressure was 140/90 mm. Hg. The thoracic cage was fixed in inspiration, movement was poor, and there was hyper-resonance on percussion of the chest with absent cardiac and liver dullness. Air entry was good, breath sounds were vesicular with occasional scattered rhonchi.

The results of laboratory and other investigations are summarized in Table 7.

APPENDIX II

Physico-chemical Examination of the Serum and Urine Proteins in Some Cases of Cadmium Poisoning

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Although Friberg (1950) in his monograph on cadmium poisoning gives some data concerning the electrophoretic and ultracentrifugal behaviour of the serum and urine proteins from such cases, the provision of further data in connexion with the present series described by Bonnell (1955) seemed advantageous.

Methods

Treatment of Urine and Serum.—In general the concentration of protein in the urine was too low to permit a satisfactory physico-chemical examination to be made in the usual manner, that is, after simple dialysis to equilibrium against a suitable buffer.

Initially 24-hour samples, but later overnight samples, of urine were dialysed at 2 to 4° immediately after voiding against phosphate buffer pH 8.0 I = 0.02 in order especially to remove urea. Following repeated changes of buffer during 48 hours, the dialysed material, after centrifuging off any slight precipitate which formed, was freeze-dried in 10 ml. quantities in a centrifugal freeze-drying plant. The dry residue was reconstituted in 0.1 of the initial urine volume of distilled water to provide a solution of urinary proteins in phosphate buffer pH 8.0 I = 0.2. This solution was immediately dialysed for 24 hours at 2 to 4° against a large volume of phosphate buffer pH 8.0 I = 0.2 before electrophoretic and ultracentrifugal examination.

Serum samples were dialysed to equilibrium against phosphate buffer pH 8.0 I = 0.2 at 2 to 4°, and diluted with buffer to give a suitable protein concentration for subsequent examination.

Protein concentrations were determined refractometrically on the dialysed solutions of serum or urine proteins.

Electrophoresis Measurements.—These were made in phosphate buffer pH 8.0 I = 0.2 in the Tiselius (1937) apparatus at 0° and a potential gradient of 6. V/cm. Optical observations by the diagonal Schlieren method (Philpot, 1938) were photographically recorded on Ilford half-tone panchromatic plates, using a high pressure Hg arc as a light source from which monochromatic light $\lambda = 546 \text{ m}\mu$. was isolated by a suitable filter.

For the analysis of sera the total protein concentration was 2 g./100 ml. in each instance. For the urine protein analysis the total protein concentration was between 1.1 and 1.5 g./100 ml.

Ultracentrifuge Measurements.—The urine proteins were examined at concentration of 1 g./100 ml. in phosphate buffer pH 8.0 I = 0.2 + 0.15M NaCl. The solutions were subjected to 250,000 g. in the Svedberg oil-turbine ultracentrifuge using a 12-mm. cell, the optical recording being as described under electrophoresis.

Results and Discussion

In the Table the electrophoretic analyses of the sera from four cases of cadmium poisoning are presented together with the values for normal human serum obtained under the same experimental conditions. In two instances the proportion of gamma globulin is abnormally high and in all cases the alpha globulin proportion is slightly above the normal value. There seems, however, to be no uniformly consistent deviation from the normal attributable unequivocally to the effects of cadmium poisoning.

TABLE
THE ELECTROPHORETIC ANALYSIS OF SOME SERA FROM PATIENTS WITH CADMIUM POISONING

| Serum Sample | Total Protein (g./100 ml.) | Electrophoretic Analysis | | | |
|---------------|----------------------------|--------------------------|-------|------|-------|
| | | Globulins | | | |
| | | Albumin | Alpha | Beta | Gamma |
| A3 | 7.25 | 53.8 | 9.2 | 16.6 | 20.5 |
| B3 | 6.94 | 56.9 | 9.5 | 10.8 | 22.9 |
| A1 | 6.84 | 65.7 | 9.9 | 12.0 | 12.4 |
| B2 | 6.26 | 67.8 | 7.0 | 13.1 | 12.2 |
| Normal values | 6.75 | 65.1 | 6.4 | 15.1 | 13.6 |

In Fig. 1 electrophoresis and ultracentrifuge diagrams of the urinary proteins are given. Except in one instance the electrophoretic characteristics of the urinary proteins were similar to those shown in Fig. 1a, where there appears to be a very large number of ill-defined components covering a mobility range similar to that of the serum proteins. In the divergent case (A3, Fig. 1b) four relatively well defined components were present but in this patient the total urine proteins at about 0.5 g./100 ml. were very much higher than in any other instance.

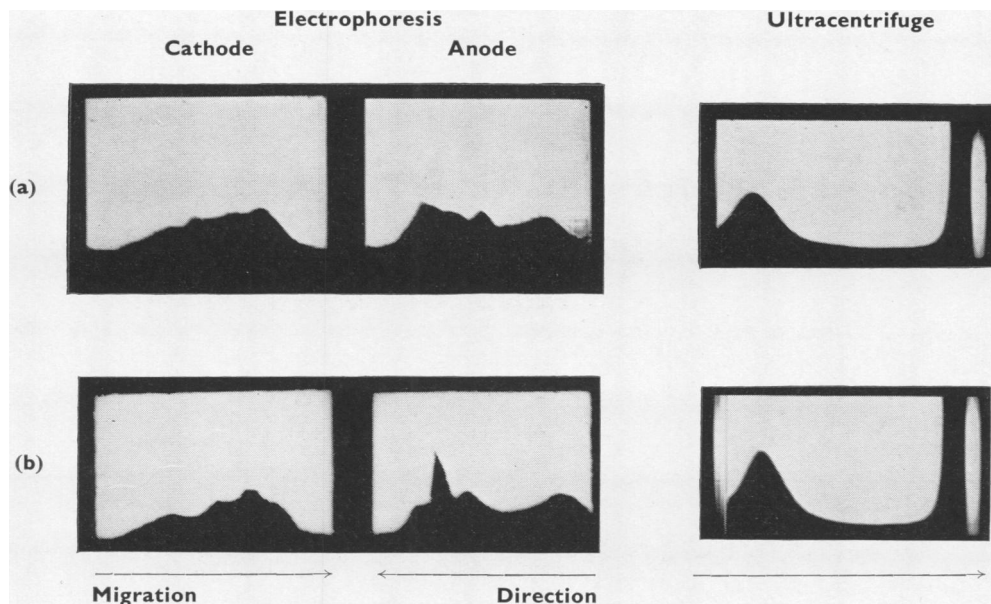


FIG. 1.—Electrophoresis and ultracentrifuge diagrams of urine proteins (a) Patient B3: electrophoresis after three hours at 15 mA., pH 8.0 I = 0.2. (b) Patient A3: ultracentrifuge after 80 minutes at 54,000 rev./min.

The urine proteins sedimented in the ultracentrifuge as a single component (Fig. 1), which is somewhat surprising in view of the complexity of the electrophoretic behaviour. Values for the sedimentation constant determined on solutions containing 1 g. protein/100 ml. varied from 2 to 2.2 S. These would correspond with a molecular weight in the range 20,000–30,000 which is very much lower than that of any known serum protein.

The data for the sera are similar in some instances to those given by Friberg (1950): the sedimentation coefficients obtained for the urine proteins are of the same order as the values quoted by him. In general a more complex electrophoretic behaviour was observed for the urinary proteins, but this may have been due to the fact that Friberg in many cases concentrated the urinary proteins by precipitation with ammonium sulphate. This procedure may not

have provided such representative preparations as would be obtained by freeze drying the total urinary protein.

Summary

The serum and urinary proteins from patients suffering from cadmium poisoning have been examined physico-chemically.

While the serum proteins show divergencies from the normal electrophoretic distribution, no characteristic deviation appears consistently.

The urinary proteins show a large number of electrophoretic components but sediment as a single component of a molecular weight in the range 20,000–30,000.

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