Case Report

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Cardiomyopathy accompanying industrial cobalt exposure

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A case of cardiomyopathy in a 41-year-old metal worker is described. High concentration of cobalt in the organs and the morphological findings in the heart suggest cobalt cardiomyopathy to be the underlying disease.

The toxicity of cobalt has recently been discussed in association with the so-called beer drinkers' cardiomyopathy. This disease was reported first from Quebec City where 48 cases were observed clinically with 20 fatalities (Bonenfant, Miller, and Roy, 1967; *Journal of the American Medical Association*, 1966; *Canadian Medical Association Journal*, 1967). Similar cases were published from Omaha, Nebraska (McDermott *et al.*, 1966), and from Belgium (Kesteloot *et al.*, 1968). It was felt that cobaltous sulphate added to the beer was mainly responsible for the myocardial damage (Morin and Daniel, 1967). In animal experiments, it was possible to produce acute myocardial damage by treatment with excessively high doses of cobalt compounds (Grice *et al.*, 1969a,b; Kaspersek, Siller, and Knieriem, 1969; Knieriem and Herberthz, 1969). Nutritional factors appeared to predispose to cobalt toxicity (Alexander, 1969).

In medical practice, cobalt salts were used for the treatment of anaemias with considerable success (Berk, Burchenal, and Castle, 1949; Fountain and Dales, 1955). Undesired side effects have been reported (Wintrobe, 1967); cardiomyopathy, however, did not appear. Neither have there been any reports of cobalt-induced cardiomyopathy in industry, in spite of the intensive and long-lasting exposure to cobalt of workers with hard metal alloys. The disease has been reported so far only as cardiomyopathy of beer drinkers.

The following is a case of fatal disease in a metal worker who had been exposed to

cobalt for some time. The necropsy findings, together with the results of the determination of cobalt in the tissues, indicate a causal relation.

Case report

A 41-year-old man was admitted to the hospital on 6 March 1966, with the symptoms of a general malaise, non-productive cough, and oppressive pain below the left costal margin. During previous medical checkups he had always been reported as healthy, with normal chest x-rays and routine laboratory value examinations, except slightly raised RBC count (around 5,800,000), Hb values (17-20 g/100 ml), and haematocrit (50%).

Physical examination on admission showed congestion of the conjunctivae, auscultatory rales over the chest, and enlargement of the heart. A chest x-ray showed enlargement of the heart to both sides (Fig. 1). Laboratory findings: RBC 6,700,000, Hb 20 g/100 ml, WBC 6,800, ++ proteinuria with granular casts. Non-protein nitrogen was 33 mg/100 ml on the day of admission, rising to 55 mg/100 ml on the second day. Serum aspartate and alanine transferases were within normal limits. Electrocardiogram showed sinus rhythm with low voltage in the extremity leads, high and widened P in leads II and III, and biphasic P in V. PR interval 0.14 sec, QRS 0.08 sec, right axis deviation, and transition zone in the chest leads in V₅. The electrocardiographic pattern was described as suggestive of right ventricular hypertrophy.

On the second day of admission the patient complained of oppressive pain under the left costal margin. He vomited and became irritated. There was cyanosis, increased filling of the cervical veins, tachycardia 120/min, and soft pulse. Blood pressure dropped to immeasurable values and right-sided hemiparesis developed.

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FIG. 1 Chest x-ray taken 2 days before death. The heart appears very enlarged.

Temporary improvement resulted from norepinephrine infusion, and injections of strophanthin and aminophylline; however, further deterioration led to death on 9 March, 3 days after admittance to hospital.

Necropsy findings Heart weighed 490 g. Both atria and ventricles were dilated, the left ventricular wall was thickened (13 mm), the right ventricular wall showed trabecular hypertrophy. Myocardium of both ventricles was pale. Cardiac valves were normal, and coronary arteries were patent with only a few atherosclerotic plaques. Minimal atherosclerotic changes were found in the aorta. The lungs showed congestion and slight oedema. The thyroid gland was moderately enlarged. There were effusions in both pleural cavities (500 right and 150 ml left side) and in the pericardial sac (500 ml).

Microscopical examination Histological study of several areas from the ventricles showed a similar pattern: the myocardial fibres were mostly thickened, fragmented, with obvious focal vacuolar change. The interstitial connective tissue separating the fibres was diffusely increased and oedematous (Fig. 2). There was no inflammatory reaction in any of the areas studied. The endocardium showed diffuse thickening, with occasional small parietal thrombi. The intramural

FIG. 2 Representative area of the left ventricular myocardium. Note irregularity, thickening, and vacuolar degeneration of the muscle fibres and the loose interstitial connective tissue. (H and E. $\times 250$.)

coronary branches were patent. Histology of the thyroid showed normal structure except several areas where the alveoli were small, lined with columnar epithelium, and contained little colloid. The lungs were congested. Histology of the liver, kidneys, and spleen revealed both acute and chronic congestion. Examination of sternum, rib, and vertebral body showed normal pattern of haemopoietic tissue.

In summary, the necropsy revealed cardiomegaly with cardiomyopathy of an unknown origin. The myocardial changes could not be attributed to the minimal atherosclerotic changes present in the coronary arteries. There were no valvular deformities and, microscopically, no signs of inflammation. Thyroid gland showed focal signs of activation. The cause of death was cardiac insufficiency.

A sample from the left ventricular myocardium was analysed for the content of cobalt. The value found was $37 \mu\text{g}/100 \text{ g}$ wet weight of the heart muscle or $140 \mu\text{g}/100 \text{ g}$ dry tissue weight (Table).

TABLE Organ concentrations of cobalt in case of cardiomyopathy and in two control cases

Organ	Cardiomyopathy		Controls			
	$\mu\text{g}/100 \text{ ml}$ wet weight	$\mu\text{g}/100 \text{ ml}$ dry weight	Uraemia		Cor pulmonale	
			$\mu\text{g}/100 \text{ ml}$ wet weight	$\mu\text{g}/100 \text{ ml}$ dry weight	$\mu\text{g}/100 \text{ ml}$ wet weight	$\mu\text{g}/100 \text{ ml}$ dry weight
Heart	37	140	5	20	2	10
Lung	17	107	7	40	3	20
Liver	34	135	3	10	3	10
Spleen	19	87	4	20	1	10
Kidney	29	140	3	10	1	10

Discussion

This report describes a case of cardiomyopathy in a patient who had been exposed for 4 years to cobalt. Clinical features (age, sudden manifestation of the disease, short clinical course with a fatal outcome, clinical signs of cardiac insufficiency, electrocardiographic findings) resembled beer drinkers' cardiopathy. Low serum enzyme values (SGOT, SGPT) were not in disagreement with the diagnosis of cardiomyopathy; in the Quebec cases high levels of serum enzyme were ascribed more to the secondary liver damage than to the myocardial involvement. Postmortem chemical analysis showed massive accumulation of cobalt in tissues. In the myocardium the concentration exceeded the values given by Sullivan, Parker, and Carson (1968) in fatal cases of beer drinkers' cardiopathy. Necropsy findings also corresponded with the pathological findings in cases of beer drinkers' cardiopathy (Bonenfant *et al.*, 1967; Grinvalsky and Fitch, 1969; McDermott *et al.*, 1966; Rona, 1968).

The toxic effect of cobalt is known since the experimental work of Webb (1962, 1964). Cobalt apparently inhibits several enzymes, most probably by competition with magnesium and calcium ions that are necessary for the enzymatic activity. It thus interferes with the breakdown of metabolites in the Krebs cycle, with the metabolism of pyruvate, fatty acids, and with the terminal electron transport mechanism (Dingle *et al.*, 1962; Hall and Smith, 1968; Levy, Levinson, and Schade, 1950; Webb, 1962, 1964; Wiberg, Munro, and Morrison, 1967). Enzymatic inhibition may be combined with partial replacement of calcium on sites where it is necessary for muscular contraction. As stressed by Kaufmann and Fleckenstein (1965), this leads to myocardial insufficiency characterized by a defective utilization of the high energy phosphates.

The interference of cobalt with the cardiac metabolism causes obvious myocardial weakness with dilatation of the heart and secondary parietal thrombosis, a picture similar to the description of the acute fulminating form of beri beri heart disease. Light microscopical findings are similar (Grinvalsky and Fitch, 1969).

Histochemical studies of Hall and Smith (1968) in animals intoxicated with cobaltous sulphate or chloride showed an abundance of glycogen, some increase in the overall enzymatic activity of beta-hydroxybutyric dehydrogenase, and decrease in activity of succinic dehydrogenase. The findings have

been interpreted as a sign of metabolic changes in the heart muscle caused by cobalt. However, an obvious loss of body weight was reported in this study dealing with the histochemical changes after poisoning with cobalt. It seems that, in addition to the toxic effect of cobalt, accumulation of glycogen and enzymatic changes may have resulted from starvation.

Ultrastructural changes after an experimental intoxication with cobalt (Grice *et al.*, 1969a, b; Hall and Smith, 1968; Knieriem and Herbertz, 1969) show severe damage to the cardiac muscle cells with disappearance of the myofibrils, aggregation of mitochondria, fatty degeneration, and final disappearance of the cells and fibrosis. Similar findings were reported in human cases examined with the electron microscope (Alexander, 1968; Auger and Chenard, 1967). The ultrastructural observation of one case by Wellman (1968), though it resembles findings in experimental cobalt intoxication, lacks some important information (intake of cobalt). Clinical findings and the electron microscopical pattern in this case also differ slightly from the Quebec cases.

Little is known so far about the conditions responsible for the individual differences in toxicity of cobalt for man. It seems that cobalt alone is not responsible for the cardiotoxicity, and that additional features such as deficient diet, alcohol, viral infection, and electrolyte imbalance (Wiberg *et al.*, 1969) sensitize the tissues to excessive intake of cobalt. This would explain the appearance of beer drinkers' cardiomyopathy in only a small percentage of the population consuming high quantities of beer with increased concentration of cobaltous sulphate and the apparently rare occurrence of cobalt cardiomyopathy among metal workers. Lung fibrosis may be more frequent as a complication in workers with hard alloys (Bech, Kipling, and Heather, 1962), and it may cause secondary heart insufficiency.

In the history of the case presented it is difficult to specify any possible contributory factor. There is no indication of an excessive alcohol (beer) intake and an inadequate diet. The findings in the heart and thyroid are similar to those found in cases of beer drinkers' disease. It is felt that, because of the high content of cobalt found in the organs, especially in the heart muscle, and because of the lack of any other causal factor for the myocardial lesion, the case may well be an example of cobalt cardiomyopathy secondary to an industrial exposure to this metal.

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