All chambers of the heart are affected in experimental cobalt cardiomyopathy, with atrial pre-
dilection. The primary morphological alteration is mitochondrial damage that possibly reflects
an enzymatic block of oxidative decarboxylation at pyruvate and ketoglutarate levels. In acute
cobalt toxicity chelation of calcium may also be a contributory factor, resulting in deficient
utilization of high-energy phosphates. Experimental cobalt cardiomyopathy requires precon-
ditioning factors: protein deficiency appears to be one of them. Vegetative polypoid endocarditis
is an important accompaniment in the model used, suggesting that in rats on a protein deficient
diet cobalt produced endothelial damage in addition to a cardiocyte injury.

In 1965 investigators in Quebec (Morin et al., 1967) and Omaha (McDermott et al., 1966) observed an endemic cardiomyopathy in heavy beer drinkers. Though epidemiological studies suggested a multicausal origin, cobalt, a beer additive, appeared to play a major part (Kesteloot et al., 1968). Since the Quebec outbreak, studies on experimental animals have been carried out in collaboration with Dr. C. J. Chappel to reproduce the characteristic vacuolar and dystrophic ‘myo-
cardosis’ of humans (Bonenfant, Miller, and Roy, 1967; Rona, 1968) and to gain an insight into the pathogenesis of this condition, using cobalt administration alone or in combination with hormonal and nutritional factors.

Methods and results

Male Sprague-Dawley rats weighing 200–250 g. were used. Cobalt sulphate alone, adminis-
tered orally in high dosage (100 mg./kg.), was cardiotoxic. However, the incidence of myo-
cardial changes was low as the rats died prematurely in systemic circulatory failure. The lesion consisted mainly of fatty change, contraction bands, and hyaline myofibre necrosis (Fig. 1). This acute cardiotoxicity of cobalt was probably related to a competitive inhibition of Ca (Kaufmann and Fleckenstein, 1965) that resulted in an inability of cardiac muscle cells to utilize high energy phosphate and to sustain mechanical tension in the state of excitation.

As cobalt inhibits the biosynthesis of thy-
roxin and cobalt administration results in thyroid alterations (Bonenfant et al., 1967),
the predisposing role of hypothyroidism was considered. Though both prior treatment with propylthiouracil and thyroidectomy aggrava-
ted the myocardial changes of cobalt-
treated rats, no distinct dystrophic-vacuolar cardiomyopathy was produced. The same results were obtained after the simultaneous
administration of a sympathomimetic drug
(isoprenaline) and cobalt, or by a combination
of thiamine deficiency and cobalt.
A combination of protein-deficient diet and
cobalt administration was also studied. In
these experiments cobalt sulphate, containing
from 4.0 to 12.5 mg./kg. cobalt ion, was given
daily in 1.0 ml. distilled water by gavage to
280 rats for two weeks. Before this procedure
the rats were preconditioned for 10 days by
protein restriction. Severe cardiomyopathy
occurred in rats receiving the low protein diet
consisting of 4 per cent casein and treated
with 12.5 mg./kg. cobalt ion. All chambers of the
heart were involved; apparently the atrial
myocardium underwent more extensive dam-
gage than that of the ventricles. At the light
microscopical level the swollen cardiac muscle
cells contained coarse irregular myofibrils.
Hydropic vacuoles alternated with stippled
basophilic areas. The latter change was particu-
larly prominent in 1 μm. thick sections of
Epon embedded material stained with tolu-
dine blue (Fig. 2). In advanced cases there was
partial or complete lysis of the muscle cells
leaving empty sarcolemmal sheaths behind.
The most ubiquitous fine structural feature
of the myocardial lesions was swelling of the
mitochondria, with decreased matrical density
and, finally, disruption of the cristae and the
outer membrane (Fig. 3). In addition, dilata-
tion of sarcoplasmic reticulum and intra-
sarcomplasmic oedema were noted. The myo-
filaments were pushed to the periphery of the
cell or occupied a perinuclear position.

Discussion
These histological and fine structural altera-
tions correlate well with the metabolic de-
rangement of protein deficiency (Svoboda,
Grady, and Higginson, 1966) and cobalt
toxicity (Grice et al., 1969; Hall and Smith,
1968). Cobalt interferes with myocardial
energy metabolism, as it irreversibly chelates
with the dithiol form of lipoic acid (Dingle
et al., 1962; Webb, 1962), inactivating the
coenzyme required for the oxidative decar-
boxylation of pyruvate to acetyl coenzyme A
and alpha ketoglutarate to succinate (Alexan-
der, 1969). Pyruvate and lactate accumulation
in the mitochondria increases osmotic pressure

FIG. 2 Pale perinuclear areas of cardiocytes represent swollen mitochondria. (Epon embedded 1 μm. thick section, stained with toluidine blue. × 1280.)

FIG. 3 Electron microscopic presentation of swollen mitochondria, dilated sarcoplas-
mic reticulum, and intrasarcoplasmic oedema. (× 20,800.)
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and results in water binding, oedema, and finally structural disruption. Aminoacids combine readily with cobalt and prevent its chelation with sulphhydryl groups of the myocardial tissue (Alexander, 1969; Wiberg et al., 1969). Protein deficiency blocks this protective mechanism. Whereas the fine structural changes the mitochondria presented are non-specific, a pathognomonic feature of cobalt intoxication was the appearance of dense osmophilic intramitochondrial particles, measuring 0.3–0.4 μm. in diameter (Fig. 4), considered to represent cobalt-protein complexes (Knieriem and Herbertz, 1969; Kasperek, Siller, and Knieriem, 1969). These differed from the fine granular intramitochondrial calcium deposit described in a variety of myocardial injuries.

In addition to the myocardial lesion, polypoid vegetative endocarditis developed in 10–35 per cent of rats receiving the low-protein diet and treated with cobalt. The mitral valve was affected predominantly (Fig. 5), but vegetations also occurred occasionally on the aortic and tricuspid valves and on the parietal endocardium. A non-necrotizing granulomatous inflammatory process developed around the vegetations (Fig. 6). Blood cultures from these rats were negative. Electron microscopical findings consisted of endothelial cell alteration leading to endothelial discontinuity that allowed platelets to be carried into the subendothelial stroma. In the depth of the valve there was polymerized fibrin among proliferating fibroblasts (Fig. 7). Though it is conceivable that endothelial damage may be the primary factor in the genesis of endocarditis, platelet conglutination may also be important, since oxidation of the free SH groups on the platelet surface, a step in platelet conglutination (Skålhegg, Hellem, and Ødegaard, 1964), may be affected by cobalt and protein deficiency.

FIG. 4 Electron dense intramitochondrial particles represent cobalt-protein complexes. (× 16,300.)

FIG. 5 Gross presentation of polypoid endocarditis in the mitral valve of a rat on protein-deficient diet treated with 12.5 mg./kg. cobalt ion daily.
References


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