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Chemical exposures at work and cardiovascular morbidity

Atherosclerosis, ischemic heart disease, hypertension, cardiomyopathy and arrhythmias

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KURPPA K, HIETANEN E, KLOCKARS M, PARTINEN M, RANTANEN J, RÖNNEMAA T, VIIKARI J. Chemical exposures at work and cardiovascular morbidity: Atherosclerosis, ischemic heart disease, hypertension, cardiomyopathy and arrhythmias. *Scand J Work Environ Health* 10 (1984) 381—388. Relatively little systematic research has been directed towards the potential effects, either etiologic or aggravating, of industrial chemicals on cardiovascular diseases. While some evidence indicates that exposure to certain pesticides might affect lipoprotein metabolism in man, there is no consistent documentation to support the view that atherosclerosis is caused in man by chemical exposures in industry. In this respect results from some animal studies are highly interesting, eg, exposure to some carcinogens, but the hypotheses presented have not yet been vigorously tested in man. Exposure to carbon monoxide is detrimental to the myocardium, especially in patients with ischemic heart disease, but there are no reliable data on elevated cardiac mortality due to carbon monoxide exposure in industrial populations. A few studies have reported arrhythmias or sudden deaths among workers exposed to solvents and organic nitrates. The effects of lead and cadmium upon human blood pressure have remained controversial, although the bulk of controlled epidemiologic studies suggests that they, if at all existent, are not strong.

Key terms: arsenic, cadmium, carbon disulfide, carbon monoxide, lead, nitrates, organic solvents, pesticides, polynuclear aromatic compounds, serum lipids.

Cardiovascular diseases (CVD) comprise one of the most important public health areas in modern industrialized societies. However, only a few reviews on chemical exposures in relation to CVD morbidity have been published. Rosenman (70) has reviewed the subject, and also the American Heart Association (33) has published a report on the impact of the environment on CVD. Although most typical textbooks of toxicology have not included a chapter on the cardiovascular system, special books are now available on cardiovascular toxicology (10, 89).

A number of chemicals acutely influence cardiovascular function. The insidious long-term effects are, however, more interesting perhaps from the occupational health point of view. The objective of this article is to scrutinize briefly some of the CVD for which data have incriminated chemical exposure

of either etiologic or aggravating importance. It is apparent that many such topics still remain highly controversial.

Atherosclerosis

Atherosclerosis is a disease, or a group of diseases, with etiologies and mechanisms that have puzzled researchers for decades. Although several propositions for the genesis of atherosclerosis have been put forward, no general consensus on their details prevails among scientists. However, during the last ten years, most published data are in favor of the so-called response-to-injury theory in its expanded form (71).

Carbon monoxide

Rabbits fed a very rich cholesterol diet and exposed to about 200 ppm of carbon monoxide (carboxyhemoglobin approximately 15 %) for a few months (7) showed an increased cholesterol content of the aorta. Even rabbits exposed to carbon monoxide without a cholesterol diet showed atherosclerosis (92). The proposed mechanism, increased permeability of the endothelial membranes to plasma components, was in line with the infiltration and the response-to-injury theory of atherosclerosis. However, later experiments on normocholesterolemic rabbits by partly the

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same investigators failed to reveal any arterial histotoxicity of carbon monoxide (42, 43). Carbon monoxide exposure induced atherosclerosis of the coronary arteries in *Macaca irus* monkeys (82) and in squirrel monkeys on a high cholesterol diet (93), but not in the aorta or carotic arteries (93).

The cynomolgus monkey is an excellent animal for the study of atherosclerosis (47). Atherosclerotic lesions were not detected in monkeys with carboxyhemoglobin levels of 5–10 % for 14–24 months (31) or when the carboxyhemoglobin intermittently reached levels of 21 % (14, 58). Cynomolgus monkeys exposed to carbon monoxide for a year showed a rise in plasma and tissue free fatty-acid concentrations, but the ratios of plasma triglycerides and high-density lipoprotein (HDL) to total cholesterol remained unchanged (14). Long-term exposure to carbon monoxide did not increase the plasma cholesterol level of monkeys on a high cholesterol diet (58, 93).

Carbon disulfide

Especially in the 1950s and 1960s reports were published suggesting that viscose rayon workers exposed to carbon disulfide showed an increased occurrence of atherosclerotic disease. The mechanisms through which carbon disulfide would cause atherosclerosis are not well understood. Effects upon glucose and lipid metabolism and blood coagulation and direct toxicity upon the arterial walls have been suggested. Carbon disulfide exposure is possibly associated with elevated serum cholesterol levels (67, 88), though the increase is not remarkable. In men exposed to carbon disulfide concentrations of 30 mg/m³ the changes in serum lipids were found to be negligible (27). An inhibitory effect of carbon disulfide on thyroid function has been suggested (57); such an effect would raise the low-density lipoprotein cholesterol concentration and lead to atherosclerosis. However, in tests of the thyroid function of men exposed to carbon disulfide, no such effect was indicated (88).

Pesticides

Serum cholesterol, especially low-density lipoprotein cholesterol, is a central promoting factor in atherosclerosis. High-density lipoprotein is considered to protect against atherosclerosis (11, 64, 81). The protective effect is thought to be exerted by HDL₂ (35, 65).

Interestingly, pesticide exposure is associated with increased serum lipid concentrations (1, 16, 44, 79). The mechanism(s) of the effect is unknown. In one study 40 % of the men exposed to lindane and DDT (chlorophenothane) showed hyper-HDL-lipoproteinemia (16). Among these subjects there was no evidence of alcoholism, which is also known to be associated with increased high-density lipoprotein concentrations in serum (45).

Tetrachlorodibenzo-p-dioxin (TCDD) induces hyperlipoproteinemia in animals (59, 98) and humans (91). In guinea pigs a single dose of TCDD induced a 19-fold increase in the very low-density lipoprotein concentration, and a fourfold increase occurred in the low-density lipoprotein concentration (79).

Metals

There is limited information on the effects of metal exposures on lipid metabolism and atherosclerosis. Cadmium in the drinking water of pigeons reduced high-density lipoproteins in serum and accelerated the formation of atherosclerotic plaques. Total aortic lipids increased when rats received cadmium in drinking water during their entire lifetime, while serum cholesterol decreased. [See the report of Revis (69).] In a Russian study rabbits exposed to lead while on a diet of cholesterol showed more accelerated atherosclerosis than rabbits fed the same diet but without lead exposure. Lead alone did not exert such an effect [See the review of Rosenman (70).].

Polynuclear aromatic compounds

Vascular lesions in atherosclerosis are not uniformly distributed; instead they are isolated patchy formations in the arterial walls. This phenomenon is compatible with the monoclonal hypothesis of atherosclerosis (13), according to which atherosclerotic lesions might be derived from the proliferation of a single cell and could be considered benign tumors. If so, initiators or promoters of atherosclerotic lesions could be regarded as analogous to those that are associated with carcinogenesis.

Treating chickens with polynuclear aromatic compounds accelerates atherosclerosis without markedly altering the serum cholesterol level (2, 15). To act as a carcinogen benzo(a)pyrene must be metabolized by aryl hydrocarbon hydroxylase. So far two animal species susceptible to atherosclerosis have shown aryl hydrocarbon hydroxylase activity in the aorta in contrast to two species that are resistant to atherosclerosis (40). Such findings emphasize the need of screening for chemicals that promote the growth of aortic smooth muscle cells. Some chemicals might foster both carcinogenesis and atherogenesis.

The results of one epidemiologic study could, perhaps, be interpreted along the lines already described. Chimney sweeps are exposed to carcinogens, including polynuclear aromatic compounds. A mortality study of 713 Danish chimney sweeps found 12 cancer deaths versus 5.3 expected and 12 deaths from ischemic heart disease against 5.4 expected (32). These figures might suggest that some carcinogens are associated with human atherogenesis. A larger cohort of 2 071 Swedish chimney sweeps showed 80 deaths from diseases of the circulatory system as against 77.7 expected (41).

Ischemic heart disease

Carbon monoxide

Relatively low carboxyhemoglobin concentrations can precipitate anginal pain in exercising subjects with coronary heart disease. In two double-blind studies, patients with angina showed reduced exercise time on a bicycle ergometer prior to the onset of anginal pain at a carboxyhemoglobin level of 2.8 % (3, 4). Coronary blood flow increases in healthy man when carboxyhemoglobin is rapidly raised to about 6–12 % (9). A decline in the partial pressure of oxygen in the coronary sinus blood was detected in almost all the patients with coronary heart disease, and the myocardial metabolism showed signs of tissue hypoxia (9).

In the United States a population study suggested an association between atmospheric levels of carbon monoxide and increased mortality from myocardial infarction in Los Angeles (21), but potential confounders were not effectively controlled. By contrast, a similar study in Baltimore (49) showed no association between ambient carbon monoxide levels and myocardial infarction or sudden death.

Epidemiologic studies on the relation between carbon monoxide exposure and ischemic heart disease in industrial populations are scarce. The prevalence of angina among Finnish foundry workers showed an exposure-response relationship with regard to carbon monoxide exposure, but no such result was found for ischemic electrocardiographic findings (38). The potential effect of heat stress was not effectively controlled.

Methane-derived halogenated hydrocarbons

Methane-derived di- and trihalogenated hydrocarbons, such as methylene chloride, are metabolized into carbon monoxide (25). Two myocardial infarctions followed by a third, fatal episode, each of the three occurring after exposure to methylene chloride, has been reported for one patient (77). A life-table analysis of men continuously exposed to low levels of methylene chloride did not reveal excess mortality due to exposure (28).

Carbon disulfide

All mortality studies of workers exposed to carbon disulfide have reported an increased mortality from ischemic heart disease. Tiller and his co-workers (83) reported that cardiovascular deaths amounted to 42 % among the exposed workers as against 24 % among other workers in the same factory.

The cardiovascular mortality of Finnish men exposed to carbon disulfide has been monitored since 1967 (38, 39, 66, 67, 84). The first results showed a 4.7-fold mortality from ischemic and other heart diseases. The rate difference for total mortality was almost identical with that for coronary heart disease

alone. There was also an excess of angina prevalence, higher levels of blood pressure, and pathological electrocardiographic findings in the exposed group. The effect of carbon disulfide on coronary mortality was largely independent of the diastolic blood pressure and age (67). Exposure to carbon disulfide and hydrogen sulfide had probably been about 20 to 40 ppm in the 1950s, and 10 to 30 ppm in the 1960s. Hygienic improvements in 1972–1974 reduced the exposure to less than 10 ppm. The rate ratio of cardiovascular deaths became 1.0 after the intervention. Estimates indicated that 59 CVD deaths related to carbon disulfide exposure, instead of the actual 19, would have occurred without the intervention.

Results regarding morbidity from myocardial infarction and anginal pain are not consistent. The rate ratio of 2.8 for nonfatal infarctions was shown among the exposed in Finland (86). Yet, in Holland, no excess of ischemic heart disease was found (90). A low occurrence of coronary heart disease and a high occurrence of retinal microaneurysms in Japan, as compared to the corresponding occurrences in Finland (78, 85), may reflect the importance of the interaction between various genetic, environmental, and nutritional factors.

Organic nitrates

In the explosives industry so-called “Monday deaths” have occurred in the “abstinence phase,” ie, 36–72 h after the last exposure to nitroglycol or nitroglycerin (17). [See also the studies of Hogstedt (41), Morton et al (60), and Symansky (80).] The mechanism(s) of these deaths has remained elusive, although arrhythmia and coronary artery spasm are both conceivable candidates.

The deaths were sometimes preceded by symptoms simulating angina pectoris. Nine patients with chronic exposure to nitroglycerin and “Monday morning angina” on withdrawal from exposure have been studied (51). Four of these patients had myocardial infarction. Angiography showed that all four had normal or nearly normal coronary arteries. One of the four developed a coronary artery spasm with anginal pain when studied 74 h after removal from exposure. Nitroglycerin taken sublingually immediately relieved the symptoms and angiographic findings. This aspect will be further discussed in conjunction with arrhythmias.

Swedish workers exposed to nitroglycerin and ethylene glycol dinitrate for at least 20 years showed a crude rate ratio of 2.5 for cardiovascular mortality. An increased risk of death was not found for exposure periods shorter than 20 years. [See the report of Hogstedt (41).]

Arsenic

A crude rate ratio of 2.2 for cardiovascular mortality was reported for workers exposed to arsenic at a copper smelter in Sweden (8). There was a dose-

response relationship over the categories of exposure. The results were congruent with those of one earlier study on arsenic-exposed smelter workers (54).

Hypertension

Cadmium

Cadmium induces high blood pressure in various animals (52). Several attempts to clarify such hypertensive mechanisms have remained inconclusive.

Experimental studies on cadmium have shown an intriguing biphasic response. Contractility of isolated arteries to nerve stimulation was increased by low doses and decreased by high doses of cadmium (63). Hypertension was observed in rats whose drinking water contained a cadmium content of 5 mg/l, whereas hypotension ensued at a dosage of 50 mg/l (69). An 18 month's study on 520 rats found that systolic blood pressure increased 20 % at a cadmium intake of 10 $\mu\text{g}/\text{d}$. Heavier cadmium exposure lowered, not raised, the blood pressure. The results indicate, according to the authors, that cadmium induces maximum cardiovascular changes in rats at levels to which the average American is exposed (46). It is possible that the concentration of cadmium in the vascular tissue determines whether the response is hypotensive or hypertensive.

Some studies have associated environmental cadmium exposure to human hypertension (18, 72, 73), but others have not [see the reports of Lauwerys (53) and Staessen et al (76)]. Occupational exposure to cadmium has not been associated with hypertension [see the report of Lauwerys (53)], nor is there such evidence among patients with cadmium-induced itai-itai disease [see the review edited by Tsuchiya (87)]. The biphasic cadmium effect on blood pressure in experimental animals should be of interest in the design of future epidemiologic research.

Lead

Attempts to produce hypertension in experimental animals by prolonged treatment with lead have remained inconclusive (95). Such a controversy could be due to species differences. [See the report of Revis (69).]

Hypertension is rarely seen in the early phase of clinical lead intoxication (19). Yet, in the United States, workers exposed to lead were reported to have an increased prevalence of hypertension (55, 56). These studies did not employ concurrent reference groups however. The high prevalence of cardiovascular disease in a small community in Scotland was recently blamed on a lead-associated high hypertension rate (12). In contrast, a more extensive population study in Belgium found no evidence that environmental lead exposure contributed to blood pressure variability (76).

A study on workers with prolonged exposure did not uncover an increased occurrence of hypertension

among the "lead-affected" workers when compared with those not "lead-affected" (22). A pilot study of 130 Kenyan workers exposed to lead showed no association between blood pressure and exposure strength or exposure duration for up to 15 years (50). The blood lead concentration varied between 20 and 120 $\mu\text{g}/100\text{ ml}$ (0.96 and 5.79 $\mu\text{mol}/\text{l}$) (median 60 $\mu\text{g}/100\text{ ml}$, 2.90 $\mu\text{mol}/\text{l}$).

Nitrates

Acute reactions to organic aliphatic nitrates include hypotension. [See the study of Morton (60).] Textbooks have linked occupational exposure to nitrates to an increased risk for hypertension.

A cross-sectional study on Swedish dynamite workers (26) is often presented as evidence that exposure to organic nitrates induces changes in blood pressure. Yet the authors stated that the systolic blood pressure was within normal limits. They also stated that during nitroglycol exposure the diastolic blood pressure tended to rise, while the systolic pressure declined. In the two factories studied the small changes found in blood pressure were in opposite directions. Studies on blood pressure in Japanese explosives plants have also produced inconclusive results. [See the studies of Morton (60) and Yamaguchi et al (96).]

Pesticides

Workers formulating chlorophenoxy and other pesticides had blood pressures similar to those of referents (61). An increased hypertension rate was, however, reported for DDT workers (34). An association was also reported between blood pressure and the dietary intake of polychlorinated biphenyl (48). Extraneous variables rendered the association insignificant for systolic blood pressure, but the association still remained for diastolic blood pressure.

Cardiomyopathies

Cobalt was previously added to beer as a foam stabilizer. In many countries, a high incidence of cardiomyopathy, with a mortality rate of 22 %, was reported for beer drinkers in the 1960s. [See the review of Rosenman (70).] The disease disappeared when cobalt sulfate was no longer added to beer. It is puzzling, however, that the estimated daily intake of the afflicted beer drinkers did not exceed 6–8 mg of cobalt. Patients receiving 60–75 mg of cobalt a day for sickle cell anemia or other diseases do not develop cardiomyopathy. [See the reports of Revis (69) and Rosenman (70).] Therefore, increased cobalt intake alone does not explain the detected cardiomyopathy. Cardiomyopathy was usually associated with poor nutrition, particularly with a protein poor diet. Nutritional or subclinical alcoholic heart disease might have made these patients susceptible to the metabolic effects of cobalt (30).

Oral cobalt administration to rats results in cardiomyopathy. Old rats are more vulnerable than young ones (30). Cardiotoxicity was enhanced when the animals were maintained on beer for about a month before the cobalt administration. [See the report of Revis (69).]

The cardiomyopathy of moonshine drinkers has been associated with lead (6). Rats fed on lead show myofibrillar and sarcoplasmic degeneration (5). Experimental studies indicate that both the electrical and contractile properties of the myocardium are affected. [See the report of Revis (69).]

Arrhythmias

Organic solvents

The first deaths attributed to solvent sniffing were reported in the 1960s. They were sudden and without demonstrable pathology at autopsy. The sniffing practice encompassed numerous aerosol products, including frying pan lubricants, hair sprays, deodorants, and antiseptics. The gas in most cases consisted of halocarbons and hydrocarbons such as fluorocarbons, trichloroethylene, isobutane, and toluene. Reinhardt and his co-workers (68) have listed 41 anesthetic agents which can sensitize the heart to epinephrine.

High blood concentrations of propellant gas can be achieved in extreme situations. Samples assayed from plastic bags, filled in the manner of the deliberate sniffer, have reached 350 000 ppm (24). Such exposure concentrations can only occur in industry under very exceptional circumstances.

Various mechanisms have been postulated for sniffing deaths (68). The underlying mechanism of cardiac sensitization probably involves a disturbance in the normal conduction of the electric impulse. Garb & Chenoweth (29) suggested that hydrocarbons render parts of the myocardium less irritable than others and, therefore, give rise to small temporary blocks which disturb conduction and elicit arrhythmias in the presence of catecholamines. The suppressive effect of hydrocarbons on the sinus or atrioventricular nodes and on the ventricular conduction system might permit the emergence of ectopic foci of pacemaker activity (68).

Sniffing deaths have typically occurred after sudden exertion, such as running up a flight of stairs (68). The explanation most often given is that solvents sensitize the myocardium so that the surge of catecholamines elicited by sudden activity induces ventricular arrhythmia.

Among pathology residents exposed to fluorocarbon aerosols (300 ppm of fluorocarbon 22 for 2 min) during the processing of cryostat sections at a hospital, both resting electrocardiograms and 24-h electrocardiographic monitoring indicated premature atrial contractions, paroxysmal atrial fibrillation, and an increase in premature ventricular beats. These results

were totally unexpected in a group of young, clinically healthy adults (75).

Trichloroethylene is one of the most potent cardiac sensitizing solvents (68). Metabolic interactions may further increase its arrhythmogenic potential. Pretreatment of rabbits with ethanol enhances the blood concentration of trichloroethylene. Concomitantly, the incidence of arrhythmias increases (94).

Organic nitrates

Sensitivity of the heart to epinephrine increases in animals 24–48 h after the last exposure to nitrate esters, the result being more frequent ventricular ectopic beats and increased mortality of exposed animals (20, 97).

The possibility that sudden deaths among healthy male dynamite workers could be caused by ventricular fibrillation during the abstinence phase has been studied in Sweden (41). The mean number of ectopic beats and the frequency of subjects with any ectopic beat was similar for the exposed and nonexposed groups. The mean QT time was not longer in the abstinence phase than during, or soon after, exposure.

Metals

Patients with lead poisoning show disturbances in atrioventricular conduction (62). Tachycardia, sinus block, nodal rhythm, premature atrial contractions, wandering pacemaker, and other arrhythmias have been reported in children (74). Rat pups and adult rats treated with lead during the first weeks of life have shown increased sensitivity to the arrhythmogenic action of epinephrine (36, 37).

Carbon monoxide

Tachycardia, bradycardia, and extrasystoles are common signs of acute carbon monoxide intoxication. In cynomolgus monkeys with an experimentally induced myocardial infarct, carbon monoxide exposure (carboxyhemoglobin 12.4 %) increased the vulnerability of the heart to induced fibrillation. Infarction and carbon monoxide exposure showed an additive effect when combined (23).

Concluding comments

Reliable data on chemical effects upon cardiovascular morbidity among humans are scanty. At present, there is no tenable proof that human atherosclerosis is caused by exposure to industrial chemicals. Some evidence suggests that at least a few pesticides or their impurities (lindane, DDT) or compounds arising in the combustion of some chemicals (TCDD) might affect lipoprotein metabolism in man. Clinical and physiological documentation has shown that carbon monoxide detrimentally affects myocardial function and aggravates symptoms of ischemic heart disease. Yet reliable proof for increased cardiovascular mor-

tality due to environmental or industrial exposure to carbon monoxide is lacking. Cardiovascular mortality seems elevated among workers exposed to carbon disulfide in some Western countries. Exposure to organic nitrates in industry has caused cardiac deaths.

In man, hypertension induced by environmental or industrial exposure to cadmium or lead is a controversial matter. The preponderance of evidence from a few controlled studies suggests that such an association is weak if at all existent. As to the proposed association between pesticide exposure and hypertension, the documentation is too sparse to allow scientific judgment. Cobalt ingestion, probably in combination with poor nutrition, has caused cardiomyopathies, but systematic studies of industrial cohorts are lacking. Exposure to organic solvents has obviously resulted in deaths due to cardiac arrhythmias in very high exposures ("sniffers"), but there is no well-corroborated documentation of such incidents in nonaccidental industrial exposures.

As to the lack of dependable associations between cardiovascular diseases and chemical exposures, an old remark is in order, ie, the absence of evidence should not be taken as evidence of absence. Although much data have been published on the effects of chemicals upon the cardiovascular system, these data are still rather fragmentary. They mainly come from solitary studies and are less often the result of systematic research programs to solve a certain problem. Many of the interesting hypotheses suggested by experimental studies on animals have not been tested at all by the epidemiologic approach. Quite a few studies on industrial cohorts have been invalidated by reckless design or other errors that lessen the quality of the results. There is now plenty of room for healthy skepticism regarding currently prevailing opinions. On the other hand, there is also room for the genuine enthusiasm of an explorer, who may, indeed, find the terrain ahead poorly mapped.

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