Cardiovascular disease and environmental exposure

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ABSTRACT This paper reviews the possible association between cardiovascular disease and occupational and environmental agents. The effects of carbon monoxide, fibrogenic dusts, carbon disulphide, heavy metals, noise, radiation, heat, cold, solvents and fluorocarbons are discussed. New directions for investigation are suggested.

There has been a growing awareness of the relationship between the quality of the environment and the incidence of human disease, particularly in relation to chemical carcinogenesis and lung disease. In contrast, studies of the aetiology of coronary arteriosclerotic heart disease (CAHD) have not usually been concerned with exposure to environmental toxins. Those studies which have examined cardiovascular disease in relation to occupation have largely been concerned with the effect of sedentary as opposed to active work (Morris, 1959; Karvonen *et al.*, 1961; Pell and D'Alonzo, 1963; Paffenbarger and Hale, 1975; Baxter *et al.*, 1976; Menotti and Puddu, 1976) or the psychological stress of the work (Jenkins, 1976). The United States Public Health Service published tables in 1963 showing mortality rates from specific diseases (including cardiovascular) by occupation, industry and socio-economic levels (United States Public Health Service, 1963), and mortality statistics are published in Britain every few years (Office of Population Censuses and Surveys, 1978). However, there have been few attempts to correlate specific chemicals, gases, dusts, and/or fumes or mixed exposure with subsequent change in incidence or prevalence of CAHD. This deficit is not unique to the medical literature. An examination of the table of contents of a typical textbook of toxicology (Casarett and Doull, 1975) shows such chapter headings as Toxicology of the Liver, Toxicology of the Kidney, Toxicology of the Central Nervous System. Toxicology of the cardiovascular system stands out by its absence. Some may argue that the deficiency is justifiable, and attributable to a lack of effect rather than a lack of knowledge. Up to approximately

30 years ago CAHD was generally felt to be a non-modifiable degenerative process of ageing. This concept has changed with subsequent epidemiological and clinical studies. Our understanding of CAHD (the leading cause of death in the United States of America) has not progressed to such an extent that one could easily maintain that the present list of accepted risk factors is complete.

The information presented in the following discussion will explore possible environmental risk factors and, in the process, new means of intervention may be suggested. The inconclusiveness of much of the data, rather than indicating an absence of effect, underlines the need for further study.

The discussion of cardiovascular disease will be mainly limited to possible environmental aetiological factors of CAHD. By inference one might assume that many of these same factors would be important in the incidence of cerebrovascular disease. Included in the discussion of CAHD will be agents that cause arrhythmias or vasospasm. Although these two physiological responses are not necessarily related to arteriosclerosis it is impossible, without good autopsy data, to separate sudden death caused by these mechanisms from sudden death secondary to myocardial infarcts of atherosclerotic origin. Agents having a direct effect on myocardial tissue will also be reviewed. Environmental causes of congenital heart disease will not be discussed.

The Table lists those environmental agents which have been associated, with various degrees of confidence, with heart disease in humans. Their potential importance in terms of human disease varies not only with their degree of toxicity but also with the number of individuals exposed: this applies, for example, to the relative importance of carbon monoxide and carbon disulphide. The predominance

Received for publication 24 April 1978

Accepted for publication 7 July 1978

Table *Suspected and proved environmental risk factors in cardiovascular disease*

Coronary arteriosclerotic heart disease
Carbon disulphide*
Carbon monoxide*
Fibrogenic dusts
Heavy metals
Hypertensive agents
Lead
Cadmium
Physical agents
Noise
Radiation
Heat
Cold
Non-atheromatous ischaemic heart disease
Nitrates*
Cardiac arrhythmias
Hydrocarbons*
Fluorocarbons*
Direct myocardial tissue damage
Cobalt*
Antimony
Arsenic
Arsine
Yellow phosphorus

*Well documented.

of men in the workplace, where one finds the highest exposure to the agents in the Table, may contribute, to some extent, to the known differences in incidence of heart disease between the sexes. Carbon monoxide may be an important factor in the strong association between cigarette smoking and CAHD. Carbon disulphide-exposed workers may have more CAHD because of increased blood pressure and/or cholesterol levels. Certain heavy metals may increase the incidence of CAHD by their toxic renal effect which may subsequently cause hypertension.

The monoclonal theory of arteriosclerosis (Benditt, 1977) suggests a possible mechanism for environmental agents. Cells in aortic atherosclerotic plaques from women heterozygous for X-linked glucose-phosphate dehydrogenase deficiency were examined at autopsy for their clonal origin. The cells in fibrous plaques were found to be of monoclonal origin, compared with cells in normal intima (Benditt and Benditt, 1973). Fatty streak cells were found to be intermediate for the presence of monoclonal cells (Pearson *et al.*, 1975). Some investigators have interpreted this as a change in the genetic information transcribed by abnormal plaque cells which then causes them to proliferate. Atherosclerotic plaques may be a type of benign neoplasm (Benditt, 1977).

This theory is consistent with currently known risk factors that are thought to increase the incidence of CAHD. The first of these is cigarette smoking: chickens exposed to benzo(a)pyrene (a suspected carcinogen present in cigarette smoke and other forms of

air pollution) have an increased number of atherosclerotic plaques at autopsy (Benditt, 1977). The second factor is hypercholesterolaemia: benzo(a)pyrene was shown by serum electrophoresis to be carried by the same protein factors as cholesterol (Benditt, 1977); cholesterol epoxides, increased in individuals with hypercholesterolaemia, are carcinogenic in mice and rats (Benditt, 1977). Hypertension is the third factor: DNA of hypertensive subjects is more susceptible to breakage by mutagens than is the DNA of those with normal blood pressure. It is possible that the same types of factors that have caused the increase of cancer in this century are responsible for the earlier increase of CAHD. If this is so, the relationship between environmental exposure and CAHD may well be of considerable significance.

Carbon monoxide

Reports on smoking and CAHD are numerous; those on CAHD after chronic exposure to carbon monoxide are scant. The association between cigarette smoking and an increased frequency of CAHD is well documented (Coburn, 1970; Astrup and Kjeldsen, 1973; Goldsmith and Aronow, 1975; US Department of Health, Education and Welfare, 1975), but the aetiological agent(s) in cigarette smoke responsible for this association are not as yet equally well documented. Carbon monoxide and nicotine appear to be the most likely causal agents although nitrogen oxides, hydrogen cyanides, arsenic, cadmium, radioisotopes and chemical mutagens have also been suspected.

Both rabbits and monkeys develop atherosclerotic changes when exposed to carbon monoxide (US Department of Health, Education and Welfare, 1975), although some of the original investigators of carbon monoxide exposure in non-cholesterol fed rabbits have recently stated that it was the lack of a double-blind reading of the pathological slides which was responsible for their initial positive findings (Hugod *et al.*, 1978). When cholesterol is added to the diet of rabbits and monkeys exposed to carbon monoxide the atherosclerotic changes are even more marked, however (US Department of Health, Education and Welfare, 1975). These studies were based on exposures causing 10–21% carboxyhaemoglobin (COHB) levels over short periods of time (weeks to months).

In the same publication it is postulated that carbon monoxide enhances atherosclerosis by its known ability to cause increased endothelial permeability. Carbon monoxide in perfused arteries causes an increased uptake of cholesterol (Astrup and Kjeldsen, 1973). It has also been shown to increase

platelet adhesiveness (US Department of Health, Education and Welfare, 1975).

In occupationally exposed workers, COHB levels in non-smokers may be as high as, and sometimes higher than, those in non-exposed smokers. Wald *et al.* (1973) have shown that smokers with COHB levels exceeding 5% run 20 times the risk of having atherosclerotic heart disease as do smokers of the same age and sex with COHB levels below 3%. However, this is not proof of a causal relationship, because increased carbon monoxide levels may indicate only increased inhalation and therefore only increased exposure to another agent (Wald and Howard, 1975).

There are few epidemiological studies of human exposure to carbon monoxide. In 1955, a syndrome called Shinshu myocardosis was described in Japan (Goldsmith, 1970). Its aetiology was ascribed to repeated exposure to carbon monoxide. The population at risk spent the winter working in enclosed rooms heated by charcoal fires, and COHB levels reached 20–30%. One thousand and twenty-two individuals were examined, of whom 35% had abnormal heart findings. Excluding other known causes, 18% of the total were thought to have the syndrome. Symptoms varied, according to severity, from stiffness of shoulders, backache, fatigue, vertigo, facial oedema, dyspnoea on exertion, substernal tightness and pain at work with some numbness of the upper extremities, to paroxysmal nocturnal dyspnoea and anginal attacks. Cardiac enlargement was found on radiography, and electrocardiographic abnormalities included arrhythmia, low voltage, depressed S-T segments and prolongation of the ventricular complex. After remodelling of the rooms where exposure took place, cardiac morbidity decreased by 50%.

Finnish investigators showed that 26% of 145 non-smoking foundry workers had COHB levels exceeding 6% (Virtamo and Tossavainen, 1976). In a prevalence study of CAHD in Finnish foundry workers (Hernberg *et al.*, 1976) with a much larger cohort than above, 14% of those examined were found to have angina. The prevalence in non-smokers without carbon monoxide exposure was 2%, while the prevalence in smokers with carbon monoxide exposure was 19%. Non-smokers with carbon monoxide exposure had the same prevalence of angina as ex-smokers with or without carbon monoxide exposure and smokers without carbon monoxide exposure. Electrocardiograms, interpreted by the Minnesota code (Rose and Blackburn, 1968), showed no differences in subjects grouped according to exposure and smoking history. The authors felt that they were unable to determine whether carbon monoxide caused increased CAHD

or merely aggravated symptoms. In a companion study (Koskella *et al.*, 1976) no increase of mortality in men working more than five years in the foundry was found in furnacemen or casters, who are thought to have the highest carbon monoxide exposure, although no actual COHB levels were measured. The authors concluded that, despite the negative results, the study did not rule out a possible effect of carbon monoxide upon CAHD mortality. They cite the lack of substantial difference between the carbon monoxide-exposed and non-exposed group (some furnacemen and casters have no exposure while some of the comparison group, coremakers, do), and the possibility of selection by state of health. A third study showed that 14% of workers who ceased work after less than one year, 7% who left employment after five years, and 1% of those still working, had a history of myocardial infarction.

It was concluded from a study of blast furnace workers in England that, although the workers showed a mean carboxyhaemoglobin increase of 2.0–2.6% at work, there was no increase in CAHD (Jones and Sinclair, 1975). Confounding problems include using other steel workers as controls (frequency of job transfers between departments, carbon monoxide exposure to controls), no matching for other risk factors, and comparison of the deaths of only those workers under the age of 65 who were actually working at the time of death.

In American mortality studies of steelworkers (Lloyd *et al.*, 1970; Lerer *et al.*, 1974; Mazumdar *et al.*, 1975; Redmond *et al.*, 1975; Rockette and Redmond, 1976) certain job classifications had a significant relative increase of associated cardiovascular disease. These included men working as janitors, maintenance mechanics, crane operators and workers in the batch pickling and sheet drying areas. Men in the coating department and masons had increased hypertensive heart disease. In janitors and maintenance mechanics, the increase was thought to be attributable to health selection. These were jobs into which men were moved as they became ill or grew older. The other areas where increases in cardiovascular disease were noted were thought to be significant, and the disease to be related in some way to the men's occupation. There have been no industrial hygiene surveys of these areas or attempt to elucidate the possible aetiological factor(s). Although many of the workers are exposed to carbon monoxide it does not appear that this could explain all of the increases found. Exposures in the batch pickling area, for example, seem to be mainly to sulphuric acid and sodium hydroxide. Appropriate industrial hygiene studies and confirmation of the suspected increase of CAHD might identify new risk factors.

Stationary engineers and firemen (who operate and maintain equipment for power generation, heating, ventilation, humidity control, refrigeration and air conditioning, and thus are potentially exposed to carbon monoxide from steam boilers) have been shown in a preliminary study to have an increased frequency of deaths from CAHD, compared with the general population of the United States of America (Decoufle *et al.*, 1977).

Besides having a possible aetiological role, increased exposure to carbon monoxide has been shown, both under experimental conditions and in driving on the Los Angeles Freeway, to be associated with aggravation of pre-existing CAHD (Aronow *et al.*, 1972). Exercise time was decreased for patients suffering from either angina or intermittent claudication when exposed to carbon monoxide (Anderson *et al.*, 1973). These changes took place with increases of carboxyhaemoglobin as low as 1.7% above pre-exposure levels. In addition, in Los Angeles it was found that there was an increased rate of fatal cases of myocardial infarction in high pollution areas during periods of relatively increased ambient carbon monoxide (Cohen *et al.*, 1969). A study of monkeys tested for their susceptibility to ventricular fibrillation gives a possible reason for the above observation. The results showed a continuum from the group least susceptible to ventricular fibrillation, no infarct, COHB 1.1%; to infarct, COHB 1.2%; to no infarct, COHB 8.4%; to the most susceptible group, infarct, COHB 10.2% (DeBias *et al.*, 1976).

Electrocardiographic changes during exercise have also been noted, in individuals clinically free of CAHD, at carboxyhaemoglobin levels of 5.7–7% (US Department of Health, Education and Welfare, 1975).

An acute increase in carboxyhaemoglobin from 0.98% to 8.96% causes a reduction in mixed venous oxygen tension. Patients with non-coronary heart disease were able to compensate with an increased coronary blood flow while coronary heart patients could not (US Department of Health, Education and Welfare, 1975).

Carbon monoxide clearly aggravates the symptoms of individuals with CAHD and may well accelerate atherosclerosis. The latter effect has been demonstrated in animal studies. There are no positive studies, in workers exposed to carbon monoxide, to confirm the animal data.

Although cigarette smoking is strongly associated with mortality from CAHD, the presence of nicotine in cigarettes does not allow one to conclude that carbon monoxide is solely responsible for the association. The pharmacological actions of nicotine probably contribute to acute death; it is therefore at least partly responsible for increased

mortality in cigarette smokers. However, its lack of atherogenic effect (US Department of Health, Education and Welfare, 1975) tends to support the experimental evidence of the aetiological importance of carbon monoxide in atherosclerosis.

The present industrial standards, which allow a carboxyhaemoglobin level of 7.36%, and the newly recommended American standard (National Institute of Occupational Safety and Health, 1972) which would allow a blood level of 5% carboxyhaemoglobin, appear to be inadequate. Disregarding a possible atherogenic effect, these levels could cause aggravation of symptoms in workers who already have clinical CAHD, and could adversely affect the CAHD mortality rates among them. While further study is needed to clarify the effect of carbon monoxide on the pathogenesis of atherosclerosis in humans, the present evidence is consistent with the need for further reductions in carbon monoxide levels, both in industry and in the whole community.

Fibrogenic dusts

The relationship between restrictive lung disease and occupational exposure has been well worked out for certain diseases, such as asbestosis, silicosis, beryllium lung disease and farmer's lung. With a sufficient exposure a certain percentage of individuals will be so severely affected that right-sided heart failure will occur. That there is any relationship between the presence of lung disease and the subsequent development of CAHD is not as clear-cut. It was first suggested by an analysis of the results of the Framingham study, that a decreased vital capacity was a risk factor for CAHD. This finding was disputed by Keys *et al.* (1972), who analysed the data from a world-wide epidemiological survey of approximately 6000 men. They showed that the association between pulmonary function and CAHD lost statistical significance if the age factor was better controlled. In contrast, another investigation refuting the finding of Keys *et al.* was recently reported among patients in the Kaiser health system, who had had a thorough physical examination including measurement of pulmonary function (Friedman *et al.*, 1976). Those individuals developing a documented myocardial infarction had shown, on average, statistically significantly lowered vital capacities during their previous examinations. This study was well controlled for other CAHD risk factors, including age.

There is some indication that coal miners have increased mortality rates for CAHD (Enterline, 1964). Although there is some carbon monoxide exposure in coal mines, the lung is the site of

pathological changes. Studies that have disputed the increased incidence of mortality from CAHD generally suffer from deficiencies in data analysis, for example, no mention is made of years of exposure, years from onset of exposure, or respiratory function. Despite such deficiencies, one study (Costello *et al.*, 1975) did show a small excess of ischaemic heart disease in non-working miners (retired, left for health reasons or for other jobs).

In a prevalence study of CAHD in Marion County, West Virginia, no differences were found in the rates for miners, ex-miners and non-miners (Higgins *et al.*, 1969). However, there was an association between low ventilatory capacity (FVC in all age groups, FEV_{1.0}/FVC in all age groups except 50–59) and CAHD. This difference was present among all three occupationally defined cohorts and could not be explained by cigarette smoking. Another study, from Sweden (Tibblin *et al.*, 1975), showed a higher than expected death rate from CAHD in those individuals with decreased peak expiratory flow.

The evidence suggests that decreased pulmonary function is a risk factor for CAHD although it is still possible that decreased pulmonary function may be a consequence of subclinical heart disease. At the least, lung function must be considered whenever cohorts at risk for pulmonary disease are analysed in terms of CAHD. The widespread prevalence of such a preventable health change merits determination of its strength as a risk factor.

Carbon disulphide

Carbon disulphide exposure and its association with CAHD both in laboratory studies and human epidemiological studies has been reviewed in the past (Davidson and Feinleib, 1972). The major uses of carbon disulphide are in the manufacture of rayon and carbon tetrachloride. Its use in the rubber industry is limited to the cold curing process, not widely practised in the United States of America. It is estimated that, in the USA, some 500 000 workers are exposed to carbon disulphide.

Because of the chronic effects of carbon disulphide on the central nervous system, pathologists first became aware of its atherogenic potential in the cerebrovascular system. It was later realised that the atherosclerosis was not limited to cerebral vessels. Animals which inhaled carbon disulphide in experimental studies were also shown to develop atherosclerosis. Later, case reports and subsequently population studies, confirmed the increased incidence of CAHD in humans exposed to carbon disulphide. A mortality study (Tiller *et al.*, 1968) of male workers from 1933 to 1962 showed that

42% of deaths in exposed workers were certified to CAHD compared with 24% of deaths in other workers of the same age, 17% of deaths in local men, and 14% in the Registrar General's tables. The results of other studies confirmed the increased incidence of CAHD with carbon disulphide exposure (Gavrilescu and Lilis, 1966; Hernberg *et al.*, 1970; Tolonen *et al.*, 1975). Many studies were undertaken in Europe, as the cold curing process for rubber was widely used there. Some showed an increase in the average blood pressure and/or cholesterol in exposed groups (Hernberg *et al.*, 1970; Manu *et al.*, 1972; Tolonen *et al.*, 1975). Decreased fibrinolytic activity has also been reported (Gavrilescu and Lilis, 1966). The exact mechanism of the toxic effect is unknown. Possibly, the effect on atherosclerosis is secondary to its reported hypertensive, hypercholesterolaemic and/or antifibrinolytic action, or perhaps to a mutagenic influence. The elucidation of its role in the pathogenesis of atherosclerosis would be useful in understanding atherosclerosis in non-exposed people as well (Schilling, 1970). The present exposure levels of workers are lower than in the past, but a 'no chronic effect' level is uncertain. The level of exposure currently allowed in Finland, where much of the recent work on carbon disulphide has been done, is one-half that of the USA.

Nitrate

Those nitrates which are used to make dynamite have been definitely associated with sudden death and non-atheromatous heart disease. The substances involved include glyceryl trinitrate (nitroglycerin), ethylene glycol dinitrate and alkyl nitrates (Hamilton and Hardy, 1974). Sudden death from nitrates, when it does occur, often happens on Monday morning before reaching work, and is dubbed 'Monday morning death'. A mortality report from an explosives plant in Pennsylvania showed an increase in deaths attributable to coronary artery disease (Carmichael and Lieben, 1963). Four of the six men dying were younger than 45 yr. In addition, about 50 instances of sudden death in munition workers have been reported for the period 1936–60. Three-quarters of the deaths occurred after a one- or two-day absence from work.

In a clinical study of nine munition workers with cardiac chest pain and without any other predisposing coronary risk factors, one patient died, and five had myocardial infarctions (Lange *et al.*, 1972). They had worked in the plant from one to four years before having chest pain. All five individuals who were given coronary arteriography were found to have normal vessels. The disease and symp-

toms in these workers appeared to the author to be related to withdrawal from nitroglycerine. This same conclusion was reached in another study of nine munition workers with longer exposures of from two to 27 years (Lund *et al.*, 1968). The presence of a withdrawal phenomenon has relevance to patients taking nitroglycerine medicinally over long periods. There is the possibility of rebound vasospasm in patients taking either high doses of nitroglycerine and/or of the long-acting nitrates, if such patients suddenly stop taking their medication.

A recent case-control study from Sweden reported a 2.5 times increased risk of cardiocerebrovascular disease in explosives workers with over 20 years' exposure (Hogstedt and Axelsson, 1977). All but three of the deaths occurred months or years after exposure. The authors cite evidence, from experiments with animals, that long-term exposure to erythrol tetranitrate at concentrations producing tissue hypoxia causes enhanced atherosclerosis.

The question of long-term exposure to nitrates and its relationship to CAHD should be examined in other workers at risk, including employees in pharmaceutical firms.

Metals and trace elements

Metals and trace elements are ubiquitous. Epidemiological studies have attempted to correlate them with variations in prevalence of cardiovascular disease. Various studies have associated different metals and trace elements in drinking water with the prevalence of CAHD. The corrosiveness of soft water appears to be the factor, explaining why different studies have found different metals to be important. Depending on the geographic region and the presence or absence of soft water (the latter usually being associated with areas of increased prevalence of cardiovascular disease), different metals would become dissolved in the drinking water (Schroeder and Kraemer, 1974). There have been conflicting reports regarding the possibility of increased risk factors for CAHD disease in populations drinking soft water (Elwood *et al.*, 1971; Stitt *et al.*, 1973). If there were differences in known risk factors, such as blood pressure or plasma cholesterol, it is not clear whether these are secondary to the difference in the hardness of the drinking water or a cause of the difference in the observed CAHD mortality. Others have suggested, at least in Great Britain, a correlation between soft water and high rainfall and low temperature as possibly having some significance (Editorial, *British Medical Journal*, 1978). All one can conclude at present is that the mechanisms of action and/or the presence of specific causal relationships have not been determined.

Studies in rats showed that 'focal myocardial fibrosis, probably healed coronary occlusion' occurred with increased frequency compared with control animals, when test animals were fed niobium, zirconium, lead, vanadium, cadmium and antimony (in order of increasing positivity of the results); human data exist on exposure to antimony, cadmium and lead (Schroeder and Kraemer, 1974). One hundred and thirteen workers making resinoid wheels, who were exposed for up to two years to levels of antimony trisulphide from 0.58 to 5.5 mg/m³ were examined for possible cardiac disease (Brieger *et al.*, 1954). The study was started after eight workers had died (six suddenly and two from long-standing heart disease). Thirty-seven ECGs of a total of 75 were judged to be abnormal (mostly T wave changes). These changes persisted in 12 of 56 workers monitored after antimony was removed from the workplace. The authors mentioned six studies in animals which confirmed these observations. They also pointed to reported ECG changes in patients being treated with antimony for parasite infestation. Further, compositors and typesetters exposed to lead and antimony fumes were found to have an increased cardiovascular death rate compared with other printing craftsmen. There are no further epidemiological studies to confirm or negate the findings on workers exposed to antimony trisulphide. The adequacy, for long-term exposure, of the present US standard of 0.5 mg/m³ has never been evaluated.

The chronic effects of lead on the cardiovascular system have long been considered. There is widespread evidence that lead can cause chronic nephropathy (Wedeen *et al.*, 1975). Whether this leads to the suspected increase of hypertension in lead workers requires further investigation. A clinical study in Great Britain compared the lead levels of the first 135 patients in a hypertension clinic with a control group matched for age and sex (Beevers *et al.*, 1976). The hypertensive group had higher lead levels. This association may be a consequence, rather than a cause, of their hypertension. The prevalence of increased hypertension among lead workers in general remains unsettled, as is the possibility of an increased incidence of cerebrovascular disease (Lane, 1964; Malcolm, 1971). An industry-sponsored mortality study of lead workers in smelters and battery plants from 1947 to 1970 (Cooper and Gaffey, 1975) showed that the number of deaths was approximately equal to that expected. This is not necessarily a negative study as the healthy worker effect usually causes a lower than expected rate for at least a number of years after the onset of observation, except in cases where there are industrial hazards. Statistically

significant increases in the expected number of deaths for the categories of 'other hypertensive disease' and 'chronic and unspecified nephritis' were found, although there were few actual deaths. Other investigators have found a relationship between CAHD and increased aortic lead levels (Voors *et al.*, 1973). Rabbits fed on cholesterol and lead developed more atherosclerosis than did rabbits fed on cholesterol alone (Kuzminskaya, 1965). Rabbits fed on lead alone did not develop atherosclerosis despite the apparent synergism between cholesterol and lead.

Epidemiological studies have associated increased cadmium levels with hypertension (Schroeder and Buckman, 1962; Schroeder, 1974). Rats fed on cadmium develop hypertension (Schroeder and Buckman, 1962; Schroeder, 1965; 1974). A study comparing serum cadmium levels in an untreated hypertensive group with those in a normotensive control group found statistically significantly higher average cadmium levels in the former (Glauser *et al.*, 1976). This was in agreement with previous studies, using autopsy specimens, which showed high cadmium levels in the kidneys of hypertensive patients. As with the increased lead levels, so the increased cadmium levels may have been a consequence, rather than a cause, of hypertension. Among other toxic effects, morbidity studies have shown kidney disease in the form of low molecular weight proteinuria in workers exposed to cadmium (Axelson and Piscator, 1966). Cadmium levels in the air have been correlated with cardiovascular death rates. This association is independent of the effect of urbanisation and other types of air pollution (Carroll, 1966). Cadmium is present in cigarette smoke, and smokers have increased blood cadmium levels, but its aetiological role in cigarette-associated disease is unknown. Neither the presence of hypertension in exposed workers, nor its long-term consequences, have been adequately explored.

Arsenic has, in the past, been considered a possible aetiological factor for the known increase of CAHD in cigarette smokers (Astrup and Kjeldsen, 1973). Since arsenic-containing insecticides have been abandoned by tobacco growers, the levels in cigarette smoke are much lower. There are reports of plasma arsenic concentration increased up to ten times in patients with endemic peripheral arteriosclerosis resulting from arsenic in drinking water (Astrup and Kjeldsen, 1973). A recent mortality study from Sweden showed a significant dose-related increase in cardiovascular disease in workers exposed to arsenic in a copper smelter (Axelson *et al.*, 1978). This report cites conflicting results from past studies of the incidence of cardiovascular disease in smelter

workers. The authors also stress the difficulty of isolating the offending agent in a mixed exposure. Arsenic and arsine have also been reported to cause changes in ECG, although these probably are not related to atherosclerosis. A case report in 1960 documented non-specific T wave changes lasting for 14 days after acute arsenic poisoning (Weinberg, 1960). Animal studies attest to a direct cardiotoxic effect. Arsine, known for its haemolytic properties (Fowler and Weissberg, 1974), also appears to have a direct effect on the heart. In a report describing 13 men exposed to arsine, four of whom died, the clinical impression and results of autopsy suggested that the cause of death was not attributable to anaemia but probably to acute myocardial failure. The nine men who recovered all had ECG changes which, in one case, lasted for ten months (Pinto *et al.*, 1950). It is possible that the increased incidence of cardiovascular disease seen in batch picklers in the steel industry may be partly caused by the acid used in the process combining with arsenic impurities in the steel to form arsine.

Cobalt cardiomyopathy was seen as a small epidemic in the autumn and winter of 1965-6 (*Quebec Beer-drinkers' Cardiomyopathy*, 1967). The mortality rate of the 48 cases reported in Canada was 21.6%. Other series were reported from Nebraska and Minnesota in the USA, and from Belgium. Cases began to be seen one month after cobalt was added as a foaming agent to beer. All individuals were heavy beer drinkers who mainly drank beer treated with a higher than usual concentration of cobalt (1.2 ppm compared with 0.075 ppm). Those who recovered and were studied one year later showed no residual heart failure. The myocardium in all the dead victims showed similar tissue destruction, and thrombi in the heart and major arteries. It was never adequately explained why estimated doses of 8 mg cobalt/24 pints of beer caused such a toxic effect when physicians had previously been prescribing drugs containing 60 mg cobalt/day. Animal studies suggest that nutritionally deprived rats have an increased rate of heart disease caused by cobalt (Grice *et al.*, 1969). However, these studies were not controlled for the effect of thiamine deficiency. The synergistic effect of alcohol, cobalt and a protein-poor diet on enzyme metabolism has been suggested as being the mechanism responsible for the occurrence of this pathologically unique cardiomyopathy (Alexander, 1969). However, there is one case report of cobalt cardiomyopathy in a metal worker exposed to cobalt for four years, who was thought to have had neither a nutritionally inadequate diet nor an excessive alcohol intake (Barborik and Dusek, 1972). No other cases have been reported from industrial settings. There are reports of patholo-

gical changes in the heart after acute yellow phosphorus poisoning (Talley *et al.*, 1972) and animal experiments confirm the direct cardiotoxic effect. There are also reports of ECG changes after mercury poisoning (Dahhan and Orfaly, 1964). Fluorine poisoning, by causing hypocalcaemia, has also been reported to have a cardiotoxic effect (Goodman and Gilman, 1975). In the Russian and German literature there are isolated reports of cardiovascular damage from chromium, manganese and mercury in the workplace (Kosmider and Wocka-Markowa, 1968; Klavis, 1970; Kleiner *et al.*, 1970).

Hydrocarbons and aerosol propellants

Most of the literature on the cardiac toxicity of halogenated hydrocarbons is concerned with their ability to cause arrhythmia. There are, however, reports on the direct cardiotoxicity of certain solvents and propellants. 1,1,1-trichloroethane, after inhalation by dogs, has a direct depressive effect on their hearts; it was suggested that there was inhibition of myocardial contractility (Herd *et al.*, 1974). The same conclusion was reached in studies on the cardiac effect of fluorocarbons (freons) in mice, rabbits and in isolated human papillary muscle removed at surgery (Harry, 1973; Taylor and Drew, 1975b). One hundred and fifty individuals suffering from 'moderate chronic poisoning by benzene derivatives' were found in a Russian study to have a 26.6% incidence of ischaemic cardiopathy and a 28% incidence of hypertension, prevalence rates which were considered to be increased (Reznik and Vajsmian, 1974).

The interest in animal studies with 1,1,1-trichloroethane arose after 18 deaths had occurred following the use and abuse of a nasal decongestant containing 1,1,1-trichloroethane as a carrier solvent. These sudden deaths were reported throughout the USA and led to banning of the use of this compound as a carrier solvent in drugs. Much of the earlier information on the arrhythmic effects of these compounds resulted from their use as anaesthetic agents. There are at least five reports of arrhythmias and sudden death after exposure to trichloroethylene (Geiger, 1943; Waters *et al.*, 1943; Bell, 1951; Bernstine, 1954). One report details five sudden deaths after exposure to trichloroethylene, of which four appeared to be caused by ventricular fibrillation (Kleinfeld and Tabershaw, 1954). An attempt has been made, using dogs, to classify compounds according to the strength of their cardiac-sensitising properties (Reinhardt *et al.*, 1971). The most active compounds were said to be benzene, chloroform, heptane and trichloroethylene: carbon tetrachloride and halothane were considered to have an inter-

mediate degree of toxicity. The numerous weak sensitising agents include methylene chloride and vinyl chloride. Fluorocarbons were also classified according to their ability to sensitise the heart with consequent ventricular fibrillation (Taylor and Drew, 1975b). All fluorocarbons have some effect, though at varying concentrations and to different percentages of dogs. Combined exposure to noise and a fluorocarbon was more sensitising than exposure to the fluorocarbon alone (Reinhardt *et al.*, 1971).

The effects on humans who abuse products containing these substances is well documented. One hundred and ten sudden sniffing deaths were reported from 1964 to 1969 (Bass, 1970). The deaths were not caused by suffocation, as the victims were usually found at varying distances from the plastic bags filled with the substance they had been inhaling. The six autopsied cases reported in this series showed no anatomical cause of death. The substances used were fluorocarbons, benzene, 1,1,1-trichloroethane, petrol, toluene and other unspecified hydrocarbons.

There have also been reports of adverse effects with normal use of propellants (Taylor and Harris, 1970; Aviado, 1975; Food and Drug Administration, 1975). Pathologists have experienced palpitations when using a spray freezing agent which contained a fluorocarbon propellant. Both resting electrocardiograms and 24-hour electrographic halter monitoring indicated premature atrial contractions, paroxysmal atrial fibrillation and increased premature ventricular beats. These results were totally unexpected in this group of young, clinically healthy adults (Speyer *et al.*, 1975).

In the 1960s, both epidemiological studies and case reports tended to associate an increase in sudden death in asthmatics at that time with the use of over-the-counter bronchodilator aerosols. It was felt that the propellant was at least partly responsible, in combination with the sympathomimetic bronchodilators, in causing cardiac arrhythmias.

The effects of these compounds in the home and industry in relation to their potential cause of sudden death have never been studied, although many people are exposed to them. The compounds are used in cleaning, degreasing, and painting, and in starting and carrier compounds in the chemical industry. It is estimated that, in the USA, over 300 000 workers are exposed to trichloroethylene alone. The incidence of sudden death in cases without massive exposure is not known. Their effect in precipitating fatal episodes in the course of CAHD is also unknown. Subjects previously suffering from heart disease would probably be at increased risk. Animal studies showed that such compounds caused arrhythmia

at lower concentrations in hamsters with hereditary cardiomyopathy than in healthy animals (Taylor and Drew, 1975a). The rate of accidents and/or accidental deaths actually attributable to syncope from induced arrhythmias is not known. The additive effect of stress, such as that associated with loud noises, on the arrhythmic effect of the offending chemicals should also be considered. Studies with continuous electrocardiographic monitoring during actual solvent and propellant use would be the initial method of investigating some of these problems (Valić *et al.*, 1977). Their direct effect on cardiac smooth muscle should also be determined.

Physical agents and stress

Marked physiological changes have been noted under stressful conditions. Chronic exposure to stress, especially psychogenic, has been considered to be a risk factor for CAHD. Most work on cardiovascular effects of stress has been concerned with psychological factors. There has been very little study of the chronic effects of physical agents.

There is limited information on the non-auditory effects of noise. A three-hour exposure to noise ranging in intensity from 105 to 115 dB in 18 subjects showed increased catecholamine excretion, and increased cholesterol, triglycerides, free fatty acids, plasma 11-OHcortisol levels and blood pressure (Ortiz *et al.*, 1974). Only the cortisol levels showed attenuation during exposure. These findings, if continuously present, could have a detrimental effect on the coronary arteries. One study of steel workers found a higher prevalence of heart problems in the noisier areas (Kryter, 1970). This is another possible explanation for the mortality findings in the American steel industry already described. Animal experiments have shown that the platelets of subjects exposed to noise have increased adhesiveness (Maass *et al.*, 1973). The investigators were considering their results in relation to a possible mechanism for auditory loss, but an increased tendency to clotting could have important cardiovascular implications.

In rats, and possibly man, high levels of noise may be associated with hypertension. A comparison was made between urban dwellers and an African tribe in the southern Sudan which has a very low exposure to noise (Schiff, 1973). The latter group, as well as lacking the hearing loss associated with age (presbycusis) seen in industrial populations, had a low prevalence of hypertension. Individuals in both groups responded with prompt vasoconstriction to noise levels of 90 dB. However, the blood vessels of the tribe members relaxed much more quickly. This difference in vessel elasticity between

the two groups suggests an explanation for the low prevalence of hypertension found in the quieter environment. A study in Iran of workers in silos (a noisy environment) showed a higher prevalence of hypertension than expected (Kavoussii, 1973).

The physiological effects of hot and cold environments have been studied. Among other physiological phenomena, strenuous exercise in a hot environment causes the maximal heart rate to be reached at lower levels of oxygen consumption (*Occupational Medicine: Principles and Practical Applications*, 1975; Selye, 1976). Heavy work and/or the increased effort of breathing caused by wearing a respirator would be more likely to precipitate an ischaemic attack in a susceptible worker under hot conditions than during more comfortable temperatures. However, the chronic effect of heat on the pathogenesis of atherosclerosis has not been thoroughly investigated. A mortality study of open-hearth steel workers (to assess the effects of their excessive exposure to heat) showed less heart disease than expected (Redmond *et al.*, 1975). The problem of selective bias and disease among the control group of other steel workers makes evaluation difficult.

There is the common impression that strenuous work in the cold (such as shovelling snow) is associated with ischaemic attacks. Experiments have shown that peripheral vasospasm is associated with coronary artery vasospasm (Mudge *et al.*, 1976). A study (*Occupational Medicine: Principles and Practical Applications*, 1975) of 300 men working in a cold climate for three months did not show any changes in ECG (tests included Master two-step exercise testing both before and after the three-month period). Despite this study, the long-term pathogenic effects of a cold environment on workers are still unknown.

There is some evidence that radiation may cause atherosclerosis. Experimental studies in animals have suggested that radiation increases atherosclerosis (Sheehan, 1944). There are also case histories of patients developing myocardial infarctions and premature atherosclerosis after being treated with radiotherapy for cancer (Fajardo *et al.*, 1968): for example, a 15-year-old boy died of myocardial infarction after receiving 4000 rad to his mediastinum as therapy for Hodgkin's disease; an autopsy showed atherosclerosis of his coronary arteries only. Finally, there is additional evidence from 33 autopsies: α -ray emission from atherosclerotic plaques was found to be twice as high in those subjects (50%) who died from CAHD, compared with that in those dying of other causes (Elkeles, 1968). Cigarettes are a common source of radiation for the general population (Martell, 1975). It is suspected that the use of phosphate fertiliser, contaminated with uranium,

on tobacco plants is the source of the radiation found in cigarette smoke. The ^{210}Po and ^{210}Pb (α -emitters) which are found in cigarette smoke, besides having a possible causal role in lung cancer, might also contribute to the pathogenesis of CAHD. That radiation might be an aetiological factor accords well with the monoclonal theory of atherosclerosis. Long-range mortality and morbidity studies concerning CAHD are necessary for workers exposed to radiation.

Working and living in electromagnetic fields has been suggested as a possible risk factor (Sheppard and Eisenbud, 1977). In the USA, where only the thermal properties of these waves are generally accepted, no work has been carried out to confirm or refute this suggestion.

Summary

This paper has examined CAHD by reviewing known and less well documented associations between environmental factors and CAHD. Admittedly, much of the information is scanty and incomplete but, to a large extent, it represents the amount of research done in this area. Despite the many advances in the field of CAHD, the origin and mechanism of atherosclerosis remains a matter for conjecture. New areas of research and new methods of preventive intervention are needed. There are now more sensitive and specific non-invasive methods to assess the presence of CAHD than the questionnaire and electrocardiogram previously used in cardiovascular epidemiological surveys, and these new techniques could be adapted for surveys in such areas. This discussion of environmental risk factors does not negate the importance of other known risk factors for CAHD. Rather, the question may properly be put whether their interaction with such other factors might not have additive, or even multiplicative, effects.

Special thanks to Dr I. J. Selikoff for his continuing inspiration and encouragement and to Julia Roberts for her patient preparation of the manuscript. This research was supported in part by Center Grant ES 00928 of the National Institute of Environmental Health Sciences and by Training Grant 00219 of the National Institute for Occupational Safety and Health.

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