
Weetman DF, Wood D (eds): Risk Factors for Cardiovascular Disease in Non-Smokers. Int. Workshop, Washington, Tyne and Wear, 1991. Basel, Karger, 1993, pp 118-128

Carbon Monoxide Exposure as a Risk Factor for Cardiovascular Disease

F.J.C. Roe

Consultant in Toxicology, Wimbledon Common, London, UK

In this paper I shall attempt to answer the following questions: (1) What are the short-term effects of carbon monoxide (CO) and how long does it stay in the body? (2) Are the short-term effects of exposure to low ambient levels of CO harmful to normal individuals or to individuals with reduced cardiovascular function? (3) Does repeated exposure to CO predispose to atherosclerosis and/or myocardial infarction in humans or in animals? (4) How and to what extent are non-smokers exposed to CO from other people's tobacco smoke, other indoor sources or vehicular exhaust fumes?

What Are the Short-Term Effects of CO and How Long Does It Stay in the Body?

Oxygen (O_2) is transported from the lungs to the tissues in the form of a relatively loose association with haemoglobin (Hb). The O_2 diffuses through the normally thin alveolar wall into the serum, and from there it is taken up by the Hb in the red blood corpuscles. The amount of O_2 taken up by each gram of Hb is determined by the concentration of O_2 in the serum which, in turn, is determined by its concentration in the alveoli. The amount of O_2 carried to other tissues is determined by the amount taken up by each gram of Hb, by the amount of Hb per unit volume of blood, and by the rate of blood flow. Removal of O_2 from oxygenated Hb is influenced by the O_2 tension in the tissues through which it passes. Heavy use of O_2 results in reduced O_2 tension and increased dissociation of oxygenated Hb as blood passes through the tissue concerned. The heart is a heavy user of O_2 .

Unfortunately, Hb has an affinity for CO (to form carboxyhaemoglobin (COHb)) that is over 200 times its affinity for O₂. Thus, COHb is readily formed even under conditions where the tension of CO in the alveoli is relatively low. Hb that has combined with CO is not available for carrying O₂. Apart from the effects of the replacement of oxyhaemoglobin by COHb, there is evidence that the presence of CO in the blood slows the release of O₂ from oxyhaemoglobin. CO also combines reversibly with myoglobin, a protein in muscle cells. It has been suggested that this effect per se contributes to the toxic effects of CO on, for instance, the functioning of the heart [1]. COHb eventually dissociates again into CO and Hb on prolonged exposure to air which is substantially free from CO. In other words, CO is gradually lost by the same route as it is acquired.

The rate of loss of CO (i.e. the rate of dissociation of COHb) is dependent not only on the difference between the concentrations of CO in both the blood and the alveolar air, but also on the rates of respiration and blood flow through the lungs. Exercise, by increasing the respiration rate, hastens the loss of CO; lack of exercise retards it. During deep sleep, even in a CO-free atmosphere, COHb levels fall only very slowly. According to Dr P.V. Cole [pers. commun.], COHb levels fall faster in men than women, presumably because the number of red blood cells per unit volume of blood is lower in women.

CO combines even more avidly with fetal Hb than with adult Hb. Cole et al [2] found COHb levels in the fetus to be 80% higher than those in the mother after a pregnant woman has been exposed to CO. Also, after exposure ceases, the COHb concentration falls more slowly in the fetus than in the mother.

The anatomy of the lungs is ideal for gaseous exchange between the blood and the atmosphere (i.e. alveolar air): O₂ passes readily in and carbon dioxide (CO₂) passes readily out. CO enjoys the same easy passage in both directions, but the strength of its association with Hb severely limits the rate it is lost from the body.

According to Dalhamn et al [3], absorption of CO through the epithelium of the nose and pharynx is negligible: it is also negligible in the trachea and bronchi down as far as the respiratory bronchioles, although there is no information available on this [G. Cumming, pers. commun.]. It is reasonable to assume that little CO would escape from the body except via the lungs. Less than 0.1% of absorbed CO is oxidized to CO₂.

Apart from the CO which is taken into the body from the surrounding air, it is noteworthy that some CO is formed endogenously as a by-product of haem metabolism [4, 5].

Are the Short-Term Effects of Exposure to Low Ambient Levels of CO Harmful to Normal Individuals or to Individuals with Compromised Cardiovascular Function?

In Normal Individuals

The normal body is able to compensate for changes in oxygen demand and supply by increasing the respiration rate (to raise alveolar O₂ tension), by increasing blood flow (by increasing heart rate and stroke volume) and, over a longer period, by increasing numbers of red blood cells and Hb per unit volume of blood. These compensatory changes are very similar to the adaptive changes which occur when people living at low altitudes climb to higher altitudes where the air is more rarified. The changes are reversible and there is no evidence, or real likelihood, that permanent or accumulative effects are produced in healthy individuals, provided that peak COHb levels do not rise above 10%. It is only in some heavy smokers that COHb levels regularly reach as high as this, and, although heavy smoking is associated with increased incidence of coronary heart disease, cerebrovascular disease and peripheral vascular disease, it is not known whether this association is with exposure to CO or with that to other components of tobacco smoke.

Ayres et al. [6] reported that a rise of COHb concentration to 9% is associated with an increase in coronary blood flow in humans, while Adams et al. [7] showed that a 5% increase in COHb was associated with a 14% increase in coronary blood flow in dogs.

Although it has not been proven that intermittent low peak levels of COHb do no permanent harm, it seems likely that the healthy body can compensate for them completely.

Cohen et al. [8] found an increased fatality rate from myocardial infarction in areas with high rates of air pollution, but only during periods of high CO pollution. However, they were uncertain whether the association indicated a cause-effect relationship.

In Individuals with Compromised Cardiovascular Function

Theoretically one would anticipate that in subjects with atherosclerotic coronary vessels which are unable to expand or contract, there could be no compensatory increase in coronary blood flow as COHb levels rise. In turn, this could lead to a reduction in the functional cardiac reserve and an earlier onset of anginal pain upon exercising. In line with this expectation, Ayres et al. [9] reported disturbed lactate and pyruvate metabolism, indicative of myocardial hypoxia, when COHb levels rose in subjects known to have coronary heart disease. Also, Anderson et al. [10] and Allred et al. [11] saw ECG changes (increased S-T depression) in anginal

patients when they were exposed to 50 ppm CO in ambient air. Calverley et al. [12] observed reduced exercise tolerance in 15 patients with severe chronic bronchitis and emphysema after they had been exposed to enough CO to raise their COHb levels to 9%. Allred et al. [11] found that a rise in the COHb level to between 2 and 3%, as could occur in subjects confined to heavily contaminated air in a badly ventilated room, was enough to reduce exercise tolerance.

A difficulty with the interpretation of laboratory studies of the kind that have been reported by Ayres et al. [9], Anderson et al. [10] and Aronow [13] is that simply being in an investigative laboratory is stressful for subjects with compromised cardiovascular function. The release of catecholamines as a result of this stress and the consequential increase in blood pressure is apt to complicate the interpretation of the findings in such studies. The same problem virtually prevents any meaningful investigation of the possible effects of CO derived from other people's tobacco smoke on cardiovascular parameters in either normal subjects or patients with existing cardiovascular disease. The characteristic smell of tobacco serves to inform the subject when he/she is being exposed to CO as distinct from uncontaminated air, and if he/she has been conditioned to believe that environmental tobacco smoke is dangerous, fear or annoyance caused by the smell of it may trigger off a rise in blood pressure.

Does Repeated Exposure to CO Predispose to Atherosclerosis and/or Myocardial Infarction?

In Humans

Autopsy studies suggest that there is an association between cigarette smoking and increased atherosclerosis of the aorta and coronary arteries. However, this does not tell us whether CO, per se, is implicated in the causation of atherosclerosis and at least one other component of tobacco smoke, namely nicotine, attracts as much attention as CO in this context.

Theoretically, raised COHb could predispose to atherosclerosis in various ways: (a) By reducing oxygen tension and thereby damaging the lining of arteries or the deeper structures of the walls of arteries. (b) By an effect on circulating blood lipids. (c) By increasing the risk of mural thrombus formation either by increasing platelet stickiness or by some other mechanism.

Evidence that exposure of humans to CO predisposes to atherosclerosis has been provided by a study reported by Wald et al. [14]. In this study, 1,085 subjects were questioned about their smoking habits and history of symptoms of vascular disease. They were then physically examined and

asked to provide a sample of venous blood. A better correlation was found between COHb concentration in the blood and evidence of atherosclerotic disease than between smoking history and such disease. As the authors of this paper themselves point out, their findings do not prove that CO per se is atherogenic. COHb levels are not only an index of the inhalation of the CO in tobacco smoke, they are also an index of absorption of nicotine from the smoke. The evidence of Wald et al [14], therefore, does not point more strongly at CO than at nicotine, or any other component of cigarette smoke, for that matter.

The mechanisms involved in the development of atherosclerosis are the subject of continuing debate. According to several theories, high levels of circulating cholesterol and/or free fatty acids (FFA) predispose to atherosclerosis. A demonstration that CO, independently of dietary cholesterol intake, raises blood cholesterol and FFA levels could, according to these theories, be taken as evidence that exposure to CO predisposes to the development of atherosclerosis.

Kjeldsen and Damgaard [15] saw no significant changes in total fatty acids, phospholipids or triglycerides in the blood of 8 volunteers given 5 half-hour exposures to 0.5% CO on 8-10 successive days (COHb = 12.5%). However, there was a significant increase in serum cholesterol during the last 3 days of exposure.

In Animals

Lipid Deposition in Walls of Arteries. The results of some animal studies suggest that exposure to CO increases the risk of deposition of lipid in the walls of the aorta and coronary arteries when animals are fed a high-cholesterol diet. Cholesterol-fed rabbits continuously exposed to CO for 10 or 12 weeks [16, 17] and cholesterol-fed squirrel monkeys intermittently exposed to CO for 7 months [18] showed excessive deposition of lipid in the intima of the aorta and coronary arteries when compared with animals exposed to CO but fed on a normal diet, or with animals fed on a high-cholesterol diet without CO exposure. Malinow et al. [19] saw no evidence of atherosclerosis or raised serum cholesterol levels in cynomolgus monkeys when fed either a standard or a high-cholesterol diet and exposed to CO. Armitage et al. [20] observed more lipid in the intima of the aorta and coronary arteries of White Carneau pigeons fed a high-cholesterol diet than in control birds. Birds exposed for 52 weeks to both a high-cholesterol diet and CO showed marginally, but not significantly, more lipid deposition than birds exposed to cholesterol only. Exposure of birds on a normal diet to CO (COHb = 11-12%) had no effect on the arteries.

Webster et al. [18] exposed cholesterol-fed monkeys to CO over a 7-month period. They saw significantly more atherosclerosis of the coro-

nary arteries in them than in cholesterol-fed monkeys exposed only to room air.

Kjeldsen et al. [15] reported that hypoxia, achieved without exposure to CO, also gave rise to increased lipid formation in the lining of the aorta in cholesterol-fed rabbits. Later, Kjeldson et al. [21] reported that hyperoxia (achieved by exposing animals to 28% O₂) protected cholesterol-fed rabbits against the development of lipid deposits in the wall of the aorta.

Intimal Oedema. Kjeldsen et al. [22] and later Hugod et al. [23], using the electron microscope, reported the occurrence of intimal oedema of the aorta in rabbits fed on a normal diet and exposed to 180 ppm CO continuously for 2 weeks. Later, however, Astrup and Kjeldsen [24] reported that they were unable to confirm that CO produces any effects on the intima of arteries.

Pfrender [25], in a critical résumé of chronic carbon monoxide poisoning, stated, 'Almost all pathologic lesions can be explained on the basis of simple tissue anoxia, as can the late sequelae'.

Raised Haematocrit. Other studies, such as those of Eckardt et al. [26] in which monkeys were exposed to CO for 2 years and those of Jones et al. [27] in which rats, guinea pigs, monkeys and dogs were exposed to CO for 90 days, have shown mainly negative results except for an elevation of mean Hb levels and haematocrit values. However, these are of no real value in relation to atherosclerosis, since no special attempt was made to assess the animals for the extent of lipid deposition in the aorta or coronary arteries at post-mortem, and information on the cholesterol content of the diets given to the animals was not provided.

Serum Cholesterol. According to Kjeldsen [28], continuous exposure of rabbits to CO may increase serum cholesterol concentrations either when the animals are given a normal diet or when they are given a diet containing 2% added cholesterol.

Since these various animal studies were conducted, the focus has moved away from cholesterol per se as the particular lipid likely to be implicated in atherosclerosis. Instead, suspicion falls far more heavily on low-density lipoproteins (LDLs). Unfortunately, no data have been reported from studies in which animals have been exposed to high LDL diets and CO.

Platelets. Birnstingl et al. [29] reported that after exposure to 400 ppm CO for 6–14 h, which increased their average COHb levels to 17.5%, rabbits showed a highly significant increase in platelet stickiness. This was

followed 24 h later by a fall to significantly below the pre-exposure level. Immediately after exposure, platelet counts were normal, but 24 h later they were reduced to 60% of normal. This reduction is consistent with the possibility that hyper-sticky platelets had stuck to the walls of damaged blood vessels.

Kjeldsen et al. [22] saw platelets and red blood cells adhering to the lining of the aorta denuded of intima as a result of an exposure of animals (rabbits) to CO.

How and to What Extent Are Non-Smokers Exposed to CO from Other People's Tobacco Smoke, Other Indoor Sources or Vehicular Exhaust Fumes?

CO from Other People's Tobacco Smoke

Various workers have measured CO levels in tobacco smoke-filled rooms and the COHb levels in non-smokers confined to such rooms. COHb levels of the same order as those of policemen on point duty (traffic direction) have generally been found.

Russell et al. [30], for instance, exposed 11 non-smokers for an average of 79 min to a smoky atmosphere 'made worse than would be likely encountered in natural social conditions' by closing all the windows and switching off the ventilation. The level of CO averaged 38 ppm. The mean initial COHb level in the 11 subjects was 1.6 (+0.6)% and this rose to a mean of 2.6 (+0.7)% after an average of 79 min. Srch [31] found 90 ppm CO in a stationary tobacco smoke-filled car with all the windows closed and a rise of from 2 to 5% in the COHb levels of 2 non-smoking occupants of the car during a period of 1 h. During the experiment, the car was kept with the engine turned off in a closed garage. The car was apparently a small one (internal volume = 2.09 m³). Harke [32] reported a rise in the mean COHb concentration, from 0.9 to 2.1%, in 7 non-smokers housed for 90 min in a smoke-filled room. The concentration of CO averaged 30 ppm. Based on measurements of COHb and of nicotine (and presumably cotinine) in urine, Harke, in Dontenwill's laboratory, concluded that, in normally ventilated rooms, non-smokers absorb of the order of less than 1% of the amounts of smoke constituents absorbed by smokers. Because some components of smoke, and especially of side-stream smoke, e.g. acrolein, are irritants to the eyes and to the mucous membranes of the upper respiratory tract, persons confined to smoke-filled spaces tend to open windows. For this reason in particular, the extreme conditions of high smoke and CO concentrations used by some investigators are unrealistic.

CO from Other Indoor Sources

In the UK prior to the replacement of coal gas by natural gas, there were between 1,500 and 2,000 deaths from CO poisoning each year. By 1979, the number of deaths in England and Wales had fallen to about 100 [33].

Gas fires, kerosene heaters and open coal or wood fires are sources of CO, particularly under conditions of incomplete combustion. However, ambient levels only rise to potentially dangerous levels if chimneys and/or other ventilation outlets are blocked. In some oriental countries, such as Korea, heating is commonly achieved with the 'Ondol' system in which coal briquettes are burnt directly under the floor on which people sleep. The system is very economical but there is always a danger that CO will seep through unrecognised cracks in the floor. Many thousands of cases of CO poisoning caused in this way are admitted to hospitals in Korea and hundreds of people so affected die. In many regions of the world where ambient temperatures are very low during part or all of the year or where they can fall to low levels during the night, it is not uncommon for kitchens to be completely unventilated. Women who spend, sometimes, several hours in such kitchens are exposed to dangerous levels of fumes including, inter alia, high levels of CO.

Vehicular Exhaust Fumes

In western countries it is not uncommon for people to commit suicide by driving a car into a garage, closing and sealing the doors and then running the car engine in the enclosed space. Death from CO poisoning is easily achieved in this way.

In many big cities, especially in the Orient, there can be high ambient levels of CO in cars stuck in traffic jams in road tunnels and on the streets in general, and the latter can result in similarly high levels in the houses and shops lining streets with heavy traffic.

Levels of 25–100 ppm CO have been commonly found in London street air by Lawther and Commins [34] and in Toronto street air by Godin et al. [35]. Non-smoking policemen on point duty in heavy traffic conditions in London had COHb levels mainly between 1 and 2%, but one had 3.8% COHb [34]. Other studies have given similar results [36–39]. For instance, levels of up to 3% COHb are common in non-smokers exposed to vehicular exhaust gases in Los Angeles [40, 41].

Conclusion

There is no clear evidence that exposure to CO is associated with an increased incidence of any form of cardiovascular disease. In the labora-

tory, the incidence of atheromatous-like deposits in the intima of arteries has been reported when animals have been exposed both to a high-cholesterol diet and to CO, but not where there is exposure only to CO. It is not certain, however, that the lesions produced by such double exposures are really analogous to any form of cardiovascular disease that occurs in humans.

At the present time, there is increasing interest in the possibility that lipid peroxidation is implicated in the aetiology both of ageing-related diseases, such as atherosclerosis and cancer. The oxidants involved can be either exogenous or endogenous in origin. In either case, protection is afforded by antioxidants and particularly by vitamin E. CO is neither an oxidant nor an antioxidant. Hence, if the above theory is right, there is no a priori reason to expect CO to influence the risk of atherosclerosis in either direction.

References

- 1 Susuki T: Effects of carbon monoxide inhalation on the fine structure of the rat heart muscle. *Tohoku J Exp Med* 1969;97:197-211.
- 2 Cole PV, Hawkins LH, Roberts D: Smoking during pregnancy and its effects on the fetus. *J Obstet Gynaecol Brit Commonwealth* 1972;79:782-787.
- 3 Dalhamn T, Edfors M, Rylander R: Retention of cigarette smoke components in human lungs. *Arch Environ Health* 1968;17:746-748.
- 4 Coburn RF, Blakemore WS, Forster RE: Endogenous carbon monoxide production in man. *J Clin Invest* 1963;42:1172-1178.
- 5 Schmid R: Hyperbilirubinemia; in Stanbury JB, Wyngaarden JB, Fredrickson DS (eds): *The Metabolic Basis of Inherited Disease*. New York, McGraw-Hill, 1972, pp 1141-1178.
- 6 Ayres SM, Mueller HS, Gregory JJ, Giannelli S, Penny JL: Systemic and myocardial hemodynamic responses to relatively small concentrations of carboxyhemoglobin (COHB). *Arch Environ Health* 1969;18:699-709.
- 7 Adams JD, Erickson HH, Stone HL: The effects of carbon monoxide on coronary hemodynamics and left ventricular function in the conscious dog; in: *Proc 1st Annu Conf on Environmental Toxicology*. Aerospace Medical Research Laboratory, 1970, TR-70-102, pp 107-124.
- 8 Cohen SI, Deane M, Goldsmith JR: Carbon monoxide and survival from myocardial infarction. *Arch Environ Health* 1969;19:510-517.
- 9 Ayres SM, Giannelli S, Mueller H: Myocardial and systemic responses to carboxyhemoglobin. *Ann NY Acad Sci* 1970;174:268-293.
- 10 Anderson EW, Andelrnan RJ, Strauch JM, Fortuin NJ, Knelson JH: Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris. *Ann Intern Med* 1973;79:46-50.
- 11 Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney J, Pagano M, Sylvester RH, Walden SM, Warren J: Short-term effects of carbon monoxide on the exercise performance of subjects with coronary artery disease. *N Engl J Med* 1989; 321:1426-1432.
- 12 Calverley PMA, Leggett RJE, Flenley DC: Carbon monoxide and exercise tolerance in chronic bronchitis and emphysema. *BMJ* 1981;283:878-880.

- 13 Aronow WS: Smoking, carbon monoxide, and coronary heart disease. *Circulation* 1973;48:1169-1172.
- 14 Wald N, Howard S, Smith PG, Kjeldsen K: Association between atherosclerotic diseases and carboxyhaemoglobin levels in tobacco smokers. *BMJ* 1973;1:761-765.
- 15 Kjeldsen K, Damgaard F: Influence of prolonged carbon monoxide exposure and altitude hypoxia on serum lipids in man. *Scand J Clin Lab Invest* 1968;22(suppl 103):16-19.
- 16 Astrup P, Kjeldsen K, Wanstrup J: Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. *J Atheroscler Res* 1967;7:343-354.
- 17 Wanstrup J, Kjeldsen K, Astrup P: Acceleration of spontaneous intimal-subintimal changes in rabbit aorta by a prolonged moderate carbon monoxide exposure. *Acta Pathol Microbiol Scand* 1969;75:353-362.
- 18 Webster WS, Clarkson TB, Lofland HB: Carbon monoxide-aggravated atherosclerosis in the squirrel monkey. *Exp Mol Pathol* 1970;13:36-50.
- 19 Malinow MR, McLaughlin P, Dhindsa DS, Metcalfe J, Ochsner AJ, Hill J, McNulty WP: Failure of carbon monoxide to induce myocardial infarction in cholesterol-fed cynomolgus monkeys (*Macaca fascicularis*). *Cardiovasc Res* 1976;10:101-108.
- 20 Armitage AK, Davies RF, Turner DM: The effects of carbon monoxide on the development of atherosclerosis in the White Carneau pigeon. *Atherosclerosis* 1976;23:333-344.
- 21 Kjeldsen K, Astrup P, Wanstrup J: Reversal of rabbit atheromatosis by hyperoxia. *J Atheroscler Res* 1969;10:173-178.
- 22 Kjeldsen K, Astrup P, Wanstrup J: Ultrastructural changes in the rabbit aorta after a moderate carbon monoxide exposure. *Atherosclerosis* 1972;16:67-82.
- 23 Hugod C, Hawkins LH, Kjeldsen K, Thomsen HK, Astrup P: Effect of carbon monoxide exposure on aortic and coronary intimal morphology in the rabbit. A re-evaluation. *Atherosclerosis* 1978;30:333-342.
- 24 Astrup P, Kjeldsen K: Model studies linking carbon monoxide and/or nicotine to arteriosclerosis and cardiovascular disease. *Prev Med* 1979;8:295-302.
- 25 Pfrender RE: Chronic carbon monoxide poisoning: A critical résumé. *Ind Med Surg* 1962;31:99-103.
- 26 Eckardt RE, MacFarland UN, Alarie YCE, Busey WM: The biologic effect from long-term exposure of primates to carbon monoxide. *Arch Environ Health* 1972;25:381-387.
- 27 Jones RA, Strickland JA, Stunkard JA, Siegel J: Effects on experimental animals of long-term inhalation exposure to carbon monoxide. *Toxicol Appl Pharmacol* 1971;19:46-53.
- 28 Kjeldsen K: Smoking and Atherosclerosis. Copenhagen, Munksgaard, 1969, pp 1-145.
- 29 Birnstingl MA, Brinson K, Chakrabarti BK: The effect of short-term exposure to carbon monoxide on platelet stickiness. *Br J Surg* 1971;58:837-839.
- 30 Russell MAH, Cole PV, Brown E: Absorption by non-smokers of carbon monoxide from room air polluted by tobacco smoke. *Lancet* 1973;i:576-579.
- 31 Srech M: Über die Bedeutung des Kohlenoxyds beim Zigarettenrauchen im Personenraffwageninneren. *Dtsch Z Gesamte Gerichtl Med* 1967;60:80-89.
- 32 Harke HP: Zum Problem des 'Passiv-Rauchens'. *Münch Med Wochenschr* 1970;112:2328-2334.
- 33 Editorial: Carbon monoxide, an old enemy forgot. *Lancet* 1981;ii:75-76.
- 34 Lawther PJ, Commins BT: Cigarette smoking and exposure to carbon monoxide. *Ann NY Acad Sci* 1970;174:135-147.

- 35 Godin G, Wright G, Shephard RJ: Urban exposure to carbon monoxide. *Arch Environ Health* 1972;25:305-313.
- 36 Ramsey JM: Estimating recent carbon monoxide exposures. *Arch Environ Health* 1962;5:308-318.
- 37 Moureu H: Carbon monoxide as a test for air pollution in Paris due to motor vehicle traffic. *Proc R Soc Med* 1964;57:1015-1020.
- 38 Curphey TJ, Hood LPL, Perkins NM: Carboxyhemoglobin in relation to air pollution and smoking: Post-mortem studies. *Arch Environ Health* 1965;10:179-185.
- 39 Cohen SI, Dorion G, Goldsmith JR, Permutt S: Carbon monoxide uptake by inspectors at a United States-Mexico border station. *Arch Environ Health* 1971;22:47-54.
- 40 Goldsmith JR, Terzaghi J, Hackney JD: Evaluation of fluctuating carbon monoxide exposures. *Arch Environ Health* 1963;7:647-663.
- 41 Haagen-Smit AJ: Carbon monoxide levels in city driving. *Arch Environ Health* 1966;12:548-551.

