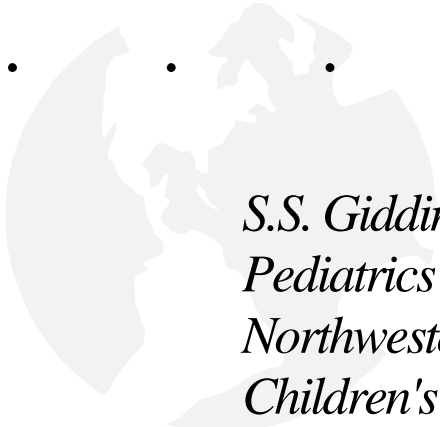


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# Background Paper

## Effects of Passive Smoking on the Cardiovascular System in Children and Adolescents

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The adverse cardiovascular effects of passive smoke exposure in adults have been well studied and recently reviewed both by individuals and scientific advisory panels for government and major health organizations (Glantz and Parmley, 1991; Taylor et al, 1992; Wells, 1994; Glantz and Parmley, 1995; California Environmental Protection Agency, 1997; Thomas, 1997; Law et al, 1997; Wells, 1998; United Kingdom Department of Health, 1998). A 20 to 40% increase in cardiovascular morbidity and mortality has been consistently observed in non-smokers with exposure to environmental tobacco smoke both at home and in the workplace as compared to those who have not. These epidemiologic observations are supported by studies in both humans and animal models which provide evidence of a pathophysiologic basis for the epidemiologic associations. Adverse cardiovascular effects of passive smoke exposure include the production of atherosclerotic lesions, vascular endothelial dysfunction, increased oxidation potential of LDL cholesterol, diminished HDL cholesterol, increased blood coagulation, and diminished systemic oxygen transport.

The substantial all cause morbidity of both smoking and tobacco smoke exposure in childhood and adolescence is well recognized and has been reported by the Surgeon General and in a Scientific Statement from the American Heart Association endorsed by the American Academy of Pediatrics (US Department of Health and Human Services, 1994; Gidding et al, 1994; Gidding and Schydlower, 1994). However, research into the specific cardiovascular effects of passive smoke exposure in children has suffered from methodologic limitations. These include the absence of easily measured cardiovascular disease endpoints, absence of reliable measures of environmental smoke exposure other than medical history of parental smoking, and justified ethical constraints on chronically exposing children to environmental tobacco smoke for research purposes. As yet, there are no good non-invasive measures of early atherosclerosis to test prospectively the hypothesis that environmental tobacco smoke exposure causes premature atherogenesis in children. Conclusions about the cardiovascular effects of environmental tobacco smoke in children and adolescents must rely on animal, adult, and pediatric cross-sectional studies with intermediate endpoints as opposed to cardiovascular events or mortality.

This chapter will review literature on environmental tobacco smoke exposure relevant to children in several areas: initiation of atherosclerosis, oxygen transport, lipoproteins, vascular function, coagulation, and fetal and infant exposure. In interpreting the effects of environmental tobacco smoke on children, the conclusions of studies performed in children, adolescents, and young adults will be given the strongest weight, with weight also given to studies in adults and animal models which can be plausibly be generalized to younger populations.

### ***Initiation of atherosclerosis***

The effects of passive smoking on the initiation of atherosclerosis have been reviewed many times with the conclusion that environmental tobacco smoke exposure can initiate the atherosclerotic process (Glantz and Parmley, 1991; Taylor et al, 1992; Wells, 1994; Glantz and Parmley, 1995; Thomas, 1997; Wells, 1998).

Endothelial injury secondary to passive smoking has been demonstrated in a number of ways. Blood endothelial cell counts are increased in individuals exposed to environmental tobacco smoke as is platelet aggregability (Davis et al, 1989; Davis, 1990). This suggests that exposure to tobacco smoke can perpetuate the earliest events in plaque formation following endothelial injury. This effect may be mediated by nicotine or more likely, other chemicals in smoke such as 1,3-butadiene (Zimmerman et al, 1987; Lin et al, 1992; Penn et al, 1996a; Penn et al, 1996b; Roberts et al, 1996). A later step in atherosclerosis, accumulation of LDL in the carotid arterial wall has recently been demonstrated (Roberts et al, 1996). There appears to be a synergistic effect between environmental tobacco smoke and LDL which facilitates the binding of oxidized LDL to the vessel wall (Roberts et al, 1996; Scanlon et al, 1996). Two studies in cockerels have conclusively shown that both constant and intermittent exposure to environmental tobacco smoke for a period as short as 17 weeks increases the development of atherosclerotic plaque (Penn et al, 1993; Penn et al, 1994). In a separate animal model with greater smoke exposure, the cholesterol-fed rabbit, similar findings were

obtained (Zhu et al, 1993). The development of atherosclerosis was not attenuated by metoprolol treatment suggesting the sympathetic nervous system is not involved in this process (Sun et al, 1994). Cigarette smoke exposure has also been associated with the accumulation of glycosaminoglycans and glycoproteins in vascular tissues of rats, another early event in atherogenesis (Latha et al, 1991).

Clinical correlation with these basic research findings has been demonstrated by two cross-sectional studies and one follow-up longitudinal study of carotid wall thickness in smokers, passive smokers, ex-smokers, and non-smokers without passive smoke exposure (Howard et al, 1994; Diez-Roux et al, 1995; Howard et al, 1998). Carotid wall thickness is an accepted measure of atherosclerotic burden with good correlation to coronary atherosclerosis. Non-smokers with environmental tobacco smoke exposure have significantly greater wall thickness than non-smokers without environmental tobacco smoke exposure. The progression of atherosclerosis is also greater in those exposed to environmental tobacco smoke. These findings are independent of other cardiovascular risk factors. However, in individuals with diabetes mellitus, rates of atherosclerosis progression are accelerated with environmental smoke exposure. The magnitude of the effect was less than in regular smokers but highly significant.

That these results are generalizable to children and adolescents can be inferred from two studies. In the Pathobiological Determinants of Atherosclerosis in Youth Study, postmortem serum thiocyanate levels were used as a marker of smoking status in individuals aged 15 to 35 years who died of other causes (PDAY Research Group, 1990; Scanlon et al, 1996). Atherosclerosis was increased in those with increased thiocyanate levels. Most important, the incorporation of oxidized LDL into early arterial atherosclerotic lesions was strongly associated with thiocyanate levels. Elevated thiocyanate levels are present in children whose parents smoke, though thiocyanate can be present from other causes as well (Moskowitz et al, 1990).

### ***Oxygen transport:***

Some of the earliest observations of the physiologic effects of passive smoking were made with regard to oxygen transport (Gidding et al, 1994; Glantz and Parmley, 1995). This is because carbon monoxide, an important component of tobacco smoke, binds tightly to hemoglobin displacing oxygen and thus reducing oxygen carrying capacity. In children, the concentration of red cell 2,3-diphosphoglycerate, a compound which regulates oxygen delivery at the tissue level, is higher in children of smokers and proportional to serum thiocyanate levels, a measure of smoke exposure (Moskowitz et al, 1990; Moskowitz et al, 1993). This suggests that children exposed to environmental tobacco smoke have experienced some tissue hypoxia similar to children with anemia, cyanotic heart disease, chronic lung disease, and at high altitude.

Physiologic effects on oxygen transport of environmental smoke exposure have been carefully studied in adults (Glantz and Parmley, 1995). Exercise performance and time to recovery of baseline heart rate are impaired in both healthy adult males and male survivors of myocardial infarction; these changes have been related to carbon monoxide levels (McMurray et al, 1985; Leone et al, 1991). Myocardial ischemia is more likely to be seen during exercise in myocardial infarction survivors exposed to environmental tobacco smoke (Allred et al, 1989).

Animal studies of oxygen transport have focused on myocardial metabolism and tissue injury following myocardial infarction. A critical finding for extending findings in adults to younger age groups has been the effect of fetal, neonatal, and childhood exposure to environmental tobacco smoke on infarct size in young rats (Zhu et al, 1997). This adverse effect related to early exposure is similar to that found in exposure during adulthood (Zhu et al, 1994). Potential explanations for this finding include increased myocardial oxygen needs after smoke exposure, increased carboxyhemoglobin levels, abnormal mitochondrial cytochrome oxidase activity, and sensitivity to ischemia/reperfusion injury (Gvozdjakova et al, 1984; Gvozdjakova et al, 1992; Aronow, 1978; van Jaarsveld et al, 1992).

The impact of environmental tobacco smoke on limiting systemic oxygen transport in children is well demonstrated and can be measured (Moskowitz et al, 1990). It is possible, based on experimental data in animals, that the effect of smoke exposure early in life may have adverse consequences on ischemic events later in life (Zhu et al, 1997). The clinical significance of these effects on children, other than impaired exercise performance, remains unknown because vascular ischemic events in children are rare and are often related to abnormal blood coagulation, congenital anomalies, or inflammatory diseases such as Takayasu's arteritis or Kawasaki disease. Further study is needed to determine if environmental smoke exposure either exacerbates vascular events in children or is a risk factor.

### ***Lipoproteins:***

Just recently, effects of environmental tobacco smoke on lipoproteins have been observed. HDL cholesterol, a known coronary risk factor, has been shown to be lower, that is, adversely effected, in smoke-exposed children in the United States (Moskowitz et al, 1990; Feldman et al, 1991). HDL cholesterol is a known independent risk factor for coronary artery disease with an inverse association between blood level and risk. The magnitude of change was in the range of 5-10 %. Studies in Japan and Turkey have shown conflicting data (Misawa et al, 1989; Iscan et al, 1996). A small, non-significant difference in HDL cholesterol was identified in smoke-exposed Japanese children and no difference in Turkish children. However, LDL cholesterol and the LDL/HDL cholesterol ratio were adversely affected in the Turkish children exposed to tobacco smoke. Collectively, the combined findings of these studies are comparable to lipoprotein changes induced by regular smoking (Craig et al, 1990). Mechanisms for this effect may be inhibition of plasma lecithin:cholesterol acyl transferase activity and altered chylomicron remnant clearance by the liver (Bielicki et al, 1995; Pan et al, 1997). A recent important confirmatory observation of these findings was made in children with severe hypercholesterolemia; lower HDL cholesterol was identified in high risk children whose parents smoked as compared to those whose parents did not (Neufeld et al, 1997).

Perhaps more important is the recent association of LDL oxidation to environmental smoke exposure. As previously noted, in pathologic studies of adolescents and young adults, the level of smoke exposure as measured by thiocyanate level is directly related to the presence of atherosclerosis and amount of oxidized LDL in early atherosclerotic lesions (Scanlon et al, 1996). Oxidative stress has been associated with exposure of adults to environmental tobacco smoke in three studies (Tribble et al, 1993; Howard et al, 1998; Valkonen and Kuusi, 1998). The first described decreased serum levels of ascorbic acid. The second, conducted in a work environment, demonstrated in those exposed to tobacco smoke the presence of higher levels of the oxidative DNA mutagen 8-hydroxy-2'-deoxyguanosine, as well as catalase and glutathione peroxidase. The third showed that environmental smoke exposure causes decreased ascorbic acid concentrations, serum antioxidant defense, and the capacity of LDL to resist oxidation. Increased components of lipid peroxidation appeared in serum. LDL from smoke-exposed subjects was more readily taken up by cultured macrophages. Changes in antioxidants similar to these clinical studies have been observed after exposure of human plasma to tobacco smoke in the laboratory (Bielicki et al, 1995). Another link between lower HDL and LDL oxidation may be the fact that HDL is the major lipoprotein carrier of cholesterol ester hydroperoxides. In vitro, HDL may decrease lipid peroxides generated on LDL during oxidation (Mackness et al, 1993, Mackness et al, 1995).

### ***Vascular function:***

A critical link in understanding the role of smoking in the pathogenesis of coronary disease has been the association of smoking induced atherosclerosis with endothelial dysfunction, an assessment which can be made noninvasively in humans who are otherwise healthy (Celermajer et al, 1993; Rangemark et al, 1992). The response of the endothelium to smoke exposure is dose dependent and suggests the presence of vascular injury. Endothelial

dysfunction has been associated with the presence of autoantibodies to oxidized LDL (Heitzer et al, 1996).

Endothelial dysfunction has been identified not only in smokers, but in adolescents and young adults exposed to environmental tobacco smoke (Celermajer et al, 1996). Effects were dose dependent, but high exposure showed adverse effects similar to chronic tobacco use. Similar evidence for vascular dysfunction has been found in cardiac catheterization studies of aortic elasticity in adult males with chest pain. Comparisons were made between smokers and non-smokers before and after passive smoke exposure. Again, passive smoke exposure had adverse effects similar to smoking (Stefandis et al, 1998). Effects on endothelial function may be expressed differently in different races as Chinese women do not appear to respond in the same way as Caucasians (Woo et al, 1997).

There is extensive confirmation in laboratory studies of the presence of endothelial dysfunction after environmental smoke exposure (Jorge et al, 1994; Hutchison et al, 1997a). These effects may be exacerbated by testosterone (Hutchison et al, 1997b).

Endothelial dysfunction as measured noninvasively using ultrasound is indicative of vascular injury. The presence of endothelial dysfunction in adolescents and young adults suggests that environmental tobacco smoke exposure initiates the atherosclerotic process early in life. What remains unknown, however, is the magnitude of the effect, the severity of the injury and its reversibility if smoke exposure is abolished or diminished.

### ***Thrombosis:***

Myocardial infarction can be described as the initiation of a thrombotic event by an acute event within an atherosclerotic plaque. Important to understanding the importance of smoking to the pathogenesis of myocardial infarction has been the demonstration of enhanced potential for thrombosis after exposure to tobacco smoke, either actively or passively (Glantz and Parmley, 1991; Law et al, 1997). This may be the mechanism for the observed increase in ischaemic events observed in adults with passive smoke exposure (Law et al, 1997). Prothrombotic effects on bleeding time and platelet aggregability have consistently been observed in animal studies of passive smoke exposure (Zhu et al, 1993; Zhu et al, 1994). Studies in humans have confirmed this finding, adding the observation that the non-smoker exposed to environmental tobacco smoke may be acutely more sensitive to the pro-thrombotic and platelet aggregating effects (Burghuber et al, 1986; Davis et al, 1989; Davis, 1990). The impact of passive smoking on platelet function has recently been reviewed with the conclusion that tobacco smoke interferes with platelet-activating factor. The mechanism relates to the many toxins in tobacco smoke which reduce the effectiveness of platelet-activating factor acetylhydrolase in neutralizing platelet activating factor activity (Kritz and Sinsinger, 1996). There is no reason to suspect differences between adults and children with regard to this finding.

### ***Fetal and infant exposure:***

Metabolites of tobacco smoke have been identified at birth in the hair of infants born to mothers who smoke (Eliopoulos et al, 1994). Cardiovascular effects on the fetus of maternal smoking may be in part responsible for adverse outcomes. Maternal smoking leads to significant increases in carboxyhemoglobin in maternal and fetal blood with higher levels in the fetus than the mother because of increased fetal affinity for carbon monoxide (Cole et al, 1978). This results in reduced oxygen carrying capacity and a reduction of the pressure at which oxygen is delivered to fetal tissues. The vasculature of the placentas of mothers who smoke have ultrastructural changes consistent with diminished placental blood flow (Asmussen, 1980). Maternal smoking during pregnancy has been shown to impair microcirculatory function during the first few days of life (Ahlsten et al, 1987). Reduced prostacyclin biosynthesis demonstrated in the blood vessels of smokers and in umbilical arteries of infants of smoking mothers may explain this reduced capacity for vasodilation (Ahlsten et al, 1986).

Infants born with persistent pulmonary hypertension are more likely to have detectable cotinine in their cord blood and have higher cotinine levels than normal infants

(Bearer et al, 1997). The maternal smoke exposure can be active or passive. Studies of passive smoke exposure in cholesterol-fed rabbits show pulmonary as well as systemic arterial involvement with atherosclerosis (Zhu et al, 1993).

One may speculate on the role of tobacco smoke exposure on the cardiovascular system in infants who succumb to sudden infant death syndrome. A relationship between prolonged QT interval and sudden infant deaths has recently been established (Schwartz et al, 1998). It is also known that tobacco use increases arrhythmias in patients with coronary ischemia (Sheps et al, 1990). As yet, no prospective electrophysiologic studies of infants and smoke exposure have been performed to determine if passive smoke exposure alters cardiac electrophysiologic properties or arrhythmias, though it is known that serum cotinine levels are higher in victims of sudden infant death (Milerad et al, 1998).

It has also been observed that the diet quality of low income children whose parents smoke is substantially worse than of low income children whose parents do not smoke (Johnson et al, 1996). Other health behaviors such as participation in regular physical activity, degree of overweight, and hours of television watched are adversely affected (Burke et al, 1998). Most of these differences would increase cardiovascular risk including increased intakes of cholesterol, saturated fat, total calories, and salt and decreased intakes of dietary fiber and vitamin A.

### ***Summary and Conclusions:***

This review has presented evidence for the presence of cardiovascular effects of environmental tobacco smoke on children and adolescents. These include adverse changes in oxygen transport, HDL cholesterol, and endothelial function. Adverse effects on platelet aggregability and LDL oxidation can easily be inferred from studies in adults. That passive smoke exposure can initiate atherosclerosis in youth can be inferred from pathologic studies which relate serum thiocyanate to atherosclerotic lesions in adolescents and young adults, the presence of endothelial dysfunction in adolescents exposed to environmental tobacco smoke, and many animal studies.

However, the clinical significance of these findings remains unproven. As yet, and there may never be, studies which link environmental tobacco smoke exposure in youth to cardiovascular events later in life. The relationship of environmental smoke exposure to vascular events in childhood has not been assessed. Finally, the potential for reversibility of adverse effects needs to be assessed.

A fruitful area for study may be the child or adolescent with other coronary disease risk factors. Since it is now well established that the presence of several risk factors accelerates the atherosclerotic process, it may be useful to attempt to demonstrate additive effects of smoke exposure in children who already have established and relatively immutable risk factors such as familial hypercholesterolemia, diabetes mellitus, and severe obesity with insulin resistance. These interactions may be influenced by race, gender, and family history of coronary disease (Moskowitz et al, in press). The development of newer research tools providing intermediate endpoints which correlate with the presence of atherosclerosis such as assessment of endothelial dysfunction, carotid ultrasound, and estimation of coronary calcium by ultrafast CT scanning may allow for a new understanding of the cardiovascular effects of environmental smoke exposure.

## References

- Ahlsten G et al. (1986) Maternal smoking reduces prostacyclin formation in human umbilical arteries: a study on strictly selected pregnancies. *Acta Obstet Gynecol Scand* 65:645-649.
- Ahlsten G et al. (1987) Impaired vascular reactivity in newborn infants of smoking mothers. *Acta Paediatr Scand* 76:248-253.
- Allred EN et al. (1989) Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. *N Engl J Med* 321:1426-1432.
- Asmussen I. (1980) Ultrastructure of the villi and fetal capillaries in placentas from smoking and nonsmoking mothers. *Br J Obstet Gynecol* 87:239-245.
- Aronow W. (1978) Effect of passive smoking on angina pectoris. *N Engl J Med* 299:21-4.
- Bearer C et al. (1997) Maternal tobacco smoke exposure and persistent pulmonary hypertension. *Environ Hlth Persp* 105(2):202-206.
- Bielicki JK et al. (1995) Copper and gas-phase cigarette smoke inhibit plasma lecithin: cholesterol acyltransferase activity by different mechanisms. *J Lipid Res* 36:322-331.
- Burghuber OC et al. (1986) Platelet sensitivity to prostacyclin in smokers and non-smokers. *Chest* 90:34-8.
- Burke V et al. (1998) Parental smoking and risk factors for cardiovascular disease in 10-12 year old children. *J Pediatr* 133:206-13.
- California Environmental Protection Agency (1997) Health effects of exposure to environmental tobacco smoke (<http://www.calepa.ca.gov/oehha/docs/finalets.htm>)
- Celermajer DS et al. (1993) Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in health young adults. *Circulation* 88:2149-55.
- Celermajer DS et al. (1996) Passive smoking and impaired endothelium-dependent arterial dilatation in healthy young adults. *N Engl J Med* 334(3):150-4.
- Cole PV et al. (1978) Smoking during pregnancy and its effects on the fetus. *Br J Obstet Gynecol* 79:782-789.
- Craig WY et al. (1990). Cigarette smoking-associated changes in blood lipid lipoprotein levels in the 8-19 year-old age group: a meta-analysis. *Pediatrics* 85:155-8.
- Davis JW. (1990) Some effects of smoking on endothelial and platelets. *Tobacco Smoking and Atherosclerosis*. JN Diana. Plenum Press, NY.
- Davis JW et al. (1989) Passive smoking affects endothelium and platelets. *Arch Intern Med* 149:386-389.
- Diez-Roux AV et al. (1995) The relationship of active and passive smoking to carotid atherosclerosis 12-14 years later. *Prev Med* 24:48-55.
- Eliopoulos C et al. (1994) Hair concentrations of nicotine and cotinine in women and their newborn infants. *JAMA* 271:621-3.

- Feldman J et al. (1991) Passive smoking alters lipid profiles in adolescents. *Pediatrics* 88(2):259-64.
- Gidding SS and Schydlower M. (1994) Active and passive tobacco exposure: A serious pediatric health problem. *Commentary. Pediatrics* 94:750-751.
- Gidding et al. (1994) Active and passive tobacco exposure: a serious pediatric health problem. *Circulation* 90(5):2581-6.
- Glantz SA and Parmley W. (1991) Passive smoking and heart disease. *Circulation* 83 (1):1-12.
- Glantz SA and Parmley W. (1995) Passive smoking and heart disease: Mechanism and risk. *JAMA* 273(13):1047-53.
- Gvozdjakova A et al. (1984) Smoke cardiomyopathy: disturbance of oxidative processes in myocardial mitochondria. *Cardiovasc Res* 18:229-232.
- Gvozdjakova A et al. (1992) Effect of smoking on the oxidative processes of cardiomyocytes. *Cardiology* 81:81-4.
- Heitzer T et al. (1996) Cigarette smoking potentiates endothelial dysfunction of forearm resistance vessels in patients with hypercholesterolemia. *Circulation* 93(7):1346-1354.
- Howard DJ et al. (1998) Environmental tobacco smoke in the workplace induces oxidative stress in employees, including increased production of 8-hydroxy-2'deoxyguanosine. *Cancer Epidemiol Biomarkers Prev* 7:141-146.
- Howard G et al. (1994) Active and passive smoking are associated with increased carotid wall thickness. *Arch Intern Med* 154:1277-1282.
- Howard G et al. (1998) Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA* 279:119-124.
- Hutchison SJ et al. (1997a) Chronic dietary l-arginine prevents endothelial dysfunction secondary to environmental tobacco smoke in normocholesterolemic rabbits. *Hypertension* 29(5):1186-91.
- Hutchison SJ et al. (1997b) Testosterone worsens endothelial dysfunction associated with hypercholesterolemia and environmental tobacco smoke exposure in male rabbit aorta. *J Am Coll Cardiol* 19(4):800-7.
- Iscan A et al. (1996) Effects of passive exposure to tobacco, socioeconomic status and a family history of essential hypertension on lipid profiles in children. *Jpn Heart J* 37(6):917-923.
- Johnson RK et al. (1996) The association between parental smoking and the diet quality of low-income children. *Pediatrics* 97(3):312-317.
- Jorge PA et al. (1995) Endothelial dysfunction in coronary vessels and thoracic aorta of rats exposed to cigarette smoke. *Clinical and Experimental Pharmacology and Physiology* 22:410-413.

- Kritz H and Sinzinger H. (1996). Passive smoking, platelet function and atherosclerosis. *Wiener Klinische Wochenschrift*. Springer-Verlag Austria.
- Latha MS et al. (1991) Changes in the glycosaminoglycans and glycoproteins in the tissues in rats exposed to cigarette smoke. *Atherosclerosis* 31:49-54.
- Law MR et al. (1997) Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *BMJ* 315(7114):961-2.
- Leone A et al. (1991) Indoor passive smoking: its effect on cardiac performance. *International J of Cardiol* 33:247-252.
- Lin SJ et al. (1992) Long-term nicotine exposure increases aortic endothelial cell death and enhances transendothelial macromolecular transport in rats. *Arteriosclerosis and Thrombosis* 12(11):1305-12.
- Mackness MI et al. (1993) Protection of low-density lipoprotein against oxidative modification by HDL associated paraoxanase. *Atherosclerosis* 104:129-136.
- Mackness MI et al. (1995) HDL, its enzymes and its potential to influence lipid peroxidation. *Atherosclerosis* 115:243-253.
- McMurray RG et al. (1985) The effects of passive inhalation of cigarette smoke on exercise performance. *Eur J Appl Physiol* 54:196-200.
- Milerad J et al. (1998) Objective measurements of nicotine exposure in victims of sudden infant death syndrome and in other unexpected child deaths. *J of Pediatr* 133(2): 232-236.
- Misawa K et al. (1989) An epidemiological study on the relationships among HDL-cholesterol, smoking and obesity. *Jpn J Hygiene* 44(3):725-32.
- Moskowitz WB et al. (1990) Lipoprotein and oxygen transport alterations in passive smoking preadolescent children. *The MCV Twin Study*. *Circulation* 81(2):586-92.
- Moskowitz WB et al. (1993) Univariate genetic analysis of oxygen transport regulation in children: the Medical College of Virginia Twin Study. *Pediatr Res* 33(6):645-8.
- Moskowitz WB et al. In press Childhood passive smoking, race, and coronary artery disease risk: The MCV Twin Study. *Arch Pediatr Adol Med*
- Neufeld EJ et al. (1997) Passive cigarette smoking and reduced HDL cholesterol levels in children with high-risk lipid profiles. *Circulation* 96(5):1403-7.
- Pan XM et al. (1997) Exposure to cigarette smoke delays in plasma clearance of chylomicrons and chylomicron remnants in rats. *Am J Physiol* 273(Pt 1):G158-63.
- PDAY Research Group (1990) Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations in smoking: a preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth. *J Am Med Assoc* 264:3018.
- Penn A et al. (1996a) 1,3-Butadiene, a vapor phase component of environmental tobacco smoke, accelerates arteriosclerotic plaque development. *Circulation* 93(3):552-7.
- Penn A et al. (1996b) Butadiene inhalation accelerates arteriosclerotic plaque development in cockerels. *Toxicology* 113:351-4.

- Penn A et al. (1992) Inhalation of carbon monoxide does not accelerate arteriosclerosis in cockerels. *Eur J Pharmacol* 228:155-165.
- Penn A et al. (1993) Inhalation of sidestream cigarette smoke accelerates development of arteriosclerotic plaques. *Circulation* 88(4 Pt 1):1820-5.
- Penn A et al. (1994) Inhalation of steady-state sidestream smoke from one cigarette promotes arteriosclerotic plaque development. *Circulation* 90(3):1363-1367.
- Rangemark C et al. (1992) Endothelium-dependent and independent vasodilation and reactive hyperemia in healthy smokers. *J Cardiovasc Pharmacol* 20 (suppl 2):S198-S201.
- Roberts KA et al. (1996) Effect of environmental tobacco smoke on LDL accumulation in the artery wall. *Circulation* 94(9):2248-2253.
- Scanlon EO et al. (1996) Evidence for more extensive deposits of epitopes of oxidized low density lipoprotein in aortas of young people with elevated serum thiocyanate levels. *Atherosclerosis* 121:23-33.
- Schwartz PJ et al. (1998) Prolongation of the QT interval and the sudden infant death syndrome. *N Engl J Med* 338:1709-14.
- Sheps DS et al. (1990) Production of arrhythmias by elevated carboxyhemoglobin in patients with coronary artery disease. *Ann Intern Med* 113:343-351.
- Stefanadis C et al. (1998) Unfavorable effects of passive smoking on aortic function in men. *Annals Intern Med* 128 (6):426-34.
- Sun YP et al. (1994) Metoprolol does not attenuate atherosclerosis in lipid-fed rabbits exposed to environmental tobacco smoke. *Circulation* 89(5):2260-22605.
- Taylor AE et al. (1992) Environmental tobacco smoke and cardiovascular disease. *Circulation* 86(2):699-702.
- Thomas D (1997) Tabagisme passif et maladies cardio-vasculaires. *Bull Acad Natle Med* 181(4):19-29.
- Tribble DL et al. (1993) Reduced plasma ascorbic acid concentrations in nonsmokers regularly exposed to environmental tobacco in smoke. *Am J Clin Nutr* 58:886-890.
- United Kingdom Department of Health (1998) Report of the Scientific Committee on Tobacco and Health (<http://www.open.gov.uk/doh/public/scoth.htm>)
- US Department of Health and Human Services (1994) Preventing Tobacco use among young people: a report of the Surgeon General.
- Valkonen M and Kuusi T. (1998) Passive smoking induces atherogenic changes in low-density lipoprotein. *Circulation* 97:2012-6.
- Van Jaarsveld H et al. (1992) Antioxidant vitamin supplementation of smoke-exposed rats partially protects against myocardial ischaemic/reperfusion injury. *Free Rad Res Comm* 17(4):263-9.

Wells AJ (1994) Passive smoking as a cause of heart disease. *J Am Coll Cardiol* 24(2):546-54.

Wells AJ (1998) Heart disease from passive smoking in the workplace. *J Am Coll Cardiol* 31:1-9.

Woo KS et al. (1997) Differences in the effect of cigarette smoking on endothelial function in chinese and white adults. *Annals Intern Med* 127(5):372-5.

Zhu BQ et al. (1997) Effects of second-hand smoke and gender on infarct size of young rats exposed in utero and in the neonatal to adolescent period. *J Am Coll Cardiol* 30(7):1878-85.

Zhu BQ et al. (1994) Exposure to environmental tobacco smoke increases myocardial infarct size in rats. *Circulation* 89(3):1282-90.

Zhu BQ et al. (1993) Passive smoking increases experimental atherosclerosis in cholesterol-fed rabbits. *J Am Coll Cardiol* 21(1):225-31.

Zimmerman M et al. (1987) The effect of nicotine on aortic endothelium. *Atherosclerosis* 63:33-41.