ENDOTHELIAL DYSFUNCTION IN CARDIOVASCULAR DISEASE
P.M. Vanhoutte, Institut de Recherches Internationales Servier, Courbevoie, France.

The endothelium mediates a number of responses (relaxations or contractions) of isolated arteries and veins from animals and humans. The endothelium-dependent relaxations are due to the release by the endothelial cells of potent non-prostanoid vasodilator substances. The best characterized endothelium-derived relaxing factor (EDRF) is nitric oxide (NO). Nitric oxide is formed by the metabolism of L-arginine by the constitutive NO synthase of endothelial cells. In arterial smooth muscle, the relaxations evoked by NO are explained best by the stimulation by NO of soluble guanylate cyclase that leads to the accumulation of cyclic GMP. In a number of animal blood vessels and in human coronary arteries the endothelial cells release a substance that causes hyperpolarization of the cell membrane (endothelium-derived hyperpolarizing factor, EDHF). The release of relaxing factors can be initiated by circulating hormones (catecholamines, acting on o2-adrenoceptors; vasoopressin and oxytocin, acting on V1 vasopressin receptors; and estrogens, acting at an undefined site). The release of EDRF from the endothelium can be mediated by both pertussis toxin-sensitive (alpha2-adrenergic activation, serotonin, aggregating platelets, leukotrienes) and insensitive (adenosine diphosphate, bradykinin) G-proteins. The ability of the endothelial cell to release relaxing factors can be upregulated by the regeneration of the cell membrane. The limited information available on isolated human blood vessels or obtained in situ, concur with the conclusions reached with isolated animal tissues. In addition to relaxing factors, the endothelial cells can produce contracting-substances (endothelium-derived contracting factors ; EDCF) which include superoxide anions, endoperoxides, thromboxane A2 and the potent vasoconstrictor peptide endothelin. To judge from animals studies, the propensity to release EDCF is maintained or even augmented in diseased blood vessels. This is particularly the case in essential hypertension and diabetes. The switch from a normally predominant release of EDRFs to that of EDCF may play a crucial role in vascular hyperreactivity as occn in vasospasm, hypertension and atherosclerosis.

CORONARY ARTERY DISEASE: A DEMOGRAPHIC PERSPECTIVE
D T Kelly, Hallstrom Institute of Cardiology, University of Sydney, Sydney, New South Wales, Australia.

Coronary disease mortality rate varies in different countries but prevalence and mortality are increasing worldwide. Several factors are responsible for the increased prevalence. Population ageing, a social phenomenon of the latter half of the last century, continues into this century. The rate of ageing is greater in countries that have had reduced birth rates in the last generation, such as China. As prevalence of coronary disease increases dramatically over the age of 65, prevalence is linked to population ageing.

In many countries, particularly those in Asia, the risk factor profile is increased. Urbanization has dramatically increased in developing countries, particularly Asia. By 2030 over 50 percent of Chinese will be urban dwellers. Urbanization carries increased risk of hypertension, diabetes, adverse dietary change, tobacco smoking and decreased physical activity. These risk factors are responsible for a dramatic increase in coronary disease in middle and old age.

A further cause of increased prevalence is the decreased mortality from acute coronary syndromes, particularly in developed countries, due to improved management and therapeutic strategies over the last 50 years. The endpoint of coronary disease is now not death from myocardial infarction in middle age but increasingly heart failure in old age. This, paradoxically, has increased the community disease burden and will continue in the first half of this century. Social and economic strategies to manage this increased burden of coronary artery disease must be developed.

THE CHALLENGE OF ATHEROSCLEROSIS IN THE 21ST CENTURY
Peter W.F. Wilson, Boston University School of Medicine, Framingham Heart Study, Boston, USA.

Obesity (BMI>30 kg/m2), type 2 diabetes mellitus, and the prevalence of cardiovascular disease continue to rise throughout the world. U.S. data show that there is an upswing in obesity that is especially evident in the past 10 years; virtually every age, sex, and ethnic group is affected. The incidence of type 2 diabetes mellitus is highly associated with total and regional adiposity, and lifetime risks for type 2 diabetes mellitus have been estimated at 30% in both men and women with a BMI>30 kg/m2 during their middle-aged years. Diabetes increases the risk of large and small vessel disease, and affects initial and recurrent event rates. Although the incidence of cardiovascular death has decreased in North America and Europe since the late 1960's, the
incidence of new heart disease has declined only modestly and the proportion of middle aged and older persons with vascular disease continues to increase. Importantly, heart disease is now an important cause of death in developing countries. Levels of cardiovascular risk factors remain at relatively high levels in middle-aged adults throughout the developed world and there have been only modest improvements, with a few notable exceptions. As blood pressure and dyslipidemia therapies become more common and reach a greater fraction of the population we will have to be on the alert for the development of more small vascular disease sequelae in an aging population. Sequelae such as renal insufficiency, microvascular disease of the heart and brain are other potential ways that atherosclerosis will "evolve" in the future.

004
ATHEROSCLEROSIS:
ENVIRONMENT AND GENETIC FACTORS
Jean Davignon, Hyperlipidemia and Atherosclerosis Research Group, Clinical Research Institute of Montréal and University of Montréal.

Atherosclerosis is a multifactorial and ubiquitous vascular disease with dire consequences. Its complexity has made its understanding and treatment difficult. The study of atherosclerosis and its consequences, especially coronary artery disease (CAD), has resulted in the identification of a large number of environmental and genetic "risk factors". These atherogenic factors, causing anatomical as well as functional changes, determine the rate of change of lesions throughout life. In the past, emphasis was placed on the lipid hypothesis, which delineates a clear relationship between plasma lipoprotein abnormalities and atherosclerosis. In recent years several paradigm shifts have taken place to bring attention to small vulnerable plaques, endothelial dysfunction and the role of inflammation and oxidation in atherogenesis. The notion of genetic predisposition modulated by environmental factors has further emphasized the complex interactions taking place in the etiology of this common disease.

Modulation of the impact of a variation in the CETP gene by alcohol intake, and the effect of variation at the apolipoprotein E gene locus on CAD risk and response to treatment, are prime examples of such interactions. Endothelial dysfunction, characterized by a reduced nitric oxide (NO) production, predisposes to the development of atherosclerosis. Variations in the endothelial NO synthase gene have been found to influence CAD risk. Such modulating factors exist throughout the cascade of events that lead to atherosclerosis. Gene-environment interactions influence not only the rate of progression of atherosclerotic vascular disease, but also the therapeutic response. They must be taken into account in assessing CAD risk and optimizing treatment.

005
THE ROLE OF GENDER: IN ATHEROSCLEROSIS
Katharine Detre*. University of Pittsburgh, PA, USA.

Gender has a well-known role in the risk for coronary artery disease (CAD). In their reproductive years, women are practically immune to CAD, unless they undergo surgical menopause, suffer from polycystic ovaries (Syndrome X) or from Diabetes Mellitus. However, incidence of CAD increases substantially in the sixth decade of life. To test the role of estrogen as a mechanism of the "female protection", several RCT-s in the 1970's were initiated in men with CAD using different doses of estrogen with or without lipid lowering drugs. Because of their adverse rather than beneficial affects, the estrogen arms (5 and 2.5 mg Premarin) had to be discontinued prematurely in the NHLBI funded Coronary Drug Project, but was continued for five years – with a 1.25 mg Premarin dosage, - showing no survival benefit in a similarly designed Drug-Lipid study carried out by the Veteran's Administration.

Today, decades later, the benefit of hormone replacement therapy as a prevention of CAD even in post-menopausal women remains controversial.

Psychosocial stress has also been implicated as a differential risk factor for CAD in men and women. With the advent of women's liberation, many women moved into the labor force occupying stressful positions with a high responsibility previously held only by men. In the Federal Women's Study, we studied 15-year mortality of women versus men in the highest level jobs in the Federal Government exposed to the same on the job stresses and pressures. Interestingly, the nearly 5,000 women and nearly 15,000 men, (closely matched by age, supervisory responsibilities and by civil service level, 14 and 15) both experienced more than a 50 percent reduction in a 15-year heart disease mortality rates compared with that expected on the basis of the parallel experience of the general population. Thus, the approximate twofold heart disease mortality advantage traditionally enjoyed by women persisted in this study. We concluded that the sex differential in heart disease mortality is probably not modified by conditions associated with high-level employment (i.e., on-the-job stress).

007
ANTIARRHYTHMIC AGENTS:
TARGETS FOR PHARMACOLOGIC THERAPY
Henry Duff*. University of Calgary, AB, Canada.

A number of strategies have failed to suppress arrhythmias and prolong life: pharmacologic block of sodium and potassium channels and inotropic agents. Currently, truly successful antiarrhythmic pharmacologic strategies include: beta-blockers, ACE inhibitors, spironolactone, and amiodarone. New strategies must