

## Editorial

# Atherosclerosis—a disease that begins in childhood

David S. Celermajer, Keld E. Sorensen and John E. Deanfield

**A**THEROSCLEROSIS IS A VERY OLD DISEASE, HAVING BEEN identified even in the mummies of ancient Egypt.<sup>1</sup> In the latter half of this century, this disease and its complications have caused up to 50% of deaths in the Western World. A child born today is up to 500 times more likely to die from the complications of atherosclerosis than from congenital heart disease. Although the clinical manifestations usually present in middle and late adult life, the risk factors for atherogenesis are often present in childhood, and early histopathological changes can be found in large systemic arteries in the first decade of life.<sup>2</sup>

Attention was first drawn to the childhood origins of atherosclerosis by an autopsy study conducted on young soldiers killed in the Korean War. The subjects had an average age of 22 years, and over 70% of them had evidence of atherosclerosis in their coronary arteries.<sup>3</sup> Since that time, Sary and colleagues have demonstrated a very high incidence of lipid laden macrophages in the intima of the aorta and coronary arteries of young American children killed in motor accidents, with over 50% of children aged 10-14 having some evidence of early atherosclerosis.<sup>2</sup> The early signs of disease identified in these autopsy studies almost certainly represent the same pathological process that causes late morbidity and mortality. The presence of atheroma in young people has been correlated with a high level of low density lipoproteins and with cigarette smoking, both of which are known to be important risk factors for late cardiovascular death.<sup>4</sup> The recent prospective study by Klag and colleagues,<sup>5</sup> which demonstrated that serum cholesterol levels in late teenage years are strongly predictive of cardiovascular morbidity and mortality in middle age, is further evidence that the presence of risk factors in the pediatric age range is important in determining the later development of occlusive vascular disease.

### How early can this process begin?

Evidence is accumulating that the risk of late atherosclerosis

can be programmed from an extremely early stage. Genetic influences are clearly important. Recently, the angiotensin converting enzyme genotype has been implicated in the risk equation, with the DD genotype being associated with three times the risk of late myocardial infarction compared with the II genotype.<sup>6</sup> Early environmental influences are also important, and may act as early as fetal life. Long-term epidemiological studies have shown an association between low birth weight and subsequent risk of hypertension in adult life, and also between weight on the first birthday and later risk of occlusive vascular disease.<sup>7</sup>

Apart from these genetic and early environmental influences, most of the risk factors associated with vascular disease may be manifest during the childhood years. Hypercholesterolemia, hypertension, diabetes mellitus and cigarette smoking may all be found in children and adolescents. The recent development of a noninvasive method for detecting evidence of early vascular injury in children and young adults has facilitated our understanding of the origins of atherosclerosis.<sup>8</sup>

### Endothelial dysfunction

For many decades the vascular endothelium was viewed simply as a semipermeable barrier between blood and interstitium, facilitating the exchange of water and small molecules. Over the last 15 years, however, a series of experiments has demonstrated that the endothelium has an enormous range of vital homeostatic functions, such as maintenance of thromboresistance, synthesis and secretion of peptides, regulation of vascular tone and growth and regulation of inflammatory reactions.<sup>9</sup>

There is a strong link between endothelial injury and the later development of atherosclerosis, with endothelial damage being a key early event in atherogenesis.<sup>10,11</sup> Both spatial and temporal correlation between endothelial dysfunction and coronary atherosclerosis<sup>12,13</sup> have been shown, in animal models and in man. A major functional consequence of endothelial injury is the reduced availability of endothelium-derived relaxing

factor, which is now known to be nitric oxide or a molecule elaborating nitric oxide.<sup>14</sup> Endothelium-derived relaxing factor is a local vasodilator, and also inhibits adherence and aggregation of platelets, smooth muscular proliferation, and interactions between endothelial cells and leucocytes.<sup>10</sup> The recent demonstration that L-arginine, the substrate for the production of the relaxing factor, not only protects endothelium-dependent relaxation in hypercholesterolemic rabbits but also inhibits formation of atheroma, is provocative.<sup>15</sup> It suggests that loss of normal endothelial function is not simply a marker of early disease, but may be intimately involved in the pathogenesis of atherosclerosis.

Endothelial injury has been induced experimentally by exposure to known vascular risk factors, such as smoking and hypercholesterolemia.<sup>16,17</sup> Until recently, most clinical studies of endothelial function have involved infusion of vasoactive substances into the coronary circulation, followed by quantitative angiography for measurement of arterial diameter.<sup>18,19</sup> The responses of the vessel to endothelium-dependent and independent vasodilators have been contrasted. Clearly such invasive studies are not suitable for investigation of the early development of vascular damage in young asymptomatic subjects.

### Noninvasive studies of high risk subjects

A noninvasive method to detect endothelial dysfunction in children and adults at risk of atherosclerosis has, therefore, been developed, using high resolution ultrasound to measure arterial diameter.<sup>8</sup> As flow-induced dilatation is mediated by the endothelium in normal arteries,<sup>20,21</sup> endothelium dependent vasodilatation can be assessed by change in arterial diameter in response to condition of increased flow. This is contrasted to the response to sublingual nitroglycerine, which causes vasodilatation by an endothelium independent mechanism (direct relaxation of smooth muscle). Using this method, endothelial dysfunction has been demonstrated in the systemic arteries of children and young adults with a variety of risk factors.<sup>8</sup> Endothelial dysfunction is present in children with familial hypercholesterolemia as young as seven years of age, and the degree of endothelial injury is correlated with the elevation in level of serum cholesterol.<sup>22</sup> In children with homozygous homocystinuria, another metabolic disorder predisposing to premature atherosclerosis, endothelial dysfunction can also be demonstrated in the first decade of life.<sup>23</sup> Evidence of early vascular injury has also been found in young adult smokers, and the degree of vascular injury is related to the number of cigarettes smoked.<sup>24</sup>

Another promising noninvasive technique for detection of preclinical vascular disease is the ultrasound-

based measurement of intima-media thickness in the common carotid artery. Such measurements can now be obtained in almost all subjects, and may be made accurately and reproducibly.<sup>25</sup> Intima-media thickness increases with age, and is greater in subjects with atherosclerotic disease at distant sites.<sup>26</sup> The thickness of the intima-media of common carotid arteries is increased in hypercholesterolemic compared to normal adults,<sup>27</sup> and also correlates well with carotid and femoral atherosclerosis.<sup>26</sup> Intima-media thickness, and a variety of noninvasively derived arterial wall thickness "scores," are being used in prospective, long-term epidemiological studies. In the Atherosclerosis Risk in the Community<sup>28</sup> study, increased intima-media thickness has been positively correlated with total serum cholesterol, LDL cholesterol and systolic blood pressure, findings confirmed by Salonen and Salonen in Finland.<sup>29</sup> This group have also recently shown that a thickened intima-media in the carotid arteries is related, in middle-aged men, to rates of later ischemic events.<sup>30</sup> These data establish the predictive value of measurements of the thickness of the carotid wall, although the technique seems more applicable to older adults than to children and adolescents.

The maximum potential for prevention and reversibility of atherosclerosis would be expected with intervention at an early stage of the disease, before atherosclerotic plaques are established.<sup>31</sup> Reversal of endothelial dysfunction has been demonstrated in experimental animals by important interventions such as lowering levels of cholesterol<sup>12</sup> and antihypertensive therapy.<sup>32</sup> In clinical studies, there is evidence that cholesterol lowering and smoking cessation may reverse early vascular injury and, presumably, retard the progress of atherosclerosis.

### Clinical implications

The brief of the pediatrician and pediatric cardiologist should extend to diagnosis and treatment of risk factors in both individual patients and in populations. The measurement of blood pressure, advice on diet and exercise, and an active stance against smoking should be routine parts of initial and follow-up consultations. Although population screening for serum cholesterol is not justified, lipid profiles should probably be obtained from children whose parents have hypercholesterolemia or myocardial infarction under the age of 50 years. Appropriate interventions in children with identified vascular risk factors may well have important benefits for public health. Ongoing research will define the role of what interventions are safe and effective in reversing the signs of early arterial damage, such as endothelial dysfunction.

## The future

A variety of interventions may prove beneficial for arterial health. Strategies include not only modification of risk factors but pharmacological intervention, for example using calcium antagonists or inhibitors of angiotensin converting enzyme. This latter group of drugs may be particularly useful for subjects with the high risk angiotensin-converting enzyme genotype. The administration of L-arginine, the substrate for endothelium-derived relaxing factor, may reverse endothelial dysfunction caused by hypercholesterolemia.<sup>33,34</sup> Vitamin E, acting as a scavenger for free radicals, may also retard the development of atherosclerosis. Finally, genetic manipulation may have an important impact on the progression of atherosclerosis, especially when genes involved in high risk families and appropriate methods for their delivery to the vascular endothelium have been identified.

Atherosclerosis is the disease that will cause the death of most of us and most of our patients. It is timely and appropriate for cardiologists interested in the health of children to turn their attention to the identification and treatment of our patients who might be at increased risk of vascular disease in later life. Such an approach may be at least as important as the treatment of complex congenital heart disease, especially in terms of potential impact on the health of the community.

*Cardiothoracic Unit  
Hospital for Sick Children  
Great Ormond Street  
London, WC1N 3JH, United Kingdom  
Tel. 071 404 5094; Fax. 071 831 4850*

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