CIGARETTE SMOKING AND ENDOThelial INJURY: A REVIEW

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INTRODUCTION

Epidemiological considerations

There is overwhelming epidemiological evidence that an association exists between cigarette smoking and cardiovascular disease, in particular atherosclerosis (Auerbach et al., 1965, 1976; Auerbach and Garfinkel 1980; Dawber et al., 1959; Doll and Peto, 1976; Eastcott, 1962; Kannel et al., 1976; Laing et al., 1981; Murphy and Mustard, 1966; Sackett et al., 1968; Spain and Bradess, 1970; Strong and Richards, 1976). Despite these considerable epidemiological data, the component or components of cigarette smoke responsible for this relationship and the mechanisms through which they mediate their effects remain unknown.

Cigarette smoking and atherosclerosis

The pathogenesis and pathology of atherosclerosis have been the subject of many studies and reviews (see Ross, 1986; Woolf, 1987) and are not within the realm of this paper other than to note that there is still controversy as to what constitutes the earliest lesion of the disease, and that the fibro-lipid plaque may develop by a variety of routes (Haust, 1971; Woolf, 1987). Ross (1986) has proposed a response to injury hypothesis for the pathogenesis of atherosclerosis that takes account of recent experimental evidence. Two main pathways form the basis of this hypothesis and one of these or a variation of it may be important in relation to cigarette smoking as well as diabetes and hypertension. It is hypothesised that direct stimulation of endothelium may result in it releasing growth factors promoting the migration and proliferation of smooth muscle cells which in themselves may also release growth-factors on stimulation (Ross, 1986).

Endothelium and Endothelial Injury

Vascular endothelium has been the subject of many reviews
(see for example, Petty and Pearson, 1989; Pittilo, 1988a; Bull 1988) and a consideration of its morphology and known functional roles is outside the scope of this review.

Reidy (1985) has pointed out that historically endothelial injury has been considered to be the absence of endothelium and the presence of platelets. We now know that functional alteration of intact endothelium can influence the process of atherogenesis and now have to consider that intact endothelium may be functionally abnormal and represent an injured state (see Reidy, 1985). There are data to suggest that cigarette smoking may mediate its effect on the vessel wall partly through modifying endothelial cell function (see below).

Although this review is concerned with endothelial cell injury in relation to cigarette smoking, it is important not to forget that interactions between endothelial cells and other cells, such as blood platelets, may to a large extent be due to factors independent of the endothelial cell.

Morphological Limitations in Investigating Endothelial Injury

It has seemed logical to assume that the primary target for cigarette smoke components absorbed into the blood would be the vascular endothelium. However, from a morphological viewpoint it is not a straightforward matter to distinguish between normal and injured endothelium. It has been suggested that loss of endothelial cells might be a common consequence of injury with replacement of the lost cells by neighbouring cells (Reidy and Schwartz, 1984). These events could easily escape morphological detection. There is good evidence to indicate that endothelial cell loss can occur without denudation and consequent exposure of the sub-endothelium. Reidy and Schwartz (1983) used endotoxin to increase the turnover and replication of arterial endothelial cells and demonstrated desquamating endothelial cells without denudation. Furthermore, it would seem reasonable to speculate that endothelial injury might occur without there being any morphological manifestations (Ross, 1986). In other words, the endothelium might be modified to secrete growth factors or perhaps altered amounts of prostacyclin, without morphological change.

Examining the morphology of vascular endothelium in order to detect change resulting from injury is fraught with another problem. It is well established that vascular endothelium can show considerable morphological variation depending on the preparative methodologies adopted (Hollweg and Buss, 1980). Pittilo (1988a) advocated caution when examining vascular endothelium in view of the ease by which it can be altered artefactually and the fact that structures considered normal now, may be shown in the future to result from poor preparation.

Despite the dual cautions that endothelial injury might not have a morphological manifestation, and the ease through which endothelium can be altered artefactually during preparation, morphological studies have proven useful in demonstrating that endothelial damage can result from exposure to smoke or smoke components. In conjunction with available biochemical evidence, they have provided some insight into how cigarette