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Cholesterol in the lungs of heavy cigarette smokers

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Corrin, B and Soliman, S S (1978). *Thorax*, **33**, 565–568. **Cholesterol in the lungs of heavy cigarette smokers.** Electron microscopy of "normal" lung tissue from four heavy cigarette smokers showed acicular crystal clefts thought to represent cholesterol in the cytoplasm of virtually every type II pneumocyte. Similar but less pronounced changes were found in two cases of obstructive pneumonia distal to bronchial tumours, a condition characterised by excess cholesterol. Cholesterol pneumonitis is particularly prevalent in smokers, and the changes in our smokers' lungs possibly represent an early stage in a process that if progressive would lead to this disease. The cholesterol may represent a degenerative change in type II pneumocytes or a byproduct of increased surfactant synthesis stimulated by cigarette smoke.

A recent account of idiopathic cholesterol pneumonitis indicates that this condition is particularly prevalent in smokers (Lawler, 1977). We report subcellular alterations in the lungs of heavy cigarette smokers, which possibly represent the beginning of this disease.

Materials and methods

Seemingly normal peripheral lung tissue was obtained at operation from four patients who had all smoked more than 20 cigarettes a day for many years. Two were operated on for traumatic haemothorax, one for pleurectomy after empyema, and one underwent lobectomy for a bronchial carcinoid tumour.

Two patients who had both undergone lobectomy for lung cancer were also studied. In each of these cases the lung distal to the tumour showed obstructive endogenous lipid pneumonia, and samples were taken from these areas. One was an elderly woman with a poorly differentiated squamous carcinoma who smoked 20 cigarettes a day and the other a man with an anaplastic carcinoma arising in cryptogenic fibrosing alveolitis who smoked five to ten cigarettes a day.

For electron microscopy small pieces of lung tissue were fixed in cold (4°C) 0·1M cacodylate-buffered 4% paraformaldehyde containing 7·5% sucrose immediately after removal, post-fixed in 2% osmium tetroxide and embedded in Epon. Thin sections stained with lead citrate and uranyl acetate were subsequently examined by transmission electron microscopy.

Results

HEAVY SMOKERS (CASES 1–4)

In cases 1–4 light microscopy showed no abnormality other than an increased number of alveolar macrophages. Electron microscopy was conducted on several blocks from each patient, and in every one almost every type II pneumocyte contained several empty acicular crystal clefts ranging in length from 0·25 to 4 μm (figs 1 and 2). Many clefts lacked a limiting membrane, but some were continuous with channels of the endoplasmic reticulum or the lamellar vacuoles and shared the outer membranes of these structures. The appearances suggested membrane disruption, but the point of origin of the clefts in relation to the disrupted organelles was not apparent. Apart from the clefts and focal separation of the cells from the basement membrane the type II pneumocytes appeared normal. The lamellar inclusions and surface microvilli generally showed no abnormalities. Type I pneumocytes appeared normal apart from an occasional myelin figure, and bronchiolar lining cells contained many dense lamellar bodies, both these features representing focal cytoplasmic degradation. Alveolar macrophages were greatly increased in number and contained many pleomorphic lysosomal inclusions.

OBSTRUCTIVE PNEUMONIA (CASES 5 AND 6)

Both case 5 and case 6 showed hyperplasia of type

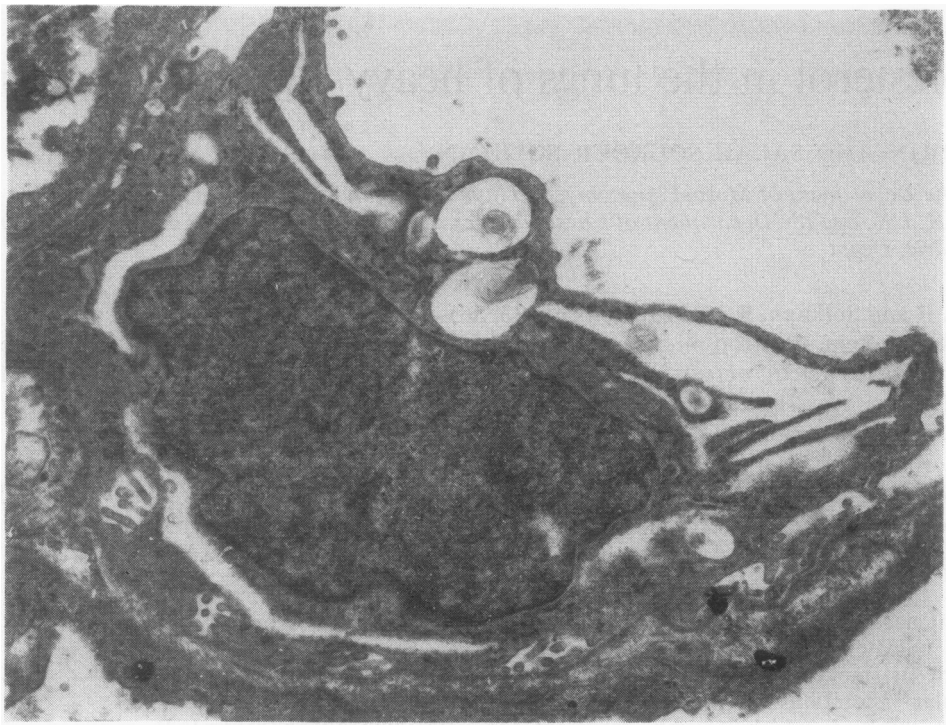

Fig 1 *Heavy smoker. Case 4. A type II pneumocyte with numerous cytoplasmic clefts, some of which intercommunicate. At several points on its basal aspect the cell has separated from its basement membrane. Electron micrograph ×12 000.*

II pneumocytes, which often formed a complete row without any intervening type I cells, a common feature of chronically damaged lung. These cells often contained acicular cytoplasmic clefts (fig 3) similar to those observed in cases 1–4, but in these chronically damaged lungs surface microvilli and lamellar inclusions were often poorly developed. Alveolar macrophages were increased in number and contained many amorphous inclusions.

Discussion

Previous reports of the fine structure of smokers' lungs (Pratt *et al,* 1971) have described the changes in macrophages noted in this study, but we are not aware of any previous descriptions of the needle-shaped clefts noted by us in the type II pneumocytes. We have occasionally observed these clefts in the past, particularly in diseased lungs, but not in the large numbers seen in the present patients. Dr Françoise Basset (personal communication 1978) has also encountered them, both in non-smokers and animals, and they evidently cannot be regarded as a specific effect of cigarette smoking. Nevertheless, they appear to be particularly numerous in heavy smokers. We presume that the clefts represent cholesterol crystals because of their shape, their solubility in the organic solvents used in tissue processing, and their presence in the two patients with obstructive pneumonia, a condition characterised by excess cholesterol (de Navasquez and Haslewood, 1954). These very small crystals possibly represent the beginning of a process which if progressive would lead to cholesterol pneumonitis, a condition which Lawler (1977) has shown to be particularly common in heavy cigarette smokers.

In discussing the pathogenesis of idiopathic cholesterol pneumonitis, Lawler (1977) suggests that there may be disordered surfactant metabolism. Relevant to this are our previous studies of the cholesterol pneumonitis that formed part of an endogenous lipid pneumonia found in rats exposed to silica dust (Corrin and King, 1969). These animals also developed alveolar proteinosis, and this process has subsequently been shown to be due to excessive surfactant secretion (Heppleston

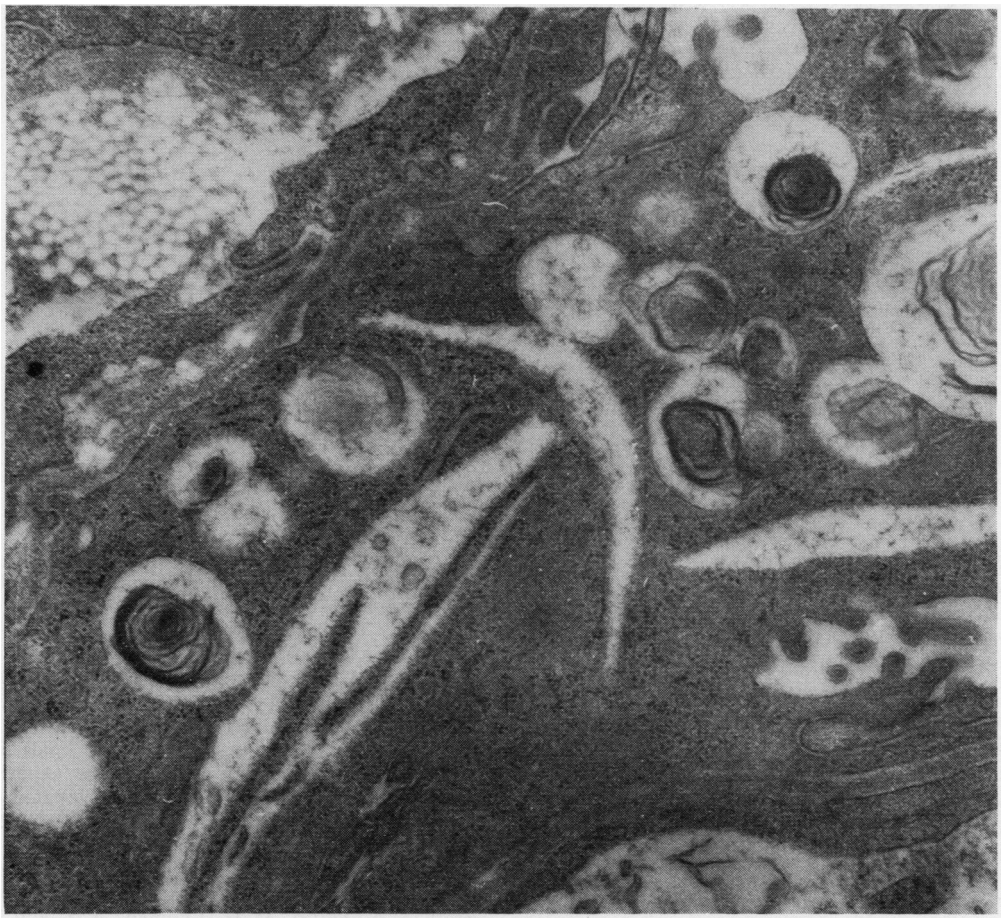

Fig 2 *Heavy smoker. Case 1. Part of a type II pneumocyte showing several elongated clefts devoid of a limiting membrane. Electron micrograph ×24 000.*

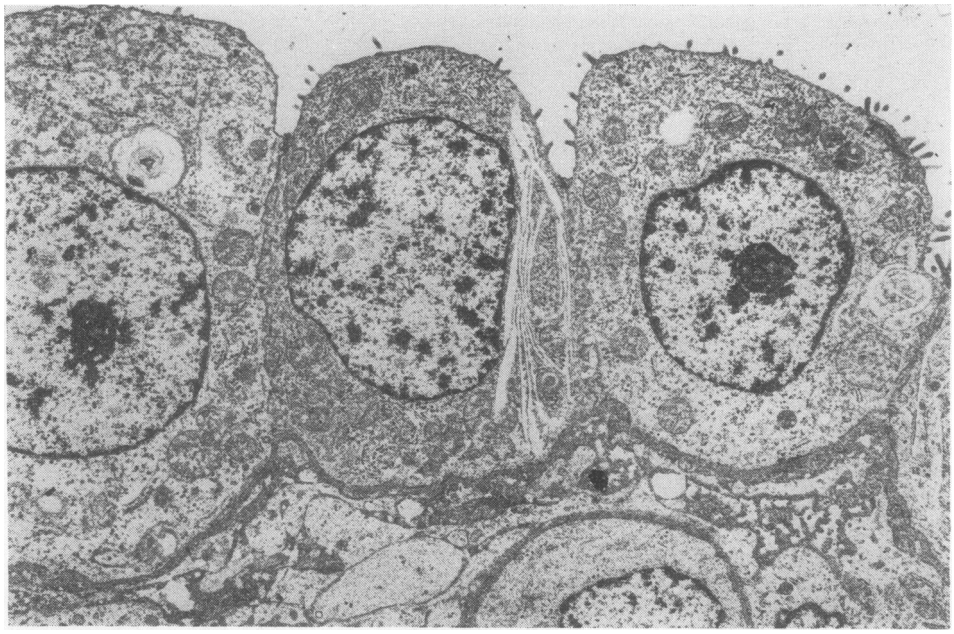

Fig 3 *Obstructive pneumonia. Case 5. Three type II pneumocytes, the middle one of which has several needle-shaped cytoplasmic clefts stacked alongside its nucleus. Electron micrograph ×5000.*

et al, 1974). Our present studies indicate that in heavy smokers cholesterol is commonly found at least at the ultrastructural level in type II pneumocytes, cells which synthesise and secrete pulmonary surfactant (Kikkawa *et al,* 1975). Although the exact relationship of cholesterol to surfactant is unclear it is noteworthy that these lipids sometimes share a common source. The cholesterol in smokers' lungs could represent either a degenerative change in type II pneumocytes caused by smoking or by a byproduct of increased surfactant synthesis stimulated by cigarette smoke.

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