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Human airway secretory cells during development and in mature airway epithelium

P.K. Jeffery*, D. Gaillard**, S. Moret**

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ABSTRACT: The combined secretions of distinct secretory cells of the airway lining mucosa serve to keep the inspired air moist and free of potentially harmful dust particles, organisms and adsorbed gases. Apart from their role in protecting the respiratory zone of the lung, mucus-secreting cells act as pluripotential stem cells during foetal development and, in the adult, following mucosal injury.

The variety of secretory cells include the mucous and serous cells of the surface and glandular epithelium, the non-ciliated bronchiolar (Clara) cell and the less frequent dense-core granulated (neuroendocrine) cell. The last-mentioned is the first type to differentiate at about 10 weeks of gestation; mucus-secreting cells are present from the 13th week of gestation, when mature ciliated cells are already present, and Clara cells begin to mature during the 19th week of human development.

The alteration of secretory cell number and chemical composition of their secretions during the second trimester of foetal life is similar to that which occurs in chronic bronchitis in the adult. However, in hypersecretory disease the extent and site of the major change appear to be inappropriate to the defence of the lung.

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The secretory cells which line the conducting airways of adult humans are of various types and have many functions. Their combined secretions serve to keep the lining mucosa moist, to humidify inhaled air and, in concert with beating cilia, clean the air by removal of potentially harmful dust particles, organisms and adsorbed gases, to the throat where they are normally swallowed. Their secretions also contain substances which discourage bacterial colonization and growth or make them susceptible to neutralization by the hosts immune system. Apart from their protective role, mucus-secreting cells may also act as stem cells, both during foetal development and in the adult during repair following injury to the mucosa. In bronchitis, increases in the number of mucus-secreting cells and alterations in the chemical composition of their secretions have similarities to those which occurs during the second trimester of foetal life. However, in hypersecretory disease the extent and site of the change appears to be inappropriate to the defence of the lung. The range of secretory cell types which occur in the normal adult human and their appearance and changes during normal foetal development form the focus of the present short review.

Sequence of lung development

The airways of the lung begin their development 22–26 days post fertilization as a central diverticulum budding from the foregut and lined by epithelium of endodermal origin. In humans the diverticulum forms two small ventrolateral buds (lung primordia) during the following 4 weeks. The trachea then becomes separated from the oesophagus by the rostral extension of an epithelial-derived septum that forms at the root of the lung buds. As the two ventrolateral buds grow, they become invested by mesenchyme derived from splanchnic mesoderm. This later condenses and differentiates around the growing bronchial tree to form cartilage, muscle, blood vessels, lymphatics and other connective tissue elements. The diverticula and their surrounding mesenchyme divide, first to form two branches on the left and three on the right, *i.e.* the five-lobed pattern typical of the human lung. As the hollow bronchial tubes branch again and again, now within their respective mesenchymal coats, the numerous blind-ended tubules give the lung the pseudoglandular appearance characteristic of the first postembryonic phase (fig. 1). Following the embryonic period in humans, three phases of lung development are recognized: 1) Pseudoglandular, during which the preacinar branching pattern of the airways is established; 2) Canalicular, when vascularization of mesenchyme rapidly increases and the respiratory portion of the lung begins to develop; 3) Terminal sac (saccular) or alveolar, when additional respiratory bronchioles develop and the future respiratory units differentiate (*i.e.* the acini, each comprised of

a single terminal bronchiole and its subsequent divisions of respiratory bronchioles, alveolar ducts and alveoli) [1–3].

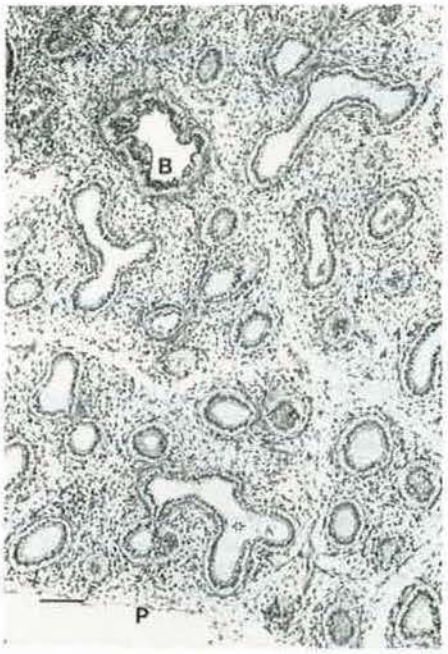

Fig 1. – Light microscopic section of human foetal lung at 18 weeks of gestation showing differentiating bronchi (B), dichotomously branching peripheral airway tubules (⁖) and pleural edge (P). Haematoxylin and eosin; (H&E) scale bar = 80 μm. (By permission from [1]).

Gestation time varies in different species as does the length of each developmental phase and the proportion of gestation which it occupies [3]. The human foetal airway mucosa is functional, with many examples of mature cells, by 24 weeks of gestation (all times given henceforth will be those from the last time of menstruation) [4]. In contrast, most of the animals, used to model foetal development, have an immature mucosa even at birth, with undifferentiated cells, secretory cells and a few ciliated cells [1, 3–5]. The species which most approximates the human in the development of its airway mucosa is the monkey [6]. These and other species differences make it difficult to extrapolate the findings from studies of many animal tissues to the human. The adult pattern of airway branching is complete by the 18th week [7]. However, after birth the size of the tracheobronchial tree increases and the distal (smallest) airways will grow until at least 8 yrs of life. The airway mucosa of the newborn is also not fully developed as the mucus-secreting cells and connective tissue elements, whilst present, must still mature.

Adult structure

The light and electron microscopic structure of the normal adult human lung has been described in some detail [8, 9]. Figure 2 shows that the airway wall comprises epithelial, lymphoid, muscular, vascular and nervous elements, in close contact with a pliable connective tissue support together arranged as: 1) a lining mucosa of surface epithelium supported by a reticular basement membrane and an ill-defined elastic lamina propria in which there are bronchial blood vessels, nerve bundles and free cells (including fibroblasts and mononuclear cells); 2) a submucosa in which lie the bulk of the mucus-secreting glands, muscle and cartilage plates; and 3) a relatively thin adventitial coat.

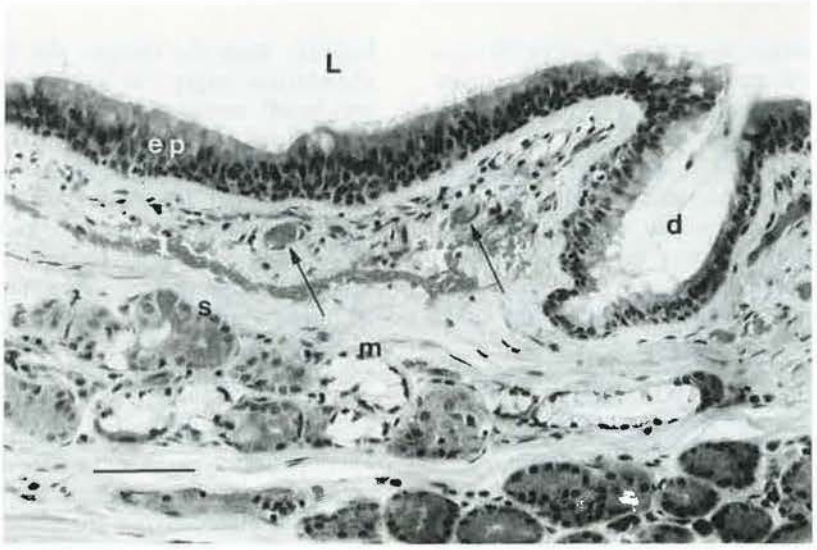

Fig. 2. – Normal human bronchial mucosa from an adult illustrating surface epithelium (ep) resting on a reticular basement membrane with underlying bronchial vessels (arrows) in the lamina propria. There is a gland duct (d) opening out onto the surface, the lumen of which is continuous with that of the mucous tubules (m) and serous acini (s) lying within the submucosa. Haematoxylin and eosin; (H&E) scale bar = 60μm. L: airway lumen (By permission from [1]).

The airway epithelium includes the surface epithelium which lines all airways (nose to alveolus) and it is continuous with that forming the tubulo-acinar

submucosal mucus-secreting glands which develop from the surface in utero [9, 10]. The stratified squamous epithelium, lining much of the larynx, gives way to one which is pseudostratified, ciliated and columnar with secretory cells when the trachea is reached. Where it is "pseudostratified" all cells rest on the basement membrane but not all reach the airway lumen (fig. 3). In man, this type of epithelium persists throughout the major bronchi, becoming simple cuboidal more peripherally within the lungs. Normally, ciliated cells predominate, interspersed by mucus-secreting (goblet) cells which are found regularly in the tracheobronchial tree but rarely in bronchioles of less than 1 mm diameter [9, 11].

Mucous cell. In adult human trachea, the normal mean density of surface mucous cells (fig. 4a) is estimated at 6,000–7,000 cells·mm^{-2} surface epithelium [16]. Following haematoxylin and eosin (H&E) staining the surface (and gland) mucous cells take up the stain poorly (fig. 2). Most contain high-molecular-weight mucous glycoprotein which is acidic due to sialic acid or sulphate groups: this cell type therefore stains well by the combined Alcian blue (AB) pH 2.5/periodic acid-Schiff (PAS) or high iron diamine/AB procedures (see below). By electron microscopy, the mucous cell contains electronlucent, confluent granules of about 800 nm diameter (fig. 4b).

Fig. 3. – Normal human bronchial surface epithelium: scanning electron micrograph (SEM) of a fracture through the epithelium demonstrating its pseudostratified, ciliated columnar arrangement: *i.e.* all cells attach to the basement membrane (arrows) but not all reach the airway lumen. Scale bar = 25 μm. (By permission from [9]).

A variety of cell types is recognized in airway surface epithelium: at least eight different epithelial cell types have now been delineated depending on species [12, 13]. In addition, cells involved in the immune response and its reactions may migrate through the epithelial basement membrane: some of these remain within the surface epithelium; whereas others are in the process of passing through to the luminal surface [8]. The terminal processes of sensory nerve fibres, the cell bodies of which lie deep to the epithelium, pierce the epithelial basement membrane, lose their myelin coat and come to lie surrounded closely by epithelial cells (of the surface and gland) where they may initiate airway reflexes such as bronchoconstriction and cough and also influence airway secretion [14, 15]. The secretory cells of both the surface and submucosal glands are now considered in further detail.

Secretory cells of the surface epithelium

Mucus-secreting cells

Two types of surface secretory cell are known to secrete mucus: the mucous (goblet) and the less frequently found epithelial "serous" cell [9, 12].

Serous cell. Serous cells of the surface have electron-dense cytoplasm, much rough endoplasmic reticulum and, in contrast to mucous cells, few discrete electron-dense granules each of about 600 nm diameter. Morphologically, serous cells of the surface epithelium resemble those present in the submucosal glands. They have been described in surface epithelium in the rat, cat, young hamster and foetal humans [3, 12, 17]. In the author's experience they are also found normally, but infrequently, in adult human small bronchi and bronchioli (fig. 5). They are thought to contain neutral mucin and there is evidence that some may also contain a non-mucoid substance, probably lipid [18].

Histochemically, the presence of intracellular mucus has been demonstrated in the human foetal trachea by the 13th week of gestation [19, 20] when mature ciliated cells are already present. The mucus-secreting cells (MSC) are sparse or gathered into small groups of cells. The columnar MSC have a centrally placed nucleus and each contains sparse apically placed PAS-positive granules. Infrequently there are goblet-shaped cells distended by their intracellular secretion which then compresses the nucleus to its base.

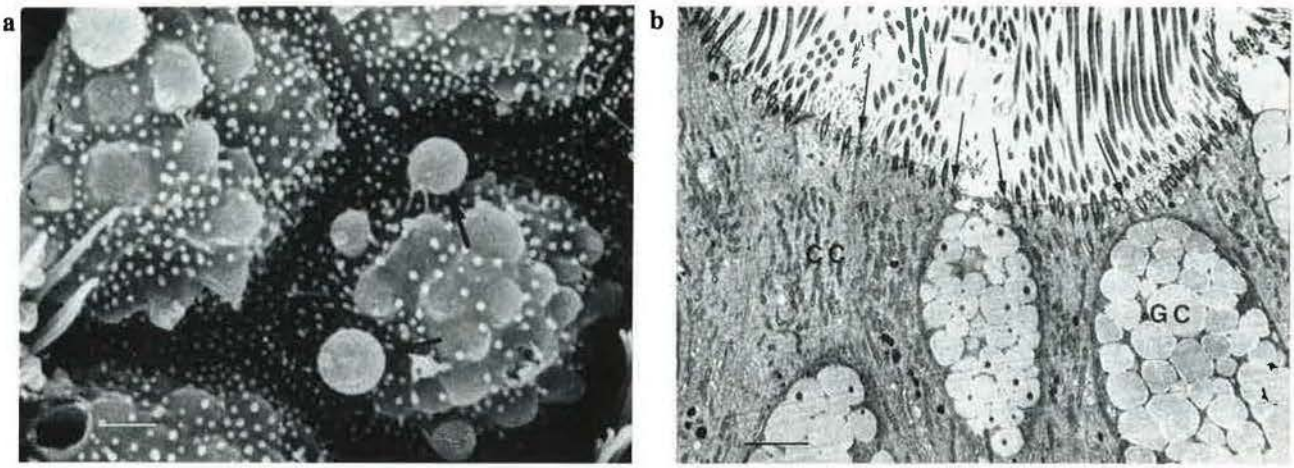

Fig. 4. – Surface epithelial mucous goblet cells: a) Scanning electron micrograph (SEM) of luminal surface of two mucous cells. There are secretory granules lying free in the lumen (arrows) and others present just beneath the cells' apical plasma membrane. Many bright microvilli project from the surface. Scale bar = 1 μm. b) Transmission electron micrograph (TEM) showing ciliated cells (CC) and goblet cells (GC) in which the majority of secretory granules are pale and confluent. Arrows show the "tight juctions" of adjacent cells. Scale bar = 1μm.

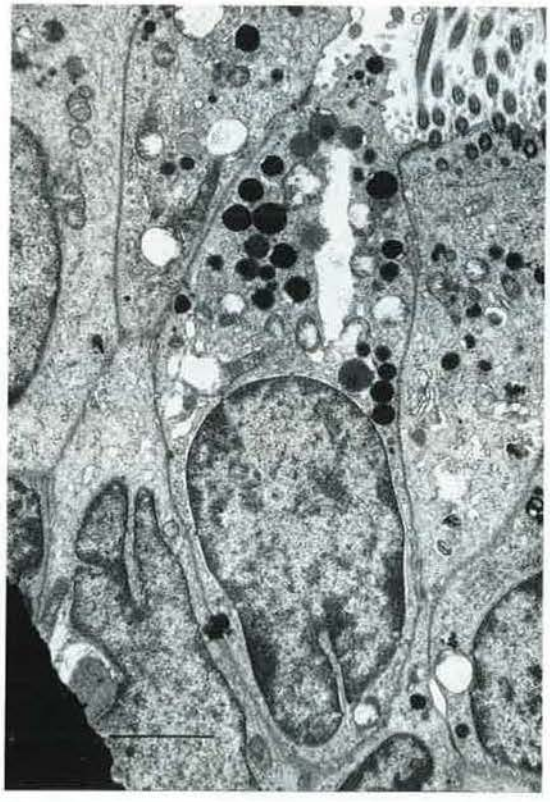

Fig 5. – Surface serous cells: In the human, cells containing electron-dense granules resembling those of rat serous cells are found in small bronchi and bronchioli. Scale bar = 2μm

Like ciliated cells, MSC appear first in the proximal (central) airways and then subsequently develop in the more peripheral airways [21]. Their number increases and peaks in the middle of gestation when they represent approximately 30–35% of the cells lining the luminal surface [43] (fig. 6a). Towards the end of the second term of gestation there is a relative decrease in the number of MSC, these being replaced by an abundance of ciliated cells. The MSC that are present during the third term and at birth are less frequent than in the adult but like the adult they are more numerous in the proximal than in the peripheral airways [22] (fig. 6b).

By electron microscopy the foetal MSC have electron-dense cytoplasm and contain glycogen, mitochondria, rough endoplasmic reticulum and ribosomes and, in addition, a well-developed Golgi apparatus in the supranuclear zone. Most of the secretory granules are electron-lucent (fig. 7a) but a few cells contain electron-dense granules or granules which are heterogeneous for density. Others contain predominantly electron-dense granules (fig. 7b) and these have been suggested to represent the epithelial serous cell [3]. However they do not show immunoreactivity for lysozyme at this time which contrasts with the findings for serous cells of the submucosal glands [23]. The antiprotease enzyme antileucoprotease (ALP), present in adult serous gland and Clara cells of human bronchioli (see below), has recently been identified in the surface epithelium of the human trachea and bronchi by 20 weeks' gestation [24]. As the submucosal glands of the second term of foetal development are not fully mature and secrete little mucus, the foetal surface secretory cells are probably an important source of the ALP required for the protection of airway epithelium against proteolysis.

In addition, the mucus-secreting cells fulfil a role as progenitors of ciliated and other epithelial cell types [4, 25, 26]. This was first suggested and hypothesized for the development of the foetal trachea of the hamster [5] and described in monkey airways [6] and in human foetal trachea also [4]. The division of surface serous and mucous cells of the rat has been shown both in the normal adult and in response to irritation by cigarette smoke [26]. The secretory cell probably, therefore, plays a major role in the repair of injured respiratory mucosa *in vivo* [27] and experimentally *in vitro* [28].

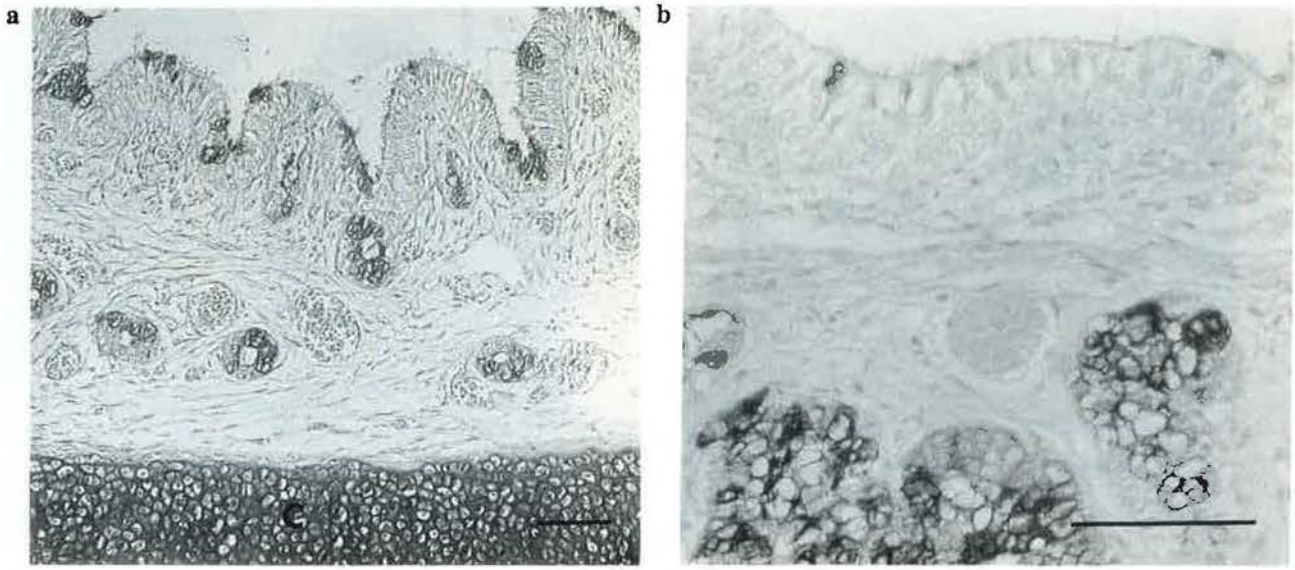

Fig. 6. – Human foetal trachea seen by light microscopy. a) 18 weeks gestation showing mucus-secreting cells of surface epithelium and submucosal glands containing sulphomucins (high iron diamine/Alcian blue (HID/AB)). Cartilage (C). Scale bar = 100 μm. b) At 37 weeks of gestation there are now few mucus-secreting cells in the surface epithelium (HID/AB). Scale bar = 100 μm.

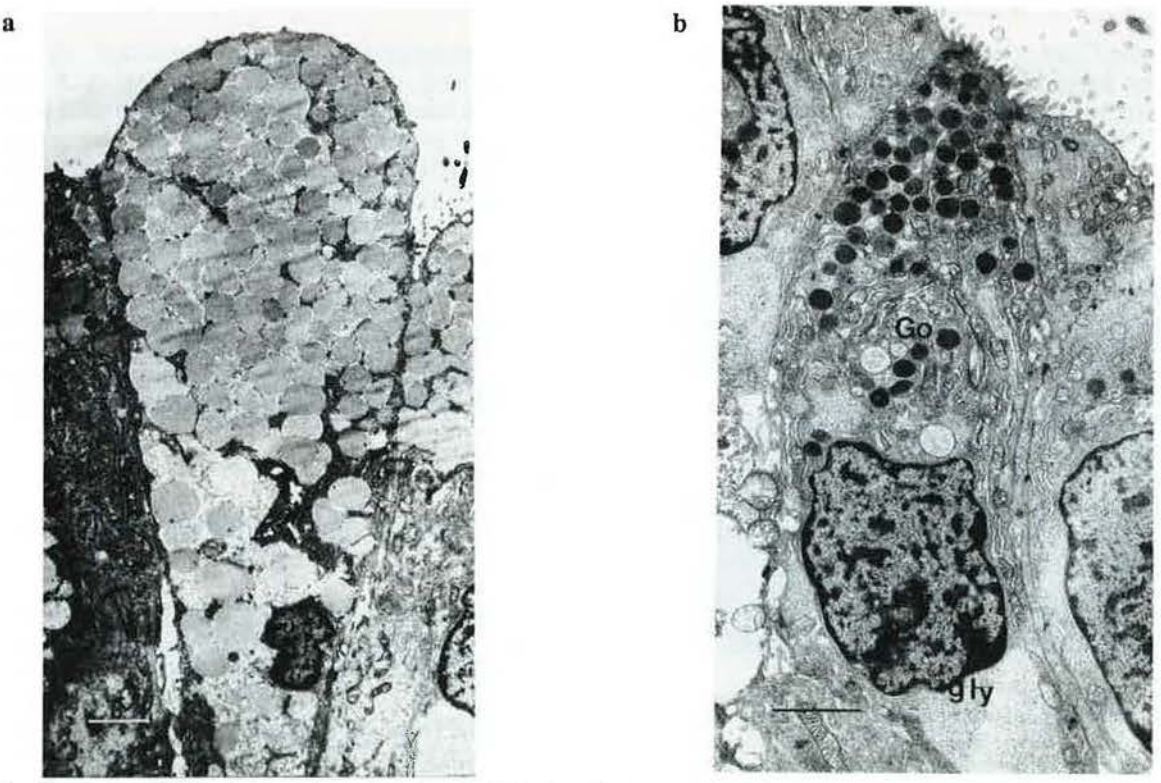

Fig. 7. – Transmission electron micrograph (TEM) of surface epithelium at 18 weeks of gestation. a) Mucous (goblet) cell filled with pale, confluent secretory granules. Scale bar = 2 μm. b) Serous cells with numerous small, discrete electron-dense granules at the cell apex, a prominent Golgi apparatus (Go) and an abundance of intracytoplasmic glycogen (gly). Scale bar = 2 μm. (from [3] by permission).

Clara cells (non-ciliated bronchiolar cells)

Clara cells in adult humans are restricted in location to the terminal bronchioles where they typically bulge into the airway lumen and contain electron-dense granules of about 500–600 nm diameter, ovoid in man but irregular in most other species [21, 29, 30] (fig. 8). The apical cytoplasm in most species, with the exception of the human, contains an abundance of smooth endoplasmic reticulum. The function(s) of this cell type is still being investigated. It may produce a carbohydrate (hypophase) component of surfactant [31] or an antiprotease [24, 32] and is known to have ion-absorbing and secreting properties [33].

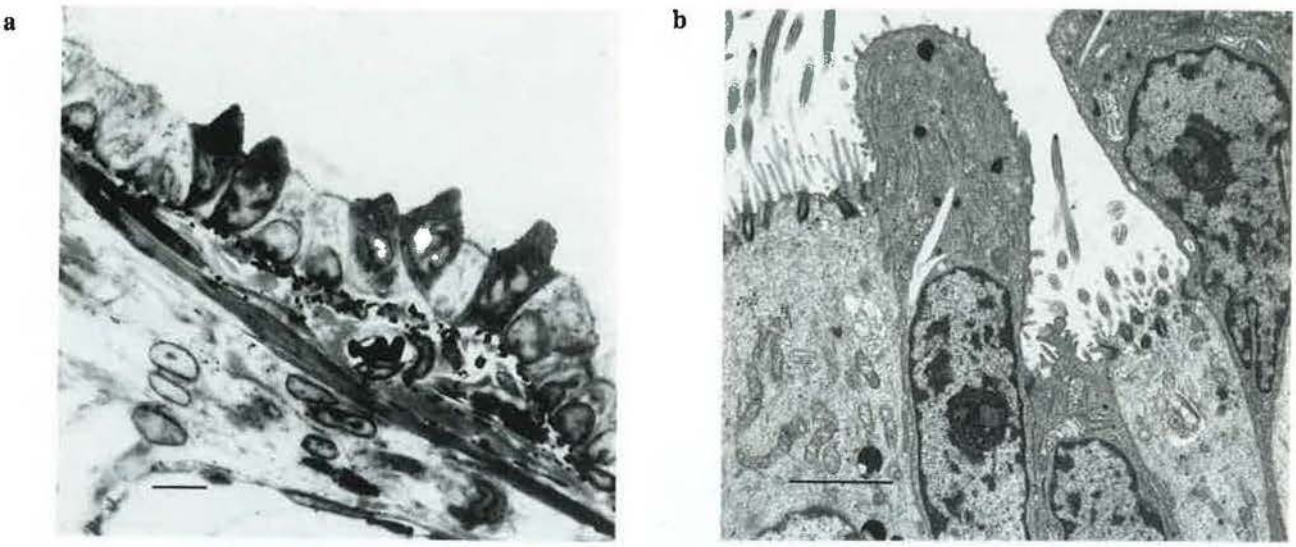

Fig. 8. – Non-ciliated bronchiolar (Clara) cells. a) Plastic section to demonstrate that the apex of each Clara cell bulges into the airway lumen. Scale bar = 8 μm. b) Transmission electron mocrograph (TEM) morphology of human non-ciliated bronchiolar cell with sparse irregularly-shaped electron-dense secretory granules. In comparison with the ciliated cell the cytoplasm is electron-dense and the nucleus has a distinct nucleolus and much heterochromatin. Unlike most other mammalian species, there is a deficiency of smooth endoplasmic reticulum in human Clara cells. Scale bar = 2 μm.

Furthermore, the Clara cell acts as the stem cell of small airways where basal and mucous cells are normally sparse: both ciliated and mucous cells may develop from the Clara cell subsequent to its division and differentiation [26].

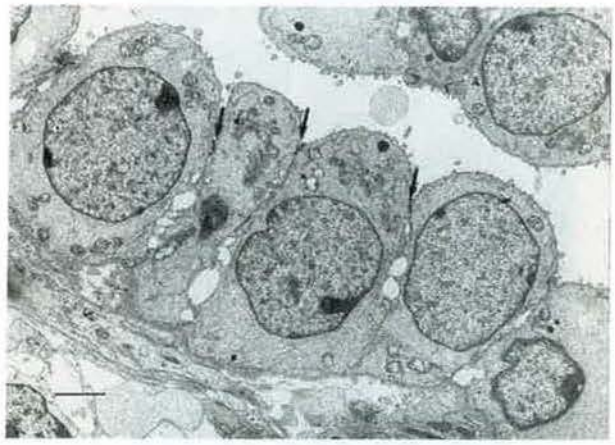

Fig. 9. – Human foetal lung at 20 weeks of gestation showing the epithelial lining cells of a pre-terminal airway. The cell apices bulge slightly into the airway lumen. There is an abundance of intracellular glycogen. The beginnings of electron-dense granules and tight junctions are evident (arrows). Scale bar = 2 μm.

Relatively little is known about the Clara cell during development. They are thought to develop during the second half of gestation from primitive, glycogen-containing, non-ciliated cells of the terminal airways (fig. 9). By 18–19 weeks' gestation, the dome-like apical protrusion (characteristic of the mature cell) has formed. Maturation involves gradual loss of cytoplasmic glycogen, increasing ribosomal content and the appearance of electron-dense secretory granules which may become numerous by 26 weeks' gestation. In the adult human lung, the low-molecular-weight ALP can be localized to nonciliated bronchiolar (Clara) cells and, in addition, is present in serous cells of submucosal glands and surface mucus-secreting cells [32, 34]. Recently, the antiprotease has been shown to be present in bronchiolar epithelium (presumed to be in Clara cells) by the 38th week of gestation [24]. These data argue for early appearance of a protective antiprotease and the maturation of Clara cells at a time prior to parturition. The timing is in marked contrast to that of the specific pathogen-free laboratory rat, where Clara cells do not begin to mature until at least 5 days after birth [3].

Dense-core granulated "neuroendocrine" cells (synonyms: Kultchitsky or Feyrter cell)

Argentaffin-positive and argyrophilic cells are identified within the surface epithelium by light microscopy [35, 36]. By electron microscopy, dense-core granulated (DCG) cells are normally infrequently found, generally basal in position but often with a thin cytoplasmic projection reaching the airway lumen [36–38]. Single cells and clusters of such cells may also be associated with nerve fibres when they are referred to as neuroepithelial bodies or neurite-receptor complexes [39, 40]. The cytoplasm of DCG cells usually contains large numbers of small (70–150 nm) spherical granules each with an electron-dense core surrounded by an electron-lucent halo. Granule subtypes have been described [41] and the cells may contain biogenic amines [42] or peptides such as bombesin [43] which, when released, may influence vascular and bronchial smooth muscle tone, mucous secretion and ciliary activity.

DCG cells are reported to be the first "mature" type to differentiate within primitive airway epithelium. Distributed singly or in pairs, they are identified at 10 weeks' gestation [44]. They are weakly argyrophilic, show immunoreactivity for serotonin and neuron-specific enolase but not, as yet, for bombesin and other peptides [44–46]. The characteristic dense-cored granules are at first sparse and smaller than those seen in the adult (fig. 10): Cutz has suggested that they represent granule precursors of the three types of granules found in the adult DCG cell. Bombesin-like immunoreactivity and serotonin positivity is found at about 12 weeks' gestation at a time when submucosal nerves and ganglia show strong immunoreaction for neuron-specific enolase [46]. During the alveolar phase of development (*i.e.* from about 25 weeks' gestation) the frequency of bombesin and serotonin-immunoreactivity DCG cells increases significantly towards term due primarily to an increase in neuroepithelial bodies in peripheral airways [45, 47]. Associated with this, bombesin-like immunoreactivity in lung tissue extracts is highest during the late foetal-neonatal period and decreases postpartum [48]. Calcitonin and leu-encephalin are detected only late during foetal development and are identified postnatally [49].

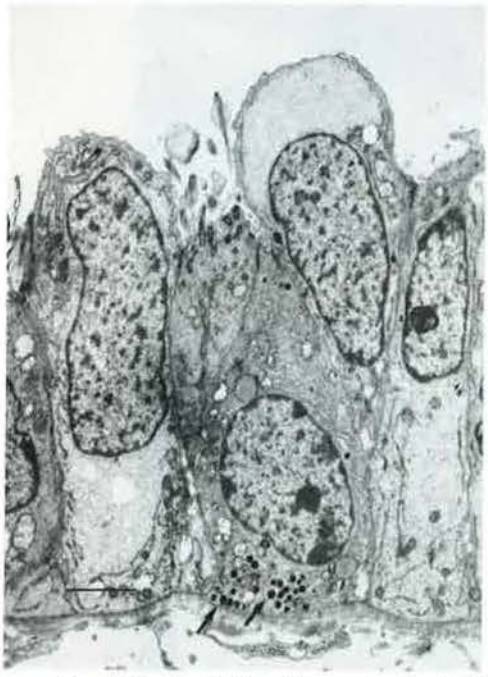

Fig 10. – Bronchiolar epithelium from a foetus of 16 weeks' gestation showing neuroendocrine cell with dense-cored granules (arrows). Scale bar = 2 μm.

The function of the DCG cell is unclear. ROSAN and LAUWERYNS [50] have suggested that it may, by its amine secretion, affect lobule growth and differentiation. With age, there is a decrease in cell number, in the number of granules per cell, and in the electron density of each granule. MOOSAVI *et al.* [51] and LAUWERYNS and COKELAERE [52] have shown that in hypoxic conditions there are intracellular changes in the bronchial DCG cell of the young rat, similar to those seen in carotid-body chief cells, which suggests that the DCG cell might have a function in the response of the young lung to hypoxia. Rarely, nerve endings in contact with DCG cells have been demonstrated in foetal lung also [53].

Submucosal glands

In the adult human trachea and bronchi, glands responsible for producing most of the mucus found in the airways are numerous. Present wherever there is a cartilage, they are located in the submucosa mainly between the cartilage and the surface epithelium. Each gland is tubulo-acinar, with a duct opening into the airway lumen. In the adult human each gland may be composed of four regions [54] the lumena of which are continuous: 1) a relatively narrow ciliated duct the lining cells of which are in continuity with the surface epithelium; 2) an expanded collecting duct lined by cells of indeterminate morphology or of eosinophilic cells packed with mitochondria (which have also been referred to as "oncocytes"); 3) mucous tubules and acini; and 4) serous acini [10, 37].

Airway submucosal glands appear in the human trachea at about 13 weeks' gestation. They first appear in proximal airways and then progressively more peripherally and reach the main carina some 7 days later [55]. In bronchi, they are present by the fourth month of foetal life, in greatest concentration proximally, decreasing peripherally and especially concentrated at airway bifurcations [56]. Each gland starts its development within surface epithelium, by division of surface basal cells, to form a sharply defined cluster of cells with dark nuclei [19, 55]. Growth then proceeds radially into the lamina propria as a solid cylinder, pushing outward and laying down new basement membrane, which maintains continuity with that of its surface epithelium. By light microscopy, these cells are polygonal, with a rounded central nucleus. Soon, mucus is secreted into intercellular space, forming a pond which expands into a canal. Subsequent subepithelial widening of the canal pushes the epithelial cells apart, thus forming an opening to the airway lumen [57].

During early development, the glands consist only of mucous acini, each cell with cytoplasm distended by pale foamy granules which flatten the nucleus to the base of the cell. At this time by electron microscopy the cytoplasm is electron-dense and is filled with electron-lucent or heterogeneous granules (fig. 11a). By both light and electron microscopy there is immunoreactivity for lysozyme in small amounts by the 16th week of gestation: initially these cells are of columnar shape and contain electron-lucent granules (fig. 11b).

A weakly eosinophilic ductal region is present as early as 24 weeks' gestation. Mucous tubules arise from the collecting duct region, with serous acini usually at their distal ends. The number of lysozyme positive cells increases as term approaches, immunoreaction for lysozyme being confined to the serous acini of the

submucosal glands and not identified in surface epithelium [45] (fig. 11c). Low-molecular-weight antileucoprotease is another marker for maturation of serous cells of the gland and can be detected from 16 weeks' gestation in glands of the trachea, main and lobar bronchi [24].

By light microscopy, the first pyramidal-shaped serous cells are found forming crescent shapes about the mucous acini at 25–27 weeks gestation (*i.e.* before the end of the second term). Their number increases during the third term. By electron microscopy, between 30 and 33 weeks there are lysozyme positive serous cell granules, some of which are electron-dense (fig. 11d).

Although the branching pattern of the submucosal glands is complete at birth, the overall density of the glands in the airway wall remains higher than that in adults and contains a larger proportion of mucous cells than would be found in the adult. The relative percentage of serous cells increases during the first two years of postnatal life. The proteins secreted by the serous cells are thought to have an important role in protecting against bacterial colonization of the respiratory tract [8] and their secretions may be relatively deficient early on in life, predisposing to bacterial colonization and repeated infections.

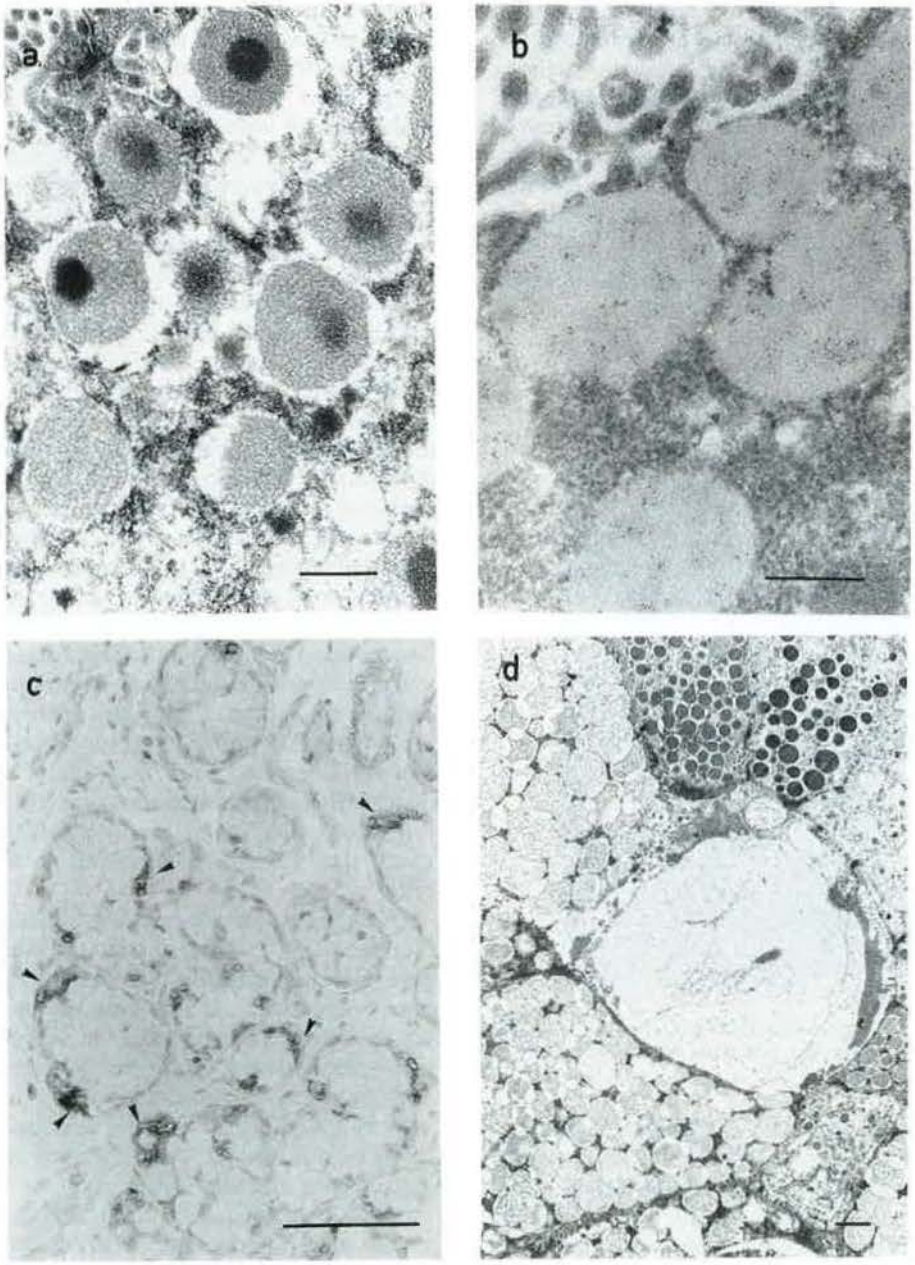

Fig. 11. – Transmission electron micrograph (TEM) of developing submucosal gland: a) 33 weeks' gestation showing heterogenous secretory granules in mucous acini. Scale bar= 1 μm. b) 27 weeks' gestation demonstrating immunogold-labelling for lysozyme localized to both pale and heterogenous granules. Scale bar = 0.5 μm. c) 37 weeks' gestation showing light microscopic immuno-labelling localized to the serous demilunes associated with mucous acini. Scale bar = 100 μm. d) 33 weeks' gestation demonstrated that characteristic electron-dense appearance of serous cell secretory granules. Scale bar =2 μm.

Following radial penetration of the muscle layer, there is continued growth and division but in a tangential or longitudinal direction, either cranially or caudally, (fig. 12). Tos [55, 57] has shown that the appearance of mucus-secreting glands in the membranous wall precedes that in the cartilaginous wall in both bronchus and trachea, and in the case of the trachea by some nine days. In the bronchus, the rate of gland formation reaches a peak during the 14th to 16th foetal week, decreasing after this and terminating during the middle of the 25th week. It has been estimated that at this time some 4,000 glands are present in the human trachea, the highest density now in the cartilaginous wall (55, 56).

Few new glands are formed in childhood, the increase in gland area being the result of an increase in gland complexity. The shape of the gland mass varies and is determined by the space available. Not until 13 yrs of age does the gland approach the form characteristic of the adult, and even then growth continues until 28 yrs of age [3].

Glycoprotein histochemistry

The epithelial mucins of the respiratory tract are polydisperse, high molecular weight glycoproteins.

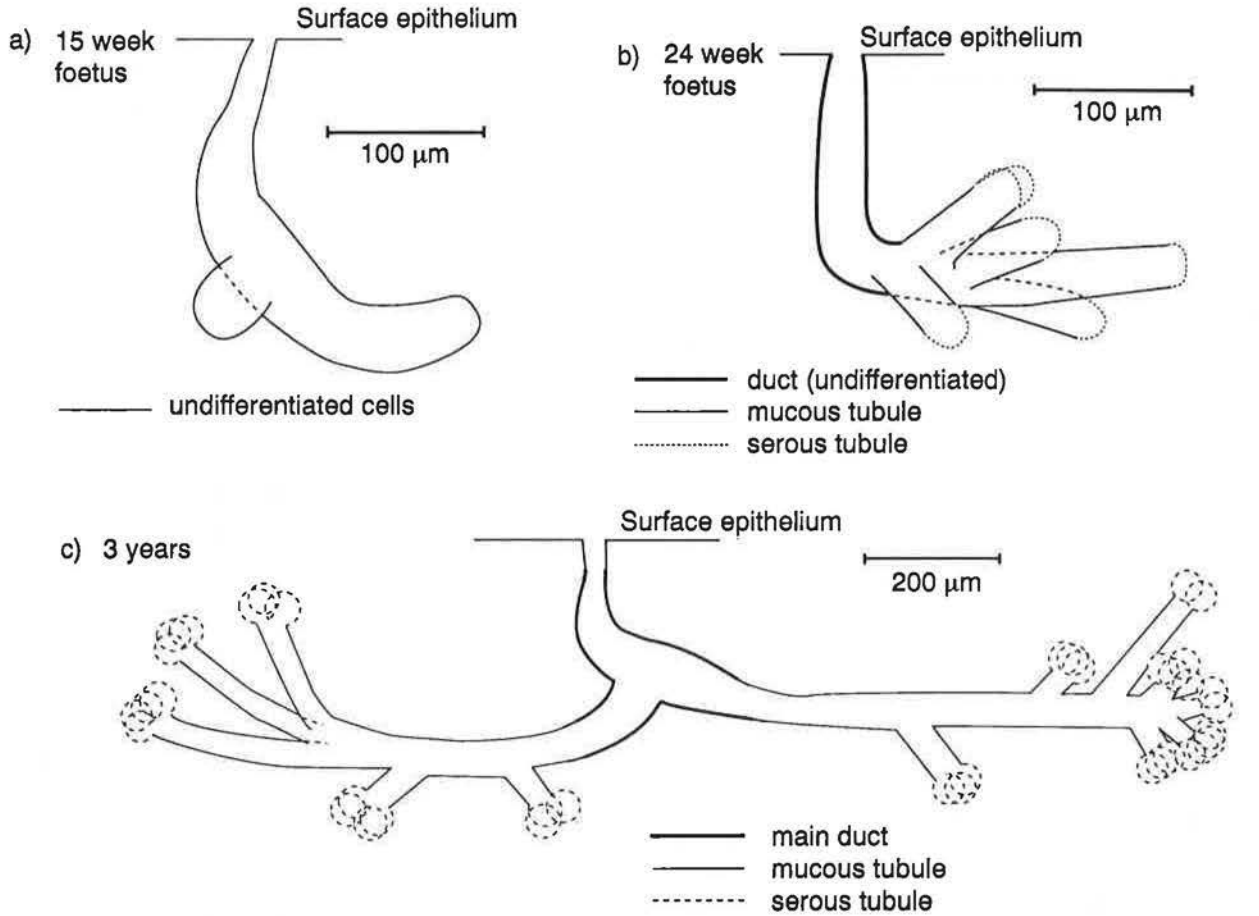

Fig. 12. – Reconstructions of developing tubulo-acinar mucus-secreting glands at: a) 15 weeks' gestation; b) 24 weeks' gestation; c) 3 years of age. (with permission from [3])

Tos [55] reports that there are no sex differences in the gland density during development, while THURLBECK and co-workers [56] found a male superiority in gland numbers, resulting from a higher concentration of glands rather than from a difference in absolute size of the trachea. The proportion of the wall occupied by gland (*i.e.* the gland-to-wall ratio or "Reid index") reaches the adult norm in late foetal life, but during childhood mucous glands form a larger proportion of the walls (major bronchi) than in the adult [58]. Thus, gland hyperplasia in response to irritation might be a more significant problem in young children than in adults.

They consist of a filamentous protein core to which oligo-saccharide side-chains are attached. The core protein contains regions that are densely glycosylated (70–80%) and there are also naked regions with cysteine residues [59–61], so that the structure of the mucin may be likened to that of a bottle brush. According to the distinct chemical composition of the oligo-saccharide side-chains, the mucins may be acidic or neutral, whilst the naked region of the peptide has an identical amino acid composition [62]. Acidic mucins appear to have a higher molar ratio of threonine, serine, sialic acid and sulphate. The sugar residues appear to play a role in determining the physical and flow properties

of the mucus and may also affect bacterial adherence. Lectins which have an affinity for specific carbohydrate residues have been widely used for the ultrastructural localization of the specific carbohydrates [63–67]. The heterogeneity of mucin types has been demonstrated in primate airway epithelia using a number of monoclonal antibodies [68]. Histochemical methods have been applied at the light microscopic level to identify those cells secreting either acidic or neutral mucins or both in combination. Alcian blue (AB) pH 2.5/periodic acid Schiff (PAS) used in combination distinguishes between the acidic and neutral mucins, respectively. The combined high iron diamine (HID)/AB pH 2.5 method demonstrates the two main types of acidic glycoprotein, those with sulphomucins which stain brown and those containing sialomucins which stain blue [69] (fig. 6).

In adult man the majority of surface epithelial cells contain both neutral and acidic glycoproteins with sialomucins and sulphomucins being represented. The ratio of radioactive sulphate to glucosamine uptake is higher in the surface epithelium than in the underlying submucosal glands and several studies indicate that a highly sulphated acidic secretion is associated with the surface [69, 70]. This is particularly true for epithelial cells cultured from patients with cystic fibrosis [71]. During development the number of surface epithelial secretory cells is relatively high particularly during the beginning of the second trimester. Both neutral and acidic glycoproteins are secreted by the same cell and the acidic component is mainly or nearly exclusively sulphomucin until birth [22]. Serous acini differ from mucous acini in producing a secretion with less carbohydrate, little or no sialic acid and no terminal or penultimate galactose [69]. There is evidence from several studies that serous cells may normally produce the secretory component of immunoglobulin A (IgA), lysozyme, lactoferrin, albumin-like molecules and a glycosaminoglycan [72]. The submucosal glands of patients with chronic bronchitis contain a relatively larger proportion of acini which are mucous in type and these secrete higher quantities of sulphomucins than is normal [73]. During development the submucosal glands which first comprise solely of mucous acini contain both neutral and acidic glycoproteins [19, 20, 22]. Only about 20% of the acidic glycoprotein consists of sialomucin. Serous cells containing a large proportion of neutral glycoprotein [72] appear relatively late.

Some parallels can be drawn between the appearance of secretions during development and that in the pathology of bronchitis: for example, the relatively higher proportion of epithelial cells which are secretory and the predominance of sulphomucins which occurs at times during development and in bronchitis. There are also similarities between development and the changes seen during injury and repair of the mucosa. Experimental models of airway damage demonstrate the role of both mucous and Clara cells as progenitor cells in response to irritation of the epithelium and their capacity, now well recognized, to proliferate and differentiate into other cell forms [25, 28]. Mucous cells with relatively few secretory granules may replicate, in the presence of vitamin A, to provide both new mucous cells and also ciliated cells [27], whereas those cells distended by secretion may play a relatively more important role as secretors than as progenitors [74]. In the adult, basal cells are present in the proximal airways and these may divide to replenish themselves and to act as stem cells. In contrast, during early development where basal cells are sparse and in the regenerating mucosa, the secretory cell may play the pivotal stem cell role.

Conclusion

In conclusion, airway secretory cells in the human appear during gestation particularly in the beginning of the second trimester and their secretions appear to be important during both foetal development and in the adult. The variety of epithelial secretory cell types and their various secretions which have been described herein, in the adult, serve to humidify and to protect the more distal respiratory portion of the lung from pollutants and infection. They also play an important role as stem cells from which other cell types may differentiate and mature during development, disease, and the repair which follows irritation and damage of the airway mucosa.

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