The Origin of Dust-Cells in the Lung.

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With Plate 27.

1. Introduction.

The aim of this paper is twofold:

Firstly, to present evidence on the origin of 'dust-'[1] and 'heart-failure cells'.[2] Such personal observations include the examination of dust-laden, nitrated, and vitally stained lungs.

Secondly, to discuss some of the recent work on the question of dust-cells and the nature of the alveolar epithelium in relation to the personal observations here recorded.

Space forbids more than the scantiest reference to the literature on dust-cells. But further references will be found in the reviews of Jaulmes (**27**), Policard (**34**), Drinker (**14**), and Carleton (**8**).

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2. The Evidence of Vital Dye and other Injections.

Permar (**31, 32, 33**) has strongly held that dust-cells are derived from the capillary endothelium of the lung, a view which

[1] It is a commonplace that, of the finer dust particles inhaled, a number fail to be arrested by the cilia and mucus of the air passages. Those which reach the pulmonary alveoli are rapidly engulfed by large and characteristic phagocytes—the dust-cells.

[2] 'Heart-failure cells' are defined in a foot-note on p. 230.

is held by many other authorities (Drinker, **14**; Foot, **17**; Haythorn, **26**).

Permar's experiments were as follows: rabbits were given daily intravenous injections of a 0·5 per cent. solution of isamine blue in 0·9 per cent. saline. The maximum dose of isamine blue was 60 c.c. over 9 or 11 days; the minimum amount—producing vital staining—was 35 c.c. in 8 days; the average dose was about 50 c.c. distributed over 8 days. Apparently the rabbits were not weighed, so that the ratio of dye-stuff to the animal kilo is unknown. During the course of the isamine-blue injections a suspension of carmine in 0·9 per cent. saline was injected with a needle into the trachea.

In my experiments a rather weaker solution of isamine blue —0·4 per cent.—was employed. This was because the higher concentration used by Permar was found to be less stable and more prone to clotting in the ear veins. Furthermore, a definite dosage of sufficient strength to give good vital staining was adhered to in all these experiments. This dosage was 4·3 c.c. of the dye solution per kilo rabbit.

Intratracheal suspensions of carmine, finely divided coal-dust and wood-charcoal were administered with aseptic precautions under ether anaesthesia. The strength of these suspensions was 5 per cent. in 0·9 per cent. saline and the dosage 1·8 c.c. per kilo animal.

In order to imitate the conditions under which foreign matter normally enters the lungs, some experiments were made in the dusting machine described elsewhere (**10**). Coal, haematite (iron ore), and wood-charcoal dusts were used for this purpose in the heaviest concentrations consistent with the avoidance of choking.

An isamine-blue injection was always given during the intratracheal one. In the case of dusted animals the vital dye was at once given after the inhalation. One to four vital-dye injections were given after the pigment had been introduced into the lungs so as to avoid Permar's criticism of Sewell's (**37**) work.

Frozen sections were made and examined in all cases; in addition, paraffin sections were prepared. When the total

duration of dehydration did not exceed 2–4 hours only a little of the dye was found to be extracted from vitally stained cells on comparing the paraffin with the frozen sections.

The lungs were fixed in 5 per cent. formol (previously neutralized) in normal saline or in distilled water. Collapse was avoided by tying off the trachea before opening the thorax. Often the formol was injected, per tracheam, till the lungs were slightly distended. They were then removed and placed in more of the fixative.

Fourteen experiments were made in all. Since the detailed protocols of each experiment would entail needless repetition, only a general summary is given.

Staining of dust-cells was but rarely observed. In some of the experiments it was completely absent, in others a small proportion of the cells—always under 2 per cent.—were stained. The endothelial cells of the pulmonary capillaries occasionally contained blue granules. It is significant that the number of vitally stained cells was not widely different in animals which had received injections of the vital dye only (i. e. controls) and in animals which had had both the isamine blue and the pigment per tracheam. The scarcity of vitally stained cells in the normal lung is well known (Goldmann, **18**; Permar, loc. cit.). In Permar's experience the number of vitally stained phagocytes increased greatly when the lungs were stimulated with carmine; the experience derived from the experiments here recorded was that the number of vitally stained phagocytes increased very slightly or not at all after the introduction of foreign particles into the lungs.

Very careful search was also made in thin and thick sections for stages in the splitting off of endothelial cells from the capillaries, and their migration towards the alveolar epithelium. Very occasionally an endothelial cell, more swollen than its fellows, could be seen. Apart from the fact that this is no formal proof of such a cell being about to leave the capillary bed for the alveoli, the number of these swollen endothelial elements was not found to be greater in lungs which had been stimulated with pigment than in those which had not. If the

capillary endothelium were furnishing phagocytes, signs of proliferative activity should have been abundant when one considers the immense numbers of dust-cells. I can only conclude that Permar mistook for endothelial elements cells (e.g. histiocytes) which were really outside the capillary walls and which were derived from other sources. The interpretation of thick sections of lungs is very difficult owing to the different types of cells that lie superimposed on one another.

The evidence of my series of vital-dye injections is that the dust-cells were derived from cells lining the alveolar cavities. At present the question of the origin of such cells is deferred (see p. 231).

The evidence of tissue culture is totally at variance with an endothelial origin of the dust-cells. Lang (**28**) and Carleton (**7**) have cultivated lung in vitro. They both found that the endothelial cells of the pulmonary capillaries were quite indifferent to pigment particles, although intense phagocytosis by other cells was easily elicited. Both these authors also remark on the absence of proliferation in the vascular endothelium in vitro.

The bearing of some recent important papers on the origin of dust-cells may be considered here.

Westhues (**40**), in 1922, after injecting rabbits intravenously with Indian ink noted that the endothelium of the lung capillaries did not take up the particles. A more recent paper by this worker (**41**), while confirming the latter observation, goes far to prove the origin of the dust-cells.

Westhues perfused a rabbit with normal saline so as to wash out the blood-cells. Next he injected Indian ink into the trachea. A piece of lung was then excised and placed in saline at 37° C. for half an hour. A control fragment of lung was cut out at the same time and fixed immediately in formol. In the latter no phagocytosis could be seen. But in the former, ' remarkable phagocytosis ' was present in the alveoli.

The origin of the pigment-devouring cells was therefore restricted either to the cells in the alveoli or to the endothelium of the lung capillaries.

Supplementary experiments were devised to test the phagocytic power of the capillary endothelium. Indian ink was injected intravenously after previous removal of the blood-cells by perfusion. Saline was then injected per tracheam. The lungs were placed in warm saline as in the first experiment. On sectioning them no phagocytosis could be seen in the capillaries—in spite of the ink particles—or elsewhere. Repetition of these experiments gave the same results. Occasional histiocytes were thought to help in the phagocytosis, but the most active cells seem to have been undoubtedly derived from the alveolar epithelium, since both the blood leucocytes (including the histiocytes brought by the blood-stream to the lungs) and the capillary endothelium were excluded.

Seeman (**36**) has shown that the intratracheal injection of sugar of iron causes the appearance of cells both inside the alveoli, and attached to the alveolar wall, which give a positive histochemical reaction for iron. When the same substance is injected intravenously it cannot be found, on applying appropriate histochemical tests, in the capillary endothelium.

Experiments made by the same author with vital-dye injections showed that the staining reactions of histiocytes and of the cells in the alveolar epithelium were different. This again suggests a different origin for the two types of cell.

This recent work of the Aschoff school seems to merit very serious consideration, coming as it does from a laboratory where the study of the reticulo-endothelial system has been pursued for many years. It is noteworthy that workers so competent to report on the role of this system should find that it is minimal in the taking up of dust by phagocytes in the alveoli.

To sum up :

The repetition of Permar's observations by Carleton and here recorded, and other personal observations on dust-laden lungs (**6**), the injection experiments of Westhues (**40, 41**) and Seeman (**36**), the data of tissue culture (Lang, **28** ; Carleton, **8**), and the oil-injection experiments of Guieyesse-Pellissier (**22, 23, 24**), which I have personally confirmed (**7**), all furnish evidence that dust-cells are not derived from the endothelium of the pul-

monary blood-vessels. The origin must therefore be sought among the cells lining the alveoli.

3. The Evidence of Tissue Culture.

Tissue culture has also been used in an attempt to identify the dust-cells. Binet and Champy (**3**) and Carleton (**7**) noted that the cubical epithelial cells proliferated *in vitro*. When stimulated with carbon or carmine particles these cells became transformed into typical dust-cells. Since the matter is fully dealt with in the papers cited above, the reader is referred to them.

Lang (**28**), making use of the same method, comes to the conclusion that while the dust-cells are derived from the elements commonly referred to as the ' cubical epithelial cells ', the latter are really histiocytic. The anucleated squames he apparently regards as epithelial.

Against this view are :

(i) The experiments of Westhues (**40, 41**) and Seeman (**36**).

(ii) The postulation of an anucleated alveolar lining makes the regeneration of damaged alveoli (e. g. after pneumonia) difficult to understand. After all, the fresh cells which reline the alveoli presumably come from pre-existing cells. If the cubical cells are histiocytes we can hardly expect them to form the endodermal squames, unless we are prepared to admit these as being histiocytic also, as suggested by Policard. This view is discussed in Part 4.

(iii) Lang's claim that the dust-cells, cubical cells, and septal cells are histiocytes would seem to be based on conviction rather than proof. The fact that cells similar to dust- and cubical epithelial cells may be found inside the alveolar septa (here forming Lang's septal cells) is no proof of a histiocytic origin for these elements.

4. The Evidence of Morbid Histology.

Much experimental work has been done in an attempt to find the origin and identity of the dust-cell. But direct observation of sections of lung in which dust particles are in process of

phagocytosis has been somewhat neglected although the data of morbid histology should preface any study on phagocytosis in the lung. For while such data may lose by the absence of the experimental method, they often gain by the absence of experimental error.

(i) Pneumoconiotic Lungs.—The study of sections of dust-laden lung shows clearly transitions between the cubical alveolar epithelial cell—a normal constituent of the alveolar wall—and the dust-cell. The essential stages of the transformation of the cubical into the dust-cell comprise a swelling and a vacuolation of the cytoplasm. Cytologically this would seem to be characterized by the appearance of large refringent globules, not stained by Sudan III, but capable of reducing osmium tetroxide (Granel, **19, 20, 21**). Doubtless the clear vacuoles, seen after ordinary methods of fixation and staining, merely outline the spaces in the cytoplasm where the granules lay.

Transitions between these cells are shown in figs. 1 and 2, Pl. 27, while the vacuolated and swollen free dust-cell is depicted in fig. 3, Pl. 27. The detachment of the cubical cell can also easily be followed. As it swells and tends to become spherical, progressively less and less of its cytoplasm rests against the alveolar wall; and, finally, a stage is reached when it breaks away, a free phagocytic unit. Dust particles may have been engulfed before detachment occurs, but phagocytosis seems to be usually associated with an increase in size of the cubical cell (see figs. 1 and 2, Pl. 27).

Another point, in favour of the derivation of the dust-cell from the cubical cells of the alveolar epithelium, is that different stages in the swelling up and phagocytosis of dust particles by the cells of the alveolar epithelium may be seen in adjacent cells in one and the same alveolus. Such cells can also be seen to form an integral part of the alveolar wall (see figs. 4 and 5, Pl. 27); they lie in between and amongst the alveolar anucleated squames as definite anatomical units. It therefore seems unlikely, on the morphological evidence, that the cells phagocytic for dust should be:

(*a*) Emigrated blood leucocytes as held by Chantemesse and Podwyssotsky (**10**), Tchistovitch (**39**), Metchnikoff (**29**), or

(*b*) Endothelial cells, as believed by Permar (**31, 32, 33**) and Foot (**17**), Haythorn (**26**), Wislocki (**42**).

Were either of these suppositions correct one should be able to detect in sections of dust-laden lung stages in the migration of these cells from the pulmonary capillaries—which is not the case.

The opinion here recorded that the dust-cells are formed from cells in the alveolar epithelium is in agreement with the results of others who have examined pneumoconiotic lungs—Charlton Briscoe (**4**), Cornil and Ranvier (**12**), Claisse and Josué (**11**) inter alia.

(ii) Heart-failure Cells,[1] when studied in sections of passive venous congestion of the lungs, would seem to have the same derivation as dust-cells. Both are phagocytic for pigment: the dust-cell for inhaled particles of various sorts, the heart-failure cell for haemoglobin derivatives (e.g. haemosiderin). Both are morphologically alike, and, what is more important still, both certainly seem to be derived from the cubical cells of the alveolar epithelium. The same stages in the swelling up and desquamation of these cells can also be observed (see fig. 6, Pl. 27).

These observations confirm those of Millian in Cornil and Ranvier (**12**) and others.

(iii) Poison Gas.—Other irritants than pigment may cause the cells of the alveolar lining to desquamate very intensively. Mustard gas may produce this in the cat (Carleton, **7**, fig. 11, Pl. xvi) to such an extent that mulberry-like masses of desquamated and swollen cells, derived from the cubical cells, lie inside the alveoli. The congested capillaries in such cases bulge nakedly into the alveolar cavities. Phosgene, again,

[1] The heart-failure cell is encountered in passive congestion of the lungs (e.g. in mitral stenosis). Its appearance is elicited by the extravasation of red blood-corpuscles from damaged capillaries. The red blood-corpuscles disintegrate in the alveoli and the pigment derived from their haemoglobin is taken up by large and characteristic phagocytes—the heart-failure cells.

causes many of the cubical alveolar cells first to swell up (see fig. 5, Pl. 27), and then to fall into the oedema fluid in the alveolar cavities, as noted by Edkins and Tweedy (**15**).

(iv) Jagziekte.—Another very striking instance of an irritiative proliferation of the alveolar epithelium has been reported by Cowdry (**13**). It occurs in a chronic catarrhal form of pneumonia—the virus of which is unknown. The disease is called 'Jagziekte' and occurs in South African sheep. The early stages are histologically characterized by capillary engorgement with macrophages and lymphocytes. The former pass in large numbers into the alveoli. Next proliferation of the alveolar epithelium sets in. Cell masses, sometimes papillomatous, grow out from the alveolar wall and fill the cavity. Invasion of the interalveolar tissue also occurs. Although some of the epithelial proliferation can be traced to the lining of the bronchioles, there seems to be no doubt as to the very active part played by the alveolar lining in the process.

(v) Pulmonary Collapse.—The appearance of cubical nucleated cells in the alveolar walls has long been noted in areas of collapsed lung. The lining of the alveoli becomes strikingly foetal in appearance. Again, in the interstitial pneumonia of congenital syphilis, similar changes may occur, though here there is the complicating factor of an inflammatory infection.

If we accept the alveolar lining as being epithelial, this return to an earlier developmental stage is not astonishing. But if we regard the alveolar lining as histiocytic, such a hearkening back to a primitive epithelial type seems most unlikely.

5. The Origin of the Cubical Cells of the Alveolar Epithelium.

The theories that dust-cells are merely blood leucocytes that pass out of the pulmonary vessels to the alveoli, or that they are derived from the endothelium of the lung capillaries have already been discussed and rejected, see pp. 230 and 223.

Evidence has been brought forward to show that both the dust-cell and the heart-failure cell are derived from the smaller

nucleated cells (' cubical epithelial cells ') normally present in the alveoli. The question now arises, whence come these cubical precursors of the alveolar phagocytes ?

Into the discussion now comes the Reticulo-Endothelial System of Aschoff (Aschoff, **1, 2**). Many authors regard dust-cells as histiocytes which have been filtered out of the circulation of the lungs. But the relationship of these histiocytes to the cubical alveolar cells is usually left unexplained.

Policard (**34**) has attempted a striking synthesis of all the discordant facts regarding the alveolar lining, and his view merits particular attention.

The foetal alveoli are formed from the ramifications of the embryonic bronchi in the surrounding pulmonary mesenchyme. These alveoli are lined by a cubical epithelium. After birth, the epithelial lining becomes much thinner, while the characteristic anucleated squames, which had begun to appear just before birth, become very evident. The current explanation of the squames is that they are formed by the cubical elements losing their nuclei. During the transformation of the collapsed antenatal alveoli into the expanded alveoli after birth, various degenerative changes occur in the alveolar epithelium.

Now, according to Policard, what occurs during the transformation period in the alveoli is n o t the production of the squames from the small cubical cells, but a wholesale degeneration of the original endodermal lining of the alveoli. He points out that the degenerative changes in the alveolar epithelium of the later stages of intrauterine life fit in with his conception of its destruction. P a r i p a s s u with the disappearance of the alveolar epithelium he holds that fresh cells, from the mesenchyme of the lung, reline the alveoli. And these cells he believes to be histiocytes.

But what of the two types of alveolar elements, the cubical cells and the anucleated squames, classically described as lining the alveoli ?

The squames Policard regards as being merely extremely thin lamellar prolongations of the cytoplasm of the histiocytes (wrongly regarded hitherto as the cubical epithelial cells). The

wavy outlines of the 'squames', so clearly shown by silver nitrate impregnation, are, according to Policard, merely the folds in the lamelliform projections of the histiocyte (or macrophage).

From the above, it follows (i) that the alveolar lining, primitively endodermal, becomes secondarily mesodermal; (ii) that the dust-cells, being derived from the histiocytes, are no longer epithelial but mesodermal in origin. In this respect they would follow the majority of the phagocytic cells in the body.[1]

The following evidence would seem to invalidate Policard's suggestive theory, though further work is necessary before the origin of the squames and cubical cells of the lung alveoli can be regarded as definitely solved.

(i) Admitting that the squames are merely lamelliform processes from the cubical (according to Policard histiocytic) cells, it is curious that continuity of these elements cannot be seen. To regard the definite outlines of both squames and cubical cells as folds in one and the same cell seems at present an hypothesis. The study of nitrated lungs led Ogawa (**30**) to reject the idea that squames and cubical cells were part of the same cell-unit.

I also have examined thick sections of nitrated lung and note that there is no relation between the number and position of the cubical epithelial cells to the squames, such as one would expect if the latter were folded lamelliform expansions of the former.

Often one can see the outlines of the cubical cells and the squames as separate and independent entities.

(ii) In transverse sections of the alveolar walls after silver nitrate impregnation the limits of the cubical cells and the

[1] But by no means all, since phagocytosis by epithelia of endodermal origin has been noted by various observers, e.g.:

Phagocytosis of spermatozoa by the epithelium of the vas deferens, after ligation of the latter (Guiyesse-Pelissier, **25**).

The same phenomenon following irradiation of the testis by X-rays (Regaud and Tournade, **35**).

The phagocytosis of coal and carmine by dedifferentiated bronchial epithelial cells in tissue cultures of lung (Carleton, **7**).

adjacent squames are clearly shown. The black nitrated cell walls extend right across the thickness of the cells. They are not incomplete—as they should be were Policard's view correct.

(iii) Transitions between the cubical nucleated cells and the anucleated plates have been described and figured by Stewart (**38**), Ogawa (**30**), and Fauré-Fremiet (**16**) in late foetal stages. The figures of these authors certainly point to a transformation of the cubical cells, by nuclear degeneration, into the squames. Ogawa (**30**) has noted similar changes following the injection of distilled water into the trachea of living animals.

(iv) It is unfortunately impossible, as remarked by Ogawa, to isolate the squames by maceration methods, on account of their fragility.

I have tried to do so by intratracheal injection of 33 per cent. alcohol or chromic acid. Good dissociations are obtainable of the pulmonary elements other than the squames by the former reagent and the various types of cell can be identified with a fair degree of certainty in suitably stained slides.

Although the alveolar squames are lacking in such preparations, the cubical cells can be identified. Their outlines are clear cut and regular. It is difficult to see how this could be so if their alleged lamelliform prolongation had been broken off or had been dissolved by the macerating fluids. One can only conclude that the cubical cells and the squames are separate entities.

(v) Seeman's experimental work, already referred to on p. 227, is against Policard's view of a histiocytic alveolar lining.

(vi) The relining of the adult alveoli collapsed lungs and in syphilitic interstitial pneumonia (see p. 231) by cubical cells resembling the foetal alveolar lining seems an unlikely act on the part of histiocytes.

In conclusion :

The present available evidence would seem to speak against the theory that the alveoli are lined by histiocytes (= the cubical epithelial cells), and that the squames are merely prolongations of the histiocytes.

6. Summary.

1. The vital injection experiments of Permar have been repeated. The transformation of endothelial cells of the lung capillaries into dust-cells, as claimed by this author, could not be established on a scale at all sufficient to account for the immense number of dust-cells.

2. The evidence of tissue culture is discussed and is claimed to favour the idea that dust-cells are derived from the cells lining the alveoli, and that these are largely cubical epithelial cells (Binet and Champy ; Carleton) and not histiocytes (Lang).

3. That dust-cells are formed from the cubical epithelial cells is urged from the study of sections of dust-laden lungs.

4. That the heart-failure cell has a similar derivation to the dust-cell is also urged. Stages in the formation of dust- and heart-failure cells are described and figured.

5. The changes caused in the pulmonary alveoli by (i) poison gas, (ii) the disease ' Jagziekte ', and (iii) collapse of the lung are discussed. The conclusion is formed that these changes favour the view that the cells lining the alveoli are epithelial rather than histiocytic.

6. Some of the recent work of the Aschoff school (papers of Westhues and Seeman) is described and discussed.

7. Policard's theory that the final alveolar lining is histiocytic (i. e. mesodermal) is described.

Difficulties for accepting this view are given.

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EXPLANATION OF PLATE 27.

Figures drawn with the Abbe camera lucida. Explanation of lettering with the description of each figure.

Fig. 1 (× 1500).—Thick (30 μ) section of a guinea-pig lung exposed to a mixture of flint and coal-dust. AS, anucleated alveolar squames seen 'en face'; C, a capillary in the interalveolar septum. On the other side of the latter are seen three nucleated alveolar cells (AC) in section. One of these contains dust and is hypertrophied. The two others are dust free, and correspond to the cubical alveolar cells. LEU, leucocyte in the capillary vessel; RBC, red blood-corpuscle. Technique: fixed absolute alcohol; stained pyronin-methyl green.

Fig. 2 (× 1500).—Thin section of lung of a human being gassed with phosgene. From a preparation of Dr. C. G. Douglas. DC, dust-cell becoming detached from the alveolar wall. Nucleated alveolar cells forming an integral part of the alveolar wall at AC. C, capillary; E, endothelial nucleus of same. Technique: formol; haematoxylin and eosin.

Fig. 3 (× 2250).—Free dust-cells from the human lung. Formol; haematoxylin and eosin.

Fig. 4 (× 1500).—Thin section of lung of a guinea-pig exposed to 'ground pitcher' (ground up porcelain) dust. Portions of two alveolar septa cut through transversely. The septa at the points depicted consisted of nucleated elements which can only be identified with the cubical epithelial cells of the normal alveolus. Absolute alcohol; safranin.

Fig. 5 (× 1500).—Section of another human lung after gassing with phosgene. From a preparation of Dr. C. G. Douglas. Here also, as in fig. 3, is the alveolar wall made up of groups of cubical epithelial cells lying between the anucleated alveolar squames (not shown). C, capillary; E, endothelial nucleus of same; RBC, red blood-corpuscle. Formol; haematoxylin and eosin.

Fig. 6 (× 2250).—Section of human lung; passive venous congestion showing the usual exudation of red blood-corpuscles (RBC) into the alveoli and the appearance of heart-failure cells (HFC) to engulf the pigment set free by the red blood-corpuscles as they degenerate. The cubical alveolar epithelial cells (AC) are swollen, and stages in their detachment (AC 1) from the alveolar wall to form heart-failure cells are shown. C, capillary; LEU, leucocytes (one lymphocyte, one polymorph, &c.) which have wandered out through the damaged capillary walls. Formol; haematoxylin and eosin.