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Granulated metrial gland cells in the lungs of mice in pregnancy and pseudopregnancy

I. STEWART

Human Morphology, Faculty of Medicine, University of Southampton, Southampton SO9 3TU, UK

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INTRODUCTION

The granulated metrial gland (GMG) cells which are found in the decidua basalis and metrial gland of the pregnant mouse uterus are large, often binucleate, cells containing many cytoplasmic glycoprotein granules and much glycogen (Stewart & Peel, 1977). Recent studies have shown that GMG cells differentiate from cells originating in the bone marrow (Peel, Stewart & Bulmer, 1983) but proliferation of GMG cells within the developing decidua basalis and metrial gland occurs and thus contributes to the increase in their numbers (Stewart & Peel, 1980). Following their increase in numbers, there is a decline and few GMG cells remain by Day 18 of pregnancy (Stewart & Peel, 1980). The fate of the GMG cells in the decidua basalis and metrial gland is uncertain; some appear to degenerate *in situ* (Stewart & Peel, 1980), but others enter the lumina of blood vessels where they are regularly seen from Day 8 of pregnancy (Stewart & Peel, 1978). Some GMG cells can be found at various stages of pregnancy in the maternal blood spaces associated with the giant cell trophoblast, junctional zone trophoblast and labyrinthine placenta (Stewart & Peel, 1978). In the labyrinthine placenta, GMG cells apparently interact with trophoblast cells lining the maternal blood spaces, suggesting that the labyrinth is a site of functional significance to GMG cells (Stewart, 1984).

GMG cells can also be identified in the lateral sinusoids of the decidua basalis and in the large venous channels of the metrial gland (Stewart & Peel, 1978; Dickson & Krcek, 1981), vessels which are believed to be draining blood from implantation sites (Holmes & Davies, 1948). Migration of GMG cells to the lungs occurs but its extent and purpose have not been established (Dickson, 1980; Stewart & Jbara, 1980). In the present study of extrauterine migration of GMG cells, the frequency of GMG cells in the lungs of mice at different stages of pregnancy is assessed. The kidneys of some animals are also examined. In addition, the loss of GMG cells from the lungs is investigated in pregnant mice subjected to bilateral hysterectomy and the results compared to normal pregnancy and to the loss of extraneous hepatocytes from the pulmonary circulation of virgin mice. The migration of GMG cells to the lungs of pseudopregnant mice with deciduomata is also assessed in order to investigate the migration of GMG cells in an environment that is not influenced by the fetal allograft. The distribution of GMG cells in deciduomata of pseudopregnancy in the mouse has not previously been studied. Therefore, in considering the extent of any migration of GMG cells to the lungs in pseudopregnant mice with deciduomata, it is also necessary to study the GMG cells in the deciduomata.

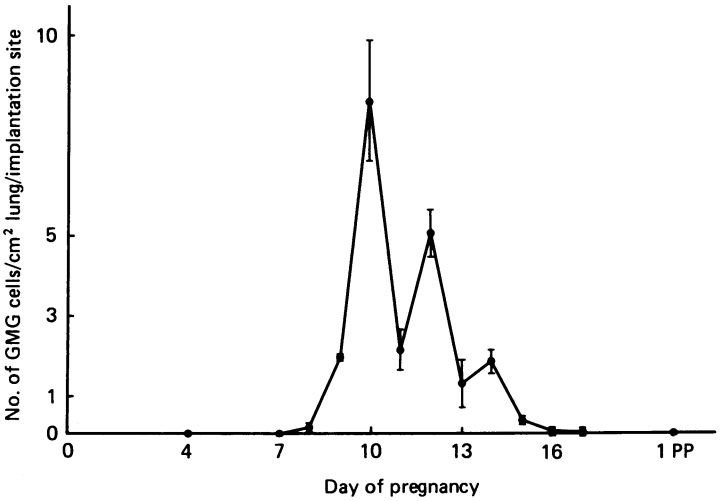


Fig. 1. The number (mean ± S.E.) of GMG cells in the lungs of mice at various stages of pregnancy.

MATERIALS AND METHODS

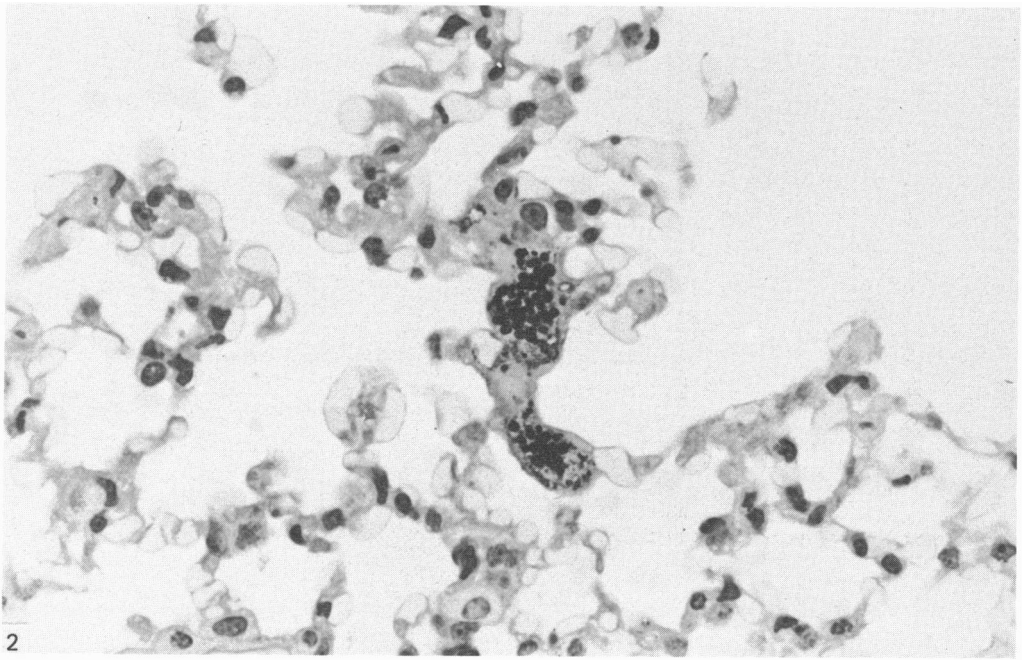
Experiment 1

Virgin Porton mice were mated overnight, and the morning on which a vaginal plug was detected was designated Day 0 of pregnancy. Virgin mice and mice at Days 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 and 17 of pregnancy were killed by cervical dislocation under ether anaesthesia. In addition, mice were killed at Day 1 post partum (the day on which live young were first detected was designated Day 0 post partum). In animals killed at Day 4 of pregnancy, the number of implantation sites was assessed by the intravenous injection of pontamine sky blue 6BX 15 minutes before death (Finn & McLaren, 1967). Animals with fewer than six implantation sites were rejected. The number of apparently healthy implantation sites and the number of resorption sites were assessed in the mice killed between Day 7 and Day 17 of pregnancy. Animals with fewer than six apparently healthy implantation sites and animals with more than one resorption site were rejected. Day 1 post partum mice with fewer than six live young at birth and mice where the number of uterine scars found at death did not equate with the number of live young at birth were rejected. At least three animals were obtained at each stage and the lungs were removed from each. The kidneys were also removed from four animals at Day 10 of pregnancy, two virgin animals and two animals at each of Days 7, 13 and 16 of pregnancy and Day 1 post partum.

Fig. 2. An apparently healthy GMG cell in the lung of a mouse. Periodic acid–Schiff and haematoxylin. Day 12 of pregnancy. × 600.

Fig. 3. A GMG cell containing a pyknotic nucleus in a blood vessel in the lung. Periodic acid–Schiff and haematoxylin. Day 12 of pregnancy. × 1200.

Fig. 4. A GMG cell (arrow) in the kidney of a mouse. Periodic acid–Schiff and haematoxylin. Day 10 of pregnancy. × 720.



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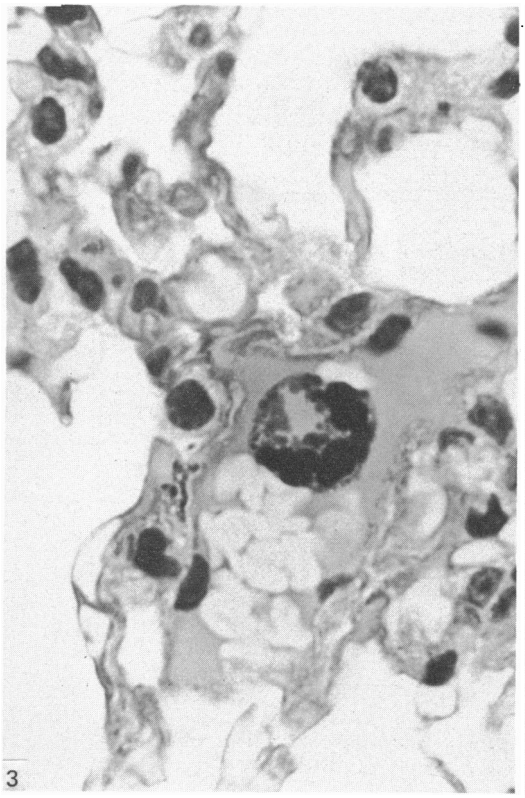

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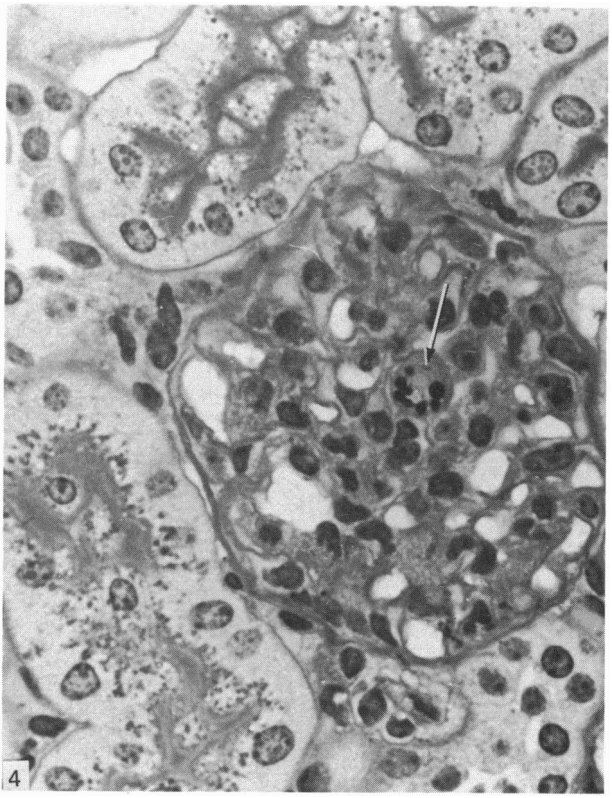

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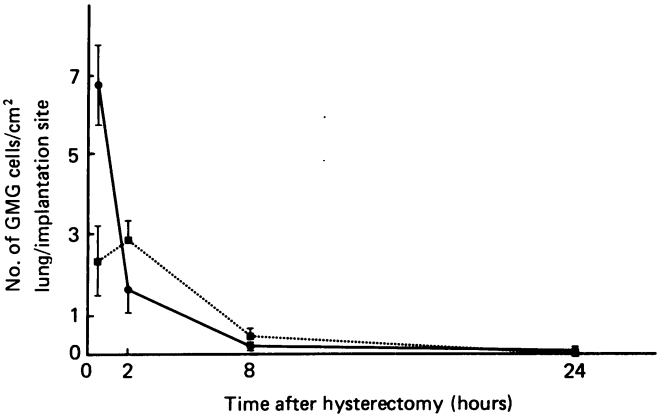
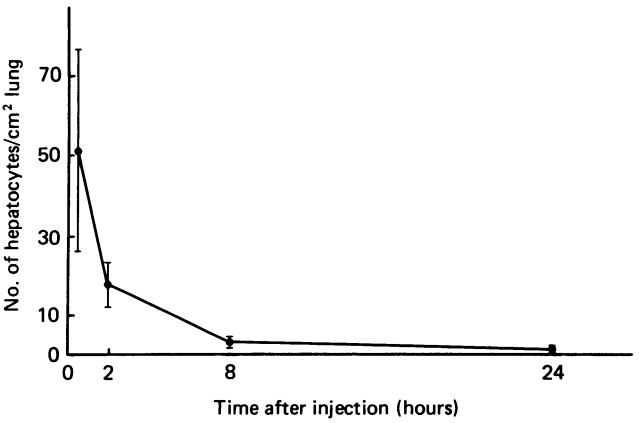
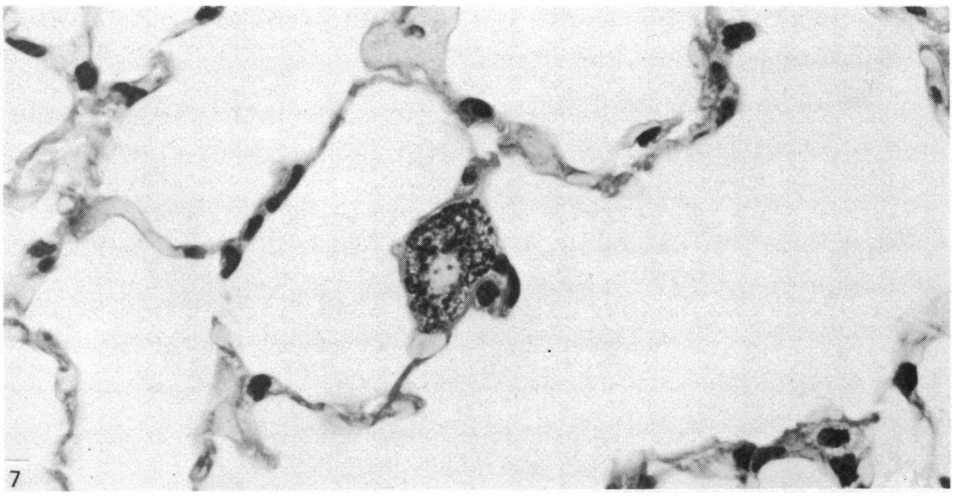

No. of GMG cells/cm² lung/implantation site
7
5
3
1
0
0
2
8
24
Time after hysterectomy (hours)

5


No. of hepatocytes/cm² lung
70
50
30
10
0
0
2
8
24
Time after injection (hours)

6



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Experiment 2

Primiparous Porton mice were hysterectomised under ether anaesthesia at Day 10 or Day 13 of pregnancy. Mice with fewer than six apparently healthy implantation sites or with more than one resorption site were rejected. The mice were killed by cervical dislocation under ether anaesthesia, at ½, 2, 8 or 24 hours after the operation. Three animals were obtained at each stage and the lungs were removed from each.

Experiment 3

Mice, of the inbred LAC129 strain, were killed by cervical dislocation and their livers removed under aseptic conditions. The isolated livers were perfused with medium consisting of Hanks balanced salt solution, without calcium and magnesium (Flow), containing 0·15% hyaluronidase (Type 1-S, Sigma), 0·15% collagenase (Type 1, Sigma), 100 IU/ml penicillin and 100 μg/ml streptomycin. This perfusion of the isolated livers was found to improve the cell yield and viability of single cell suspensions, while removing the majority of blood cells. The perfused livers were cut into pieces (2 mm × 2 mm) and incubated with constant agitation for 30–45 minutes at 37 °C in 12·5 ml of fresh incubation medium. The cells were collected by centrifugation, washed twice, resuspended in the Hanks balanced salt solution containing 100 IU/ml penicillin and 100 μg/ml streptomycin and finally filtered through a 100 mesh steel gauze to remove any cell clumps. Cell viability was assessed by nigrosine exclusion and the hepatocytes were counted in a haemocytometer. Other cell types were ignored. Only those cell preparations which showed 85% hepatocyte viability were used. Hepatocytes (5×10^5 viable) were injected into a tail vein of female virgin LAC129 mice aged 10–12 weeks. At least three mice were killed by cervical dislocation under ether anaesthesia, at ½, 2, 8 and 24 hours after injection. The lungs and uterus were removed from each animal.

Experiment 4

Virgin Porton mice were mated overnight with a vasectomised male of proven sterility and the morning on which a vaginal plug was detected was designated Day 0 of pseudopregnancy. On the morning of Day 3 of pseudopregnancy, a decidual reaction was induced by the insertion of up to 50 μl of sterile liquid paraffin oil into the lumen of each uterine horn. At least three mice were killed by cervical dislocation under ether anaesthesia at Days 7, 8, 10, 12, 13 and 16 of pseudopregnancy. The gross appearance of each uterus was examined prior to removal. The lungs were removed from each animal. Within 10 minutes of death the mesentery, the uterine tubes and the cervix were removed and the uterus was weighed. The mean weight of a dioestrous mouse uterus (100 mg, $n = 5$) was subtracted from the weight of each pseudopregnant uterus and used as an indication of the extent of the deciduomata.

There was considerable variation in the size of the decidual swellings in each uterus. Three to six decidual swellings were taken from each animal to be prepared

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Fig. 5. The number (mean ± S.E.) of GMG cells in the lungs of mice at various times after hysterectomy at Day 10 (●——●) and Day 13 (■----■) of pregnancy.

Fig. 6. The number (mean ± S.E.) of hepatocytes in the lungs of virgin mice at various times after a single intravenous injection of 5×10^5 hepatocytes.

Fig. 7. A hepatocyte in the lung of a virgin mouse 30 minutes after the intravenous injection of 5×10^5 hepatocytes. Periodic acid–Schiff and haematoxylin. × 640.

for histological examination. These were chosen from the middle of the range of sizes and showed only a small variation.

Immediately after removal, tissues were fixed for 8–24 hours in a mixture of 2% glutaraldehyde and 4% formaldehyde in 0·1 M phosphate buffer, pH 7·2–7·4. After fixation the lungs were cut into pieces and areas which showed extensive haemorrhage were rejected. Transverse slices of kidney and uterus were prepared. The tissues were dehydrated in ethanol and embedded in glycol methacrylate (Rudell, 1967). Sections, 1 μm thick, were cut and no more than two sections, spaced at least 50 μm apart, were prepared from any one block of tissue. Twenty sections of lung were prepared from each animal and, where appropriate, twenty transverse sections of kidney and ten transverse sections of uterus. The sections were reacted with the periodic acid–Schiff technique, with or without previous diastase digestion, and counterstained with haematoxylin. The numbers of GMG cells in each section whose profile showed both a nucleus and at least one of the typical glycoprotein granules were counted. The number of hepatocytes in each section whose profile showed a nucleus was determined. The area of each section of lung and kidney was measured by projecting the sections on to a sheet of graph paper at known magnification. A minimum of 1 cm^2 of sectioned lung was examined from each animal.

RESULTS

Experiment 1

GMG cells were found in the lungs of all mice killed between Day 9 and Day 15 of pregnancy and in some mice killed on Days 8, 16 and 17. None was found in the lungs of virgin mice, or in mice killed on Days 4 and 7 of pregnancy or day 1 post partum. The number of GMG cells increased rapidly from Day 8 to Day 10 of pregnancy when more GMG cells were found in the lungs than at other stages (Fig. 1). The numbers were reduced at Day 11 of pregnancy, had increased again at Day 12 but thereafter showed a general reduction in numbers until at Day 16 and Day 17 only one GMG cell was found.

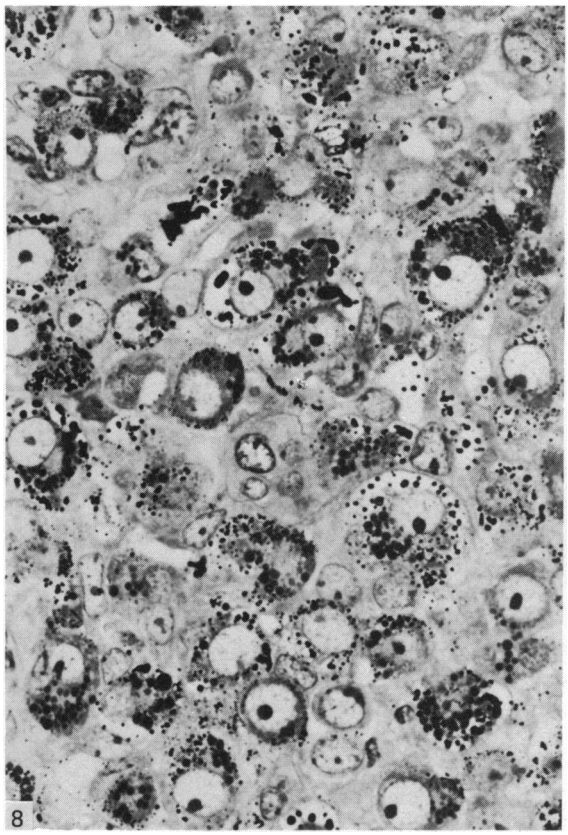
At all stages examined, the GMG cells found in the lungs usually appeared healthy. They were generally large and contained many of the typical cytoplasmic granules and glycogen (Fig. 2). Pyknotic nuclei were found in a few GMG cells but these were not related to any particular stage of pregnancy (Fig. 3).

The great majority of the GMG cells in the lung were localised in the inter-alveolar septa and these cells often had a tortuous appearance. Many were found which appeared to be lying within the lumina of capillaries but in most cases this could be neither confirmed nor excluded. Some GMG cells were found in the lumina of larger blood vessels and these were generally rounded in appearance. None was found in the lumina of the bronchial tree but occasionally a GMG cell was found in the lumen of an alveolar sac although such cells were invariably accompanied by blood cells.

Fig. 8. Large GMG cells with numerous glycoprotein granules in the compact zone of the decidua basalis at Day 8 of pseudopregnancy. Periodic acid–Schiff and haematoxylin. × 520.

Fig. 9. Small GMG cells (arrows) in the developing metrial gland at Day 8 of pseudopregnancy. Periodic acid–Schiff and haematoxylin. × 520.

Fig. 10. GMG cells in a blood vessel in the decidua basalis at Day 8 of pseudopregnancy. Periodic acid–Schiff and haematoxylin. × 520.



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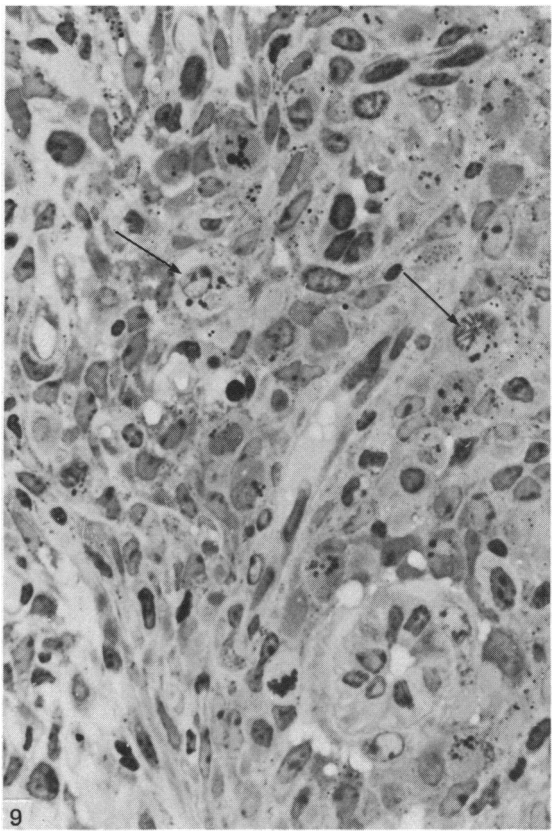

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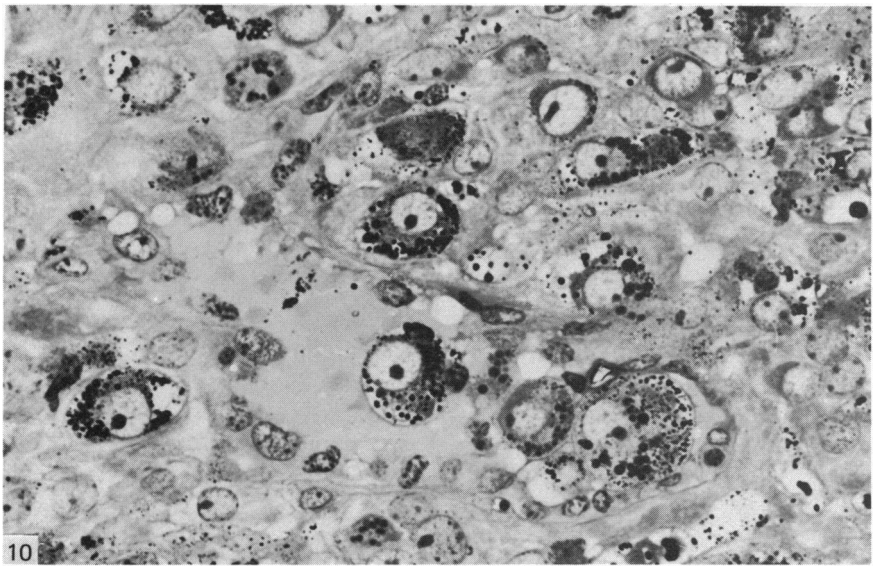

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Only five GMG cells were found in 80 transverse sections of kidney taken from animals killed on Day 10 of pregnancy, but none was found at any other stage. Each cell appeared healthy (Fig. 4) and to be located within the lumen of a capillary.

Experiment 2

In animals subjected to hysterectomy at Day 10 of pregnancy, the numbers of GMG cells in the lungs declined from ½ hour to 24 hours after the operation (Fig. 5). In animals hysterectomised at Day 13, the mean number of GMG cells in the lungs at ½ hour and 2 hours after operation was higher than the mean number of these cells found in normal Day 13 pregnant animals although the individual results were all within the range obtained at Day 13. Few GMG cells were found 8 hours after hysterectomy at Day 13 and none after 24 hours (Fig. 5). The appearance and distribution of GMG cells in the lungs of hysterectomised mice were similar to those found in pregnant animals.

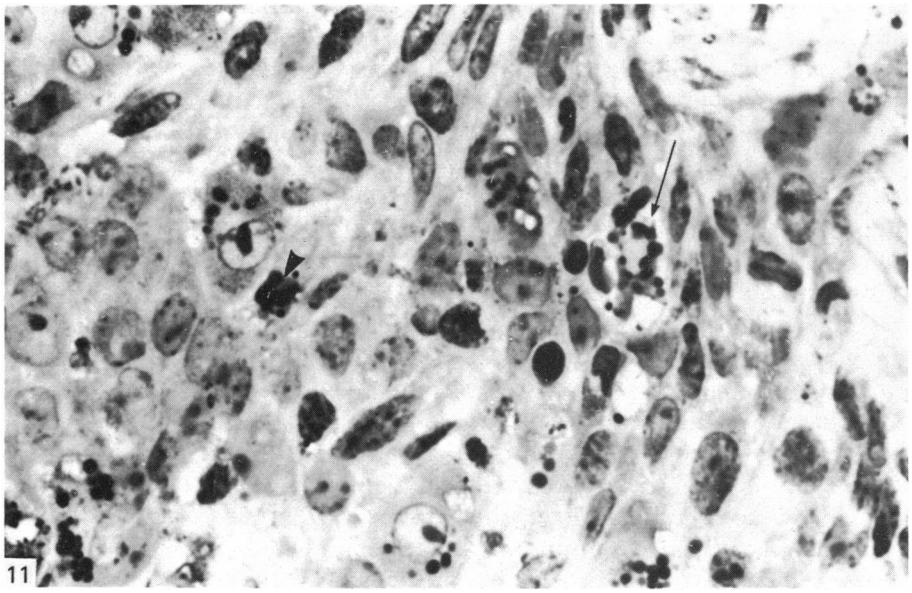
Experiment 3

In the virgin mice given an intravenous injection of hepatocytes, the numbers of these cells observed in the lungs showed a steady decline from 30 minutes to 24 hours after injection (Fig. 6). The distribution of the hepatocytes within the lungs was similar to that of GMG cells in pregnant mice with the majority being found in the interalveolar septa (Fig. 7). The uterus of each animal injected with hepatocytes was examined but no hepatocytes were found. No GMG cells were found in any of the sections of lung or uterus from the animals injected with hepatocytes.

Experiment 4

By Day 7 of pseudopregnancy, there was a well developed antimesometrial decidua consisting of large, closely packed, often multinucleate decidual cells. Towards the periphery of the antimesometrial decidua, the cells did not appear to be fully differentiated and many of these cells showed mitotic figures. No GMG cells were found in the antimesometrial decidua at Day 7 of pseudopregnancy or at any of the later stages examined. In the mesometrial decidua a compact zone was present and many of the differentiating decidual cells showed mitotic activity. GMG cells were present in the mesometrial decidua and these were mainly in the compact zone. In the compact zone, the GMG cells were mainly small with only one or two of the typical glycoprotein-containing granules but large binucleate cells with numerous cytoplasmic granules and much glycogen were also present. Some of the GMG cells contained mitotic figures and occasionally a GMG cell was seen in the lumen of a blood vessel. In the mesometrial triangle, stromal cells were hypertrophied and mitoses were common. A few small GMG cells were present in some, but not in all, of the swellings examined. Small GMG cells were found between the muscle fibres of the circular smooth muscle layer lying between the mesometrial triangle and the decidua basalis.

At Day 8 of pseudopregnancy, the decidual swellings were larger and there was greater development of the decidua. There was little evidence of decidual cell proliferation except for a few mitotic figures in the peripheral part of the compact zone lying next to the circular layer of smooth muscle. There were numerous large GMG cells in the decidua basalis (Fig. 8). In each of the decidual swellings examined at this stage there was a definite metrial gland containing numerous small GMG cells (Fig. 9). There was extensive mitotic activity in both the stromal cell and the GMG



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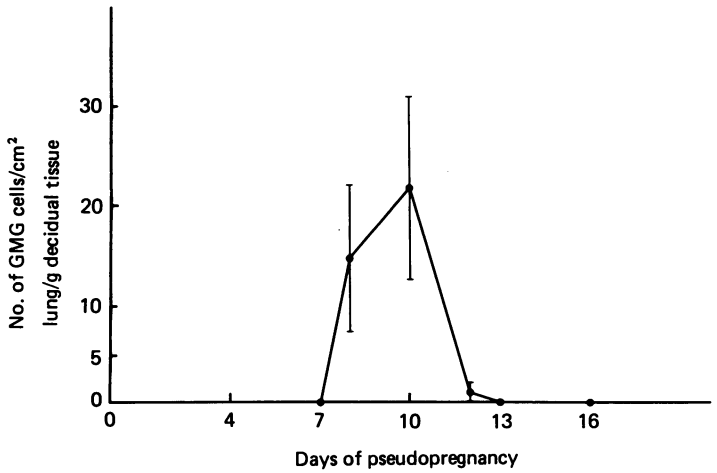

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Fig. 11. The metrial gland at Day 10 of pseudopregnancy. A GMG cell (arrow) contains a degenerate nucleus. Polymorphonuclear leucocyte (arrowhead). Periodic acid-Schiff and haematoxylin. × 875.

Fig. 12. The number (mean ± S.E.) of GMG cells in the lungs of mice at various stages of pseudopregnancy with deciduomata.

cell populations of this region. GMG cells were found in the lumina of blood vessels in the decidua basalis (Fig. 10) and also occasionally in the large venous channels at the base of the mesentery.

At Day 10 of pseudopregnancy, there was evidence of decidual necrosis in each of the decidual swellings examined. The extent of this necrosis varied between swellings but within each swelling it was always more extensive in the antimesometrial than in the mesometrial decidua. In some of the decidual swellings, the antimesometrial decidua was so necrotic that there was little evidence of cellular organisation or

detail. In the mesometrial decidua most regions appeared healthy but there was usually evidence of necrosis in the region distal to the metrial gland where pyknotic nuclei were present in both decidual cells and GMG cells. There was little evidence of degeneration in the metrial gland but whilst the metrial gland at Day 8 of pseudopregnancy appeared more developed than at an equivalent stage of pregnancy, the metrial gland at Day 10 of pseudopregnancy was poorly developed in relation to the equivalent stage of pregnancy; fewer GMG cells were present. Most of the GMG cells in the metrial gland appeared healthy but some did contain pyknotic nuclei (Fig. 11). No mitotic figures were seen in GMG cells but occasionally one was seen in a stromal cell. Polymorphonuclear leucocytes were found, to a varying extent, in the metrial gland of all decidual swellings examined (Fig. 11). Some apparently healthy GMG cells were found in blood vessels of the decidua basalis and metrial gland.

No decidual swellings were apparent in three of the four animals killed at Day 12 of pseudopregnancy or in any of the animals at Day 13. Some polymorphonuclear leucocytes and cellular remnants were found in the uterine lumen although the luminal epithelium appeared intact. In some sections, groups of cells containing a variety of periodic acid–Schiff-positive cytoplasmic inclusions were found in the mesometrial triangle, in the circular smooth muscle layer deep to the mesometrial triangle and also, but to a lesser extent, amongst the stromal cells of the adjacent endometrium. In these sections, one or two GMG cells were found in the mesometrial triangle but these generally showed some signs of degeneration.

In one animal at Day 12, decidual swellings were seen which were similar in size to those found at Day 10. Microscopical examination of these decidual swellings indicated a complete degeneration of the antimesometrial decidua and large areas of the mesometrial decidua. However, the part of the decidua basalis lying next to the metrial gland contained apparently healthy decidual cells and GMG cells, although GMG cells showing degenerative changes were also present. Healthy GMG cells, and those showing degenerative changes, were present in the metrial gland. Some apparently healthy GMG cells were found within the lumina of blood vessels in the viable parts of the decidua basalis and in the metrial gland.

At Day 16 of pseudopregnancy, some sections showed accumulations of cells containing periodic acid–Schiff-positive inclusions in the mesometrial triangle and to a lesser extent in the adjacent circular layer of the myometrium and in the endometrium. There appeared to be fewer of these cells than at Day 13. A single degenerate GMG cell was seen in the mesometrial triangle in one section, lying amongst the other cells containing periodic acid–Schiff-positive inclusions. No other evidence of deciduomata was present.

No GMG cells were found in the lungs of animals killed on Day 7 of pseudopregnancy but many were present at Day 8 (Fig. 12). There was a small increase in their frequency by Day 10 of pseudopregnancy. At Day 12 of pseudopregnancy, GMG cells were found in the lungs of the one mouse whose uterus contained large decidual swellings, but no GMG cells were found in the lungs of the other three animals killed at this stage or at Days 13 and 16. The structure and distribution of the GMG cells in the lungs of pseudopregnant mice with deciduomata were similar to those found for GMG cells in the lungs of pregnant mice.

DISCUSSION

GMG cells are found in the lungs of mice from Day 8 to Day 17 of pregnancy. These cells contain numerous glycoprotein granules and have similar morphological characteristics to the large GMG cells that are found in the decidua basalis and metrial gland of the uterus over the same period of pregnancy (Stewart & Peel, 1977, 1980). GMG cells apparently migrate across the endothelial lining to enter the lumina of blood vessels in the decidua basalis and metrial gland and they can be seen within the lumina of uterine blood vessels, including those draining the uterus, from as early as Day 8 of pregnancy and until late pregnancy (Stewart & Peel, 1978, 1980). Therefore it is likely that the GMG cells which are found in the lungs during pregnancy originate in the decidua basalis and metrial gland of the uterus and are carried to the lungs in the blood. A similar origin for the GMG cells in the lungs of pseudopregnant mice with deciduomata can be presumed.

As in the rat (Velardo, Dawson, Olsen & Hisaw, 1953) the deciduomata which develop in the pseudopregnant mice initially show a similar structure to that of the maternal placenta in pregnancy. Within the developing deciduomata, the structure and distribution of GMG cells are also similar to those found in pregnancy (Stewart & Peel, 1978). In the mouse, however, pseudopregnancy is not maintained and animals return to oestrus after about 10 days (Stewart, 1983*a*). In pseudopregnant mice with deciduomata, breakdown of the decidua becomes apparent by Day 10; decidual remnants were seen in only one animal killed at Day 12, suggesting a similar duration of pseudopregnancy with or without the presence of deciduomata. Some GMG cells are still found in the metrial gland regions in animals at Day 12 but regression of the metrial gland is evident. The animal which maintained a decidua until Day 12 showed the most developed metrial gland and some GMG cells were still to be found within the lumina of blood vessels. This animal was the only animal in which GMG cells were found in the lungs at Day 12 of pseudopregnancy. It would seem that the shorter period over which GMG cells are found in the lungs of pseudopregnant animals with deciduomata, than in normal pregnancy, can be accounted for by the earlier breakdown of the decidua and metrial gland in the pseudopregnant animals.

The great majority of the GMG cells in the lungs are found in the interalveolar septa and, by their association with blood cells and endothelium, some appear to be lying within the lumina of blood vessels. It is likely that the lumina of capillaries of the interalveolar septa represent the usual location of GMG cells in the lungs although the limitations of the techniques used in this study prevented this from being confirmed. GMG cells are large and it is likely that the capillary beds within the lungs present a physical barrier to their free circulation. GMG cells are only rarely seen in sections of kidney, and only then at a time when GMG cells are most frequently found in the lungs. In addition, hepatocytes (of the same order of size as GMG cells) which are injected intravenously into virgin mice, are detected in the lungs at all stages from $\frac{1}{2}$ hour to 24 hours after injection but none is found in the uterus of these animals. However, the drop in numbers of GMG cells after Day 10 of pregnancy (Fig. 1) and pseudopregnancy (Fig. 12) as well as following hysterectomy (Fig. 5) would suggest that GMG cells pass through the lung.

The fate of the GMG cells which enter the lungs is unclear and can only be a matter of speculation. There was no indication, in this morphological study, of any interaction between GMG cells and any cells within the lungs; an interaction appears

to occur between GMG cells and trophoblast cells lining the maternal blood spaces in the labyrinthine placenta which results in the loss of both cells (Stewart, 1984). No evidence was found to suggest that GMG cells emigrate via the bronchial tree. GMG cells with pyknotic nuclei were seen (Fig. 3), albeit infrequently, which may indicate that some GMG cells, once lodged in the lungs, begin to degenerate, become disrupted and are dispersed.

The function of GMG cells remains to be established although there are suggestions that these cells may be involved in the immunology of pregnancy. The bone marrow origin of GMG cells (Peel *et al.* 1983) is consistent with an immunological function, and studies on the GMG cells of the pregnant rat uterus indicate that these cells contain cytoplasmic immunoglobulin G (Bulmer & Peel, 1977; Mitchell, Craggs & Peel, 1980) although this latter finding has not been confirmed in the mouse (Stewart, 1983*b*). In the mouse, more GMG cells are found in the maternal blood spaces of the labyrinthine placenta in outbred pregnancies than in corresponding inbred pregnancies (Jbara & Stewart, 1982). In the labyrinth, GMG cells appear to interact with trophoblast cells lining the maternal blood spaces, resulting in the breakdown and loss of both the GMG cell and the cytotrophoblast, so indicating the possible importance of the labyrinth as a site of functional activity of GMG cells (Stewart, 1984). The numbers of GMG cells in the labyrinth appear to be greatest at about Day 14 of pregnancy (Day 0 = detection of vaginal plug) (Dickson, 1980; Jbara & Stewart, 1982) with few being found at Day 17 of pregnancy. It has been noted that the high numbers of GMG cells in the labyrinth are related in time to the period of growth of the labyrinth (Jbara & Stewart, 1982). At Day 10 of pregnancy, migration of GMG cells is well established and the number of GMG cells in the lungs is at its highest, but the development of the labyrinth has only just begun. At Day 14, when the numbers of GMG cells are at their highest in the labyrinth and there are many in the blood vessels in the decidua basalis and metrial gland (Jbara, 1983), there are relatively few in the lungs (Fig. 1). It can be concluded that as the labyrinth develops many migratory GMG cells interact with cytotrophoblast and as a consequence fewer are found in the lungs. Those GMG cells which reach the lungs are probably in excess of requirements and either have passed through the labyrinth without interacting with labyrinthine trophoblast or have taken a route not involving the labyrinth. It is important to stress that, as this migration of GMG cells occurs in pseudopregnant mice with deciduomata as well as in pregnant mice, their migration appears to be under the control of the mother, or it may be an inherent feature of GMG cells, but it is not under the influence of chemotactic factors released by the fetal placenta.

SUMMARY

A study has been made, using light microscopy, of GMG cells in the lungs of pregnant mice and pseudopregnant mice with deciduomata. GMG cells are found in the lungs from Day 8 to Day 17 of pregnancy and are mainly located in the interalveolar septa. The temporal relationship between GMG cells in the lungs and GMG cells in the blood vessels of the decidua basalis and metrial gland suggests that the GMG cells in the lungs are migrants from the uterus. The presence of GMG cells in the lungs is considered in relation to the possibility that a site of functional importance to this cell type is the labyrinthine placenta.

GMG cells are found in the uterine blood vessels and lungs of pseudopregnant mice with deciduomata. This finding suggests that the migration of GMG cells is

under the influence of the mother rather than under the control of factors derived from the fetal allograft.

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