EMBOLISM OF THE LUNGS BY TROPHOBLAST

Thesis submitted by W. Wallace Park, M.B., Ch.B., in fulfilment of the regulations for the Degree of Doctor of Medicine.

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I. INTRODUCTION

Gestational chorionepithelioma is the most tantalising of all neoplasms. Its life history is known with a degree of accuracy rarely obtainable in other neoplasms, for it can start only after fertilisation of the ovum: it shows at times a spontaneous regression that betrays its intrinsic curability in other patients could we but reproduce in them the appropriate humoral climate: and it has a unique association with hydatidiform mole. Just because it has so many peculiarities of behaviour of this kind it ought, one feels, to be so much the more susceptible to investigation, and with greater hope of success, than other more orthodox neoplasms.

One of its striking peculiarities is its ability to kill by metastasis yet show no source of origin within the uterus. Chorionepitheliomas of this type were early recognised, and the demonstration in 1893 by Dr. (later Professor) Georg Schmorl of Leipzig that particles of apparent trophoblast could be found with great frequency in the lungs of pregnant women at once raised the question: did chorionepitheliomas of this type arise by malignant transformation of placental emboli like these, or were the malignant foci in the lungs of these patients true metastases from a primary

chorionepithelioma within the uterus but a chorion-epithelioma that had been cast out, unnoticed, with the placenta?

This was the problem, posed in 1893 and unsolved to this day, that stimulated the present investigation. It seemed remarkable that so striking a phenomenon as the presence within the lung of placental tissue should have fallen so completely from the interest of pathologists and others since the first decade of the century when interest in it was at its maximum. Indeed, in an earlier communication (Park and Lees, 1949) doubt was expressed whether the phenomenon really occurred with significant frequency at all. The idea of the present work was conceived after the publication of that paper, with the ultimate object of finding out just how common an occurrence embolism of the lungs by trophoblast was. It became clear very soon after the investigation proper was begun that no doubts could be entertained about the claim that embolism of this kind did occur: but it also became equally clear that remarkably little was known about it as a physiological or perhaps quasi-pathological phenomenon.

The communication now presented attempts to add some knowledge to the matter as it stands - with the underlying theme that all matters pertaining to the behaviour of trophoblast, even if physiological, have

a very direct relevance to study of the pathogenesis of chorionepithelioma.

II. EARLIER OBSERVATIONS: AN ANALYSIS AND APPRAISAL

> "Ausser diesen ... zellen bin ich in den arteriellen Gefässen und in den Kapillaren der Lungen Eklamptischer noch anderen, höchst eigentümlichen Zellformen begegnet." (Schmorl, 1893, p.19)

With these words, Schmorl announced the discovery of the phenomenon now generally referred to as "trophoblastic cell embolism of the lung". He made the discovery while investigating the pathology of eclampsia, which was even then establishing its reputation as the "disease of theories"; and, being of the opinion that the cells were of placental origin, concluded not surprisingly that they were likely to have some aetiological significance. His original coloured illustration of these cells is reproduced here as my figure 1.

The phenomenon was, of course, an example of "parenchymal cell embolism" - though Schmorl very properly gave much thought to the question whether the cells might not have originated in the lung itself - and it is of interest to note that the existence of parenchymal cell embolism as a pathological process per se was first reported by a British pathologist, Turner (1884), who showed that, in patients with lacerating

injuries of the liver, individual hepatic cells or even small clumps of hepatic tissue could enter the portal veins. Further examples of embolism of this kind were reported shortly afterwards by Jürgens (1886) who identified hepatic cells in the right heart's blood in cases of eclampsia, and in the pulmonary capillaries in cases of delirium tremens. Unfortunately Turner's report failed to arouse the interest of British pathologists in parenchymal cell embolism. The first general review of the phenomenon was published by Maximow in 1898, and no British worker made any significant contribution to the widespread study of trophoblastic embolism of the lung carried out during the twenty years that followed Schmorl's discovery.

When Schmorl began his investigations into the pathology of eclampsia he knew of Jürgens' work, and that it had been confirmed and extended by Klebs (1888) who claimed to have seen hepatic cells in vessels of the kidney and brain in two eclamptic subjects. These workers had paid little attention to the detailed changes in the liver itself, regarding them as simple focal haemorrhage. Not until the work of Pilliet (1888) were they recognised as foci of tissue necrosis, an important and correctly recognised difference, and a form of tissue change which Schmorl regarded as a very plausible explanation for the

presence of hepatic cells within the circulating blood. In his own material from eclamptic patients Schmorl, too, saw what he considered to be undoubted liver cells in the portal venous and hepatic arterial vessels, in pulmonary vessels, and in veins of the kidney and brain. But he suspected artefact. Doubts were raised by his seeing, in venous channels in the kidney, cells which he felt sure were renal cells; but these were the same kind of cells as those which Klebs had claimed to be young hepatic cells.

It is well recognised now, but was obviously not so widely appreciated in the 1890's, that cells or clumps of cells may easily be transferred artificially during a necropsy from one organ to the vessels or tissue spaces of another, or from the parenchyma of an organ into its own vessels or spaces, by scraping surfaces with an unwashed knife, by laying one organ upon another, by rinsing or other manual procedures. Schmorl at least was well aware of this. He gave precise directions on how to avoid such artefact and, with these precautions, prepared fresh sections from much of his own material. Examination of the new sections revealed hepatic cells in hepatic veins, pulmonary arteries and capillaries, and only very occasionally in veins of the kidney and brain: they were never seen in vessels of the hepatic arterial and portal venous systems, nor in arteries or

capillaries of any other organ.

The whole matter of hepatic cell embolism of organs would be almost irrelevant in the context of trophoblastic cell embolism were it not for the fact that its reported occurrence, and possible aetiological significance, in eclampsia made it inevitable that Schmorl should examine the cellular content of blood vessels in the lung with especial care.

His first series (1893) consisted of seventeen patients: all had died with eclampsia. The lungs, taken as a whole, showed essentially four abnormal changes: focal haemorrhage; inflammatory exudation, varying in extent from microscopic foci to areas involving the greater part of a lobe, and accompanied by what would now be called "hyaline membrane" formation on many alveolar walls; multiple thrombi in arteries, veins and capillaries; and "cells of an extremely peculiar formation", that is, the cells which he identified, after careful consideration of the various other possibilities - to which I shall refer again later - as <u>placental giant cells</u>. In summary, the results of his microscopic examination of various tissues in these seventeen patients were:-

placental giant cells seen in the lungs of fourteen patients, and in no other organs.

liver cells seen in the kidney of one, the brain of one, and the lungs of ten, patients.

His "control series" consisted of only four patients who died soon after delivery, two of haemorrhage, two of uterine rupture; and he was unable to find a single placental giant cell in the lungs of these patients, despite careful search of many sections. His deduction from this negative evidence was understandably cautious, namely, that if embolic escape of placental cells occurred at all in non-eclamptic women, wholesale entry of these cells such as he saw in his eclamptic patients certainly did not occur. Nevertheless he was sufficiently impressed by the negative findings in these patients to feel justified in advancing the hypothesis that eclampsia was a disease of placental origin in which, in some way, escape of placental giant cells into the blood stream was concerned. It may seem strange now that Schmorl should have advanced an hypothesis of eclampsia, not in a preliminary communication but in a major monograph, with so few control observations - an act which, in the light of later developments, he probably regretted; but no criticism was ever levelled at his work, on these grounds at least, by later writers on the subject.

Virchow himself had examined the lungs of patients with eclampsia. He had described his findings in 1886, seven years before the publication of Schmorl's monograph, saying that he had seen fat

emboli in the lungs of four out of five patients with this disease: yet there is no mention of his having seen any multinucleated masses of the kind later described by Schmorl. Any pathologist would hesitate long before suggesting that Rudolf Virchow overlooked anything as histologically striking as the giant cells of Schmorl - but on this occasion at any rate one wonders.

It was and still is frequently stated that Schmorl regarded the escape of placental cells into the circulation, and the release of disintegration products therefrom, as itself the cause of eclampsia. This is not so. The essential lesion in eclampsia was, in his view, widespread intravascular thrombosis, resulting from the action of some thrombogenic substance produced in the placenta. So far as its mode of production was concerned he considered two possibilities: one, that the thrombogenic substance was derived from, or was itself, a decomposition produce of the released giant cells; the other, that the substance was elaborated in the placenta itself, the deported giant cells in this case merely providing some supporting evidence that there was placental abnormality of some kind. In fact, he rather preferred the second view - albeit mainly for reasons contained in the morbid anatomy of a single pregnant rabbit that had died with violent fits late in

pregnancy. This animal had a mottled yellow and red liver showing much focal necrosis; multiple intravascular thromboses in kidneys and lungs; and, in the lungs, only very scanty giant cells of apparently placental origin. So far as one can tell from Schmorl's account of the incident, it was the disparity between the widespread distribution of the thrombotic lesions and the paucity of giant cells in the lung in this one animal that finally determined his preference for the placenta itself rather than its deported giant cells as the source of the eclamptic "toxin".

The first comment on these views was made by Aschoff (1893) in a short review of the whole question of capillary embolism by "giant-nucleated cells" (riesenkernhaltigen Zellen). This author did not make any distinction between the cell containing <u>many nuclei</u> and the cell containing <u>a large nucleus</u> - a very important difference in the present context - with the result that much of his criticism of Schmorl's observations was misdirected. Aschoff examined the lungs of two patients with eclampsia: he failed to find multinucleated giant cells of the type clearly described by Schmorl, but did find large cells, each with a prominent multilobed nucleus. From his observations on tissues elsewhere he concluded, almost certainly correctly, that the cells with multilobed

nucleus had come to the lung from the bone marrow; and then remarked that if these cells and those described by Schmorl were of the same origin, Schmorl's view that the thrombosis seen in eclampsia was produced by placental tissue in the blood stream would be untenable. In these circumstances that would, of course, have been true: but Aschoff had not identified the cells correctly - "his" cells and "Schmorl's" cells were not identical.

Aschoff's remarks did not invalidate Schmorl's claims to any extent that mattered, and indeed confirmation of Schmorl's view that placental cells could be seen in the lung was published shortly afterwards by Lubarsch (1893) who had identified placental giant cells in the lungs of nine out of fourteen patients with eclampsia but saw none in the lungs of three other patients who did not have eclampsia. This worker made the interesting observation that he had seen these cells in the lungs of a patient who had died with chorea gravidarum, and concluded therefrom that the placental tissue had been dislodged from the uterus by the patient's convulsions. This led him to consider that the presence of placental tissue in the lung was not peculiar to eclampsia, thus disagreeing with one of Schmorl's tenets; and to the further view that placental cell embolism of the lung occurring in diseases accompanied by convulsions was

a result of such convulsions, not the cause.

Two years later, Leusden (1895) published a long paper on the pathogenesis of puerperal eclampsia, based on his experience with two fatal cases. His views were similar to those of Lubarsch, agreeing that placental emboli could be seen in the lungs but disagreeing that they were peculiar to eclampsia - he saw identical structures in two patients who did not have eclampsia - and disagreeing also that they were thrombogenic, for he was unable to demonstrate thrombus formation in any of the tissues that he examined. His own observations were not entirely flawless for in one of the illustrations of placental giant cells, his figure 3, he shows what is almost certainly a giant cell of bone marrow origin; but his observations otherwise were well founded.

Opinions were now gradually coming to agree that Schmorl was right in his reported facts - placental cells did occur in the lungs during pregnancy - but wrong in his interpretation of their significance - they did not appear to be a specific accompaniment of eclampsia. Pathologists of the day had to thank Lubarsch for making known to them, in a supplement to a further publication (1899), the results of investigations into the subject by Kassjanow who, working in the laboratory of Winogradow, eventually communicated his results in an Inaugural Dissertation at

St. Petersburg in 1896. The text of this Dissertation, written in Russian, appears to have been as inaccessible to pathologists then as it is now. Kassjanow had seen syncytial giant cells with great frequency in the lungs of eleven patients who had died accidentally for various reasons and had not had eclampsia. He considered that the occurrence of the phenomenon was not dependent upon the birth act since he saw it in one patient (but only in one patient) who died undelivered at the fifth month of pregnancy; and he was the first worker to hold the view that placental cell embolism of the lung was a physiological occurrence, probably happening in every pregnancy, since he could regularly demonstrate morphologically identical giant cells in the uterine wall of parturient patients dying of diseases other than eclampsia.

In the same year Apfelstedt and Aschoff (1896) reported, for the first time, blood-borne transport of whole chorionic villi; not, however, to the lungs but to the vaginal wall in the case of a patient bearing a hydatidiform mole and who later died of metastatic chorionepithelioma. From this finding they postulated that the escape, not only of syncytial giant cells but of whole villi, might be an accompaniment of normal pregnancy. This view was contested shortly afterwards by Pick (1897) who had found whole

chorionic villi in a vaginal node in a patient who had a simple non-invasive hydatidiform mole. He considered that whole villi might be transferred to the lungs in a molar pregnancy but not in normal pregnancy; and, indeed, that transfer of whole villi might well be related to molar pregnancy as transfer of giant cells was related to normal pregnancy. He drew attention to the fact that, however much pathologists and gynaecologists might care to speculate, no one had ever yet seen a complete chorionic villus in the lung: this was not to happen for a further four years.

During the year that followed Pick's observations a review of the whole question of parenchymal cell embolism of the lung vessels was published by Maximow (1898) who had himself carried out a number of investigations into the frequency of occurrence of the phenomenon in rabbits. He was unable to find any placental giant cells in the lungs of 40 pregnant rabbits killed at various stages of pregnancy, and concluded, reasonably, that transfer of placental tissue to the lungs was not a normal occurrence in this species at any rate. He was able to produce the phenomenon artificially, by massage of the uterine horns through the abdominal wall, achieving this with five animals during the second half of pregnancy but not with one other animal during the first half of

pregnancy. One point in particular he mentioned: pulmonary vascular thrombosis could be produced readily by injection of emulsions of tissue of various kinds such as bone marrow and kidney. He was therefore unable to agree with Schmorl that placental tissue possessed any specific thrombogenic properties.

The first workers to observe whole chorionic villi in the lung were Solowij and Krzyszkowski (1900). The pregnancy was pathological. The patient, aged 47, para 10, died of uterine haemorrhage and sepsis soon after the removal of a hydatidiform mole. Necropsy revealed penetration of the uterine wall at the site of the mole, and several small haemorrhagic nodes in the lower lobe of the left lung. Sections from many of these nodes showed, besides plentiful placental giant cells, undoubted chorionic villi (their Plate IV, figure 3, is certainly a convincing illustration). The haemorrhagic character of the nodes was owed to rupture of vessel walls in the neighbourhood, - certainly a result, direct or indirect, of continued metabolic activity or active growth by the trophoblastic tissue of the villi. The question of the growth potential of embolically transferred trophoblast, whether as part of a whole villus or as detached clumps, is clearly of more than academic interest; yet Solowij and Krzyszkowski, in whose patient's lungs there had clearly been continuing

trophoblastic activity of some kind, paid remarkably little attention to it. This matter, raised originally by Pick in the paper already quoted, was not seriously discussed again until the publication some years later of a further paper by Schmorl (1905) and one by his pupil, Dunger (1905).

The next important analysis of the phenomenon of haemic transfer of placental tissue was that of Veit (1901) who was responsible for the introduction of a term which, from the day of its appearance, has caused much confusion and been frequently misinterpreted. "Ueber Deportation von Chorionzotten (Verschleppung von Zotten in mütterliche Blutbahnen)" - thus, in the title of Veit's paper, was the term "deportation" presented to gynaecologists and pathologists.

A single case of tubal pregnancy, with living foetus, was the basis of Veit's observations. In sections from the wall of the gestational sac Veit saw, at two places, chorionic villi lying within maternal veins though still properly attached to the placenta, an occurrence which, he remarked, had been frequently observed by other workers. To this anatomical circumstance, the occupation of the lumen of maternal veins by still-attached villi, he applied the term "deportation", adding emphasis to the point that the villi are not detached by remarking later in his paper that " ... we have no evidence that, in the

uterus under normal circumstances, the deported villi tear off .." It is true that he regarded the process of embolism of the lung by escaped placental giant cells as a consequence of deportation, not as deportation itself; but there are passages in his paper where he does refer to the blood-borne escape of placental tissue as deportation. He may have done this inadvertently but it did expose him later to the charge of using the one term to describe two distinct processes. Schmorl was one of his severest critics.

Veit was not primarily concerned with such embolic phenomena as might accompany or develop in consequence of "deportation". He was more interested in the development of the inter-villous space, and the part played in this process by chorionic villi lying within and, by their physiological growth, expanding maternal vessels that communicated with the space. However, almost from the day of publication of his paper, the term "deportation" was widely adopted and interpreted as meaning a mechanical carrying-away of tissue from the placental site. The original significance of the term has been practically forgotten.

In concluding an article on the escape of chorionic villi from the placental site, Poten (1902) stated that "The escape of torn-off chorionic villi or their epithelium into the maternal bloodstream is

very frequent and probably happens in every pregnancy." Yet at this time chorionic villi had been seen in the lungs only once, and then only in a case of destructive hydatidiform mole - that is, the already mentioned case of Solowij and Krzyszkowski - and there is little doubt that Poten's assessment of the position was greatly influenced by the increasing number of case-reports in which authors described the finding of chorionic villi in vaginal nodes or metastases accompanying hydatidiform mole. He himself described such a case (Poten and Vassmer, 1900). Poten hoped to throw some light on the particular question, Do chorionic villi escape from the placenta in normal pregnancy?, and dismissed Veit's evidence at the outset on the grounds that Veit's case, being a case of tubal pregnancy, was abnormal. Poten had noted the double sense in which Veit used the term "deportation" and carefully avoided the use of it himself, entitling his article "Die Verschleppung der Chorionzotten."

Poten's arguments were based in his findings in large numbers of sections made from the placental site in seven patients who had died undelivered. He claimed to have found chorionic villi, free and unattached to either placenta or maternal vessel walls, in all cases. From this he derived the conclusion, already quoted, that villi escape to the lungs in

probably every pregnancy. This work was severely criticised by Schmorl in one of his later publications (Schmorl, 1905) but Poten's conclusion has persisted - otherwise unchallenged - and is incorporated in most of the standard texts of today.

The question whether escaped fragments of placental tissue in the lung might continue to grow had been briefly discussed by Pick (loc. cit.) but, rather surprisingly, had attracted little attention during the succeeding 8 years. Pick had been of the opinion that fragments of the normal mature placenta probably had little, if any, residual growth potential, but that continued growth might be expected of embolic particles from the young placenta, "destructive placental polyp", or hydatidiform mole. In 1905 the question was being given much closer attention, for the gynaecologists of the day were now acquainted with, and trying to solve, the problem of the patient who dies from multiple metastatic chorionepithelioma yet has normal uterine tubes and uterus. The most popular view, championed by Pick and by Marchand, was that embolically displaced trophoblast from a normal embedding ovum, regarded as a "physiological" chorion-epithelioma, might become malignant at its new site. Why it should "become malignant", and why so rarely, was not explained. Schmorl's opinions veered. Initially he thought the explanation must lie in a

localised placental chorionepithelioma, expelled wholly with the placenta and thus overlooked, the uterine wall suffering no damage. Then he considered that the Pick-Marchand view had most to commend it. Finally he decided to re-examine his own large volume of material in a search for evidence that might help to clarify the matter.

His second paper (Schmorl, 1905) dealt entirely with the fate of escaped placental fragments. This paper contains few clinical details of the cases discussed, and no illustrations of the morbid appearances in the lungs, but these matters are amply, indeed exhaustively, dealt with in a supplementary article by his pupil, Dunger (1905). By this time Schmorl had examined in detail the lungs of 158 women who had died during pregnancy, eighty three of them having had eclampsia. He claimed to have found embolic trophoblast in all the eclamptic patients - a finding which sustained his belief that trophoblastic pulmonary embolism and eclampsia were in some way aetiologically related - and in some eighty per cent of the non-eclamptic patients; but, for the purposes of the present problem, he directed his attention particularly to the lungs of those patients who had died during the earlier months of pregnancy. He selected forty seven cases: twenty five patients who had died undelivered; and twenty two cases dying after

abortion during the first and second month.

Of the twenty five undelivered cases, he saw trophoblast in three, and apparent proliferation of the trophoblast in none.

Of the twenty two cases of early abortion, he saw trophoblast in eight and apparent proliferation of the trophoblast in two.

The lungs of the last-mentioned two cases in the abortion series showed not only apparent proliferative growth of the trophoblast but contained trophoblast in quantities such as Schmorl had never seen in any other case with a structurally normal placenta, not even in instances of placenta praevia, manual removal of the placenta or rupture of the uterus - the conditions which he regarded as providing the opportunity par excellence for escape of trophoblast in large amount. Since the circumstances in both cases were those of an apparently simple abortion, Schmorl conceded that the finding of actively growing trophoblast within the lungs could be held to constitute evidence in favour of Marchand's view of the aetiology of extragenital chorionepithelioma, namely, malignant transformation in the lung of normally occurring trophoblastic emboli. The crux of the matter, however, as Schmorl clearly saw, was that these were cases of only <u>apparently</u> simple abortion. Both patients had been admitted to hospital several days after the abortion, both were gravely ill and

unable to give a detailed history, and in neither had the placenta been examined. The possibility that both placentas had shown early or partial hydatidiform change could not, therefore, be excluded: and Schmorl adduced strong, even if indirect, evidence to suggest that they had; namely, that he had seen proliferative growth of trophoblast within the lung, of the kind present in the two "abortion" cases under discussion, on only three other occasions, and on each of these three occasions the uterus had contained an undoubted hydatidiform mole. He no longer regarded as evidence of continued trophoblastic growth a histological pattern he had seen earlier in the lungs of a fourth case - apparent outgrowth of syncytium from the vessels to form a layer or "tapestry" on the alveolar walls - having since observed changes of the same kind in aspiration pneumonia in non-pregnant patients. He took the precaution of adding that he had seen no evidence of continued trophoblastic growth in the lungs of a further patient with hydatidiform mole although "very numerous emboli" of trophoblast were present. Thus, it seemed, only some hydatidiform moles could produce emboli capable of apparent growth, though possibly all could produce emboli in unusually large amount. Schmorl could give no certain reason why some embolic molar trophoblast should behave in this way but the possible connection with chorion-

epithelioma was obvious, and, indeed, Dunger (loc. cit.) remarked of the pulmonary lesions in these cases that they were histologically indistinguishable from the early metastases of a chorionepithelioma. Whether these two cases were in fact examples of early true chorionepithelioma prevented from achieving full development only by the untimely death of the patients could not and cannot, of course, be told.

Shortly after Schmorl and Dunger described their observations, and in the same year, Veit (1905) published a monograph on the matter of "zotten-deportation", giving his earlier views at greater length. One notes with interest that the word "deportation" was no longer part of the main title of his monograph: it was relegated to the subtitle, thus exchanging places with the formerly subsidiary "verschleppung" of his 1901 paper. The term "deportation" had been widely criticised, and indeed Veit himself admitted in one passage that it was not perhaps the happiest word to use to describe the presence of villi within maternal uterine veins. He was now mainly interested in possible biochemical and immunological implications of the presence of villi and trophoblast, attached or free, within the maternal vessels - I shall make further reference to this aspect later - and added little that was new to the

views of the day on placental cell embolism of the lungs as such.

After the year 1905, in fact, interest in the phenomenon diminished greatly and has remained at a low level ever since. Many questions, however, remain unanswered. Many people, indeed, still doubt whether placental tissue ever does reach the lung except in its malignant form as part of a chorionepithelioma. It was in an attempt to resolve this question and some of the uncertainty still surrounding the presumptively physiological phenomenon of "embolism of the lung by trophoblast" that the present investigation was carried out.

III. THE PROPOSED INVESTIGATION

General Remarks

Personal experience has shown that many pathologists and others still doubt whether normal placental tissue can in fact be demonstrated in the lungs. A question frequently raised is whether such large cells as may be seen are not perhaps megakaryocytes. It will be appropriate therefore to establish, so far as present techniques will allow, the identity of any structures that possibly could be trophoblast seen in the lungs of pregnant women; and, if this can be achieved with fair certainty, to determine the criteria whereby one particular type of structure can be correctly identified as trophoblast in the future. Consideration will also be given to the various other structures that could be misinterpreted as trophoblast. Chorionic villi, should any be seen, would be unlikely to cause diagnostic difficulty to the histologist of reasonable experience.

Besides this essentially qualitative aspect of the phenomenon, there are certain quantitative aspects of trophoblastic embolism of the lung about which knowledge is at present slight. Questions which naturally arise, and which one could hope to answer by examining appropriate material, include the following:

whether trophoblastic embolism occurs more

frequently in the earlier stages of pregnancy, when trophoblastic "invasiveness" is at its maximum, than in later stages;

whether the act of parturition per se has any influence on the frequency;

whether, as the early observers claimed, trophoblast is in fact seen more frequently in the lungs in eclampsia than in other diseases - if there is any significant aetiological connection between the presence of trophoblast in the lungs and eclampsia, one would expect trophoblast to be present with comparably high frequency also in states of pre-eclampsia;

what the frequency of occurrence is in diseases other than eclampsia and pre-eclampsia.

To all these questions the answer will be twofold: it will state the proportion of patients (in the series being examined) in whose lungs trophoblast appears; and, in these patients, the amount of trophoblast that is present.

Any other possibly relevant abnormalities seen in sections of lung from women dying during pregnancy, parturition or the puerperium will be noted and commented upon.

Finally, the investigation will include an

analysis of the results of experiments upon animals wherein trophoblastic tissue was introduced into the blood stream in various experimental circumstances. This was done in an attempt to determine the means of disposal of embolic trophoblast, and to assess the capacity of such trophoblast for continued growth.

Materials and methods

Hospital patients

Portions of lung were available from 120 pregnant, parturient or puerperal women. In eighty nine cases the patients had come to necropsy in the Royal Infirmary, Edinburgh; in twenty two cases in hospitals in the Dundee area; and in nine cases in hospitals elsewhere.

In all of the Edinburgh cases, fourteen of the Dundee cases and four of the other cases the material consisted of routinely prepared paraffin blocks of lung, and was obtained from the files of the Departments of Pathology concerned. In the remaining cases the material was obtained as unprocessed lung tissue, fresh or in fixative solution.

One block of tissue only was available in ninety one cases, two to five blocks in nineteen cases, and six blocks or more in ten cases. The total number of blocks was 247. On average, eight sections, 7

microns thick, were examined from each block; giving approximately 2000 sections in all.

For purposes of qualitative assessment of trophoblast in the lungs, some sections from all cases were stained with haematoxylin and eosin. In selected cases, where adequate material was available, other staining procedures were used. These included the periodic acid-Schiff, toluidin blue, picro-Mallory, Verhoeff elastica, reticulin and alcian blue-phloxin methods. All are standard methods except for the alcian blue-phloxin procedure which was introduced only recently by Attwood (1956) as a method for demonstration of the foreign material in the lungs in cases of amniotic embolism.

For control purposes, that is, in order to determine whether and with what frequency structures similar to particles of trophoblast may be seen in the lungs of patients other than pregnant women, a formal investigation was carried out on sections of lung from 100 unselected patients coming to necropsy. This has been further supplemented by observation on all sections of lung examined during routine biopsy and necropsy reporting during the past three years, so that there is in effect an informal or "unofficial" control series amounting to some hundreds of sections.

For purposes of quantitative estimation of trophoblast within the lung, the area of the sections

was measured and the number of trophoblastic particles within them counted. By simple calculation a "trophoblastic index" was determined - the number of such particles per 1000 sq. mm. of lung. In order to avoid the chance of counting the same structure more than once, serial sections were not used for this part of the investigation. Sections used for quantitative estimates were at least 10 microns distant from one another so that, in effect, a different area of lung was used for each count.

Other large protoplasmic masses may frequently be seen in the lung, the so-called megakaryocytes. In so far as they are sometimes mistaken for trophoblast in the lungs of the pregnant woman they merit some attention here. Their frequency in the sections was also measured and expressed as a "megakaryocytic index" - the number per 200 sq. mm. of lung.

Experimental observations

Animals. Stock female albino mice, three to six months old at the start of the experiments and obtained from a dealer, were used. Water and standard rat cake (Banner Mill, Aberdeen) were freely available.

An emulsion of placental tissue was prepared and injected into pregnant and non-pregnant animals under various experimental conditions:

Experiment I: injection into normal non-pregnant animals.

do. II, III: injection into non-pregnant animals treated with hormonal substances (oestrogen, progesterone, chorionic gonadotrophin).

do. IV: injection of autologous trophoblast into pregnant animals.

do. V: injection of emulsions of tissue other than placenta into normal non-pregnant animals.

Preparation of the emulsion. The donor animals were normal pregnant mice of the same stock as the experimental animals. They were killed by cervical dislocation during the second week of pregnancy; the uterus was opened aseptically; and the placentas removed from the uterine wall. A layer of tissue approximately 1 mm. thick was shaved from the foetal surface of the placenta and emulsified with pestle and mortar in warm sterile 0.9% saline to form a final concentration of 0.5 gram of placental tissue per 10 ml. of saline. By this means it was hoped to obtain an emulsion purely of trophoblast but the

possibility that some decidual tissue was also included could not be ruled out.

In the case of the pregnant recipient animals, autologous placenta was used. At the time of the experiment the animals were in the second half of pregnancy. Partial hysterectomy was performed under ether anaesthesia and the terminal two to four gestational sacs removed. A placental emulsion was then prepared from the contained placentas as described above and injected usually before the animal had fully recovered from the anaesthetic.

Technique of injection. In all cases 0.05 ml. of the placental emulsion was injected on one occasion only into a tail vein over a period of thirty seconds. Agitation of the emulsion during filling of the syringe, and constant slow rotation of the syringe during the injection, ensured uniform suspension of the placental particles. The concentration and amount of material injected, and the rate of injection, were determined by the results of several preliminary experiments. A more rapid rate of injection or a greater concentration of tissue than those quoted caused an unduly high immediate death rate. Even with the quantities used occasional animals still died either during the injection or within two minutes of its completion. This difficulty was countered by

having two spare animals per cage for use as replacements when required.

Extracts of human placenta have long been known to be toxic to experimental animals when introduced intravenously (Schneider, 1947). A simple preliminary experiment showed that this holds also for the murine placenta. Three groups of six mice were injected intravenously with 0.2 ml. of a 20% emulsion of murine kidney, liver and placenta. All died during or immediately after the injection, probably from simple mechanical pulmonary embolism. Three further groups of six animals were injected with the same volume of a particle-free filtrate of these emulsions. Of those receiving kidney and liver filtrate, one kidney recipient died: of those receiving placental filtrate, five died. This showed clearly that placental filtrate possessed a lethal property not possessed by filtrates of kidney and liver, at least in the quantities used. The toxic substance in crude placental extracts of this kind is considered by Schneider to be thromboplastin. Its presence in the dilute suspensions used in the main experiments now reported did not interfere significantly with the results since, as just mentioned, spare animals were used to replace the few that did die during or immediately after injection, presumably from the effects of thromboplastin.

Hormonal preparations. In the experiments where animals were treated with hormonal preparations (Experiments II and III), the following schemes of dosage were used:

(a) Oestrogen (Oestroform, B.D.H.), 0.05 mg. by subcutaneous injection weekly for 12 weeks before introduction of placental emulsion, and weekly thereafter until death.

(b) Progesterone (Progestin, B.D.H.), 0.75 mg. weekly for 12 weeks, and as above.

(c) Chorionic gonadotrophin (Gonan, B.D.H.), 10 I.U. weekly for 12 weeks, and, in Experiment II, as above. In Experiment III injections were continued for six weeks after introduction of placental emulsion, not until death.

Animals were killed by cervical dislocation at varying intervals after injection of the emulsion (see Results); the lungs fixed in formol-sublimate solution, sectioned at 7 microns, and stained routinely with haematoxylin and eosin. Other staining procedures were used in selected cases as in the case of the human lung material.

IV. RESULTS

The first aim in examining the collected series of lung sections from (a) 120 pregnant, parturient or puerperal patients, and (b) 100 non-pregnant subjects, was to find whether the sections from either group contained unusual cellular structures; and, if so, whether any particular form of cellular structure is peculiar to pregnancy.

1. Unusual cellular objects within pulmonary blood vessels: their interpretation

For the purposes of this investigation, a cellular structure was regarded as "unusual" if it was larger than a macrophage and not obviously a pathological finding such as a multinucleated giant cell of foreign-body type or an embolic particle of bone marrow. Within this definition, unusual cellular structures were frequently seen in the lungs in both groups of cases. One particular form, however, does appear to occur only in association with pregnancy.

The most frequently occurring types of unusual nucleated elements in the series of 120 cases now under examination are those shown in figures 2, 3 and 4, and referred to meantime as Types I, II and III. In a preliminary analysis of the first 106 cases in this series a few years ago (Park, 1952; and see Appendix III) an attempt was made to define the morphology of these structures, and the following

criteria, quoted from that communication, were suggested:

"Type I: Nucleus: a mass of chromatin of varying shape but essentially uniform in architecture, i.e. not multilobular. Cytoplasm: minimal in amount, if indeed visible at all.

Type II: Nucleus: a mass of chromatin of any shape but undoubtedly multilobular in architecture. Cytoplasm: as in Type I.

Type III: Nucleus: a definitely multinuclear architecture. Cytoplasm: variable in amount but clearly recognizable."

Typical examples of the Type I structure are shown in figures 5 to 8, and of the Type II structure in figures 9 to 14. With examples such as these there is a clearly recognizable difference between the two types: a mainly uniform cylindrical or rod-shaped nucleus in the one, and a more irregular multilobular nucleus in the other. However, further experience has shown that division of these elements into two varieties is without practical significance. Intermediate forms exist, forms which are difficult to allocate with certainty into either group; and it may be taken as virtually certain that Type I and Type II structures are but morphological variants of the same type of cell. They are not peculiar to pregnancy.

They can be seen on occasions, and were seen frequently during the present investigation, in the lungs of both pregnant and non-pregnant subjects: but it is remarkable how often they are overlooked - unless they happen to be present in the lungs of a pregnant woman. They are then undoubtedly apt to be regarded as particles of trophoblast. I have even seen them exhibited as structures of placental origin in a formal demonstration to a scientific society. The Type I/Type II structures are in fact the structures referred to, rightly or wrongly, by many workers as megakaryocytes: but they remain a very real source of confusion in the lung of the pregnant patient, and for that reason merit further comment.

Cells with Multilobular Nuclei : Megakaryocytes

The following description of the megakaryocyte as it appears in capillary vessels in the lung and other organs is quoted from an article by Brill and Halpern (1948):

> "With routine hematoxylin and eosin stain, the appearance of the megakaryocyte in the peripheral capillaries differs somewhat from that in the bone marrow. In the latter site the megakaryocyte is round; it possesses an abundant, homogeneous pink cytoplasm, the edge of which may or may not be irregular; the

> nucleus is large, vesicular or pyknotic, and may have few or many lobules. In the tissue capillaries, the megakaryocytes assume various shapes, being distorted by the channels in which they lie; their cytoplasm is often not discernible and the nucleus may appear naked. To a great extent, identification of megakaryocytes depends on their intravascular location and their enormous size, and especially on the large multilobulated nucleus which is most often pyknotic."

These structures were noted by Schmorl (1893) in two of his original seventeen cases, Cases 4 and 10, where he referred to them as "large, irregularly-formed, chromatin clumps", thinking that they might be fused placental cell nuclei. It is rather surprising that he made no mention of bone marrow as a possible source for these structures for he had given very careful consideration to the bone marrow as a possible source for his "other cells of an extremely peculiar type" before finally concluding that in their case at any rate the starting point was the placenta.

Aschoff (loc. cit.) discussed the nature and origin of these chromatin clumps at some length. He had seen them often in the pulmonary capillaries in a wide variety of conditions, particularly in such

inflammatory diseases as pneumonia, tuberculosis, erysipelas and typhus but also in, amongst other conditions, puerperal pyaemia and eclampsia. At first he thought their most likely source to be the lymph nodes and spleen but later, as a result of clinical and experimental observations, abandoned this view in favour of the bone marrow. Aschoff commented on Schmorl's claimed discovery of placental giant cells in the lung, published earlier in the same year, basing his comments on the fact that in two cases of eclampsia which he himself had examined he was able to identify only multilobular cells, i.e. megakaryocytes, and no multinuclear cells. He was thus moved to some misdirected criticism of one of Schmorl's views; arguing that, if the multilobular cell and multinuclear cell were derived from the same source, the thrombotic lesions in the lung thought by Schmorl to be caused by some product of the placenta (for, to Schmorl, the multinuclear cells in the lung were evidence that placental material of some kind at any rate was reaching the lung) could not be caused in this way since the multilobular cell was derived quite certainly from the bone marrow. We know now, of course, that the two types of cell did not in fact share a common source.

Whether Aschoff would have confused the two cell types had both been present in his two eclamptic cases

we can only guess; but the effect of the absence of multinuclear masses in these cases was that he had nothing, as it were, with which to compare the cells he rightly regarded as having come from the bone marrow. Leusden (loc. cit.), on the other hand, did have an opportunity to compare the two types. The first two of his illustrations show multinucleated placental cells (of my Type III variety) while the third illustration shows quite certainly a megakaryocyte: yet he regarded both types of cell as having had their origin in placenta. This error was noted by Maximow (loc. cit.) but in putting forward what he thought to be the correct explanation he in fact fell into error in quite the opposite direction. Since Leusden's third illustration showed a structure of bone marrow origin, Maximow concluded that the cells, which really were placental cells, in the two preceding figures must also have come from the bone marrow. At this time, then, two kinds of mistake were being made. Some workers, seeing in their preparations placental cells and what we now know were megakaryocytes, interpreted the placental cells as megakaryocytes: others, in the same circumstances, interpreted the megakaryocytes as placental cells. Dunger (loc. cit.) and Schmorl were of the latter group. In Dunger's paper, irregular chromatin clumps are mentioned as lying in close association with chorionic cells that

appeared to be lining a small, partly eroded, pulmonary artery. Dunger did remark that they were seen more frequently in the tissues around the affected vessel than in the vessel wall itself but stated that they could be seen amongst the chorionic cells, and implied strongly, though he did not say so directly, that he regarded them as syncytial elements derived from the larger chorionic cells in the lumen, penetrating the vessel wall and eroding the adjacent pulmonary tissue. As in Schmorl's original monograph, there is again in Dunger's paper no mention of any search having been made of a control series of lungs for the presence of chromatin clumps of similar character.

The status of the pulmonary megakaryocyte was reviewed some years later by Ogata (1912). His extensive searches had shown that large, irregularly shaped nuclei, usually naked but clothed sometimes with a little cytoplasm, could be found in the lungs of foetal and adult rabbits, and in the human foetus, child and adult. He regarded the naked nucleus as the final pyknotic stage of a bone marrow megakaryocyte that had lost its cytoplasm through long-continued nipping-off to form blood platelets, and then been swept out of the marrow as an effete remnant. He confirmed Aschoff's observation that the megakaryocyte was found most frequently in the lung in

states of febrile systemic disease, a by-product or reflection of marrow hyperplasia. Ogata's views were generally acceptable at that time and, apart from one rather curious alternative hypothesis advanced many years later and shortly to be mentioned, have remained so. It has, for example, long been taught that megakaryocytes are frequently to be seen in the lungs in lobar pneumonia: this phenomenon is depicted very well in an illustration in MacCallum's Textbook of Pathology (1936) and has been reviewed more recently by Williams (1942). The most comprehensive recent account of the occurrence and significance of megakaryocytes in the lungs and other tissues in human autopsy material is that of Smith and Butcher (1952) who found them in 88% of a series of "sudden death" cases and in 100% of a series of "hospital death" cases, the number of megakaryocytes per unit area of lung being nearly three times as high in the "hospital death" patients as in the hitherto healthy "sudden death" patients.

It is clear that the distinction between a cell with many nuclei and a cell with a single large lobulated nucleus is important, for, if megakaryocytes exist in a multinuclear as opposed to a monomuclear form, the correct identification of multinucleated structures within the lung immediately becomes more difficult. The morphology of the megakaryocyte in

health and in various diseases was reviewed at some length a few years ago by Dameshek and Miller (1946). Amongst the opinions of others that they quote is that of DiGuglielmo (1925) who considered that the megakaryocyte arises by differentiation from a "polykaryocyte". In the view of Dameshek and Miller, the polykaryocyte is probably identical with the osteoclast; and the osteoclast is an undeniably multinucleated cell. DiGuglielmo's opinion was supported by several workers - all Italian like DiGuglielmo himself - but rejected by many others, not all Italian. The opinion held by Dameshek and Miller, and by all other modern haematologists whose works I have consulted, is that the megakaryocyte does not exist in multinucleated form: its nucleus is always single and in varying degree lobulated.

The alternative hypothesis already referred to was one put forward by Howell and Donahue (1937). These workers argued, from experimental observations in the cat, that megakaryocytes are a physiological component of the lung, arising by differentiation from certain myeloblastic cells which they claimed to have identified in the pulmonary capillaries, and that platelet production therefrom is a normal occurrence. Their arguments, and there were many, did not carry conviction, and were adequately refuted a few years later by Jordan (1940). Amongst Jordan's illustrations

is one showing fragmentation of a megakaryocyte producing the appearance of "smaller spheroidal nuclei in close series" in a pulmonary capillary - the type of arrangement that might well be misinterpreted in the lungs during pregnancy as that of a particle of syncytial trophoblast.

The view that these chromatin clumps in the lung are in fact effete megakaryocytes that have been swept from the bone marrow rests mainly on evidence that is purely morphological: that is, the structures in the lung have a similar microanatomical appearance to other structures seen in the bone marrow and known there to be megakaryocytes; and partly on evidence by exclusion: that is, in the absence of any other suitable cellular candidate that might explain the findings in the lung, the megakaryocyte hypothesis is the best available. There is however in further support, the well-recognised fact that megakaryocytes can on occasion be seen in the peripheral blood (Whitby, 1948) so that, on the whole, the hypothesis is reasonably well founded. Additional evidence of a histochemical type would clearly be welcome as a "cross-check" but would obviously be difficult to obtain in an object that is virtually a naked nucleus with little or no cytoplasm with which to display tinctorial properties.

One histochemical difference does exist between syncytium and the megakaryocyte - but only the

megakaryocyte that is healthy and present in the bone marrow. Alkaline phosphatase is present in increasing amount in the syncytium from mid-term onwards (Dempsey and Wislocki, 1947) but is absent from the cytoplasm of megakaryocytes in the bone marrow (Wislocki and Dempsey, 1946). This difference is not difficult to demonstrate in appropriate material. Unfortunately the large "cells" which we call megakaryocytes in the lung are a different matter - for the reason just mentioned, that they rarely bear more than a marginal thread of cytoplasm, even if that. I have searched very many sections of "pregnancy" lung, appropriately fixed in chilled acetone, in the hope of finding together in the one section particles of syncytium and megakaryocytes with cytoplasm, so as to demonstrate simultaneously the difference in phosphatase content - but so far without success. The megakaryocytes have always been virtually naked nuclei, stripped too completely of their cytoplasm for histochemical use. The matter, it is true, is not one of crucial importance for the form of the placental giant cell is usually so unmistakable. Nevertheless, one regrets very much the nudity of the intra-pulmonary megakaryocyte.

The nature of the other types of nucleated structure found within pulmonary blood vessels during this investigation, those covered by the definition

given for the Type III structure, that is, multinucleated cells, may now be considered.

Multinucleated Cells: Placental Cells and Others

Cells included under the definition for Type III structures were seen in pulmonary vessels both in the pregnancy series of 120 cases and in the control series of 100 cases. As suggested in my 1952 communication, this would appear at first to cast some doubt on the specificity of the multinucleated cells seen in the lungs of pregnant women and claimed to be of placental origin. In fact it does not. Further study of the morphology of the multinucleated structures seen in both series has shown that with few exceptions the type that is seen in pregnancy has a remarkably constant and quite characteristic appearance.

Typical examples of this kind of cell are shown in figures 15 to 25. They are composed of a mass of closely packed, spherical nuclei of approximately equal size and some 10 microns in diameter, lying in a background of cytoplasm that varies in amount but rarely forms more than a narrow rim. Such masses are clearly multinucleated, not multilobular, and are found always within blood vessels. Comparison of the cells in these illustrations with those depicted in Schmorl's monograph (my figure 1) shows clearly that they are of the same type. When cells of this type

are as well preserved as those shown in these illustrations their appearance is quite distinctive. In fact, if sections of "pregnancy" lung are included unlabelled in a random group of lung sections, it is always possible to pick them out correctly from such a mixed group provided that they contain structures of this kind. This can be done with complete reliability after only a short acquaintance with their morphology.

These cells are peculiar to the lungs of pregnant women. Multinucleated masses of this type were never seen in my control sections from the lungs of non-pregnant subjects, nor have I seen them since in any other sections of lung in these circumstances.

It is in practice very much easier to recognise multinucleated cells of this kind under the microscope than to frame an exclusive definition whereby they could be recognised by other workers unacquainted with them. In fact, for structures possessing such a distinctive morphology, a completely exclusive definition is unnecessary. The nature and origin of these cells will be discussed presently, but one may anticipate the outcome by saying that they are undoubtedly placental cells. Therefore, the term "Type III structure of pregnancy" need not be used.

It is well to note, however, that the characteristic placental cells illustrated in these

figures are fully developed or at any rate well-preserved forms that have presumably arrived only recently from the placental site. Like any other nucleated tissue, they are liable to suffer degenerative change, manifest as nuclear pyknosis of varying degree. Placental cells of this more degenerative type are shown in figures 26 to 29. Sometimes, therefore, in a lung containing "healthy" placental giant cells there will be seen other structures, similar in form but, because of nuclear pyknosis, difficult to recognise as such with certainty. In practice this happens relatively infrequently: it is rare for every nucleus - and there may be fifty or more - in such a structure to be completely pyknotic; but difficulty does sometimes arise when a small cell of this type reaches the stage of complete nuclear pyknosis with apparent fusion of the nuclear chromatin into a multilobular mass. It then becomes difficult to distinguish from a megakaryocyte. The nucleated mass shown in figure 29, seen in the lung of a recently delivered woman, may be compared with that shown in figure 30, seen in the lung of a man with bronchopneumonia. One is almost certainly of placental origin, the other almost certainly a megakaryocyte; yet there is some similarity. The fact remains, however, that border-line examples such as this are few in the lung in

pregnancy. So long as one accepts as peculiar to pregnancy only structures that are multinucleated and not multilobular, confusion with megakaryocytes will rarely arise.

The multinucleated masses that were seen in the control series of lungs are of very varied appearance and lack altogether the characteristic arrangement of nuclei and cytoplasm seen in the placental cells. In fact, their main purpose has turned out to be that of emphasising just how characteristic the placental giant cell is. Some of the forms that were seen are shown in figures 31 to 36.

The multinucleated mass shown in figure 31 came from the lung of an 80 years old man dead of ulcerative endocarditis involving the left side of the heart only. The most likely explanation for the appearance is, I think, artefact; the result of detachment and coalescence of vascular endothelium after death, and a variant of the artefact seen in its more familiar form in figure 32.

Figure 33 shows a multinucleated mass found in a woman of 73. She died of massive retroperitoneal haemorrhage from a highly vascular papillary adenoma of the kidney. Although the adenoma was regarded as histologically benign, the particle of tissue illustrated here was almost certainly derived from it. This particle shows some similarity to a typical

placental giant cell.

The apparent embolus in figure 34 came, like that in figure 29, from a man dead of bronchopneumonia following chronic bronchitis. Its nature is uncertain but it may be a portion of detached endothelium. It also has some resemblance to the placental type of cell. The clump of tissue seen in figure 35 came from a man of 63 dead of a massive cerebral haemorrhage. It is purely an artefact due to the plane of section's passing through the vessel near its bifurcation. It is quite unlike a syncytial mass.

The multinucleated structure in figure 36 is of interest in that it came from a 75 years old woman who died of bronchopneumonia, the ultimate result of an untreated chronic subdural haematoma, and whose lung also contained particles of bone marrow (one such is illustrated later). The particle of tissue seen here could thus conceivably be an osteoclast. The history of the original head injury was vague but she had fallen and "injured her ribs" on the day before admission to hospital, three weeks before she died. No fracture of rib was found at necropsy but there is still a fairly reasonable explanation for embolism of the lungs by bone marrow, either as single cells like the possible osteoclast here or as larger fragments. The mainly peripheral distribution of the nuclei in this cell is not seen in placental emboli.

Figure 37 shows a large cellular mass in a

pulmonary vessel of another pregnant patient, Case No. 108. It is clearly a particle of bone marrow and could hardly be mistaken for placental tissue. Its morphology may be compared with that of the rather larger embolus of bone marrow (fig. 38) seen by coincidence in the "control" lung of the patient just mentioned who had a subdural haematoma and a history of probably significant injury to bone. There is no doubting the similarity. What the explanation is for the presence of marrow in the lung of the pregnant patient, No. 108, is unknown.

In the case of another of the pregnant women in this series, Case No. 110, multinucleated cells other than placental cells were seen in the lung. These are shown in figures 39 and 40. They are easy to distinguish from placental cells since, firstly, they lie outside blood vessels, and, secondly, some of them contain clearly recognisable asteroid bodies. It is possible that on rare occasions a normal placental giant cell might erode the wall of its containing vessel and pass into the surrounding tissues - its malignant counterpart, as a metastasis from a chorion-epithelioma, naturally can - but this was never seen in any of my series of sections. In the examples illustrated here, either the nearest vessel wall is intact (fig. 39) or there is no vessel nearby (fig. 40). Furthermore, I have never seen in placental cells

asteroid bodies such as these. Such bodies are frequently seen in the giant cells of sarcoidosis, but this patient showed no evidence of sarcoidosis, and the true nature of these cells remains an unsolved problem.

Three of the patients in this series died from amniotic embolism, Cases No. 40, 114, 116. The pattern shown by the mucin and squames in many of their pulmonary arterioles is shown in figures 41 and 42. Vessels plugged in this way are easy to overlook but, again, their content is unlikely to be mistaken for placental cellular tissue (especially if use be made of the alcian blue/phloxin staining technique of Attwood (loc. cit.)).

It will be recalled that several of the early workers on the phenomenon of placental cell embolism of the lung - Jürgens, Klebs, Schmorl - claimed to have seen hepatic cells in the pulmonary vessels. So far as my own series is concerned, I have never seen undoubted hepatic cells in any of the sections. This has also been the experience of a colleague, Dr. H. D. Attwood, who has recently examined sections of lung from many pregnant patients in a search for cases of amniotic embolism. I can think of only one explanation for this discrepancy, namely, that the more refined histological techniques in use today have reduced artefact and allowed more accurate

identification of cells. It may be that the earlier workers were seeing clumps of monocytes; but, whatever the correct explanation, the discrepancy remains rather puzzling.

Two of the other obvious possible explanations for the appearance of multinucleated masses within the lung, clumped leucocytes and proliferative vascular endothelium in the pulmonary vessels themselves, were carefully considered by Schmorl and other early workers but rejected on good grounds - mainly for the reasons that no such clumped nuclear masses were to be found elsewhere in the body, as could reasonably be expected if they were composed of leucocytes, and that no areas of endothelial hyperplasia were visible in the lung. It may be noted, however, that plugging of vessels by hyperplastic endothelium of local origin has been seen in the lung since then - but under highly artificial conditions. Scott and Thatcher (1926) saw such vascular plugging in the lungs of doubly adrenal-ectomised rats dying after parenteral administration of various toxic agents such as egg albumin, bacterial suspensions and diphtheria toxin; but not in non-adrenalectomised control animals. Further experiments (Thatcher and Robinson, 1927) in which Indian ink was mixed with the albumin showed that the cells of the plugs, seen to be budding from the endothelial lining of the vessels, contained carbon and were therefore

phagocytic. From this these workers concluded that the cells were "endothelial phagocytes", thus agreeing with Foot (1925) whose arguments favouring the existence of endothelial phagocytes as a true entity are very convincing. It seems, therefore, that endothelium may well behave in this way sometimes and cause plugging of pulmonary vessels but I myself have seen no such activity in my own sections from the lungs in pregnancy.

The various arguments on the nature of the multinucleated cells vis-a-vis megakaryocytes I have already discussed. There remain to be considered, therefore, the various tissues at the placental site which can or conceivably could produce emboli in the lung - syncytiotrophoblast, cytotrophoblast, decidual stromal cells, decidual endothelial cells and the cells of "benign chorionic invasion".

Cells of Placental Origin: their Sources, Actual and Potential

Syncytiotrophoblast. Histological examination of the placental site makes it quite clear that this is the tissue that acts in almost every instance as the source of the multinucleated giant cells seen in the lungs of pregnant women. Typical masses of syncytium in the placenta are shown in figures 43 to 46. They present the same arrangement of closely-packed uniform

spherical nuclei as that seen in the pulmonary masses, and are in fact morphologically identical. Serial sections of appropriate blocks of tissue show that clumps of nucleated tissue of this kind lie freely in the intervillous maternal blood lake and could certainly be expected to escape into the placental venous sinuses and reach the general circulation, ultimately to be filtered out in the pulmonary capillary bed. As would be expected, degenerative change, including nuclear pyknosis, is seen more often and in greater degree when cellular masses like this lie in the lung than when they are still in the placenta: otherwise the range of morphological patterns is essentially the same at the two sites.

Cytotrophoblast. In my own series of sections I have seen within the vessels in only one case tissue that was probably of this type. Some of the cellular masses that were seen in this case (Case No. 97) are shown in figures 47 to 50. This finding is particularly interesting because the patient was pregnant with a hydatidiform mole; and it is in cases of this kind that cytotrophoblast would be most likely to enter the maternal circulation. From mid-term onwards the amount of cytotrophoblast covering the normal chorionic villus rapidly lessens until during the last months of pregnancy it is virtually absent. There is therefore a sound reason why the lungs of

women dying in the later months of a normal pregnancy should not contain particles of cytotrophoblast. In patients dying with a hydatidiform mole, on the other hand, not only does death usually occur during the first three or four months but the amount of trophoblast of both types in the placenta is almost always greatly increased, forming tenuously attached hyperplastic masses on the surface of the villi.

It is interesting too to note that the patient in the case illustrated here died from cardiac asthma, due mainly no doubt to her essential hypertension and failing left heart but very possibly augmented to some extent by blockage of pulmonary arterioles and capillaries with emboli of this kind. The number of emboli was not as great as in many other cases in my series but in no other case were the emboli so consistently large.

There are in the literature at least two accounts of a patient dying with severe respiratory embarrassment and with a hydatidiform mole still in the uterus (Hughes, 1930; Trotter and Tieche, 1956). In both cases the lungs had shown a flooding of the arterial vessels with masses of trophoblastic tissue. A somewhat similar but rather less convincing case was reported by Marcuse (1954), that of a patient who complained of shortness of breath during the sixth month of pregnancy and died with the signs and symptoms of asphyxia soon after admission to hospital. Necropsy

showed a healthy foetus and placenta in situ. Microscopically the lower lobes of the lungs contained many small infarcts associated with the presence of syncytial cells and hyaline thrombi of uncertain type within the arterioles and capillaries. I myself have not seen a case of this severity but the signs and symptoms in one of the patients in my series, Case No. 105, were such that placental embolism was seriously considered in the differential diagnosis. This patient, in her eighth pregnancy, had been treated continuously with hexamethonium compounds from the seventeenth week of pregnancy for severe hypertension. Tachypnoea became evident during the thirty-fifth week, and the patient's condition worsened, with increasingly severe respiratory embarrassment and cyanosis, until death six days later. Examination of the lungs after death, however, showed only scanty syncytial giant cells but the characteristic gross and microscopic appearances of the so-called "hexamethonium lung". Full details of this case have been published elsewhere (Park and Cockersole, 1956: see also Appendix III).

It is clear from Schmorl's monograph that he saw tissue of apparently cytotrophoblastic type in the lungs of some of his original cases but his illustrations depict giant cells only of syncytial origin.

Decidual tissue. It is rare for decidual tissue to

appear in the lung, at least in large enough amount to be recognisable as such, but it does occur. What seems to be the first recorded example was described recently by me (Park, 1954). It was discovered in sections from one of the patients in the present series (Case No. 13), and a reprinted account of the structure of the tissue and an assessment of its significance are submitted in Appendix III. As will be seen from that account and from the original photomicrographs reproduced here as figures 51 to 54, there seems to be no doubt on grounds of pure morphology and histochemical reactions that the tissue is indeed decidua. There was nothing particularly unusual in the history of this patient's pregnancy and terminal illness to distinguish it from many others in the series, and no reason therefore to regard the decidua per se as having produced any particular clinical effects.

Since this case was reported, I have found a further example of the phenomenon also in one of the patients in this series (Case No. 107). The histological appearances of the focus of decidua in this case are shown in figures 55 and 56. The section in figure 56 has been stained to show the reticulin pattern. As in the earlier case (fig. 54), the reticulin fibres are seen to enclose individual cells. This is characteristic of normal intrauterine decidua, and is an important criterion of distinction

from cytotrophoblast. Cytotrophoblastic cells, like other epithelial cells, are never enclosed individually by reticulin fibres. There is again nothing especially unusual in the clinical data of this case to mark it out from many other cases in the series.

Following the publication of my original case-report, two further accounts of the finding of decidual tissue in the lung have been recorded, one by Hartz (1956), the other by Lattes et al. (1956). In Hartz's case, a patient of 24 years with mitral stenosis, dying of cardiac failure in the fourth month of pregnancy, the histological appearances were evidently rather similar to those in my own two cases - a mass, 500 microns in diameter, composed of large cells up to 30 microns across, lying within the pulmonary parenchyma close beneath the pleura. I have not seen the actual sections in this case but Hartz's illustrations show morphological patterns certainly similar to mine. In the case described by Lattes and his colleagues the decidual tissue produced a much more florid picture, both clinically and histologically. It caused symptoms, haemoptysis and pain in the chest, which neither of my examples nor that of Hartz achieved, and was demonstrable radiologically. The patient, aged 34, had had intermittent haemoptysis for almost three years before

being admitted to hospital with a threatened abortion, and a complaint of pain in the right side of the chest, in the third month of pregnancy. Radiology showed a nodular opacity in the right middle lobe. Partial lobectomy one month later revealed within the parenchyma of the lung a solid, well-circumscribed, pale mass 18 mm. in diameter. Sections showed it to be composed of typical decidual tissue, this time, however, including glands of endometrial type. Through the kindness of Dr. Lattes I have been able to examine some of the sections of this "deciduoma", and the appearances are most striking. One minor point, but a rather puzzling one, is that the well-developed glands within the decidual mass show no resemblance at all to "pregnancy glands" such as one frequently sees in the uterus along with a decidual stromal reaction as well developed as this was. This point is clearly shown in Dr. Lattes's illustrations. He has no explanation to offer for this apparent refractoriness of the glands towards the pregnancy hormones: nor have I.

The presence of decidual tissue in the lung is a phenomenon of great interest that raises many questions:

Could it arise by coelomic metaplasia, of the visceral pleura, rather than by vascular

spread from the uterus?

Does it arrive as such during pregnancy or does it arrive originally as a particle of endometrium (i.e. metastatic blood-borne endometriosis) which remains dormant until stimulated by the hormonal climate of pregnancy?

Is continued growth possible, and to what extent - can there, in fact, be a true deciduoma malignum, albeit in the lung?

I have discussed these questions at some length in my case-report and can summarise the position at present thus:

Decidual tissue does on occasion appear in the lung during pregnancy and, in the four examples known to exist so far, forms a relatively large multicellular mass.

The size of the masses indicates that cellular proliferation does occur: the presence of occasional mitotic figures amongst the cells supports this view.

Whether true neoplastic behaviour can develop is not known. Such tissue may have a restricted growth potential, manifest only during pregnancy.

Origin by blood-borne escape from the

uterus, either as endometrium before pregnancy or as decidua as such during pregnancy, seems likelier than origin by coelomic metaplasia.

Continued growth of trophoblast within the lung could not produce the appearances seen in the four examples quoted.

Some further mention will be made of decidual embolism of the lung in connection with placental vascular endothelium.

Placental vascular endothelium. This tissue requires consideration as one of the possible sources of multinucleated masses within the lung for the reason shown in figures 57 to 60. This is a very striking appearance and is seen quite frequently in endometrial curettings containing decidua from cases of abortion. The blood sinuses are lined completely or incompletely by large pale cells of soft appearance (with haematoxylin staining they have a pale pastel blue shade). Cells of the same kind are present also in the tissue surrounding the wall of the sinus, throughout the thickness of the wall itself, and as clumped masses lying free within the lumen.

This appearance was well recognised by early workers on placental structure but rarely excites comment nowadays. Opinions have varied on its interpretation. Cullen (1900), in his classical

work, "Cancer of the Uterus", included a very faithful drawn illustration of the tissue pattern, calling it "Typical decidual cells derived from the endothelium of the blood-vessels" (Case Gyn.-Path. No. 754). Another interpretation was that of Johnstone (1914) who, in his very fine article on early stages of placentation, clearly illustrated and described this intravascular burgeoning of tissue. He said, 'In one area my first ovum shows ... a blood space lined with "syncytium". The cells have lost their outlines and the nuclei are elongated and pale. The protoplasm contains the brownish granules which are found throughout the syncytium in this specimen. I believe, however, that this tissue is not syncytium in the sense of plasmoditrophoderm, but rather a degeneration of the maternal tissues lining the space. In other words, it corresponds to what ... Jung describes as "symplasma matermum conjunctivum".' This view was in accord with that of the observer who first described the occurrence, Friedländer (1876): he considered that the large cells lining and growing into the sinuses were derived from the connective tissue around the vessels, that is, the decidua. This interpretation was supported the following year by Leopold (1877). Some time later, Lubarsch (1893), in trying to establish the nature of giant cells in the lungs during pregnancy, put forward the view that

decidual cells might escape from the placenta to the lungs but did not discuss these appearances in the decidual sinuses. This possibility was considered also by Schmorl (1893) in the "differential diagnosis" of the giant cells he had discovered but he thought the cells unlikely to be of decidual origin, mainly for the reason that decidual cells normally lie outside the blood vessels. He had not seen, or at any rate did not mention, the striking tissue pattern described by Friedländer: had he seen it he would almost certainly have considered at greater length than he did the likelihood of a decidual origin for the cells he had discovered.

The same striking change in the vessels was certainly noticed by Veit (1905). He agreed with Friedländer that the cells had "wandered into" the placental sinuses but thought them much more likely to be Langhans' cells: that they might be decidual cells or swollen endothelium he found difficult to accept, but did consider that clumps of syncytium might sometimes behave in this way. In my own sections it has usually been possible to recognise both Langhans' cells and syncytium as such when they have grown into and are lining the sinuses. The kind of appearances produced are shown in figure 61.

One further interpretation was advanced by Leusden (loc. cit.). Although it was proposed many

years before the views of Veit, I have postponed mention of it till now because it raises a further question, namely, the significance in this context of the tissue pattern that became widely known later as "benign chorionic invasion". This is a well-known phenomenon – permeation of the decidua by large cells of varying shape, generally considered rightly or wrongly to be cells of the trophoblast, that have migrated into the decidua from the surface of the villi or the trophoblastic shell, presumably by amoeboid penetration: a detailed microanatomical description is not called for here. Leusden made a curious error in thinking that the decidua-like cells that Friedländer described as lining the placental sinuses were the giant cells of benign chorionic invasion, and therefore trophoblastic in nature. Leusden then argued that, since the Friedländer type of cell must be regarded as having wandered into the decidua from the surface of the villi, it accordingly must have the same origin as those cells that entered the blood stream directly from the intervillous space. A distinction between the two could therefore not be made. His argument was sound but his premise wrong: Friedländer did not regard his cells as chorionic.

There is good evidence that vascular endothelium in the maternal placenta can undergo remarkable hyperplasia in some of the lower animals. Maximow (loc.

cit.) mentions the formation in the rabbit of an endovascular plasmodium or, quoting an earlier worker, the "couche plasmodiale endovasculaire" of Duval; while the occurrence of a very similar pattern is well recognised in placentation in the rhesus monkey. Figure 62 is a reproduction of an illustration published originally by Wislocki and Streeter (1938) showing a blood vessel in the decidua compacta of a rhesus monkey at the 29th day of pregnancy. The opinion of these observers (whose article contains a very useful summary of the various interpretations of what they call epithelioid cytomorphosis of placental vessels) is that the proliferative tissue is probably endothelial in nature.

I myself have never seen, in human decidua, cellular proliferation of the degree known to occur in the monkey, nor have I found any description of it by other workers: one may reasonably doubt whether it occurs to anything like this extent, if at all, in the human. From my own interpretation of the appearances in the human (figures 57 to 60), I would regard the cells within the sinuses as being of decidual type, thus agreeing with the original view of Friedländer. This opinion is based solely on interpretation of the microscopic anatomy, but the persistence of obviously unaltered endothelial cells immediately beside the swollen cells; the lack of cells of intermediate

appearance in these areas; and the great similarity of the cells in the lumen, and of those on and in the wall, to those forming the decidual stroma make it hard to believe that the endothelium of the sinuses is really the prototype tissue.

If cells of this type were to reach the lung singly it is very doubtful whether they would be identifiable as such. Were they to reach the lung in clusters they should be recognisable, but I have never seen them: the only cells within pulmonary vessels that looked at all like them were those seen in the case of the patient with a hydatidiform mole, where cytotrophoblast seemed a much likelier explanation. Yet their disposition in the placental sinuses suggests strongly that they must escape into the venous blood stream sometimes: either, then, they reach the lung but shrink on the way and become morphologically indistinguishable from the characteristic clumps of syncytium - which is rather difficult to believe; or they are rapidly destroyed in the blood stream. Destruction is probably their fate: but if the decidual tissue seen in the lung by Hartz, Lattes and myself had arisen by blood-borne escape from the uterus during pregnancy, as seems likely, it is tempting to accept a vessel such as those shown in figures 59 and 60 as the starting point.

There remain to be mentioned two further aspects

of the phenomenon of placental tissue's appearance in the lung: the possible confusion of such tissue with metastatic cells from a chorionepithelioma in the uterus or uterine tube, and the matter of escape to the lungs of whole chorionic villi.

Metastatic chorionepithelioma. The statement is sometimes made that particles of trophoblast appearing physiologically in the lung may be mistaken for small metastatic deposits from a chorionepithelioma. The morphological appearance of fragments of chorionepitheliomatous tissue within a pulmonary vessel is shown in figures 63 and 64. That confusion might well arise between cellular masses of this kind and cellular masses similarly derived from a hydatidiform mole is certainly understandable - the distinction is often difficult enough or even impossible to make in tissue obtained directly from the uterus itself. These masses are, however, quite different in appearance from the characteristically clumped multinucleated masses of syncytial origin illustrated earlier (figures 48 to 50), and it is difficult to believe that confusion could arise between these two types of structure, certainly in the mind of anyone who has a more than minimal acquaintance with the phenomenon.

The question is obviously one that has little clinical significance.

Chorionic villi in the lung. The remaining question, whether chorionic villi escape to the lungs during pregnancy, is also of essentially academic interest only (at least, in so far as it is considered apart from the escape of placental tissue in general) but my own experience has been so at variance with current teaching on the matter that some comment is necessary. There is hardly a standard text on obstetrics and gynaecology that does not state that escape of chorionic villi to the lungs is a common, if not constant, occurrence during every pregnancy.

We may recall here the views of Schmorl who, in his later paper, said that he had seen whole villi in the lungs but rarely, and only in cases of long continued labour associated with mechanical damage to the placenta, namely, in cases of manual removal of the placenta, placenta praevia, and rupture of the uterus. A further relevant fact is that, so far as my reading has gone, the only other circumstances in which chorionic villi had been seen in the lungs up to that time, or have been seen in the lungs since, were those in which the uterus had contained a hydatidiform mole, usually of deeply invasive type, as, for example, in the already quoted cases of Solowij and Krzyszkowski (loc. cit.) and of Poten and Vassmer (loc. cit.). It is not surprising that the combination of degeneration of the villi and massive extravasation

of blood such as characterises the deeply invasive mole should result sometimes in the entry of detached villi into the blood stream.

I have seen chorionic villi in the lungs twice: in neither case was the pregnancy normal; in both, the uterus had contained a deeply invasive and destructive hydatidiform mole. These cases are not included amongst my series of 120. One of them was filed in the series of some 400 cases of chorion-epithelioma and hydatidiform mole that comprise the Mathieu Memorial Chorionepithelioma Registry (supervised by Dr. Emil Novak), and the other amongst the equally large volume of similar material at the Armed Forces Institute of Pathology, Washington. Each of them was regarded by the Curator of the collections as something of a curio - an attitude that supports my own belief that the appearance of villi within the lung, far from being a common occurrence, is an extremely rare event. I have never seen it in the lungs from cases of normal pregnancy, nor have I met any other observer who has.

2. Frequency of occurrence of trophoblastic tissue in the lungs of 120 pregnant, parturient and puerperal women

Particles of tissue identifiable as trophoblast according to the morphology described in the last section were found in sections of lung from 53 of the 120 patients, i.e. an incidence of 44%. This is, at first sight, a surprisingly low incidence in view of the generally held belief that escape of trophoblast to the lungs occurs probably in every pregnancy. However, a partial explanation at least would seem to lie in the limitations of the material available in the present series. As already mentioned, in ninety one cases only one block of tissue was available; in nineteen cases two to five blocks; and in ten cases six blocks or more.

When one analyses the numbers of cases "with" and "without" trophoblast in these three groups, the picture shown in Table A emerges*. Of those patients represented by only one block of tissue, 42% showed trophoblast in the lung; of those represented by two to five blocks, 42% also showed it; while for those represented by more than five blocks 70% showed it. Experience with a few further cases examined after the present series was "closed" at 120 cases confirms the

* Tables are in Appendix II.

obvious implication behind these figures, namely, that the greater the number of blocks and sections of tissue examined, the greater the chance of finding a particle or particles of trophoblast. It is thus probably true that, if one had been able to examine more than five blocks of tissue in all cases, the incidence of trophoblast in the lung would have been of the order of 70%; and if ten or twenty blocks or more, possibly over 80%. There is regrettably no record of the amount of tissue that Schmorl used in achieving a figure of 80% for the proportion of patients showing trophoblast in the lung but my own findings suggest that he must have examined something of the order of ten blocks per patient at the least.

This analysis shows that the validity of the figure indicating the number of patients in any series such as this whose lungs are found to contain trophoblast is inversely proportional to the number of blocks of tissue examined. It appears to be true, therefore, that an accurate figure for the simple number of "positive" or trophoblast-containing cases in a series like this is likely to be obtained only if five, or preferably ten blocks of lung, and several sections from each, have been examined. Two further points are, however, directly relevant here:

Analysis of such cases as do show trophoblast

in the lungs, and any conclusions derived from such an analysis, will remain valid.

Examination of cases in the present series has shown that, if no trophoblast is found in six sections from one block of lung of average sectional area, about 200 sq. mm., the chances of further blocks yielding a trophoblastic index (the average number of particles of trophoblast in 1000 sq. mm. of lung) greater than 1 are extremely small.

It is therefore possible that those patients classified as having a trophoblastic index of 0, might, had more material been available, have had an index of 1: but the chances that they might have had an index greater than 1 are negligible.

3. Factors influencing the frequency of occurrence of trophoblastic pulmonary embolism

There are three factors that would be expected, a priori, to have some influence on the frequency with which trophoblast passes into the lungs from the placental site: the occurrence of uterine contractions, separation of the placenta, and the gestational age of the pregnancy. A fourth factor that might be expected to have some influence and whose effect can be analysed is the type of disease that caused death. It has generally been maintained, following Schmorl's original view, that eclampsia is the condition above all in which trophoblast may be seen in the lungs in great amount.

Since all four factors apply in the case of each patient, it is not easy to decide which has played the main part in causing trophoblast to appear in the lungs. For example, in a patient who dies of eclampsia with convulsions within twenty-four hours of separation of the placenta during the eighth month of pregnancy, and whose lungs contain trophoblast, it is difficult to decide which is the main factor causing the displacement of trophoblast - the eclampsia, the convulsions, the separation of the placenta or the fact that death occurred before the expected day of delivery. The only way by which one can hope to gain some idea of the relative importance of these various

agencies is to carry out a multifactorial type of analysis, subdividing the patients into various groups. The manner of the grouping will be described first, and the method of analysis and its results thereafter.

Uterine contractions, normal and abnormal

There are few observations in the literature concerning the part played by the birth act itself in causing particles of trophoblast to leave the placental site and enter the maternal blood stream. Kassjanow (loc. cit.) considered that the presence of cellular emboli in the lung was not necessarily dependent on the act of parturition since he had seen them in a patient dying undelivered at the fifth month of pregnancy; while Dunger (loc. cit.) reported that Schmorl had seen trophoblastic emboli in the lungs of only three out of twenty-five patients dying undelivered. In more recent times, Wiener (1946) considered that greater rises in rhesus antibody titre seen after parturition than during the course of a pregnancy were to be explained by the greater escape of foetal erythrocytes (contained "in chorionic villi") during parturition than during the pregnancy up to that time.

In patients who die during pregnancy, parturition or the puerperium, the amount or degree of uterine contraction may naturally vary widely. For purposes of analysing the part played by uterine contractions as such, the 120 cases in the present series have

first been divided into three groups:

Group aa: cases where uterine contractions were absent or minimal - as in some of the undelivered patients ("Contr. 0")

Group bb: cases where uterine contractions were excessive; that is, cases of eclampsia with convulsions, and cases of prolonged labour not associated, so far as one could deduce from the clinical data, with primary uterine inertia ("Contr. ++")

Group cc: the remainder, with "ordinary" contractions ("Contr. +")

This subdivision is shown in Table B. The numbers of patients in each of the three groups, and the proportions showing trophoblast in the lungs, are: 4/17 (24%), 22/35 (63%), and 27/68 (40%). Table B shows also a measure of the amount of trophoblast in the lungs of those patients who showed it, i.e. the trophoblastic indices.

Separation of the placenta

The part played by separation of the placenta in causing trophoblast to be displaced into the maternal circulation is clearly difficult to dissociate from that played by the uterine contractions that precede the separation, but some idea of the relative contributions made by the two factors may be gained by dividing the

cases in another way:

Group dd: cases where the patient died before separation of the placenta ("unsep.")

Group ee: cases where the patient died within twenty-four hours of separation of the placenta ("less than 24 h.")

Group ff: the remainder, dying later ("more than 24 h.")

This grouping is shown in Table C. Only thirteen of the fifteen undelivered patients in the series are included in Group dd. In the other two patients (Cases Nos. 107 and 120), although the infant was still in utero, separation of the placenta had occurred.

Gestational age of the pregnancy

Whether or not it is appropriate that the term "invasiveness" should be used to describe the process whereby the ovum becomes embedded in the uterine wall - a matter which has been discussed elsewhere by Park and Lees (1949) and, in reply, by Javert (1951) - there is no doubt that the embedding and early growth of the ovum is attended by a great deal of disruption of tissue at the junctional zone. It may be assumed that the process of disruption continues at a gradually decreasing rate but over a gradually increasing area until the tissues at the placental

site achieve a state of relative stability at about the third or fourth month of pregnancy. It might be expected, therefore, that the production of penetrating particles of trophoblast, and their displacement to the lung, would be greater during the earlier months of pregnancy. There is admittedly the possibility that in the early months the potential increase in the number of emboli reaching the lung would be offset by the smaller area of the placental bed from which they could arise, but to what extent these two factors cancel each other there is no direct means of knowing.

In order to analyse the effect, if any, of the duration or gestational age of a pregnancy upon the frequency of pulmonary embolism by trophoblast, the cases can be divided in another way into two main groups: those patients dying before the expected day of delivery (E.D.D.), and those dying on or after the expected day of delivery. The proportion of patients in the first group, before E.D.D., whose lungs contained trophoblast is 16/40; and in the second group, after E.D.D., 37/80. The proportions are almost equal. (These groups are shown in the tables of classification of causes of death, Tables Ea and Eb).

This analysis, however, gives no information on the frequency with which trophoblast was seen in the

lungs at various stages of pregnancy in those patients who died before term: more information is required before one can try to answer the question, for example, whether trophoblast is seen in the lung more often during the fourth or fifth month of pregnancy than during the eighth or ninth. In an attempt to produce information of this kind the cases have been subdivided into those dying during the first, second and third trimesters, and on or after E.D.D. ("1st trim.", "2nd trim.", "3rd trim.", "E.D.D. and beyond"). These data are shown in Table D.

The different diseases causing death

The list of diseases from which the 120 patients died is shown in detail in Tables Ea and Eb. For purposes of more direct comparison and analysis the cases have been divided further into four main groups: haemorrhage and shock, eclampsia and pre-eclampsia, sepsis, and "other". These groups are shown in Table F. Two points of indirect interest emerge from this table, (a) puerperal sepsis caused the smallest proportion of deaths, as would be expected since the series covered the years 1938 to 1955, (b) of patients dying before the expected day of delivery, the highest proportion died from conditions other than haemorrhage/shock, eclampsia/pre-eclampsia and sepsis.

Since eclampsia is characterised by convulsions

apt to induce an undue degree of uterine contraction, the high frequency with which trophoblast was seen in the lungs in this group of cases may be a non-specific effect due to the convulsions and excessive uterine contractions, not to the eclamptic disease as such. To assess this alternative it will be appropriate,

(a) to analyse more finely the group of "excessive uterine contraction" in Table B (Group bb), comparing the amount of trophoblast in the lungs of patients dying with eclamptic convulsions with that in those dying after prolonged labour; and

(b) to compare the amount of trophoblast in the lungs of those patients who had eclampsia and those who had pre-eclampsia.

For the first of these analyses the data are available, as indicated, in Group bb of Table B. This group, of "excessive uterine contraction", contains fifteen cases of eclampsia with convulsions (Subgroup gg) and twenty cases of unduly prolonged labour (Subgroup hh). These two subgroups, with the relevant trophoblastic indices, are shown separately in Table G.

For the second of these analyses the data are shown in Table H where subgroup jj consists of patients with true eclampsia and convulsions ("Ecl.") and subgroup kk those with pre-eclampsia and no history of

convulsions ("P.E.T.").

Analysis of the data in Tables B to H

In order to analyse the interrelationships between the various factors already mentioned that might be expected to influence the amount of trophoblast appearing in the lung, it is appropriate to construct manifold tables wherein the various groups of patients are broken down into smaller subgroups accordingly as they share various characteristics. Text-table VV shows the distribution between patients with pre-eclampsia and eclampsia and the gestational age of the pregnancy.

Text-table VV

	Ecl. + P.E.T.	Others	All	Proportion with trophoblast in lungs
1st trim.	1	8	9	56%
2nd trim.	2	14	16	31%
3rd trim.	5	10	15	40%
E.D.D. and beyond	24	56	80	46%
All	32	88	120	
Proportion with tr. in lungs	56%	40%		44%

It will be seen that patients with eclampsia and

pre-eclampsia are disproportionately frequent in the "E.D.D. and beyond" group. Therefore, if toxaemia per se has any effect in promoting the appearance of trophoblast in the lungs, it will have an undue influence on cases in this later group wherever they appear in the analysis.

The two other main factors that might be concerned in causing escape of trophoblast are the strength or degree of uterine contraction and the time of death relative to separation of the placenta (unseparated; less than 24 hours; more than 24 hours). The distribution in the case of these factors is shown in text-table WW. This table shows also, in brackets, the numbers of cases of pre-eclampsia/eclampsia within the different cells. Groups aa to ff are the original groups from Tables B and C.

Text-table WW

	Contr.0 (Group aa) (E)	Contr.+ (Group cc) (E)	Contr.++ (Group bb) (E)	All	Proportion with trophoblast in lungs
Unsep. (Group dd)	10 (2)	2 (0)	1 (1)	13	23%
> 24 hr. (Group ff)	7 (0)	45 (12)	16 (7)	68	31%
< 24 hr. (Group ee)	0 (0)	21 (3)	18 (7)	39	74%
All	17	68	35	120	
Tr. in lungs	24%	40%	63%		44%

The proportion of patients dying within twenty-four hours of separation of the placenta whose lungs were seen to contain trophoblast was 74%. The difference between those patients who died soon after separation of the placenta and the remainder is highly significant ($P < 0.001$). The difference between the values for the three groups of degrees of contraction (24%, 40%, 63%) is also significant but at a less high level (P just < 0.05). The figure of 63% is, however, artificially high for the reason that eighteen of the thirty-five patients in the "excessive contraction" group died within twenty-four hours of placental separation.

In order to minimise the disproportionate effect produced by such cases as Case No. 118, where the trophoblastic index was 210, and others with indices of 60 and over, it was considered preferable to transform the values of the indices to their log. values. This was done so that the tests of significance, used to assess the amounts of trophoblast seen in the lungs in the various groups of patients, could be applied to a more nearly normal distribution than would be the case if the crude values were used. For purposes of applying these tests, the 120 patients are subdivided in the following way. Groups aa to ff refer, as before, to the original groupings in Tables B and C.

Text-table XX

	Mean trophoblastic index	Mean log.(T.I. + 1)	
1. Eclampsia and pre-eclampsia	15.7	0.68	t = 1.6
All others	5.7	0.38	0.1 < P < 0.2
Contr. 0 (Group aa)	1.8	0.20	
2. Contr. + (Group cc)	3.8	0.35	t = 2.07
Contr. ++ (Group bb)	18.9	0.76	0.2 < P < 0.5
Placenta unsep. (Group dd)	18.0	0.35	
3. Sep. > 24 hr. (Group ff)	2.7	0.29	t = 3.5**
Sep. < 24 hr. (Group ee)	13.9	0.79	P < 0.01
1st trim.	8.3	0.58	t = 1.32
2nd trim.	2.5	0.29	0.2 < P < 0.3
4. 3rd trim.	22.6	0.59	t = 1.25
E.D.D. and beyond	6.2	0.46	0.2 < P < 0.3
Total mean	7.9	0.45	
Standard deviation	22.7	0.599	

The mean log. values for each group have been calculated from the totals under "All" in text-tables VV and WW, but the tests of significance are based on comparisons between the subgroups within the cells in the body of these two tables. The figures chosen for tests of significance are the highest in each of the four groups. From these tests, the only significant difference found is the greater amount of trophoblast in the lungs of those patients dying within twenty-four hours of separation of the placenta. As has already been shown, the number of patients in this group whose lungs contained trophoblast was also significantly higher than that in any of the other groups.

When tests were applied to the marginal totals in text-table WW it was found that there was a significant difference between patients in the "excessive uterine contraction" group and the rest. When, however, allowance is made for the unequal distribution of cases in the body of that table, and the figures are analysed as indicated in table XX, the significance of the difference falls just below the 0.05 level. It is, however, possible that if a greater number of cases had been available the difference would have remained significant.

Of all patients with pre-eclampsia/eclampsia,

56% showed trophoblast in the lungs, with a mean trophoblastic index of 15.7. Both these values are higher than the averages for patients without pre-eclampsia or eclampsia but not significantly so by statistical standards. To gain some further information on the two questions whether eclampsia is a more potent producer of trophoblast in the lung than unduly prolonged labour, and whether eclampsia with its convulsions causes more displacement of trophoblast than pre-eclampsia, text-table YY has been constructed.

Text-table YY

	No.	Proportion with trophoblast in lungs	Mean T.I.	Mean log. (T.I. + 1)
"Ordinary" cases	68	33%	2.7	0.27
P.E.T. (no convulsions) (Group kk)	17	53%	6.5	0.55
Prolonged labour (Group hh)	20	65%	13.3	0.76
Eclampsia (convulsions) (Group jj)	15	67%	26.3*	0.76

(*Includes Case No. 118 with a trophoblastic index of 210)

From this table there is seen to be a gradation of effect from the "ordinary" cases, with a mean log.

value of 0.27, through pre-eclampsia (0.55), to both eclampsia (0.76) and prolonged labour (also 0.76). The values for cases of eclampsia and of unduly prolonged labour have emerged equal. This cannot be gainsaid, but the fact that three of the four patients with the highest trophoblastic indices, Cases Nos. 118 (T.I. 210), 112 (T.I. 75) and 117 (T.I. 60), all had eclampsia suggests that a larger series might have shown the excessive uterine contractions of eclampsia to be a stronger stimulus to escape of trophoblast than simple undue prolongation of labour. The difference between the "ordinary" cases and those with pre-eclampsia, though not statistically significant, at least suggests that toxaemia as such does promote the passage of trophoblast to the lungs, an effect which is augmented in eclampsia itself by the convulsions. The well-known degeneration or "premature ageing" shown by the placenta in eclampsia is no doubt also a contributory factor.

Trophoblast and megakaryocytes

One further matter was investigated that might possibly be related to the amount of trophoblast seen in the lung, namely, the numbers of megakaryocytes that appeared in the sections.

For each patient, as mentioned earlier, a "megakaryocytic index" was calculated as well as a trophoblastic index. The main reason for doing this was to see whether there was any relation between

the number of particles of trophoblast and the number of megakaryocytes seen simultaneously in the lungs. There is no obvious reason for expecting that increased amounts of trophoblast in the lung should be accompanied by increased numbers of megakaryocytes but one wondered whether, for example, uterine sepsis might cause both factors to rise, the sepsis causing both a loosening or breaking-up of any placental tissue that might not yet have separated from the uterine wall and, at the same time, hyperplasia of the bone marrow. The matter is simply investigated for the series as a whole by making a dot diagram, plotting the values for megakaryocytes against those for trophoblast. This is shown in figure 65a.

This figure shows that there is a general tendency for a high incidence of megakaryocytes in the lung to accompany a high incidence of trophoblast. Beside the dots representing the highest values of both indices I have inserted a letter indicating the group of diseases in which the patient concerned had been classified (H = haemorrhage, E = eclampsia, S = sepsis, O = other), and it will be noted that with two exceptions the highest values are accounted for by haemorrhage and eclampsia. This can be explained, at any rate for the "haemorrhage" group on the grounds that haemorrhage would lead to hyperplasia of the bone marrow and a consequent sweeping-out of

megakaryocytes, "caught in the rush", as it were; while the excessive haemorrhage from the uterus might have led to undue kneading of the organ with displacement of trophoblast. In the case of the "eclampsia" group it seems reasonable to suppose that the general systemic disturbance and severe exertion accompanying convulsions cause equally a vaso-dilatation in the bone marrow analogous to that accompanying any severe muscular exertion, and, because of undue uterine contractions, undue displacement of trophoblast. It is at first sight rather surprising that cases of sepsis do not figure more prominently in this diagram. The reason would appear to be that of the eighteen patients dying of sepsis only seven died within five days of delivery, by which time, as will be shown later, any trophoblast that might have been present in the lungs would have largely disappeared.

Since the data were available it was thought of interest also to see whether the number of megakaryocytes in the lungs of the pregnant patients differed appreciably from that found in the control series (enlarged for this purpose also to 120 patients). Figure 65b shows the numbers of patients in the two series, and their megakaryocytic indices by groups according to the size of the indices. It is seen that there tend to be more patients with higher

indices amongst the pregnant patients than amongst the controls. This is presumably again a result of bone marrow hyperplasia and is an interesting reflection of the fact that, as Pitts and Packham (1939) showed, the total nucleated cell count per c. mm. of bone marrow in pregnant patients is about twice that in nonpregnant females and in males.

4. The Fate of Trophoblastic Pulmonary Emboli

Although it has long been accepted that particles of placental tissue may normally reach the lungs of the pregnant woman, little is known of the behaviour and fate of these fragments of tissue beyond the belief that they probably always disappear entirely and cause no trouble. Some information may be gained on this question,

(a) from an examination of the lungs of experimental animals into whose lungs trophoblast has been introduced by intravenous injection. As mentioned on page 29 a series of experiments of this kind has been carried out: an account of the main results has already been given elsewhere (Park, 1957c);

(b) by a study of the structural variation shown by the trophoblastic particles themselves as they lie in the pulmonary vessels in the human; by noting the presence or absence of cellular reaction of whatever kind in the walls of these vessels and in the surrounding connective and parenchymal tissues; and finally by observing the rate at which emboli disappear from the lungs of the pregnant woman after separation of the placenta.

a. Evidence from experiments with animals

I have found no published information suggesting that embolism of the lungs by trophoblast occurs in any species but the human, and only one account of a systematic investigation of the matter; that of Maximow (loc. cit.) who was unable to find any placental tissue in the lungs of forty normal rabbits killed at various stages of pregnancy. This observation of Maximow is of interest in that the placenta of the rabbit has at one stage of its development a haemo-chorial structure which would provide some opportunity at least for the blood-borne escape of trophoblast. Yet, trophoblast appears not to escape; and perhaps the factor that promotes the escape of particles of trophoblast from the human placenta is its villous structure. Anthropoid apes also have a highly developed villous placenta: whether embolism of the lungs by trophoblast occurs in them also is, so far as my own search for information has gone, not known.

It seems probable, then, from the available evidence that trophoblast does not normally reach the lungs of pregnant mice, and I myself have seen none in these circumstances. However, it was considered that a study of the effects produced in the lungs by the experimental introduction of placental material

would give some information on the reactions of pulmonary tissue towards trophoblast, and the method of disposal of the embolic particles. There was also the hope, in the background as it were, that treatment of some of the animals with synthetic hormonal substances would so influence the pulmonary tissues as to support continued growth of the artificially introduced trophoblast. The administration of these hormonal materials was empirical to the extent that no attempt was made to simulate the naturally occurring behaviour of hormone levels in the normal pregnant mouse (for example, the mouse, like all but a very few mammals, does not secrete a chorionic gonadotrophin), yet not altogether empirical to the extent that, in the human, the behaviour of both embolic trophoblast and the pulmonary tissues, and their reactions towards one another, are almost certainly determined and controlled by hormonal factors of some kind.

Experiment I. Injection into normal non-pregnant animals

Twenty normal non-pregnant female mice were injected with placental emulsion and killed by cervical dislocation, one per day, at 2-day intervals thereafter. Placental pulmonary emboli were seen in those killed at 2, 4, 6, 8, 12, 14, 18 and 22 days

after injection but not in the others.

All emboli, whatever their size, showed some degree of degenerative change in the form of nuclear pyknosis, loss of cell boundaries, and fusion of cytoplasm into a granular mass. None showed evidence of active growth. Several 2-day emboli had the appearance seen in figures 66 and 67, a fine fraying of the surface suggesting a process of simple solution or lysis. Further sections of these particular emboli showed no covering of endothelium and no evidence of reaction in the underlying vessel wall. Other 2-day emboli are shown in figures 68 and 69. That in figure 69 is causing distortion of the wall of the vessel, but again there is little evidence of an active tissue response to the presence of the embolus. Blood has not leaked from the vessel at any point, a fact which suggests that any lytic property the trophoblast might have had has been inoperative. Figure 70 shows a 4-day embolus. It has a partial covering of flattened cells but the appearances here (and in further sections) suggest that these cells belong to the embolus and are not of endothelial origin. No ingrowth of capillaries from the vessel wall can be seen. A small 8-day embolus is seen in figure 71. It has been covered by endothelium and incorporated into the vessel wall. A much larger mass, eighteen

days old, is shown in figure 72. It is still recognisably cellular though most of its cells are pyknotic. Attachment to the vessel wall is restricted to a relatively small area but from its margins endothelium continues over the whole of the surface of the mass except for a small area where dissolution appears to be occurring. There is no capillary formation at the point of contact with the vessel wall, and no evidence of any surrounding inflammatory reaction.

II. Injection into hormone-treated non-pregnant animals

Four groups of twenty animals were used. The animals in each of three groups were treated with oestrogen, progesterone, and gonadotrophin as described: no hormone treatment was given to the fourth group. All were injected with placental emulsion on the same day with material from the same donor animal. One animal in each group was killed by cervical dislocation two days after introduction of the emulsion, and a further animal from each group killed at 2-day intervals thereafter.

Examination of the lungs produced the results shown in figure 73. Particles of injected tissue were seen more frequently and at later dates after injection amongst the gonadotrophin-treated animals

than amongst those in the other groups. The fact that emboli were seen in 9 out of 20 animals in this group compared with 7, 6 and 7 in the other three groups is not significant; but the persistence of emboli to a later date at least suggested that this hormonal treatment tended to promote survival of the emboli. The morphological appearance in two of these animals, those killed at twelve and thirty-eight days, seemed at first to provide further suggestive evidence.

In the 12-day animal the mass of tissue was relatively very large (fig. 74), as were its healthy-looking component cells which did not resemble young fibroblasts either individually or in their general disposition. The original endothelial lining of the vessel was still intact around most of the mass though in close contact with it at several places, and, where there was contact, neither ingrowth of capillaries nor inflammatory cell reaction was evident.

The cellular mass in the 38-day animal (figure 75) was rather similar in appearance though its texture varied from place to place. This figure shows a long narrow band of tissue filling one limb of the vessel, and an almost spherical mass occupying the "bay" at the top of the figure. In fact, serial sections showed the two masses to be continuous. The looser texture of the spherical part may be due to its having

had more room for expansion.

The question posed by the clumps of tissue in both these animals was: are they fibroblastic, perhaps organising thrombi, trophoblastic or decidual? The considerable similarity of part of the tissue in the 38-day animal to decidua is shown in further sections in figures 76 and 77. In the case of both animals the tissue failed to give convincingly positive reactions with connective tissue stains, thus confirming the impression gained from the haematoxylin and eosin sections that neither mass as a whole resembled fibrous tissue very closely. A distinction can be made between trophoblast and decidua, which may at times resemble each other greatly otherwise, by noting their reticulin pattern (see, for example, my earlier comments on decidual tissue in the human lung). Here, reticulin staining showed in fact that in both cases the pattern was that of decidua, not trophoblast. The reticulin pattern of the 38-day mass is shown in figure 78. The hope, therefore, that artificially introduced trophoblast might be induced to grow in the lung of the mouse was not fulfilled; but it was of some interest none the less, particularly in view of its occurrence in the human, that decidua at least had apparently continued to grow.

In consequence of these results it was decided

to carry out a further experiment, this time on animals that had been treated only with chorionic gonadotrophin.

III. Injection into gonadotrophin-treated non-pregnant animals only

Sixty-four animals were used. Two animals were killed per day on alternate days up to the 40th day, and the remainder left until the 150th day when one half were killed. The experiment was ended on the 300th day when all survivors were killed. The intervals to death, and the proportions of animals showing pulmonary emboli, are shown in Table J.

The scheme whereby animals were killed at regular intervals was disturbed slightly by the development of an intestinal infection amongst the animals in one cage (ten animals instead of only four had to be killed during the 18th to 20th days); by occasional single deaths after the 32nd day; and by the loss of three animals that died and were largely eaten by their cage-mates. These small deviations from the original scheme do not interfere materially with results in a "dying" experiment such as this.

The results were disappointing in that suggestive evidence of continued growth of placental tissue comparable to that seen in Experiment II was not found in any of the animals, although emboli were seen

in almost the same proportion of animals (21 out of 46 killed up to the 40th day) and in about the same quantity in the lungs. Of the animals killed after the 40th day, the lungs of two killed at the 150th day each showed one very small focus of calcification in the wall of a small vessel, possibly the remains of a former placental embolus (fig. 79).

IV. Injection of autologous placental tissue into pregnant animals

Twenty pregnant animals were injected intravenously with a suspension of their own placental tissue. Two animals aborted on the day after operation. Two were killed before delivery, one at the 2nd, one at the 4th day after operation. One animal died 22 days after operation with confluent pulmonary abscesses. The remainder littered normally and remained healthy until they were killed at intervals varying from 2 to 150 days after injection.

Placental emboli were seen in the lungs of those killed at 2, 4, 6, 8, 12, 16, 22 (the animal dead of pulmonary abscesses), 28, 40 and 65 days; but not in others killed at 14, 18, 33, 60, 70, 90 and 150 days (two animals). In those animals whose lungs contained placental emboli the tissue responses towards the emboli differed in no appreciable way from those seen in the non-pregnant animals in the previous

experiments. Emboli disappeared at about the same rate, and the pulmonary tissues showed the same slow and indifferent response towards them. In the case of the animal that died with multiple abscesses in the lungs, it is presumed that bacterial contamination of the emulsion had occurred.

V. Injection of emulsions of liver and kidney into normal non-pregnant animals

Twenty animals were used in a control experiment designed to show whether there was any difference in the response of pulmonary tissues to placental emboli and to cellular emboli of other kinds. Eight of the animals were injected intravenously with a 5% emulsion of mouse kidney in saline, and eight with a similar emulsion of mouse liver. The preparation of the emulsions and the technique of injection were the same as those already described for injection of placental tissue. One animal from each group was killed and the lungs examined at 3, 7, 10, 14, 17, 21, 24 and 28 days after injection. Of the other four animals, two each were injected with filtrate of the kidney and liver emulsions and killed and examined at 7 and 14 days after injection.

Persisting emboli were seen in all eight animals injected with kidney, and in five of those injected with liver. An acute inflammatory reaction of

varying intensity, characterised by infiltration of polymorphonuclear leucocytes and monocytes, was present in the walls of the arterioles and in the surrounding tissue in seven of the animals injected with particles of kidney but not in the remaining animal killed at the 24th day. Typical examples of the inflammatory reaction are shown in figures 80 and 81. In the animal killed at the 28th day early ingrowth of blood vessels into the embolus was evident. Particles of liver were apparently more easily destroyed than particles of kidney, the particle-free animals in this group being those killed at 17, 24 and 28 days; that is, particles of liver did not persist for as long as particles of kidney. The degree of inflammatory response was also, on the whole, less marked than in the kidney-injected animals but was present in those killed at 3, 7, 10 and 21 days. No inflammatory reaction was present around the few emboli present in the animal killed at the 14th day. There was no inflammatory reaction in the lungs of the animals injected with filtrates of the tissue emulsions. It is unlikely, therefore, that the inflammatory reaction seen around the emboli in the emulsion-treated animals was due to bacterial contamination of the material injected.

It is evident from this experiment that, on the whole, emboli of this kind cause the pulmonary tissues

to react in a way that differs markedly from the sluggish or virtually absent response shown towards placental particles.

Comment

The experimental observations on mice have shown that particles of placental tissue introduced intravenously into the lungs appear to behave as peculiarly bland emboli. They excite little or no reaction in the form of leucocytic infiltration, capillary ingrowth or even, for some eight days at any rate, proliferation of the vascular endothelium. This behaviour differs markedly from the response to particles of liver and kidney introduced in the same way: in these circumstances many emboli cause a brisk leucocytic response. It differs also from the acute inflammatory arteritis found by Barnard (1953) to follow a single intravenous injection of particles of human fibrin into the lungs in mice.

To judge from the rapidity with which all but the larger particles of tissue disappear from the lungs, and the frequent absence of any recognisable tissue reaction in the pulmonary vessels, particles smaller than about 20 microns in diameter appear to be removed by simple lysis by about the tenth day after injection. The morphological appearance of the edge of some of the larger masses supports this view. Particles

which are larger than this gradually become covered by endothelium and are incorporated into the vessel wall: the speed with which this is achieved depends upon the size of the particle. In the present series as a whole, emboli were seen in only fourteen animals out of ninety-eight killed after the twentieth day following injection, the oldest embolus being seen at the sixty-fifth day. Some of these had become fully covered by endothelium and were blended with the vessel wall as just described, while in others it was difficult to know whether the covering of flattened cells was endothelial or due to simple compression of the superficial cells of the embolus; but there was still no evidence of inflammatory reaction around any of them. A few nuclei of viable appearance persisted in all. None of the emboli had caused fibro-elastosis of the wall, and none was associated with lesions of atheromatous type. A small focus of calcification was found in the wall of an arteriole in two of the animals killed 150 days after injection. Such foci may well represent former placental emboli but calcification cannot be a frequent result since it was seen only twice.

This rather unusual indifference of the pulmonary tissues towards placental material may be compared with the curious absence of organisation sometimes notable in placental polyps in the human.

Polyps of this kind may be composed of obviously viable chorionic villi yet have a quite avascular base and be unaccompanied by the formation of granulation tissue. I do not know of any reason why such placental polyps should be ignored in this way by the endometrium at their base, particularly since they clearly cause an inflammatory response elsewhere, but the phenomenon may well have something in common with the indifference of the pulmonary tissues in my experimental animals.

The placental emboli in the lungs did not cause thrombosis, and fibrin emboli were seen only rarely. Two conclusions may be drawn from this: one, that placental tissue in the circulation does not cause thrombosis in its immediate neighbourhood; the other, which is relevant only to these experiments, that the strength of placental emulsion that was used contained only negligible amounts of thromboplastin, the substance thought by Schneider (1951) to be responsible for "fibrin embolism" in human pregnancy.

Evidence of continued growth of injected tissue was seen in only two animals. Both were in the original group of animals treated with chorionic gonadotrophin, but since no such growth was seen in any of the similarly treated animals in the later experiment the association may be regarded as fortuitous. The morphology and staining reactions

of both these proliferative emboli suggested strongly that they were composed of decidua, not trophoblast. This is understandable since it was not possible to be sure that some decidual cells were not included along with trophoblast in the placental emulsion. This forms an interesting parallel with the already-mentioned reports of the finding of decidual tissue in the human lung.

b. Evidence from human material

None of the trophoblastic emboli in my series of cases showed evidence of continued cellular growth, using as criteria the presence of mitotic figures within them or erosion of the vessel wall. This was only to be expected in as much as syncytium at the placental site appears to lose most of its proliferative properties from about the third or fourth month of pregnancy onwards even if, as shown by Wislocki and Bennett (1943), it continues to be metabolically active as a producer of steroid hormonal substances. It was not necessarily to be assumed, however, that it would behave equally placidly when transferred to its new site in the lungs: but apparently it does. There was also no sign of inflammatory reaction in the form either of leucocytic infiltration or thickening of the vessel walls to suggest that the placental embolus acts in any way as an irritant or,

as it truly is, as a foreign body, albeit of rather unusual type. Thrombosis was not seen in vessels containing particles of trophoblast. Also, although clumps of fibrin were seen in the vessels in several cases ("fibrin embolism"), in no case were they seen to be formed around a mass of trophoblast.

The extent to which the syncytial masses preserved their structure varied. Some were relatively large and contained many well-formed vesicular nuclei; others were very much smaller and contained only coarse irregular clumps of deeply pyknotic chromatin. It thus appears that the natural fate of the placental embolus is one of increasing pyknosis and shrinkage of nuclei, and gradual loss of cytoplasm sometimes preceded by coagulation. Very occasionally a polymorph leucocyte was seen to be included in the cytoplasm at the edge of a syncytial mass - adherent, presumably, to cytoplasm that was undergoing lysis. Such an occurrence was, however, exceptional. For the most part there was no very convincing evidence of lysis in the form of fraying or streaming of the cytoplasm: in all but the occasional example to which a leucocyte was adherent the emboli had a sharply defined edge although one did get the impression sometimes that extrusion of pyknotic nuclear material was occurring. It is difficult, on the other hand, to think of any explanation other than lysis, with or

without nuclear extrusion, for the gradual disappearance of the cytoplasm and the final extinction of the whole embolus. The occasional adhesion of a polymorphonuclear leucocyte to a syncytial mass should be regarded as an accidental or at least incidental happening. Trophoblastic emboli in the lung are not removed by phagocytosis.

It will be shown presently, from other evidence, that the great majority of placental emboli disappear within a few days of their arrival in the lung. This can be confirmed histologically to the extent that in no case was an embolus seen to be covered by vascular endothelium. Incorporation into the vessel wall does not appear to occur to any recognisable extent, a point of difference from the findings in my experimental animals in which, however, the masses of tissue that did become blended with the vessel walls were often much larger than those usually seen in the human lung.

Finally, some idea can be gained of the "natural history" of trophoblastic emboli by noting the length of time after separation of the placenta for which they may be seen in the lung. This information is contained in figure 82 which shows, by groups, the numbers of patients dying at various intervals after separation of the placenta (irrespective of the gestational age of the pregnancy): the proportion

of patients in these groups whose lungs were seen to contain trophoblast; and the amount of trophoblast that was present. Of the fifteen patients who died undelivered, two are included in this figure, Cases No. 107 and 120 wherein placental separation had occurred although the patients died with the infant still in the uterus: the remaining thirteen cases are naturally not included.

It is clear from this figure that trophoblast is seen in the lungs most often and in greatest amount in patients who die within twenty four hours of separation of the placenta, and that the incidence falls away rapidly thereafter. From this it may be concluded that the life of trophoblastic emboli is usually of the order of two to three days. In exceptional cases they may persist for up to sixteen days but in the present series none was seen in the lungs of four patients dying after the 16th day.

V. DISCUSSION

Some comment has already been made in the relevant preceding sections on most of the findings in this investigation into the nature, frequency of occurrence and fate of particles of tissue seen in the lungs of pregnant, parturient and puerperal women.

One result of the enquiry has been to confirm in general the view, originally advanced by Schmorl but to a great extent modified, exaggerated and even doubted since then, that portions of trophoblast may frequently be carried from the placenta to the lungs. The particles of trophoblast are almost always of completely characteristic appearance - islets of cytoplasm containing up to fifty or more separate, if superimposed, small spherical nuclei; frequently modified in outline by the contour of the vessel that contains them but usually round or oval in outline. The nuclei may be in varying degree pyknotic. The amount of cytoplasm is usually small. This morphology is identical with that of the syncytial trophoblastic buds seen on the surface of the chorionic villi or free in the intervillous maternal blood lake of the placenta. Two observations challenge the claim that the morphology of these intrapulmonary particles is specific: one, that effete megakaryocytes from the bone marrow, trapped in the pulmonary capillaries, may

simulate syncytium; the other, that multinucleated masses of tissue may be found in the lungs of non-pregnant subjects. These criticisms can be dismissed. Such megakaryocytes as I have seen in the lung have never been multinucleated but always monolobular or multilobular - this accords with the views of other observers; and the occurrence of multinucleated masses in the pulmonary vessels of non-pregnant subjects is an infrequent event, the morphology of masses of this kind even then rarely resembling closely that of the syncytial giant cell or bud.

I have recently reported the fact that the sex chromatin particle can be identified in both normal and neoplastic trophoblast. It can be seen in the trophoblast of early implanting human (and macaque) embryos by about the twelfth day after fertilisation (Park, 1957a) and in the trophoblast of chorion-epitheliomas and hydatidiform moles (Park, 1957b). The nature of sex chromatin and the story of its recognition by Barr and Bertram (1949) is now familiar to most medical workers, and a detailed account is unnecessary here (a useful review of current knowledge on the matter is that of Lennox, 1956). Suffice it to say that, in mature trophoblast, sex chromatin can be detected in Langhans' cells, though with some difficulty, but hardly ever in

syncytium. This is unfortunate because it means that sex chromatin cannot be identified with certainty in particles of trophoblast in the lung. In all the cases where I have sought the particle in trophoblast in the lung, either the syncytial nuclei have been almost completely pyknotic or they have shown numerous particles of chromatin frustratingly similar in shape to the sex chromatin particle, and disposed, equally frustratingly, around the nuclear membrane, the diagnostic situation for sex chromatin. For these reasons it has not been possible to show that the "sex" of trophoblast in the lung is always in keeping with that of the infant in the uterus. This would have been pleasing to show but is unnecessary as a means of identifying trophoblast in the lung, so distinctive is the morphology of the syncytial giant cell.

Cells like Langhans' cells have been seen in pulmonary vessels in the present series only once, in a patient with a hydatidiform mole, an observation which is not surprising in view of the disappearance of Langhans' cells in the later months of pregnancy, and the hyperplasia of both kinds of trophoblast in hydatidiform moles, especially in the invasive mole, the type most likely to bring a patient to necropsy.

The belief that whole chorionic villi are frequently, if not constantly carried to the lungs is

widely held. My own experience runs counter to this belief: negatively, in that no villi were seen in the 2000 or so sections in my own series; positively, in that on the only two occasions when I have seen sections of villi in the lung they were regarded as rarities, even amongst the large volume of material from moles and chorionepitheliomas in which they were filed. Loss of whole chorionic villi could well be expected to lead to blood loss from the foetus; and there is no doubt that the foetus can lose blood through the placenta. Maternal sensitisation to the rhesus factor is evidence of this - Wiener (loc. cit.) indeed postulated the existence of a pair of allelic genes, K and k, K conferring the capacity to become sensitised readily, k being the contrasting normal gene: only individuals of the rare genotype KK become sensitised during the course of a pregnancy to the small number of foetal red cells contained in, as he says, chorionic villi escaping from the placenta before parturition, while the escape of larger numbers of foetal red cells during parturition is enough to sensitise those of the less susceptible genotype Kk. That foetal red cells can pass into the maternal blood stream has been demonstrated by various agglutination techniques (see, for example, Chown, 1955). Such transplacental haemorrhage could certainly result from avulsion of chorionic villi but

that is not the only possible mechanism. Towards the end of pregnancy not only has the Langhans' cell layer disappeared but the syncytium itself becomes greatly thinned in many places leaving almost naked areas on the surface of the villi, the so-called chorionic plates (Wislocki and Bennett, loc. cit.). Erosion of the foetal capillary endothelium at areas like this, with consequent loss of blood, seems just as likely an event as avulsion of whole villi, probably more so.

The proportion of patients in the present series in whose lungs trophoblast was seen was 44 per cent. This does not necessarily weaken the claims of the early workers that escape of trophoblast to the lungs probably happens in every pregnancy. It will be recalled that in most of my cases only one block of lung was available; and even ten or twenty non-serial sections in cases like this give a very limited sample of the lungs as a whole. Had there been available, say, ten blocks instead of one in these cases, the percentage figure would no doubt have been much higher than 44 - but this deficiency in no way invalidates the conclusions I have drawn from my analysis of the figures. The simple numbers of patients whose lungs showed trophoblast within the various groups that were used - for example, "eclampsia", "non-eclampsia", "first trimester" - is of less importance than the

amount of trophoblast that was in their lungs. I have already mentioned (p. 72) that in those cases where more than one block of tissue was available, the trophoblastic index was never greater than 1. This suggests that, even if ten blocks had been available in every case, the trophoblastic indices of the sixty-seven patients whose index was 0 would have been 1, but no higher than that. Had this been the case, the simple proportion of patients whose lungs showed trophoblast would obviously have been 100 per cent - but the difference in the indices of the various patients would still remain the most important measure of difference between them. Indeed, by using for purposes of calculation the value, log. (T.I. + 1), the "negative" patients have in effect been given a trophoblastic index of 1, a quite legitimate procedure that in no way invalidates the conclusions drawn from these calculations.

The main and only statistically significant fact that emerged from the analysis of the trophoblastic indices is that the act of parturition itself is the chief factor in causing trophoblast to pass from the placental site to the lungs: the highest values both for the proportion of patients in whose lungs trophoblast was seen, and for the amount of trophoblast that was present, were found in the group of patients dying within twenty-four hours of separation of the

placenta. Since dead pregnant patients obviously come to necropsy most frequently after parturition has occurred, and only comparatively infrequently in the undelivered state, it seems likely that current beliefs regarding the amount of trophoblast that passes to the lungs during the course of pregnancy as a whole have been rather distorted by this highly selective factor.

My figures show that the amount of trophoblast seen in the lungs in patients dying within twenty-four hours of separation of the placenta is almost certainly not a fair sample or cross-section of conditions obtaining during life. In fact, if one looks again at the data for those patients who died before separation of the placenta (Group dd of Table C), it is seen that in only three out of thirteen did the lungs show trophoblast, and one of these was the quite exceptional patient, Case No. 118 (whose trophoblastic index of 210 caused a very troublesome "skewness" of distribution throughout the whole of the analysis of the figures). This finding may be compared with that of Schmorl who, as already mentioned, found trophoblast in the lungs of only three out of twenty-five of his patients who had died undelivered. Passage of trophoblast to the lungs during the course of a pregnancy would thus seem to happen on a much less voluminous scale than post

mortem evidence, and current beliefs based upon it by extrapolation "backwards" into the nine preceding months, would lead us to believe.

There is just a suggestion from the figures that trophoblast may be seen in a higher proportion of patients dying during the first trimester of pregnancy than at later stages, but no more than just a suggestion: the difference that there is could easily have occurred by chance. The most one can say on the evidence of the data in the present series is that, whatever may be the behaviour of trophoblast at the placental site in early pregnancy, the high degree of invasiveness with which it is generally credited at that time is not reflected in any striking increase in the amount that enters the blood stream and reaches the lungs. Since varying degrees of uterine contraction and placental separation as such may influence the amount of trophoblast passing to the lungs, there would appear to be only one valid way of finding out whether trophoblast reaches the lung in greater amount during the earlier months of pregnancy, simply because it is more invasive at that time; and that is to compare the sections of lung from patients who had died accidentally, for some reason unconnected with the pregnancy, and undelivered, during each of the three trimesters. This is an "ideal" unlikely to be obtained.

It has been difficult to dissociate the effect of the toxaemic part of eclampsia from its convulsive part as a producer of trophoblast in the lung. Here again no statistically significant data have emerged but the position may be summarised by saying that patients with toxaemia, pre-eclamptic or eclamptic, may have a slightly greater tendency to show larger amounts of trophoblast in the lung than other patients but that the difference is not great; that trophoblast is seen in greater amount in patients with eclampsia proper than in pre-eclampsia; and that in eclampsia itself the greater amount of trophoblast is almost certainly a consequence of the convulsions. The difference in the amount of trophoblast seen in the lungs of patients who, for reasons of eclampsia or unduly prolonged labour, were regarded as having excessive uterine contractions, and those who had "ordinary" or minimal contractions, was of borderline significance. However. bearing in mind the small numbers of patients concerned, and the rather arbitrary decision as to what was an unduly prolonged labour, I strongly suspect that excessive uterine contractions per se do indeed promote the escape of trophoblast from the uterus.

This view is supported by the relative non-appearance of trophoblastic emboli in the lungs of the patients who died before separation of the

placenta, and the greater amount seen in patients with eclampsia than in those with pre-eclampsia; and it allows the general opinion that the dominant factor in promoting embolism of the lungs by trophoblast is what I may call "placental commotion".

It is interesting to note that of the nine patients in this series in whom, according to the clinical notes, manual removal of the placenta was performed, six showed no trophoblast in the lungs. Manual removal of the placenta, it will be recalled, was one of the only three conditions (placenta praevia and rupture of the uterus were the others) in association with which Schmorl had seen, not just large amounts of trophoblast, but whole chorionic villi in the lungs. One could certainly regard the procedure as one involving "placental commotion" but the fact remains that only three of my nine cases of this kind showed trophoblastic emboli. This is perhaps a tribute to the gentleness of modern obstetricians!

Both in the experimental animals and in the human, particles of placental tissue appear to behave as unusually bland emboli and are received with equal indifference by the pulmonary tissues in both species. It is, however, relevant to remark that Pick (loc. cit.) found in some of his experiments that placental particles introduced into the lungs did cause some

degree of inflammatory reaction and thrombosis. This may be a species difference - he was using rabbits - but it may also reflect some difference in standards of aseptic technique. An occasional embolus was seen in the human lungs as late as the sixteenth day after parturition, but even three days is amply long enough for an acute inflammatory response to develop if one is going to develop; and many emboli were seen three days after parturition, still unaccompanied by any leucocytic response, erosion of the vessel wall or thrombosis. Fibrinous "plugs" were seen in pulmonary vessels in fourteen of the patients, eight of whom showed trophoblast in the lungs, but in no case had deposition of fibrin occurred in the immediate neighbourhood of any of the particles of trophoblast. The explanation of the indolence of the vascular endothelium and other tissues in the lung almost certainly lies in the fact that embolic trophoblast is treated as a form of homograft that might be tolerated, did it live long enough, for even a few weeks.

No evidence of continued growth of the embolic trophoblast was seen in any instance, not even in emboli reaching the lung during the first three months of pregnancy. Even during the third month the trophoblast must still have considerable powers of proliferation, powers which are conventionally

regarded as being "held in check" and prevented from unlimited invasion by the development of the fibrinoid stripe of Nitabuch. My own series has shown that trophoblast certainly reaches the lungs during the third month, and it must also escape, perhaps in even greater amount, during the first few weeks of nidation before a state of relative stability is reached at the placental site. No "fibrinoid stripe" is formed around the emboli in the lungs, yet continued growth does not occur, or, if it does, it very soon comes to an end. Limited growth that regresses spontaneously does admittedly appear to be achieved on occasion by trophoblast reaching the lungs in circumstances other than as metastases from a chorionepithelioma, usually in patients who have a hydatidiform mole. A short account of cases of this kind has been given by Savage (1951) and by Novak and Seah (1954). To what extent this happens, if at all, in patients who have a normal, non-molar pregnancy is difficult to know: instances are unlikely to come to light unless the growing tissue causes symptoms such as cough and haemoptysis. I have asked a number of physicians in charge of miniature mass radiography units whether they had ever noticed an unduly high proportion of pregnant women amongst their "false positive" cases; that is, patients in whom there was a definite opacity within the lung but in whom the opacity disappeared

spontaneously and in whose sputum tubercle bacilli were never found. None, however, could recall in retrospect having formed that impression. A retrospective analysis of the records of a unit of this kind might still be worth carrying out with the above point in mind: it is unlikely now, for obvious reasons, that anyone in this country at any rate would care to carry out a prospective search for regressing pulmonary shadows in the pregnant woman, involving, as it well might, much irradiation.

In the absence of any suggestive clinical evidence such as regressing opacities in the lung, and in view of the histological findings in my own series of cases, it seems likely that continued growth of the trophoblast, to any degree that affects the patient, rarely if ever occurs in normal pregnancy. It is generally assumed that particles of trophoblast which enter the circulation and become arrested in the pulmonary capillaries are removed by the action of a specific lytic agent, first postulated by Veit (1905) and named by him "syncytiolysin". A specific lysin of this kind may exist but attempts to demonstrate it have never been wholly successful. The results of the mouse experiments I have described show no striking difference between the rate of disappearance of experimentally introduced placental particles from the lungs in pregnant animals (autologous trophoblast) and

in non-pregnant animals: it disappears equally rapidly in both. Species differences naturally preclude the drawing of too close an analogy between my experimental findings and conditions obtaining in human pregnancy, but, in so far as one can compare the circumstances, it is appropriate to remark that, in the mouse at any rate, trophoblast is removed from the lungs by pregnant and non-pregnant animals with equal efficiency. There may therefore be no specific syncytiolysin in the human, but the matter is one of some importance, meriting further investigation, and I shall have occasion to refer to it again shortly.

Whatever be the physico-chemical factors involved in the removal of trophoblast from the lung - and they may be no more specific than those involved in the removal from the lungs of embolic bone marrow or liver cells in cases of bone fracture and laceration of the liver - the problem posed by the patient who has disseminated chorionepithelioma but no lesion in the genital tract remains unsolved. I have suggested elsewhere (Park, 1957a) on other evidence that this peculiar state of affairs may be due to the stimulation to neoplasia of embolic remnants of an earlier pregnancy by the hormonal climate of a new pregnancy - studies of the distribution of sex chromatin in trophoblast had shown that a chorionepithelioma of "female" type might follow the

birth of a male infant. This suggestion is not necessarily difficult to reconcile with the view that in normal circumstances embolic trophoblast in the lungs seems to disappear without trace. Any single trophoblastic cell that happened to become blended with the wall of a pulmonary vessel could not be recognised as such with present techniques; and it is just not possible to say with certainty that no single viable cell remained in the sections of lung of the "negative" patients in my series, still less in the lungs as a whole. This kind of problem is met repeatedly when examining biopsy specimens from irradiated uterine cervices, when the question is, Are any malignant cells present? The identification of a single cell, as opposed to a group of cells, as malignant is virtually impossible. This is certainly so in fixed tissues; and even cytologists with their smear preparations might agree here! This hypothesis, that the type of chorionepithelioma now being discussed may be due to malignant change occurring in embolic trophoblast inherited from an earlier pregnancy, probably does not apply in every case. Embolic trophoblast derived from a current pregnancy possibly can "become malignant" in its new situation, though why it should become malignant in these cases is another matter. It is, indeed, the problem of cancer itself.

Reference has already been made to three reported

cases (Hughes; Trotter and Tieche; Marcuse) in which death was attributed to massive trophoblastic pulmonary embolism. In the first two of these cases the patient had a hydatidiform mole, and it is just credible that enough trophoblast could escape from this kind of lesion to cause death by simple mechanical blockage rather than by some form of acute anaphylactic response. Death from amniotic embolism is in a rather different category from death by trophoblastic embolism, but there now seems little doubt that, in amniotic embolism at any rate, death is due to simple mechanical obstruction of the pulmonary vascular bed (Cron et al., 1952), not to the "anaphylactoid" reaction that some of the earlier observers of the condition postulated. To judge from the illustrations in the case reports by Trotter and Tieche and by Marcuse, the amount of trophoblast in the lungs of their patients was no greater than that shown by the rather remarkable Case No. 118 in my own series with a trophoblastic index of 210, yet this patient died of a massive cerebral haemorrhage with no conspicuous signs of asphyxia. There is no evidence that the presence of trophoblastic particles in the lung causes any interference with pulmonary function in normal pregnancy.

A great deal of work has been published by Schneider on the nature of obstetric shock and various

associated defects of blood coagulation: reference has already been made in connection with my animal experiments to some of his papers. Schneider has put forward the view, now generally accepted, that in abruptio placentae and some other conditions thromboplastin may enter the maternal circulation due to disruption of tissue at the placental site, and, by combining with fibrinogen to form fibrin, lead to dangerously low levels of circulating fibrinogen with the risk of severe haemorrhage from the placental site and elsewhere. He has also raised the question (Schneider, 1954) whether the entry of thromboplastin into the circulation in less massive amount than in abruptio placentae might not be of some significance in the aetiology of toxaemia of pregnancy. The source of thromboplastin in this case could be the embolic particles of trophoblast, either directly by their own disintegration, or indirectly by seepage of thromboplastin from their former point of attachment to the chorionic villi. Such evidence as I can produce with a bearing on the matter is scanty. Of the fourteen patients whose pulmonary vessels contained fibrin plugs of the type described by Schneider, six were in the group "eclampsia/pre-eclampsia", while of these six, four showed trophoblast also in the pulmonary vessels. This observation does suggest that "fibrin embolism" of the lung is seen rather more

frequently in patients of eclamptic type than in patients dying in other circumstances; and, in patients of eclamptic type, possibly more frequently in those who have trophoblast in the lung than in those who do not. Only a more detailed survey would allow an opinion whether or not the formation of fibrinous masses within the circulation had any aetiological import in pregnancy toxaemia. The whole matter is an interesting resurrection of Schmorl's original view that eclampsia was caused by widespread intravascular thrombosis secondary to some thrombogenic substance produced in the placenta. Whatever be the truth of the matter, the histological fact remains that fibrinous plugs do not form directly around embolic trophoblast.

In some of my experimental animals it was clear that embolic trophoblast could be incorporated into the walls of small pulmonary arterioles, though without exciting any significant degree of inflammatory reaction or any formation of lesions of arteriosclerotic type. My human material, on the other hand, gave no indication that the impaction of trophoblast caused any striking structural alteration to vessel walls. An occasional rather thick-walled arteriole was certainly seen in some of the sections but no more often than in sections of lung from male patients in the control series. The matter is not without some

relevance in connection with pulmonary hypertension. Primary pulmonary hypertension is a puzzling condition. The view has been advanced by Barnard (1954) that pulmonary hypertension and its causative pulmonary arteriosclerosis may be due sometimes to recurrent fibrinous micro-embolism, and he has succeeded in producing both pulmonary arteriosclerosis and cor pulmonale in rabbits by repeated intravenous injection of autogenous fibrin. Whether this condition is ever attributable in the human to embolism of the lungs by trophoblast, I do not at present know: if it is, it should be seen in parous women more often than in non-parous women and men, and with increasing frequency in increasing parity. Such evidence would not appear to have emerged so far from cases of primary pulmonary hypertension recorded in the literature, though one notes with interest that five out of eleven such patients reported by Wade and Ball (1957) were young parous women.

There is finally one aspect of embolism of the lungs by trophoblast about which knowledge is slight but which demands further investigation, not least because of its potential significance in the context of chorionepithelioma: that is, the inter-relationship between antigen and antibody that is almost certainly concerned in the disposal of embolic trophoblast. I have already mentioned that some further enquiry into

the existence or not of a specific syncytiolysin is certainly needed. This question was naturally one of great interest to Veit, since he it was who first postulated the existence of a lysin of this kind, and it was investigated at great length by Abderhalden (1922). Abderhalden himself had no doubts about the specificity of the lysin he claimed to be able to demonstrate in the serum of pregnant women, and the reaction by which he did demonstrate it was very generally regarded, mainly on the Continent, as a dependable pregnancy test. However, many doubts were raised about the specificity of the reaction - a useful account of the factors involved is given by Browning (1931) - and the "Abderhalden Reaction" has now been generally abandoned as a laboratory procedure.

Some interaction of molecules, however, there must be. The interaction may be no more specific than that involved in the removal from the blood stream of particles of bone marrow or fat, but I myself find it very difficult to believe that trophoblast, one half of whose chromosomes are paternal and to that extent foreign and antigenic, lying in an abnormal situation, the lungs, does not elicit some certainly specific type of antibody response. Our techniques may at present be inadequate to demonstrate it and analyse it - perhaps the newer fluorescence

techniques for demonstration of tissue antibodies will help here - but in its understanding will undoubtedly lie some part of the answer to the unique problem of chorionepithelioma.

VI. SUMMARY

An investigation of the phenomenon of embolism of the lung by trophoblast has been carried out. Sections of lung from 120 pregnant, parturient and puerperal women have been examined for the presence of embolic trophoblast; and cellular emboli morphologically identical with particles of syncytium as it occurs in the placenta found in the sections from fifty-three.

For purposes of comparison of the amount of trophoblastic tissue seen in the lungs of different patients, a quantitative measure was used, the "trophoblastic index". This denotes the number of trophoblastic emboli present in 1000 sq. mm. of sections of lung. It ranged from 1 to 210, with a mean value of 17.9 for the fifty-three patients whose lungs contained trophoblast, and of 7.9 for the 120 patients as a whole. Examination of the available material makes it seem probable that the greater the amount of tissue that is examined, the greater is the likelihood of finding trophoblast in the lung; but that if sections from one averagely-sized block of lung show no trophoblast, the trophoblastic index for that patient is unlikely to be greater than 1 no matter how many blocks and sections are examined.

From analysis of the various factors that might

be expected to have an influence on the amount of trophoblast passing to the lungs - degree of uterine contraction, the nature of the disease causing death, the gestational age of the pregnancy and the length of the interval between placental separation and death - it has been found that the most important factor promoting escape of trophoblast from the placenta to the lungs is the act of parturition itself and the separation of the placenta. Furthermore, no trophoblast was found in the lungs of ten out of thirteen patients who died before separation of the placenta had taken place. It thus appears that the amount of trophoblast seen in the lungs of a patient dying within twenty-four hours of separation of the placenta is not a true representation of the amount that passes to the lungs during the course of the pregnancy as a whole. Trophoblast probably does reach the lungs of every pregnant woman but in much smaller quantity than is generally believed.

Evidence that patients with pre-eclampsia and eclampsia are more liable than other patients to show trophoblast in the lungs did not quite reach a statistically significant level. Analysis of the data, however, suggested that with a larger series of cases such a difference might well be found.

Particles of trophoblast in the human lung appear to behave as peculiarly bland emboli. They cause no

appreciable structural change in the walls of the vessels in which they become impacted, and do not appear to cause thrombosis. These findings were confirmed by experimental observations on mice into whose lungs autologous or homologous trophoblast was introduced by intravenous injection as a saline suspension. No instance of apparent continued growth of trophoblast was seen in the lungs of either the experimental animals or the 120 patients; but small proliferative foci of decidual tissue were present in two patients. Continued growth of decidua was seen also in the lungs of two of the mice. Tissue recognisable as cytotrophoblast was present in only one case, a patient with an invasive hydatidiform mole. No chorionic villi were seen in sections from any of the patients.

To judge from the rate of disappearance of embolic trophoblast from the human lung, the life of an embolic particle would appear to be of the order of three days. The means of disposal remains uncertain but morphological evidence of gradual disintegration and lysis was occasionally seen. Emboli are not removed by phagocytosis. Whether a specific syncytiolysin is present in the blood of pregnant women has yet to be proved with conviction. Because of its potential importance in relation to the pathogenesis of chorionepithelioma, this matter requires further

investigation.

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APPENDIX I

Clinical Data, Trophoblastic and Megakaryocytic Indices of 120 Pregnant, Parturient and Puerperal Patients.

Case 1 R.I.E. necropsy 424/49, 3.9.49. Ward 54

W.S. Age 34

Died from septicaemia 7 days after delivery at term.

Histology of lung: patchy oedema; fibrin plugs in many vessels.

Trophoblastic index: 0

Megakaryocytic index: 23

Case 2 R.I.E. necropsy 273/49, 26.5.49. Ward 53

M.G. Age 31

Died from massive pulmonary embolism 10 days after normal delivery.

Histology of lung: general mild congestion.

Trophoblastic index: 0

Megakaryocytic index: 2

Case 3 R.I.E. necropsy 26/49, 15.1.49.

M.W. Age 29

Admitted in 5th month of pregnancy with complaint of abdominal pain and vomiting. Laparotomy: volvulus of small intestine with gangrene. Died undelivered 24 hours after operation.

Histology of lung: severe generalised oedema.

Trophoblastic index: 14

Megakaryocytic index: 83

Case 4 R.I.E. necropsy 390/48, 9.8.48. Ward 36

M.P. Age 29

Admitted 13 days after normal term delivery with complaint of increasingly severe epigastric pain for previous 4 days. Died on the day after admission.

Necropsy: mesenteric vein thrombosis.

Histology of lung: marked generalised oedema.

Trophoblastic index: 0

Megakaryocytic index: 4

Case 5 R.I.E. necropsy 91/48, 16.2.48. Ward 52

T.E. Age 24

Unwell for 24 hours before term delivery. Had convulsion 6 hours after delivery and became comatose. Died 18 hours after delivery without regaining consciousness.

Necropsy: massive cerebral haemorrhage.

Histology of lung: oedema; collapse; early bronchopneumonia.

Trophoblastic index: 4

Megakaryocytic index: 27

Case 6 R.I.E. necropsy 25/48, 10.1.48. Ward 54

G.H. Age 30

Admitted moribund. Severe post partum haemorrhage for 2 days at term. Retained placental fragments.

Histology of lung: mild emphysema.

Trophoblastic index: 0

Megakaryocytic index: 13

Case 7 R.I.E. necropsy 3/48, 1.1.48. Ward 51

J.S. Age 44

Admitted at term with pre-eclamptic toxaemia and left heart failure. Spontaneous delivery of stillborn infant. Developed oliguria, then anuria. Pulmonary oedema for 48 hours, coma for 12 hours, before death at 13 days after delivery.

Histology of lung: oedema; bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 12

Case 8 R.I.E. necropsy 407/47, 1.9.47. Ward 54

S.B. Age 25

Admitted at term with severe pre-eclamptic toxaemia. Died undelivered.

Necropsy: toxic change of eclamptic type in liver, kidneys.

Histology of lung: slight oedema.

Trophoblastic index: 0

Megakaryocytic index: 9

Case 9 R.I.E. necropsy 301/47, 25.6.47. Ward 53

A.T. Age 37

Mild pre-eclamptic toxaemia. Mid-forceps extraction. Died shortly after returning to ward.

Histology of lung: aspiration pneumonia.

Trophoblastic index: 0

Megakaryocytic index: 5

Case 10 R.I.E. necropsy 179/47, 14.4.47. Ward 54

J.F. Age 35

Admitted in 3rd month of pregnancy because of incomplete abortion followed by 3 weeks' vaginal bleeding. Died on the day following curettage.

Necropsy: large cerebral haemorrhage; multiple petechial haemorrhages; diagnosed as thrombocytopaenic purpura.

Histology of lung: slight oedema and emphysema.

Trophoblastic index: 5

Megakaryocytic index: 33

Case 11 R.I.E. necropsy 99/47, 24.2.47. Ward 51

A.F. Age 31

Admitted with peripheral oedema and in coma 2 days before expected day of delivery. Died undelivered 2 hours after admission. No evidence of toxaemia in antenatal records.

Necropsy: large cerebral haemorrhage; toxic changes in liver, heart, spleen.

Histology of lung: haemorrhagic pneumonia.

Trophoblastic index: 10

Megakaryocytic index: 12

Case 12 R.I.E. necropsy 78/47, 13.2.47. Ward 54

M.C. Age 22

Spontaneous abortion of hydatidiform mole during 3rd month. Heavy bleeding and collapse. Died 24 hours

Case 12 (contd.)

after admission.

Necropsy: liver showed patchy and confluent haemorrhages, diagnosed microscopically as of eclamptic type; uterus contained yellowish slough and blood clot.

Histology of lung: simple congestion and moderate oedema.

Trophoblastic index: 20

Megakaryocytic index: 124

Case 13 R.I.E. necropsy 24/47, 10.1.47. Ward 54

J.G. Age 26

Had had influenza and pleurisy for 10 days before admission. Delivered at term in ambulance on way to hospital - precipitate labour. Retained placenta. Heavy bleeding and collapse. Died 4 hours after delivery.

Necropsy: confluent bronchopneumonia with abscess formation.

Histology of lung: bronchopneumonia and fibrinous pleurisy; one small focus of decidual tissue present.

Trophoblastic index: 5

Megakaryocytic index: 62

Case 14 R.I.E. necropsy 596/46, 7.12.46. Ward 36

H.C. Age 37

Admitted with an incomplete abortion during 3rd month of pregnancy. Vaginal bleeding for 3 days. Died from haemorrhage.

Histology of lung: patchy collapse.

Trophoblastic index: 4

Megakaryocytic index: 27

Case 15 R.I.E. necropsy 485/46, 30.9.46. Ward 54

J.B. Age 25

Known to have mitral stenosis. Admitted in 3rd month of pregnancy with acute dyspnoeic cardiac failure with pulmonary oedema. Died 1 hour after admission.

Histology of lung: oedema and haemosiderosis.

Trophoblastic index: 0

Megakaryocytic index: 6

Case 16 R.I.E. necropsy 491/46, 4.10.46. Ward 52

J.O. Age 35

Term pregnancy. Ante partum haemorrhage from lateral placenta praevia. Manual removal of placenta required. Transfused. Developed jaundice and haemoglobinuria. Died 10 days later with high blood urea.

Necropsy: haemoglobinuric nephropathy; small infarct of pituitary; slight mitral stenosis.

Case 16 (contd.)

Histology of lung: infected infarct.

Trophoblastic index: 0

Megakaryocytic index: 3

Case 17 R.I.E. necropsy 370/46, 19.7.46. Ward 51

I.P. Age 36

Admitted very collapsed following post partum haemorrhage. Transfused. Developed jaundice and haemoglobinuria. Died 11 days after delivery.

Necropsy: infected blood clot in uterus; haemoglobinuric nephropathy (incompatible transfusion); septicaemia.

Histology of lung: oedema and emphysema.

Trophoblastic index: 0

Megakaryocytic index: 11

Case 18 R.I.E. necropsy 219/46, 29.4.46. Ward 54

E.B. Age 34

Persistent occipito-posterior presentation. Failed manual rotation. Prolapsed non-pulsatile cord. Perforation of head, delivery. Gradual deterioration to death at 8 hours after delivery.

Histology of lung: patchy congestion.

Trophoblastic index: 6

Megakaryocytic index: 140

Case 19 R.I.E. necropsy 76/46, 5.2.46. Ward 54

A.S. Age 22

Persistent occipito-posterior presentation. Failed manual rotation. Poor condition after delivery. Died of sepsis within 14 days of delivery.

Histology of lung: oedema and bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 42

Case 20 R.I.E. necropsy 418/45, 12.11.45. Ward 52

M.P. Age 33

Pre-eclamptic toxaemia treated for 5 weeks. Medical induction of labour at term. Internal version, breech delivery. Collapse, dyspnoea and cyanosis during 24 hours before death at 29th day after delivery.

Necropsy: small portion of retained placenta; local metritis and parametritis; septicaemia.

Histology of lung: patchy collapse and oedema.

Trophoblastic index: 0

Megakaryocytic index: 2

Case 21 R.I.E. necropsy 420/45, 12.11.45. Ward 51

H.C. Age 27

Caesarean section with delivery of still-born infant carried out at 7th month because of increasing jaundice, haematemesis, delirium. Comatose after operation. Died day after operation.

Case 21 (contd.)

Necropsy: acute hepatic necrosis.

Histology of lung: areas of haemorrhagic infarction; mild oedema.

Trophoblastic index: 0

Megakaryocytic index: 42

Case 22 R.I.E. necropsy 260/45, 7.7.45. Ward 54

J.J. Age 36

Concealed and revealed accidental haemorrhage. Delivered of still-born mature infant. Increasing renal failure. Death 8 days after delivery.

Necropsy: renal and hepatic damage of eclamptic type.

Histology of lung: oedema; fibrin plugs in several vessels.

Trophoblastic index: 16

Megakaryocytic index: 37

Case 23 R.I.E. necropsy 239/45, 20.6.45.

C.McD. Age 35

Large baby. Lower segment Caesarean section after 18 hours labour. Died from shock 3½ hours after operation. Poorly contracted uterus.

Histology of lung: severe collapse; some congestion.

Trophoblastic index: 0

Megakaryocytic index: 36

Case 24 R.I.E. necropsy 150/45, 16.4.45. Ward 50

E.I. Age 34

Breech delivery. Severe shock after delivery, died soon thereafter. Regarded as probable renal failure.

Histology of lung: much collapse.

Trophoblastic index: 0

Megakaryocytic index: 14

Case 25 R.I.E. necropsy 116/45, 20.3.45. Ward 54

R.McG. Age 40

Severe eclampsia. Five ante partum and 1 post partum fits. Never regained consciousness, died 24 hours after delivery.

Necropsy: severe eclamptic hepatic necrosis; small cerebral haemorrhage.

Histology of lung: oedema; patchy pneumonia; fibrin plugs in several vessels.

Trophoblastic index: 0

Megakaryocytic index: 23

Case 26 R.I.E. necropsy 119/45, 23.3.45. Ward 54

A.H. Age 28

Admitted 3½ months pregnant. History of increasingly severe jaundice for 2 weeks. Condition rapidly deteriorated. Died undelivered in coma associated with delirium.

Necropsy: acute hepatic necrosis.

Histology of lung: confluent bronchopneumonia;

Case 26 (contd.)

Lung (contd.): fibrin strands in many vessels.

Trophoblastic index: 0

Megakaryocytic index: 5

Case 27 R.I.E. necropsy 123/45, 26.3.45. Ward 52

I.G. Age 33

Patient a known diabetic. Caesarean section performed at term. Sudden onset of coma 24 hours later. Died without regaining consciousness within 2 days of delivery.

Necropsy: severe focal hepatic necrosis of eclamptic type.

Histology of lung: marked intra-alveolar oedema.

Trophoblastic index: 4

Megakaryocytic index: 66

Case 28 R.I.E. necropsy 83/45, 21.2.45. Ward 54

E.B. Age 28

Prolonged labour terminated by mid-forceps extraction. Manual removal of placenta. Severe shock. Complaint of praecordial pain. Died 4 hours after delivery.

Histology of lung: collapse and bronchopneumonia, ? of aspiration type.

Trophoblastic index: 71

Megakaryocytic index: 110

Case 29 R.I.E. necropsy 56/45, 8.2.45. Ward 54

M.R. Age 39

History of hypertension in previous pregnancy 2 years earlier. Admitted in 4th month of pregnancy. Pregnancy terminated. Developed right, then left, hemiplegia 2 days later. Complete paralysis by time of death on 4th day after delivery.

Necropsy: polycystic kidneys; concentric hypertrophy of left ventricle; subarachnoid haemorrhage.

Histology of lung: bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 45

Case 30 R.I.E. necropsy 402/44, 8.12.44. Ward 54

M.McK. Age 32

Admitted after 4 days in labour. Forceps delivery. Drowsy, vomiting after delivery. Died 2 days after delivery.

Necropsy: acute hepatic necrosis.

Histology of lung: early bronchopneumonia.

Trophoblastic index: 5

Megakaryocytic index: 22

Case 31 R.I.E. necropsy 322/44, 16.10.44. Ward 53

C.C. Age 32

Admitted in 5th month of pregnancy with convulsions. Pregnancy terminated. Rapid collapse to death 24

Case 31 (contd.)

hours later.

Necropsy: eclamptic necrosis of liver; petechial haemorrhages into endocardium, lung, peritoneum; small scattered haemorrhages in putamen.

Histology of lung: severe oedema.

Trophoblastic index: 5

Megakaryocytic index: 12

Case 32 R.I.E. necropsy 246/44, 24.7.44. Ward 49

E.D. Age 30

Admitted in 5th month of pregnancy. Vomiting and headaches for previous 5 weeks. Died suddenly, undelivered, 1 week after admission.

Necropsy: cerebellar glioma; acute suppurative pyelonephritis.

Histology of lung: marked oedema.

Trophoblastic index: 0

Megakaryocytic index: 9

Case 33 R.I.E. necropsy 222/44, 30.6.44. Ward 52

A.S. Age 38

Prolonged labour (50 hours) terminated by forceps extraction. Took anaesthetic badly, died shortly after delivery.

Necropsy: marked fatty infiltration of myocardium.

Histology of lung: basal congestion and oedema.

Case 33 (contd.)

Trophoblastic index: 0

Megakaryocytic index: 8

Case 34 R.I.E. necropsy 166/44, 17.5.44. Ward 54

A.H. Age 28

Admitted for elective Caesarean section because of disproportion. Complaint of headaches for 2 to 3 weeks. Labour began but no true trial of labour permitted. Caesarean section. Died 3 days later.

Necropsy: pulmonary tuberculosis; tuberculous meningitis.

Histology of lung: fibrocaseous tuberculosis.

Trophoblastic index: 2

Megakaryocytic index: 42

Case 35 R.I.E. necropsy 168/44, 18.5.44. Ward 51

E.L. Age 24

Severe eclampsia. Sixteen fits in all. Never regained consciousness. Died 8 hours after delivery.

Necropsy: multiple haemorrhages and eclamptic histology in liver.

Histology of lung: collapse and early broncho-pneumonia; fibrin plugs in several vessels.

Trophoblastic index: 10

Megakaryocytic index: 42

Case 36 R.I.E. necropsy 177/44, 26.5.44. Ward 49

E.J. Age 18

Admitted for emergency removal of high retrocaecal appendix. Recovery good until 17th post-operative day when miscarried a 3 months foetus. Developed rigor and tenderness in renal angle. Collapsed and died 8 hours after miscarriage.

Necropsy: offensive uterine content; left pyelitis; septicaemia.

Histology of lung: multiple fibrin plugs in vessels.

Trophoblastic index: 40

Megakaryocytic index: 96

Case 37 R.I.E. necropsy 183/44, 29.5.44.

Mrs.H. Age 45

Spontaneous term delivery. Severe post partum haemorrhage. Died 24 hours later with anuria.

Necropsy: perforated lower uterine segment.

Histology of lung: collapse and congestion.

Trophoblastic index: 0

Megakaryocytic index: 118

Case 38 R.I.E. necropsy 122/44, 14.4.44. Ward 51

H.H. Age 36

Prolonged labour. Died from rupture of uterus and massive collapse of left lung 10 days after delivery.

Histology of lung: marked intra-alveolar oedema.

Trophoblastic index: 0

Megakaryocytic index: 18

Case 39 R.I.E. necropsy 436/43, 11.12.43. Ward 54

J.B. Age 33

Large baby, long labour. Forceps extraction failed. Craniotomy required for delivery. Manual removal of placenta. Collapsed and died 4 hours after delivery.

Necropsy: ruptured bladder; ruptured uterus; patchy necrosis of liver.

Histology of lung: collapse and oedema.

Trophoblastic index: 29

Megakaryocytic index: 115

Case 40 R.I.E. necropsy 381/43, 23.10.43. Ward 50

M.F. Age 31

Prolonged labour (43 hours) terminated by mid-forceps extraction. Collapsed before recovery from anaesthetic, and died 1½ hours after delivery.

Necropsy: generalised hepatic necrosis; similar changes in kidneys.

Histology of lung: patchy collapse, intra-alveolar oedema; a few vessels contain squames and strands of mucin indicating amniotic embolism.

Trophoblastic index: 26

Megakaryocytic index: 55

Case 41 R.I.E. necropsy 355/43, 1.10.43. Ward 54

B.D. Age 20

Admitted at term seriously ill, complaining of vomiting and abdominal pain for 4 days. Delivered next day, died 8 hours after delivery.

Necropsy: pyelonephritis; perinephric abscess; generalised peritonitis.

Histology of lung: early bronchopneumonia; fibrinous pleurisy.

Trophoblastic index: 0

Megakaryocytic index: 195

Case 42 R.I.E. necropsy 340/43, 13.9.43. Ward 54

M.K. Age 23

Lateral placenta praevia. Medical induction. Prolonged labour. Death occurred "immediately on delivery".

Necropsy: no convincing cause of death discovered.

Histology of lung: no significant changes.

Trophoblastic index: 10

Megakaryocytic index: 188

Case 43 R.I.E. necropsy 276/43, 19.7.43. Ward 54

I.T. Age 28

Pre-eclamptic toxaemia for 1 month before admission. Eclamptic fit 10 hours after delivery; 16 more thereafter. Died 48 hours after delivery.

Necropsy: severe liver necrosis; renal tubular damage.

Case 43 (contd.)

Histology of lung: patchy oedema; early broncho-pneumonia.

Trophoblastic index: 4

Megakaryocytic index: 34

Case 44 R.I.E. necropsy 259/43, 6.7.43. Ward 53

M.R. Age 35

Prolonged labour. Caesarean section. Collapsed and died 1 hour after operation.

Necropsy: no significant lesion discovered.

Histology of lung: patchy collapse.

Trophoblastic index: 6

Megakaryocytic index: 160

Case 45 R.I.E. necropsy 120/43, 22.3.43. Ward 52

M.P. Age 42

Admitted with 5 day history of diarrhoea and vomiting, and lower abdominal pain in 6th month of pregnancy. Developed uraemic twitching and anuria. Died undelivered 6 days later.

Necropsy: renal cortical necrosis; necrotising colitis.

Histology of lung: collapse, congestion, broncho-pneumonia.

Trophoblastic index: 0

Megakaryocytic index: 17

Case 46 R.I.E. necropsy 47/43, 30.1.43. Ward 54

C.R. Age 38

Hyperemesis and some toxaemia during last 3 months of pregnancy. Developed high pyrexia after delivery, dying 4 days thereafter.

Necropsy: acute purulent pericarditis. Retained placental tissue.

Histology of lung: bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 3

Case 47 R.I.E. necropsy 1/43, 2.1.43. Ward 54

H.R. Age 28

Died 7 days after delivery with fulminating puerperal infection, paralytic ileus and bilateral pyelitis.

Histology of lung: collapse, congestion, some emphysema; fibrin plugs in a few vessels.

Trophoblastic index: 2

Megakaryocytic index: 74

Case 48 R.I.E. necropsy 8/43, 7.1.43. Ward 54

A.R. Age 37

Severe pre-eclamptic toxaemia. Concealed accidental haemorrhage during delivery. Anuria from delivery until death on 2nd day after delivery.

Necropsy: eclamptic changes in liver; renal tubular degeneration.

Case 48 (contd.)

Histology of lung: patchy oedema.

Trophoblastic index: 30

Megakaryocytic index: 29

Case 49 R.I.E. necropsy 404/42, 14.11.42

J.B. Age 38

Admitted in 7th month of pregnancy with history of toxaemic symptoms for 1 week. Developed hemiplegia. Uterus evacuated. Died 2 days later.

Necropsy: massive cerebral haemorrhage. Little evidence of toxic change in liver or kidneys.

Histology of lung: confluent bronchopneumonia; some fibrin plugs.

Trophoblastic index: 0

Megakaryocytic index: 28

Case 50 R.I.E. necropsy 329/42, 19.9.42. Ward 54

A.S. Age 36

Admitted at term with mild pre-eclamptic toxaemia. Forceps extraction because of uterine inertia. Manual removal of placenta. Died 9 days after delivery.

Necropsy: puerperal sepsis with septicaemia; pericarditis; endocarditis with septic infarctions.

Histology of lung: patchy infarction with haemosiderosis.

Case 50 (contd.)

Trophoblastic index: 0

Megakaryocytic index: 12

Case 51 R.I.E. necropsy 340/42, 29.9.42. Ward 49

M.McD. Age 39

Admitted during 5th month of pregnancy with pyelitis. Developed peritonitis 2 days later. Spontaneous abortion 9 days after admission. Condition deteriorated to death 2 days after the abortion.

Necropsy: peritonitis from perforation in a region of ileo-colitis; apical tuberculosis.

Histology of lung: pulmonary tuberculosis.

Trophoblastic index: 6

Megakaryocytic index: 52

Case 52 R.I.E. necropsy 295/42, 24.8.42. Ward 54

E.L. Age 28

Long labour associated with uterine inertia. Mid-forceps extraction. Condition poor after delivery and rapidly deteriorated to death within 24 hours.

Histology of lung: bronchopneumonia and pulmonary oedema.

Trophoblastic index: 0

Megakaryocytic index: 33

Case 53 R.I.E. necropsy 257/42, 25.7.42. Ward 54

A.K. Age 26

Prolonged labour. Mid-forceps extraction. Severe shock. Died 2 hours after delivery.

Necropsy: acute suppurative pyelonephritis.

Histology of lung: marked congestion and collapse.

Trophoblastic index: 50

Megakaryocytic index: 140

Case 54 R.I.E. necropsy 188/42, 26.5.42. Ward 36

N.J. Age 28

Incomplete 3 months' abortion. Severe vaginal bleeding for 2 weeks before admission. Died 24 hours after transfusion from ? incompatibility, ? severe anaemia.

Histology of lung: oedema and congestion.

Trophoblastic index: 5

Megakaryocytic index: 3

Case 55 R.I.E. necropsy 193/42, 29.5.42. Ward 52

M.B. Age 19

Admitted having been found comatose during 8th month of pregnancy. B.P. 240/140. Infant delivered spontaneously and died shortly afterwards. Mother remained comatose, dying 36 hours after delivery without regaining consciousness.

Necropsy: liver very autolytic but appearances resembled those of eclampsia.

Case 55 (contd.)

Histology of lung: patchy infarction; oedema; some fibrin plugs.

Trophoblastic index: 12

Megakaryocytic index: 34

Case 56 R.I.E. necropsy 169/42, 11.5.42. Ward 54

J.B. Age 30

Slight pre-eclamptic toxaemia. Easy low forceps delivery followed 1 hour later by complaint of shoulder tip pain, and rapidly developing pulmonary oedema. Died 18 hours after delivery.

Necropsy: irregular collapse and consolidation of lungs.

Histology of lung: aspiration bronchopneumonia.

Trophoblastic index: 5

Megakaryocytic index: 39

Case 57 R.I.E. necropsy 174/42, 16.5.42. Ward 54

J.H. Age 24

Long labour (66 hours) terminated by forceps extraction. Sudden death 14 days after delivery.

Necropsy: massive pulmonary embolism; urinary tract infection.

Histology of lung: collapse and congestion; a few fibrin plugs.

Trophoblastic index: 0

Megakaryocytic index: 8

Case 58 R.I.E. necropsy 127/42, 4.4.42. Ward 51

L.G. Age 28

Severe pre-eclamptic toxaemia. Inevitable abortion at 6th month of pregnancy. Almost complete anuria during the 6 days between delivery and death.

Necropsy: partial bilateral renal cortical necrosis; acute pyelitis.

Histology of lung: patchy oedema.

Trophoblastic index: 0

Megakaryocytic index: 32

Case 59 R.I.E. necropsy 79/42, 6.3.42. Ward 54

D.McL. Age 24

Peritonitis developed 12 days after delivery. Laparotomy for drainage. Death from septicaemia 3 days after the operation.

Necropsy: peritonitis; cellulitis of abdominal wall; low-grade endometritis.

Histology of lung: patchy congestion.

Trophoblastic index: 0

Megakaryocytic index: 132

Case 60 R.I.E. necropsy 91/42, 12.3.42. Ward 54

M.T. Age 27

Admitted because of failed forceps extraction. Heavy bleeding. Craniotomy performed. Died within one week of delivery.

Case 60 (contd.)

Necropsy: ruptured uterus; multilobular hepatic cirrhosis.

Histology of lung: marked emphysema.

Trophoblastic index: 0

Megakaryocytic index: 8

Case 61 R.I.E. necropsy 56/42, 21.2.42. Ward 52

M.S. Age ?

Arsenical dermatitis for 3 weeks. Premature delivery of still-born infant. Convulsion 3 days after delivery. Died the next day.

Necropsy: superior longitudinal sinus thrombosis; toxic changes in liver and kidneys.

Histology of lung: marked congestion.

Trophoblastic index: 0

Megakaryocytic index: 66

Case 62 R.I.E. necropsy 69/42, 2.3.42. Ward 54

E.G. Age 38

Admitted in 8th month of pregnancy with pyrexia of undetermined origin. Died 10 days after delivery.

Necropsy: septicaemia; septic endometritis.

Histology of lung: congestion; small fibrin plugs in several of the smaller vessels.

Trophoblastic index: 0

Megakaryocytic index: 18

Case 63 R.I.E. necropsy 16/42, 14.1.42. Ward 36

J.T. Age 30

Admitted during 4th month of pregnancy with abortion. Perforation of uterus during evacuation. Death 4 hours later from massive haemoperitoneum.

Histology of lung: some emphysema.

Trophoblastic index: 0

Megakaryocytic index: 3

Case 64 R.I.E. necropsy 455/41, 27.11.41. Ward 53

J.H. Age 31

Admitted with severe anaemia. Transfused. Normal term delivery 4 days later. Second transfusion 13 days after delivery because of increasing anaemia, followed 6 hours later by rigor and death in acute haemolytic crisis.

Necropsy: acute rheumatic carditis.

Histology of lung: marked oedema.

Trophoblastic index: 0

Megakaryocytic index: 3

Case 65 R.I.E. necropsy 411/41, 28.10.41. Ward 51

M.C. Age 20

Fulminating puerperal eclampsia; 26 fits over a period of 20 hours, starting 3 hours after delivery. No history of pre-eclamptic toxaemia.

Necropsy: eclamptic necrosis of liver, kidneys.

Case 65 (contd.)

Histology of lung: patchy oedema and congestion.

Trophoblastic index: 0

Megakaryocytic index: 22

Case 66 R.I.E. necropsy 352/41, 18.9.41. Ward 54

J.McK. Age 23

Persistent occipito-posterior presentation. Manual rotation and mid-forceps extraction. Developed vomiting with abdominal tenderness and slight jaundice. Gradual deterioration with tachycardia. Death within 48 hours of delivery.

Necropsy: toxic changes, ? eclamptic, in liver, kidneys.

Histology of lung: congestion; oedema.

Trophoblastic index: 5

Megakaryocytic index: 51

Case 67 R.I.E. necropsy 356/41, 24.9.41.

C.D. Age 28

Mid-forceps extraction because of foetal distress. Tendency to vomit during anaesthesia. Respiratory distress developed after delivery with death 8 hours later.

Necropsy: marked pulmonary congestion and oedema.

Histology of lung: haemorrhagic aspiration pneumonia.

Trophoblastic index: 20

Megakaryocytic index: 74

Case 68 R.I.E. necropsy 318/41, 16.8.41. Ward 52

J.B. Age 41

History of pre-eclamptic toxaemia. Admitted because of concealed and revealed accidental haemorrhage. Delivered of stillborn infant. Died with severe loss of blood 4 hours after delivery.

Necropsy: moderate degree of hepatic necrosis.

Histology of lung: oedema; occasional fibrin plugs.

Trophoblastic index: 10

Megakaryocytic index: 113

Case 69 R.I.E. necropsy 284/41, 12.7.41. Ward 52

M.C. Age 20

Admitted in labour following blow on abdomen during 7th month of pregnancy. Signs of some infective process developed. Gradual deterioration to death at 20 days after delivery.

Necropsy: pulmonary tuberculosis; tuberculous peritonitis.

Histology of lung: fibrocaseous tuberculosis.

Trophoblastic index: 0

Megakaryocytic index: 25

Case 70 R.I.E. necropsy 290/41, 18.7.41. Ward 35

C.W. Age 26

Myasthenia gravis diagnosed 2½ years before admission for hysterotomy in 5th month of pregnancy: had developed 6 months after birth of first baby. Second

Case 70 (contd.)

baby 11 months before admission: condition became much worse after that pregnancy. Died 48 hours after hysterotomy.

Histology of lung: oedema and bronchopneumonia, probably of aspiration type.

Trophoblastic index: 0

Megakaryocytic index: 42

Case 71 R.I.E. necropsy 269/41, 1.7.41. Ward 53

J.G. Age 24

Admitted because of failed forceps extraction. Successful forceps delivery after admission. Died 20 hours after delivery of "heart failure".

Necropsy: patchy liver necrosis.

Histology of lung: severe oedema and bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 77

Case 72 R.I.E. necropsy 154/41, 2.4.41. Ward 51

I.J. Age 28

Five eclamptic fits before admission. Low forceps delivery following induction. Condition improved thereafter but died suddenly 24 hours after delivery.

Necropsy: hepatic necrosis of eclamptic type.

Histology of lung: patchy oedema and bronchopneumonia.

Trophoblastic index: 6

Megakaryocytic index: 5

Case 73 R.I.E. necropsy 110/41, 6.3.41. Ward 52

E.F. Age 30

Long labour, persistent occipito-posterior presentation. Mid-forceps extraction. Manual removal of placenta. Gradual deterioration to death 5 days after delivery.

Necropsy: septic endometritis; patchy hepatic necrosis.

Histology of lung: focal oedema and congestion.

Trophoblastic index: 0

Megakaryocytic index: 11

Case 74 R.I.E. necropsy 76/41, 15.2.41. Ward 35

M.L. Age 22

Admitted during 4th month of pregnancy: spontaneous abortion with severe haemorrhage. Died from peritonitis and septicaemia 9 days later.

Histology of lung: patchy oedema; severe autolytic change.

Trophoblastic index: 0

Megakaryocytic index: 7

Case 75 R.I.E. necropsy 62/41, 7.2.41. Ward 41

A.O'B. Age 31

Severe pre-eclamptic toxaemia for 14 days before admission. One convulsion after admission, then labour induced. Difficult forceps delivery: contraction ring developed. Died within a few hours

Case 75 (contd.)

of delivery.

Necropsy: eclamptic hepatic necrosis.

Histology of lung: severe collapse.

Trophoblastic index: 0

Megakaryocytic index: 10

Case 76 R.I.E. necropsy 34/41, 21.1.41. Ward 52

J.G. Age 30

Admitted during 8th month of pregnancy with history suggestive of pre-eclamptic toxaemia. Died suddenly, undelivered.

Necropsy: rupture of dissecting aortic aneurysm into pericardium.

Histology of lung: patchy collapse.

Trophoblastic index: 0

Megakaryocytic index: 7

Case 77 R.I.E. necropsy 23/41, 15.1.41. Ward 54

M.M. Age 32

Admitted during 7th month of pregnancy. Membranes had been ruptured for 10 days. Purulent liquor amnii. Developed peritonitis; was improving but developed pneumonia and pleurisy with effusion. Died 30 days after evacuation of uterus.

Histology of lung: severe bronchopneumonia; some hyaline membrane formation in alveolar ducts.

Trophoblastic index: 0

Megakaryocytic index: 50

Case 78 R.I.E. necropsy 530/40, 13.12.40. Ward 54

C.S. Age 38

Admitted during 3rd day of labour at term, pyrexial with some rigors. Craniotomy performed. Died, severely shocked, 7 hours after delivery.

Necropsy: pyelonephritis.

Histology of lung: patchy collapse.

Trophoblastic index: 25

Megakaryocytic index: 60

Case 79 R.I.E. necropsy 534/40, 14.12.40. Ward 54

I.C. Age 23

Normal term delivery. Sudden collapse 60 hours thereafter; death within 6 hours of collapse.

Necropsy: fulminating infection of lower uterine segment and cervix.

Histology of lung: no significant changes.

Trophoblastic index: 0

Megakaryocytic index: 46

Case 80 R.I.E. necropsy 536/40, 17.12.40. Ward 53

A.F. Age 20

Fulminating eclampsia starting 11 days before delivery. Nine convulsions on day of delivery, controlled by sedation. Spontaneous delivery of stillborn infant. Died from collapse and "heart failure" 7 hours after delivery.

Necropsy: severe eclamptic hepatic necrosis.

Case 80 (contd.)

Histology of lung: marked congestion.

Trophoblastic index: 20

Megakaryocytic index: 15

Case 81 R.I.E. necropsy 369/40, 13.8.40. Ward 54

J.McQ. Age 33

Admitted severely shocked following abortion and extraction of 4½ months' foetus and placenta.

Necropsy: deep cervical laceration.

Histology of lung: patchy collapse, generalised congestion.

Trophoblastic index: 10

Megakaryocytic index: 52

Case 82 R.I.E. necropsy 358/40, 5.8.40. Ward 34

Mrs.W. Age 36

Admitted for myomectomy. Uterus contained 2½ months' pregnancy. Died undelivered 10 days after operation from massive pulmonary embolism.

Histology of lung: marked oedema and congestion.

Trophoblastic index: 0

Megakaryocytic index: 2

Case 83 R.I.E. necropsy 308/40, 29.6.40. Ward 52

C.J. Age 19

Admitted during 8th month of pregnancy complaining of increasing dyspnoea. Died suddenly.

Case 83 (contd.)

Necropsy: acute rheumatic pancarditis; mitral and aortic valvular lesions; chronic venous congestion of lungs and liver.

Histology of lung: unusual consolidation, similar in places to lipid pneumonia.

Trophoblastic index: 25

Megakaryocytic index: 29

Case 84 R.I.E. necropsy 313/40, 3.7.40. Ward 52

E.S. Age 30

Prolonged labour. Mid-forceps extraction. Became jaundiced 2 days after delivery; died on the following day.

Necropsy: puerperal sepsis; extensive hepatic necrosis.

Histology of lung: confluent bronchopneumonia.

Trophoblastic index: 22

Megakaryocytic index: 82

Case 85 R.I.E. necropsy 214/40, 17.4.40. Ward 53

M.L. Age 39

Prolonged labour (3 to 5 days) terminating in delivery by craniotomy. Persistent vomiting thereafter. Died of shock 24 hours after delivery.

Histology of lung: marked autolytic change only.

Trophoblastic index: 4

Megakaryocytic index: 4

Case 86 R.I.E. necropsy 167/40, 18.3.40. Ward 51

M.B. Age 31

Mild pre-eclamptic toxaemia. Spontaneous delivery at term. Died 2 hours later.

Necropsy: no cause of death discovered.

Histology of lung: congestion and slight oedema.

Trophoblastic index: 4

Megakaryocytic index: 19

Case 87 R.I.E. necropsy 169/40, 19.3.40. Ward 52

M.A. Age 26

Severe eclampsia. Many convulsions before, and one 2 days after delivery at term. Anuria developed after delivery and persisted until death 3 days later.

Necropsy: focal eclamptic necrosis of liver.

Histology of lung: marked oedema.

Trophoblastic index: 0

Megakaryocytic index: 47

Case 88 R.I.E. necropsy 122/40, 20.2.40. Ward 53

N.M. Age 32

Died 4 days after delivery of second twin. Placenta of first was retained and required manual removal.

Necropsy: septic endometritis and septicaemia; focal hepatic necrosis; necrosis of anterior lobe of pituitary.

Histology of lung: mild oedema only.

Trophoblastic index: 0

Megakaryocytic index: 13

Case 89 R.I.E. necropsy 45/40, 15.1.40. Ward 52

J.G. Age 32

Admitted at term with pre-eclamptic toxaemia. Intra-uterine foetal death; craniotomy; spontaneous delivery. Developed hemiplegia, became comatose and died within 4 days of delivery.

Histology of lung: marked oedema; purulent bronchitis.

Trophoblastic index: 0

Megakaryocytic index: 6

Case 90 St. A. Univ. Path. Dept. 25632/43.

J.H. Age 27

Admitted to hospital 9 days after instrumental delivery: perineal lacerations, oedema of vulva, abdominal distension. Developed rigors and high pyrexia. Died 28 days after delivery.

Necropsy: septic endometritis; septic infarct of lung.

Histology of lung: confluent bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 2

Case 91 St. A. Univ. Path. Dept. 29981/49.

T.McF. Age 37

Admitted at term with mild pre-eclamptic toxaemia. Caesarean section performed for uterine inertia. Died the following day with respiratory distress.

Case 91 (contd.)

Necropsy: chronic pyelonephritis; pulmonary collapse and congestion.

Histology of lung: bronchopneumonia of aspiration type.

Trophoblastic index: 0

Megakaryocytic index: 3

Case 92 Dundee R.I. necropsy 204/49, 4.2.49.

M.M. Age 37

Admitted in 5th month of pregnancy with signs of concealed accidental haemorrhage. Several rigors preceded abortion. Oliguria and high pyrexia during the 12 days between abortion and death in uraemia.

Necropsy: septic endometritis and parametritis; pyelonephritis.

Histology of lung: patchy infarction and bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 24

Case 93 Dundee R.I. necropsy 1378/47, 25.11.47.

M.McI. Age 17

Admitted at term having had 3 eclamptic convulsions. Spontaneous delivery. Convulsions continued; became hyperpyrexial and died without regaining consciousness.

Case 93 (contd.)

Necropsy: cerebral oedema; subcapsular haemorrhages over liver.

Histology of lung: early bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 38

Case 94 Royal Maternity Hospital, Glasgow, necropsy, 1951 (courtesy of Dr. A. D. T. Govan)

Mrs.L. Age 30

Spontaneous delivery of twins during 8th month of pregnancy. Retained placenta removed manually with difficulty. Severe collapse thereafter.

Necropsy: pulmonary embolism; chronic bronchitis with some emphysema.

Histology of lung: congestion and slight oedema.

Trophoblastic index: 8

Megakaryocytic index: 70

Case 95 Dundee R.I., medico-legal necropsy, 1951.

M.D. Age 24

Admitted severely ill and died 3 days later from overwhelming toxaemia. Unsuspected 3 months' pregnancy discovered at necropsy. Attempted criminal abortion.

Histology of lung: bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 6

Case 96 Dundee R.I. necropsy 464/51.

M.P. Age 26

Mild pre-eclamptic toxaemia during last month of pregnancy but normal spontaneous delivery at term. Readmitted 11 days after delivery having repeated convulsive attacks. Developed hemiplegia. Died 15 days after delivery.

Necropsy: massive softening frontal pole of left cerebral hemisphere.

Histology of lung: patchy collapse.

Trophoblastic index: 0

Megakaryocytic index: 53

Case 97 Ayrshire Central Hospital, Irvine; necropsy, February 1947, (courtesy of Professor A. C. Lendrum)

A.H. Age 25

Admitted during 20th week of pregnancy with severe vaginal haemorrhage and marked toxaemia. Had had treatment for essential hypertension with severe cardiac asthma; B.P. 200/110. Spontaneous delivery hydatidiform mole. Heavy blood loss. Was transfused but died with cardiac asthma 5 hours after delivery.

Histology of lung: gross oedema.

Trophoblastic index: 5

Megakaryocytic index: 18

Case 98 Dundee R.I. necropsy 813/46.

G.W. Age 35

Admitted having had an abortion 12 days earlier during 4th month of pregnancy; complaining of sudden swelling and pain in left lower limb. Manual removal of placenta. Gradual general deterioration to death.

Necropsy: pelvic vein thromboses; patent foramen ovale; marked right ventricular hypertrophy and dilatation.

Histology of lung: generalised congestion.

Trophoblastic index: 0

Megakaryocytic index: 62

Case 99 Dundee R.I. necropsy 451/45.

S.T. Age 35

Had been treated for refractory anaemia during pregnancy. Admitted during 8th month with pleuritic pain and signs of pulmonary infarction. Medical induction of labour which started 9 days later. Severe blood loss before and after delivery. Uterus failed to contract.

Necropsy: uterus distended with clot; three large infarctions of lung.

Histology of lung: subpleural haemorrhages.

Trophoblastic index: 0

Megakaryocytic index: 8

Case 100 Dundee R.I. necropsy 420/45.

J.McI. Age 33

Prolonged labour (60 hours). Caesarean section for uterine inertia. Condition poor post-operatively; much blood loss. Plasma infusion started but patient complained of chest pain, developed a rigor, died.

Necropsy: extensive bilateral bronchopneumonia, probably of aspiration type; marked dilatation right heart.

Histology of lung: bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 112

Case 101 Dundee R.I. necropsy 531/40

I.A. Age 37

Admitted after 3 months' amenorrhoea with severe abdominal pain. Ruptured tubal gestation found at laparotomy. Severe diarrhoea developed 11 days later. Gradual deterioration, with continuing diarrhoea, to death at 16th post-operative day.

Necropsy: ileitis and dysenteric colitis; thrombosis of left femoral and iliac veins.

Histology of lung: bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 8

Case 102 Dundee R.I. necropsy 6/39.

S.S. Age 44

Admitted at term having had 4 eclamptic convulsions. B.P. 160/100. Spontaneous delivery of stillborn infant. Temperature and pulse rate rose progressively to death 2 days after delivery.

Necropsy: toxic changes in liver; left ventricular hypertrophy.

Histology of lung: oedema; bronchopneumonia.

Trophoblastic index: 0

Megakaryocytic index: 16

Case 103 Dundee R.I. necropsy 73/39.

G.S. Age 33

Emergency admission with severe post partum haemorrhage and retained placenta. Manual removal of placenta. Pyrexial thereafter "despite Prontosil". Gradual deterioration to death 6 days after delivery.

Necropsy: septic endometritis; extensive pelvic vein thrombosis.

Histology of lung: extensive bronchopneumonia; oedema.

Trophoblastic index: 0

Megakaryocytic index: 28

Case 104 Dundee R.I. necropsy 371/38.

A.G. Age 24

A known epileptic. Had several convulsions and became unconscious 5 days after normal term delivery: never regained consciousness.

Necropsy: pyelonephritic scarring in one kidney; death considered to be due to status epilepticus.

Histology of lung: some intra-alveolar haemorrhage.

Trophoblastic index: 0

Megakaryocytic index: 3

Case 105 Kingston General Hospital necropsy, 1949 (courtesy of Dr. J. C. Lees).

W.S. Age 37

Treated with hexamethonium compounds from 17th week of the 8th pregnancy for severe hypertension. Died after spontaneous delivery at term having had increasingly severe respiratory distress for the preceding week.

Necropsy: "solid oedema" of the lungs; left ventricular hypertrophy.

Histology of lung: "hexamethonium lung".

Trophoblastic index: 1

Megakaryocytic index: 70

Case 106 Bridge of Earn Hospital necropsy, 169/52 (courtesy of Dr. J. H. Prain).

M.D. Age 32

Admitted at term in labour. Head failed to engage despite strong uterine contractions. Caesarean section performed. Patient collapsed and died a few hours after the operation.

Necropsy: massive blood clot in left broad ligament, extending upwards in the retroperitoneal tissues to surround the kidney.

Histology of lung: partial collapse; mild oedema.

Trophoblastic index: 1

Megakaryocytic index: 2

Case 107 Dundee R.I. necropsy 412/51.

V.B. Age 32

Admitted during 8th month of pregnancy with complaint of severe lower abdominal pain and some vomiting of blood. Was severely anaemic. Shortly after beginning of blood transfusion collapsed suddenly: uterus became enlarged, hard and tender. Died undelivered.

Necropsy: large retroplacental blood clot and complete separation of placenta; some retroperitoneal haemorrhage; dilated right heart.

Case 107 (contd.)

Histology of lung: oedema; fibrin plugs in some vessels; one small focus of decidual tissue present.

Trophoblastic index: 9

Megakaryocytic index: 10

Case 108 Kingston General Hospital necropsy, 1950 (courtesy of Dr. J. C. Lees).

Age 26

Pulmonary tuberculosis discovered during pregnancy. Spontaneous delivery at term. Rapid collapse thereafter to death 6 hours later.

Necropsy: fibrocaseous pulmonary tuberculosis.

Histology of lung: active tuberculous foci; congestion; two particles of bone marrow seen within vessels.

Trophoblastic index: 1

Megakaryocytic index: 86

Case 109 Kingston General Hospital necropsy, 1950 (courtesy of Dr. J. C. Lees).

Age 30

Found moribund 2 days after delivery of mature infant following concealed pregnancy. Died from toxaemia and shock within a few hours of discovery.

Necropsy: patchy hepatic necrosis.

Case 111 (contd.)

despite bronchoscopic suction, remained so, dying 24 hours after delivery.

Necropsy: haemorrhagic collapse and consolidation of lungs.

Histology of lung: aspiration bronchopneumonia.

Trophoblastic index: 3

Megakaryocytic index: 88

Case 112 Dundee R.I. necropsy 659/51.

E.R. Age 18

Admitted during 8th month of pregnancy having had 2 convulsions. B.P. 185/135. Sudden attack of left ventricular failure on the following day: partial recovery and forceps delivery of premature infant. Sudden drop in pulse rate and respiratory rate: terminal hyperpyrexia. Died 2½ hours after delivery.

Necropsy: eclamptic hepatic necrosis; pulmonary oedema.

Histology of lung: early bronchopneumonia.

Trophoblastic index: 75

Megakaryocytic index: 120

Case 113 Dundee R.I. necropsy 713/52.

A.C. Age 35

Admitted during 5th month of pregnancy with pulmonary tuberculosis for therapeutic hysterotomy. Sudden death preceded by palpitations and dyspnoea for 2

Case 113 (contd.)

hours on 7th post-operative day.

Necropsy: massive pulmonary embolism; active bilateral apical pulmonary tuberculosis.

Histology of lung: fibrocaseous tuberculosis; some oedema.

Trophoblastic index: 0

Megakaryocytic index: 6

Case 114 Dundee R.I. necropsy 1741/54.

M.C. Age 43

Admitted at term in labour. No abnormalities found during regular attendances at ante-natal clinic. Membranes ruptured (meconium-stained liquor) after 19 hours in labour. Patient felt sick within 10 minutes of rupture of the membranes and died dyspnoeic, convulsive and cyanotic 5 minutes later.

Necropsy: asphyxial cyanosis with great dilatation of the right heart; normal infant in a normal uterus.

Histology of lung: mucin and squames in many vessels - amniotic embolism.

Trophoblastic index: 0

Megakaryocytic index: 11

Case 115 Hairmyres Hospital, necropsy 1952 (courtesy of Dr. J. P. A. Halcrow).

Mrs.S. Age 30

Case 115 (contd.)

Admitted to hospital at term in state of shock having collapsed suddenly. Spontaneous delivery of still-born infant. Large retroplacental clot: severe post partum haemorrhage. Condition remained poor. Developed oliguria and then anuria during the 16 days between delivery and death in complete renal failure.

Necropsy: bilateral renal cortical necrosis.

Histology of lung: congestion and oedema.

Trophoblastic index: 8

Megakaryocytic index: 16

Case 116 Withington Hospital, Manchester, necropsy 1954 (courtesy of Dr. Lois Stent).

Age 32

Labour induced because of post-maturity. Six hours after onset of labour, appearance of liquor amnii noted. One hour later patient suddenly became cyanosed, dyspnoeic, shocked. Death followed after a further 1½ hours: "? obstetric shock".

Necropsy: no obvious cause of death: normal mature infant within the uterus.

Histology of lung: many vessels contain squames and clumps of mucin - amniotic embolism.

Trophoblastic index: 0

Megakaryocytic index: 3

Case 117 Dundee R.I. necropsy 1747/54.

H.W. Age 27

Twin pregnancy. Admitted during 8th month of pregnancy with pre-eclampsia: B.P. 150/100. B.P. continued to rise; was 170/115 three weeks later; retinal haemorrhages developed. Eclamptic convulsions began suddenly during 4th week in hospital. Forceps delivery of stillborn twins. Death followed in hyperpyrexia within 1 hour of delivery.

Necropsy: massive pontine haemorrhage; widespread subcapsular haemorrhage over liver.

Histology of lung: patchy collapse, congestion, oedema.

Trophoblastic index: 60

Megakaryocytic index: 16

Case 118 Maryfield Hospital (Dundee) necropsy 210/55 (courtesy of Dr. H. McD. Cameron).

J.M. Age 24

Admitted during 8th month of pregnancy with sudden onset of upper abdominal pain. B.P. 220/120. Gross albuminuria. Treated as pre-eclamptic toxaemia. Had several convulsions and lapsed into coma, B.P. 240/190. Jaundice evident. Jaundice and coma deepened, patient dying undelivered on the day after admission.

Case 118 (contd.)

Necropsy: massive cerebral haemorrhage; severe eclamptic necrosis of liver with many subcapsular haemorrhages; no retro-placental haematoma.

Histology of lung: marked congestion; occasional intra-alveolar haemorrhages.

Trophoblastic index: 210

Megakaryocytic index: 120

Case 119 Dundee R.I. necropsy 2046/55.

P.B. Age 21

Normal pregnancy. Died whilst under general anaesthetic for external version to correct a breech presentation. Death occurred shortly after an injection of Scoline.

Necropsy: asphyxial changes; normal infant in intact amniotic sac; uterus normal.

Histology of lung: patchy oedema and intra-alveolar haemorrhage.

Trophoblastic index: 0

Megakaryocytic index: 52

Case 120 Glasgow Western Infirmary necropsy (courtesy of Dr. J. M. Johnstone: Case Report, Johnstone, J. M. and McCallum, Scottish Med. J., 1, 360, 1956).

Age 33

Case 120 (contd.)

Foetal heart sounds ceased 3 hours after onset of labour. Labour pains became very severe. Vaginal haemorrhage profuse. Patient collapsed and died before treatment could be instituted.

Necropsy: abruptio placentae with large retro-placental clot.

Histology of lung: mild emphysema; occasional fibrin thrombi in vessels.

Trophoblastic index: 4

Megakaryocytic index: 30

APPENDIX II

Tables A to J.

TABLE A

Shows the number of blocks of lung tissue available (1, 2 to 5, more than 5), the number of cases in each of these groups, and, of these cases, the numbers with and without identifiable trophoblast.

1 block		2 to 5 blocks		more than 5 blocks	
with	without	with	without	with	without
38	53	8	11	7	3
Trophoblast therefore present in:					
38/91 = 42%		8/19 = 42%		7/10 = 70%	

TABLE B

Shows the 120 cases divided into three groups:

aa. Cases associated with absent or minimal uterine contraction;

bb. Cases associated with excessive uterine contraction, consequent upon prolonged labour (not due to primary uterine inertia) or eclamptic convulsions;

cc. Cases with normal uterine contraction - the remainder;

also the trophoblastic index (T.I.) in cases where trophoblast was seen in the lungs; and the status of the pregnancy.

(Und. undelivered; C.S. Caesarean section, elective or for primary inertia; Hys. hysterotomy; Conv. eclamptic convulsions; L.L. prolonged labour)

Group aa			Group bb			Group cc		
Case No.	T.I.	Status	Case No.	T.I.	Status	Case No.	T.I.	Status
3	14	Und.	5	4	Conv.	10	5	"Other"
8		Und.	18	6	L.L.	12	20	"
11	10	Und.	19		L.L.	13	5	"
15		Und.	20		L.L.	14	4	"
21		C.S.	23		L.L.	22	16	"
26		Und.	25		Conv.	36	40	"
27	4	C.S.	28	71	L.L.	47	2	"
29		Hys.	30	5	L.L.	48	30	"
32		Und.	31	5	Conv.	51	6	"
34	2	C.S.	33		L.L.	54	5	"
45		Und.	35	10	Conv.	55	12	"
70		Hys.	38		L.L.	56	5	"
76		Und.	39	29	L.L.	67	20	"
82		Und.	40	26	L.L.	68	10	"
91		C.S.	42	10	L.L.	81	10	"
113		Hys.	43	4	Conv.	83	25	"
119		Und.	44	6	L.L.	86	4	"
			53	50	L.L.	97	5	"
			57		L.L.	105	1	"
			65		Conv.	106	1	"
			66	5	L.L.	107	9	"
			72	6	Conv.	108	1	"
			75		Conv.	109	7	"
			78	25	L.L.	110	2	"
			80	20	Conv.	111	3	"
			84	22	L.L.	115	8	"
			85	4	L.L.	120	4	"
			87		Conv.			
			93		Conv.	plus the remaining 41 cases, none of which showed trophoblast in the lungs.		
			94	8	L.L.			
			100		L.L.			
			102		Conv.			
			112	75	Conv.			
			117	60	Conv.			
			118	210	Conv.			
Mean T.I. = 1.8			Mean T.I. = 18.9			Mean T.I. = 3.8		

TABLE C

Shows the 120 cases divided into three groups:

dd. Patients dying before separation of the placenta;

ee. Patients dying within 24 hours of separation of the placenta;

ff. Patients dying later than 24 hours after separation of the placenta - the remainder;

and the trophoblastic index (T.I.) in cases where trophoblast was seen in the lungs.

Group dd		Group ee		Group ff	
Case No.	T.I.	Case No.	T.I.	Case No.	T.I.
3	14	5	4	10	5
8		9		12	20
11	10	13	5	14	4
15		18	6	22	16
26		23		27	4
32		28	71	30	5
45		33		31	5
76		35	10	34	2
82		36	40	43	4
114		39	29	47	2
116		40	26	48	30
118	210	41		51	6
119		42	10	54	5
		44	6	55	12
		52		66	5
		53	50	72	6
		56	5	84	22
		63		85	4
		65		109	7
		67	20	111	3
		68	10	115	8
		71			
		78	25	plus the other 47 cases, none of which showed trophoblast in the lungs.	
		80	20		
		81	10		
		83	25		
		86	4		
		93			
		94	8		
		97	5		
		99			
		105	1		
		106	1		
		107	9		
		108	1		
		110	2		
		112	75		
		117	60		
		120	4		
Mean T.I. = 18.0		Mean T.I. = 13.9		Mean T.I. = 2.7	

TABLE D

Shows the numbers of patients dying at different durations of pregnancy, and the proportion of patients within each group whose lungs contained trophoblast expressed as the absolute number and as a percentage: also the trophoblastic indices where relevant, and the mean trophoblastic indices.

Stage of pregnancy	Number of patients dying	Number of patients with trophoblast in the lungs Total	T.I.	Proportion of patients with trophoblast in the lungs
1st trimester	9	5	40, 20, 5, 5, 4.	56% (Mean T.I. 8.3)
2nd trimester	16	5	14, 10, 6, 5, 5.	31% (Mean T.I. 2.5)
3rd trimester	15	6	210, 75, 25, 12, 9, 8.	40% (Mean T.I. 22.6)
On or after E.D.D.	80	37	(Remainder)	46% (Mean T.I. 6.2)

TABLE Ea

Shows the causes of death, with Case Numbers, of patients dying before the expected day of delivery (Case Numbers in red indicate patients whose lungs contained trophoblast: they numbered 16/40.

Haemorrhage and shock	14, 63, 81, 97, 107.
Eclampsia and pre-eclamptic toxaemia	12, 31, 49, 55, 58, 61, 112, 118.
Sepsis	36, 62, 74, 77, 92, 95.
Acute hepatic necrosis	21, 26.
Rheumatic carditis	15, 83.
Volvulus of small intestine	3.
Thrombocytopaenic purpura	10.
Hypertension	29.
Cerebellar neoplasm	32.
Renal cortical necrosis	45.
Renal sepsis	51.
Tuberculosis	69, 113.
Aspiration pneumonia	70
Rupture of aorta	76
Pulmonary embolism	82, 94.
Congenital heart disease	98.
Drug sensitivity (Scoline)	119.
Refractory anaemia	99.
Acute dysentery	101.
Transfusion incompatibility	54.

(One case of hydatidiform mole, No. 12, is included under "Eclampsia"; a second case, No. 97, under "Haemorrhage")

TABLE Eb

Shows the causes of death, with Case Numbers, of patients dying on or after the expected day of delivery (Case Numbers in red indicate patients whose lungs contained trophoblast: they numbered 37/80).

Haemorrhage and shock	6, 18, 23, 28, 33, 37, 38, 39, 44, 52, 53, 60, 66, 71, 78, 85, 106, 115, 120.
Eclampsia and pre-eclamptic toxaemia	5, 7, 8, 11, 22, 25, 35, 43, 46, 48, 65, 68, 72, 75, 80, 86, 87, 89, 93, 96, 102, 105, 109, 117.
Sepsis	1, 19, 20, 47, 50, 59, 73, 79, 84, 88, 90, 103.
Aspiration pneumonia	9, 56, 67, 91, 100, 111.
Transfusion incompatibility	16, 17, 64.
Amniotic embolism	40, 114, 116.
Tuberculosis	34, 108.
Pulmonary embolism	2, 57.
Acute hepatic necrosis	30
Renal sepsis	41.
Pneumonia	13.
Mesenteric vein thrombosis	4.
Toxic myocarditis	110.
Diabetes mellitus	27.
Epilepsy	104.
Unknown	24, 42.

(One case of hypofibrinogenaemia, No. 120, is included under "haemorrhage")

TABLE F

Subdivision, by disease groups, of the 120 cases.

Bracketed figures in red (thus) indicate number of patients whose lungs contained trophoblast.

	Haemorrhage and shock	Eclampsia and P.E.T.	Sepsis	Other
a. Number of patients	24 (15)	32 (18)	18 (3)	46 (17)
b. Proportion of total series	20%	27%	15%	38%
c. Number dying before E.D.D.	5 (4)	10 (6)	6 (1)	23 (6)
d. Number dying on or after E.D.D.	19 (11)	22 (12)	12 (2)	23 (11)
e. Proportion of patients within each group with trophoblast in lungs	63%	56%	17%	37%
f. Trophoblastic indices	71, 50, 29, 25, 10, 9, 8, 6, 6, 5, 5, 4, 4, 1, 1.	210, 75, 60, 30, 20, 20, 16, 12, 10, 10, 10, 7, 6, 5, 4, 4, 4, 1.	40, 22, 2.	26, 25, 20, 14, 10, 8, 6, 5, 5, 5, 5, 5, 5, 4, 3, 2, 2, 1.
g. Mean trophoblastic index	9.7	15.7	3.5	3.2

TABLE G

Shows the cases of "excessive uterine contraction" (Group bb of Table B) divided into two groups:

gg. Patients with eclamptic convulsions;

hh. Patients who had prolonged labour;

and the trophoblastic index (T.I.) in those patients whose lungs contained trophoblast.

Group gg		Group hh	
Case No.	T.I.	Case No.	T.I.
118	210	28	71
112	75	53	50
117	60	39	29
80	20	40	26
35	10	78	25
72	6	84	22
31	5	42	10
43	4	94	8
5	4	44	6
25		18	6
65		66	5
75		30	5
87		85	4
93		19	
102		20	
		23	
		33	
		38	
		57	
		100	
Mean T.I. 26.2		Mean T.I. 13.3	

TABLE H

Shows the 32 cases of eclampsia/pre-eclampsia in the series as a whole subdivided into two groups:

jj. Those patients who had convulsions;

kk. Those patients who did not have convulsions;

and the trophoblastic index (T.I.) in those patients whose lungs contained trophoblast.

Group jj		Group kk	
Case No.	T.I.	Case No.	T.I.
118	210	48	30
112	75	12	20
117	60	22	16
80	20	55	12
35	10	11	10
72	6	68	10
31	5	109	7
43	4	86	4
5	4	105	1
25		7	
65		8	
75		46	
87		49	
93		58	
102		61	
		89	
		96	
Mean T.I. 26.2		Mean T.I. 6.5	

TABLE J

Shows the proportion of non-pregnant animals, all treated with chorionic gonadotrophin, in Experiment III, whose lungs contained placental emboli at intervals after injection of placental suspension.

a.	Interval after day of injection (D)	D + 2	4	6	8	10	12	14	16	18	19	20
b.	Proportion of animals with pulmonary emboli	2/2	2/2	2/2	1/2	2/2	1/2	2/2	0/2	1/3	1/2	3/5
a.	do.	D + 22	24	26	28	30	32	34	36	38	40	
b.	do.	1/2	1/2	0/2	1/2	1/2	0/2	0/2	0/2	0/2	0/2	
a.	do.	D + 62	150	186	220	222	300					
b.	do.	0/1	0/9*	0/1	0/1	0/1	0/2					

* A minute calcific focus, possibly the remains of an embolus, was seen in the lungs of two of these animals.

Three animals were lost, eaten by cage-mates between the 150th and 300th days.

APPENDIX III

Reprinted Copies of Three Articles referred to in the Text.

[*From the Proceedings of the Physiological Society*, 18–19 July 1952.]
Journal Physiology, Vol. 118.

Trophoblastic tissue within the lungs during pregnancy. By W. W. PARK. *Department of Physiology, University College, Dundee (University of St Andrews)*

Ever since the original observation of Schmorl (1893) it has been generally accepted that there is in the human a constant passage of particles of trophoblastic tissue, and even maybe of entire chorionic villi, from the placenta to the lungs throughout pregnancy (see, for example, Novak, 1947). An attempt has been made by examining sections of lung taken from 106 women who died at varying times during pregnancy and the puerperium to assess the frequency with which this phenomenon occurs. A control series of sections of lung tissue from 52 non-pregnant subjects has also been examined.

Unusually large cellular structures were seen in many of the sections in both series. Any structure was regarded as an unusual finding in lung tissue if it was obviously larger than a monocyte, and not obviously a pathological finding such as, for example, a foreign body giant cell. For purposes of classification the structures seen were divided into three types:

Type I: Nucleus: a mass of chromatin of varying shape but essentially uniform in architecture, i.e. not multilobular. *Cytoplasm:* minimal in amount, if indeed visible at all.

Type II: Nucleus: a mass of chromatin of any shape but undoubtedly multilobular in architecture. *Cytoplasm:* as in Type I.

Type III: Nucleus: a definitely multinuclear architecture. *Cytoplasm:* variable in amount but clearly recognizable.

Type III structures were found almost exclusively within blood vessels. Type I and Type II structures were seen both within and without blood vessels.

The occurrence of Type I and Type II structures is certainly not a finding peculiar to pregnancy. They were found in many of the control sections and are regarded as megakaryocytes. Type III structures were found significantly more frequently in the sections from pregnant women, 39 out of 106, than in those of non-pregnant subjects, 5 out of 52 ($P < 0{\cdot}01$). Since, however, Type III structures are seen occasionally in non-pregnant subjects there is some doubt whether, when they do appear in the pregnant woman, they are of specifically placental origin. This matter is being investigated further.

No structures recognizable as chorionic villi were seen in any of the sections.

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Reprinted from THE JOURNAL OF PATHOLOGY AND BACTERIOLOGY
Vol. LXVII, No. 2, pp. 563-570, 1954

THE OCCURRENCE OF DECIDUAL TISSUE WITHIN THE LUNG: REPORT OF A CASE

W. WALLACE PARK

University of St Andrews, Department of Pathology, Medical School, Dundee

(PLATES CXXIX AND CXXX)

DURING histological examination of the lungs from pregnant women in a search for embolic trophoblast, one section was found containing an islet of tissue of a type foreign to the lung and not obviously trophoblastic. This report gives a description of the tissue fragment and an assessment of its possible origin.

CASE REPORT

Clinical and necropsy data

(From the records of the Royal Infirmary, Edinburgh)

The patient, aged 26, was in her second pregnancy: the date of the first was not recorded. One week before admission she had developed influenza, and, during that week, pleurisy. She was admitted 6 days before the expected day of delivery, in labour and obviously ill. A normal infant was delivered after a 3½-hours' labour. The patient's condition was poor after delivery, and was further impaired by blood loss due to trapping of the placenta in the cervix. The placenta was gently removed one hour after the birth but in spite of supportive measures the condition of the patient deteriorated, gradually and then rapidly, and death occurred 4 hours after delivery.

At necropsy the essential lesions were right-sided bronchopneumonia with abscess formation and empyema.

Microscopic appearances in the lung

The material available was one routinely processed block of lung tissue. Three sections, 5 μ thick, were cut with an interval of 20 μ between each: two were stained with hæmatoxylin and eosin, one with the per-iodic acid-Schiff sequence. When these sections were examined and the focus of possible decidua noted, 6 further sections were cut serially from the block. The tissue in question was present in 4 of the sections and then disappeared. Of these 4 sections, one was damaged and 3 were available for further study.

Hæmatoxylin and eosin staining. The section of tissue is quadrilateral, with one pleural surface. The pathological changes are a fibrinous pleural exudate, a zone of inflammatory-cell infiltration with intense vascular congestion extending inwards for 1 mm. beneath the pleura, general vascular congestion, some areas of œdema and the edge of a patch of bronchopneumonia.

At a point 6 mm. beneath the pleural surface there is a small island of tissue with an appearance foreign to the lung. It has some similarity to liver tissue but clearly resembles decidual tissue more closely than any other (fig. 1). It is roughly triangular in outline, measuring $250 \times 200\ \mu$, and, in the first of the sections, consists of about 40 cells. Calculating from this surface area and the depth of tissue cut from the block, it is estimated that the nodule contained in all some 500 cells. If the tissue had been present as a roughly spherical nodule bisected by the first section, this number would be doubled.

The individual cells measure up to $30\ \mu$ in diameter and have abundant pale mauve, finely granular cytoplasm. The nuclei are large and relatively clear, with a content of scattered granules and usually a prominent nucleolus. The colour of the nucleoli varies from deep blue to light purple. An occasional cell is binucleate, and a few show some cytoplasmic vacuolation. One cell in the first section is seen to be in the anaphase of mitosis (fig. 2).

In places the cells are closely apposed; elsewhere they are separated from each other by an eosinophilic matrix or groundwork, mostly finely granular or fibrillar, occasionally finely vacuolated. Immediately adjacent to the cells, few of which show a clearly defined cell membrane, this groundwork is condensed to form a surround of strongly eosinophilic material. This is thought to be a truly extracellular condensation of the matrix material and not marginal cytoplasmic thickening.

A large capillary vessel containing erythrocytes lies within the substance of the plaque (it was present in all 6 sections), and in one area further capillary vessels are seen, entering the margin of the plaque from the adjacent lung parenchyma. This vascularisation virtually excludes the possibility that the island of tissue had been introduced into the block of lung as an artifact.

Per-iodic acid-Schiff sequence (Pearse, 1949). This procedure gave strong fuchsinophil staining of the pericellular condensation of the matrix (fig. 3). Again it is rarely possible to distinguish cell membranes with clarity, and the impression is strengthened that the fuchsinophil material is extracellular. The rest of the matrix again has a finely granular or fibrillar appearance and blends gradually with the pericellular condensation. The cytoplasm of most of the cells assumes a neutral greyish tinge; certainly none shows sufficient fuchsinophilia to suggest an appreciable content of glycogen. The colouration of the nucleoli appears to depend on the depth of staining by hæmatoxylin. Where this is heavy the nucleoli are strongly basophilic: in the less deeply stained sections the nucleoli show a pale fuchsinophilia.

A further section was exposed to saliva for 1 hour, washed, and stained in parallel with the section described above. Neither cells nor matrix show any significant alteration; there is no reduction in the degree of cytoplasmic staining. It is concluded, therefore, that the tissue contains no demonstrable glycogen.

Toluidine blue. In the section stained with 0·5 per cent. aqueous toluidin blue the island of tissue is much smaller, containing only some 20 cells. Rather less than half of these show faint cytoplasmic metachromasia. Some of the non-metachromatic cells show slight cytoplasmic basophilia. The cytoplasm shows the same fine granularity of texture noted previously. In this section the cell membrane can be picked out distinctly in a few instances, thus enabling a clear

TABLE

Comparison of the histological and histochemical findings in the present case with those in undoubted decidua

Histological features	Lung fragment	Control sections of decidua	Description by other workers of findings in decidua
Appearances with P.A.S. staining	Fuchsinophil intercellular matrix with prominent pericellular condensation	Varying amounts of matrix but, in areas of similar texture, appearances identical with those in the lung fragment	Moderate red staining of reticulum surrounding individual decidual cells §
Cytoplasmic basophilia	Faint in occasional cells	Present in majority of cells but extremely faint	Negligible staining by basic dyes.‡ Mild basophilia after fixation in Zenker solution and staining with methylene blue §
Metachromasia .	Faint in occasional cells and matrix	Present in matrix and some cells	Interstitial matrix and some cells of decidua show metachromasia §
Glycogen . .	None demonstrable	Minimal content in occasional cells	Occurs in many decidual cells §: content diminishes as gestation advances †
Argyrophil intercellular network	Well-marked between individual cells	In areas of loose texture; appearances identical with those in lung fragment	A characteristic finding in decidua and the best method of distinguishing this tissue from cytotrophoblast *

* Wislocki and Bennett (1943)
† Dempsey and Wislocki (1944)
‡ Wislocki and Dempsey (1945)
§ Wislocki and Dempsey (1948)

distinction to be made between the cell margin and the pericellular condensation of the matrix. The nuclei have a thin, sharply demarcated, deeply basophilic nuclear membrane and contain a fine scattering of tiny basophilic granules. The nucleoli are pale blue. The intercellular matrix shows faint metachromasia in a few places; for the most part it is deeply basophilic, and the structure is better delineated than with the other staining methods. Its fine fibrillary character is clearly shown and reveals the deeply staining pericellular zone as undoubtedly a condensation of this reticular material.

Silver impregnation. One of the hæmatoxylin-and-eosin sections was taken down and used for impregnation of the reticulin by a routine method (Lendrum, 1951). This shows the presence of abundant

argyrophilic intercellular material. (fig. 4) The silver is deposited for the most part as fine granules rather than sharply defined lines. This can be taken as indicating reticulin, and exactly the same appearances were obtained in control sections of ordinary decidua.

Evaluation of the histological findings

If the tissue under discussion be not decidua, the possibility has to be considered of its being cytotrophoblast, syncytiotrophoblast, myometrium, liver or a fragment of a hepatoma, displaced or metaplastic bronchial epithelium, or a mass of alveolar epithelial cells. With the exception of this last and debatable material, all these tissues were obtained and studied after staining with the methods given above. Occasional slight resemblances were noted in the hæmatoxylin and eosin sections, particularly of normal liver, but the other methods, especially silver impregnation, left no doubt that the cellular fragment was not composed of any of these tissues. Sections of normal decidua from the uterus, however, gave results which support the view that this fragment is decidual. These results satisfy the criteria for decidua given by Wislocki and his collaborators (table), except as regards glycogen content. Aqueous fixatives were used for both my tissues and these admittedly may cause some loss of glycogen. The glycogen content of decidua is thought by Dempsey and Wislocki (1944) to vary inversely with the blood supply of the area. If this be so, the high vascularity of the present nodule and its situation within the lung would adequately explain its lack of glycogen. The fact that the pregnancy was practically at term would also mean a low content of glycogen (Dempsey and Wislocki).

In sum, the morphology and staining characteristics are strongly in favour of the tissue being decidual.

Discussion

The fragment of tissue having been diagnosed as decidual, the question arises of how it came to be within the lung. There are three possibilities: (*a*) that it was transported, as a portion of endometrial stroma, from the uterus to the lung at some time before the present pregnancy, the subsequent decidual change being brought about hormonally; that is, blood-borne ectopic endometriosis; (*b*) that it arose by a process of differentiation *in situ*; (*c*) that it was carried in the blood stream from the placental site.

The first two possibilities can be discussed together since they epitomise the whole problem of blood-borne spread of endometrium and its relation to ectopic endometriosis. Endometrial tissue apparently lying within uterine blood vessels is illustrated by Sampson (1927) and by Javert (1951), who describes the phenomenon as "endometriosis vascularum" or "stromatosis vascularum" according to the type of tissue within the vessels. Although Javert found these

DECIDUAL TISSUE IN LUNG

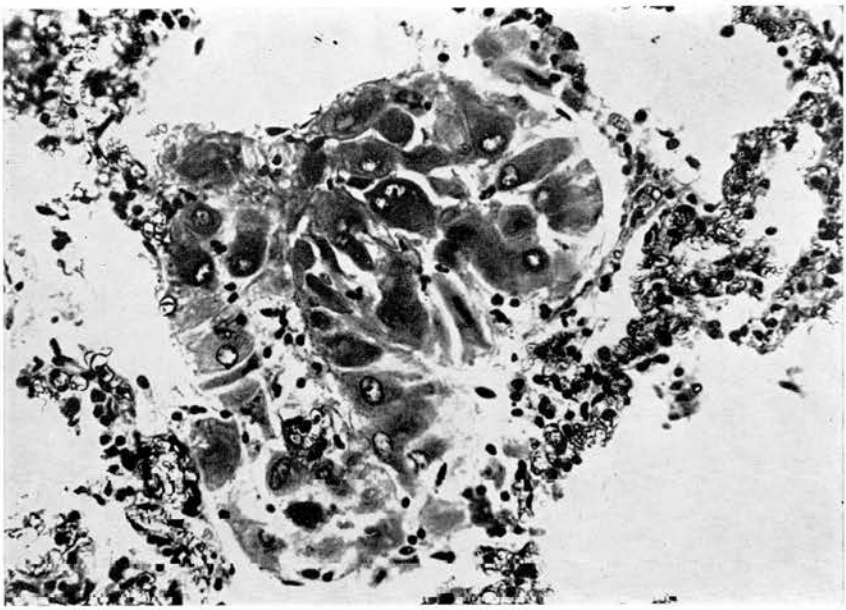

FIG. 1.—Decidual focus in the lung, showing the resemblance to hepatic cells. H. and E. ×260.

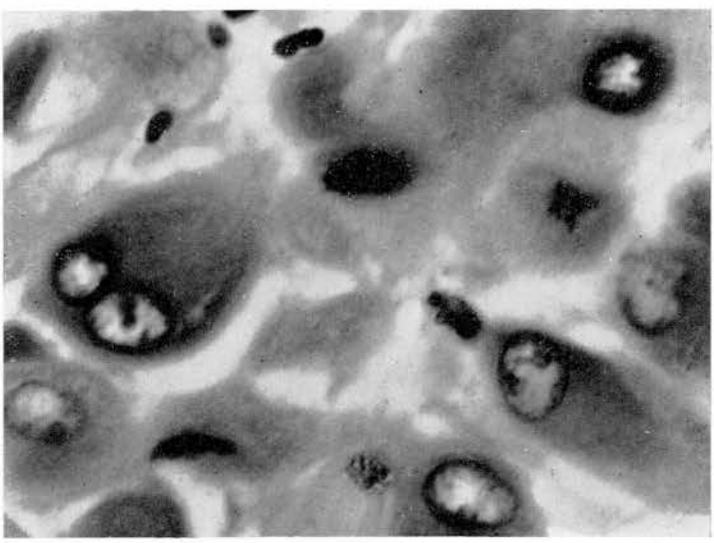

FIG. 2.—Decidual focus showing, toward the right, a cell in mitosis. H. and E. ×600.

DECIDUAL TISSUE IN LUNG

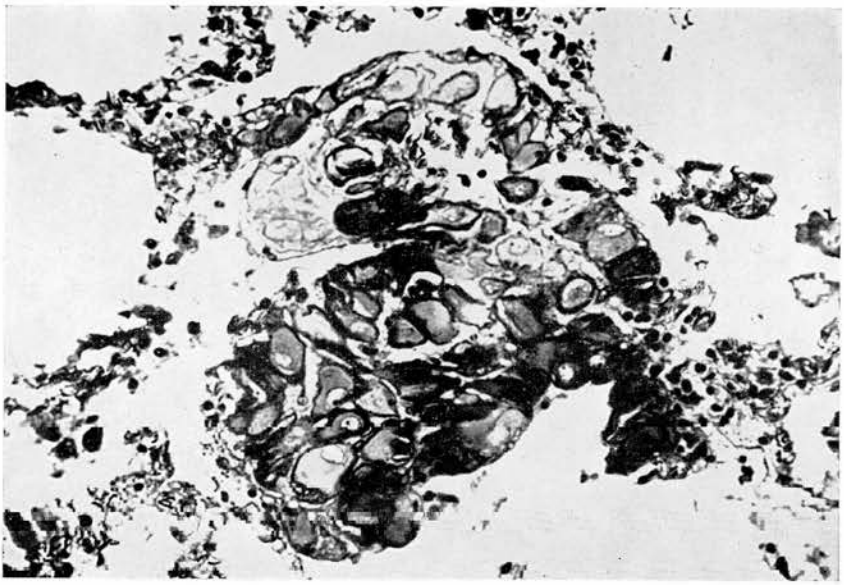

FIG. 3.—Decidual focus stained by the P.A.S. method. The cells fail to show any reaction for glycogen. The intercellular material is strongly stained. ×260.

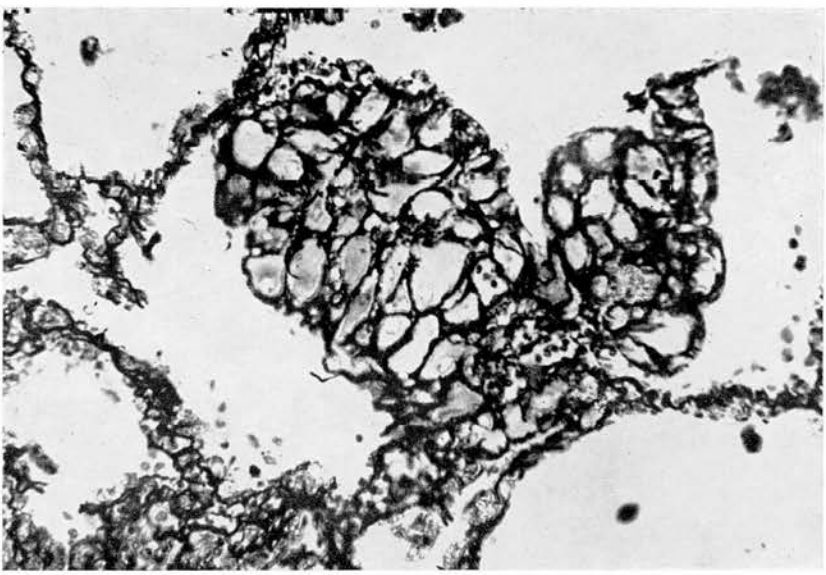

FIG. 4.—Decidual focus showing the reticulin pattern (silver impregnation). This is the type of picture given by normal intra-uterine decidua. ×260.

appearances only in uteri the seat of adenomyosis (5 cases) and never in the normal organ, he nevertheless regards this as evidence supporting the possibility of hæmatogenous spread of endometrium and reasonably to be correlated with the occurrence of endometriosis in such sites as the kidney (Marshall, 1943 ; Maslow and Learner, 1950), forearm (Biebl, 1938), thigh (Mankin, 1935 ; Schlicke, 1946) and thigh, axilla and hand (Correa da Costa, 1948). Another related case is that of Bettinger (1947), who reported finding decidual tissue in the wall of the pelvis of a hydronephrotic kidney removed during the 4th month of pregnancy.

Endometriosis of the pleura has been reported on two occasions. The finding of three small nodules on the pleura of a woman aged 42, who died of chronic pneumonia, was reported by Büngeler and Fleury Silveira (1939, case 2). The nodules showed a definite picture of endometriosis with a typical premenstrual reaction. The glands were surrounded by a very cellular stroma and compact connective tissue containing much hæmosiderin. In some areas smooth muscle could be distinguished encircling the epithelial nodules. This appears to have been the first reported case of pleural endometriosis. A second example was described by Nicholson (1951) in a woman of 25 who had had recurrent blood-stained pleural effusions over 15 months. Thoracotomy revealed an area of opaque pleural thickening 1 in. in diameter. This was removed and, on section, showed the structure of " typical endometrium ".

Before accepting vascular spread from the uterus as the complete explanation of these cases, we may recall a hypothesis put forward by Gruenwald (1942) concerning ectopic endometriosis in general. It certainly would seem that endometriosis of the kidney and limbs could only be explained by blood-spread from the uterus, but Gruenwald maintains that even in these situations the alternative explanation of cœlomic epithelial metaplasia is still applicable. If, as he has shown, cells of cœlomic origin can be incorporated during early development within the substance of a limb bud, later perhaps to have their endometrial competence manifested as endometriosis of an extremity, there is no fundamental reason why cells of the cœlomic epithelium which come to form the visceral pleura should not similarly be incorporated in the developing lung bud, later to become manifest on rare occasions as endometriosis of the pleura or even of the lung.

Vicarious menstruation from the lung has long been included among the conditions to be considered in the differential diagnosis of hæmoptysis, but I have not so far found any published account of the demonstration of endometrial tissue in the lungs of a patient with this physical sign. Suggestive cases have been described, as, for example, that of Hobbs and Bortnick (1939), where, in addition to a diminution of the patient's periodic hæmoptysis following irradiation of the ovaries, there was radiological evidence of a pulmonary tumour ; but until undoubted endometrium is found within the lung the

significance of such cases, and indeed of " endometriosis vascularum ", must remain uncertain.

The literature contains two reports of the finding of tissue of endometrial type within the lung parenchyma. Many pea- to cherry-sized nodules, mostly subpleural, were found by Hart (1912) in the lungs of a woman aged 72 who had died with " atherosclerosis and cerebral softening ". A uterine tumour had been removed 22 years earlier but no details were available. Microscopically the nodules showed a microcystic structure with a surround of smooth muscle, and Hart concluded, as the most likely explanation, that the nodules represented metastases, adenomyomatous in structure and benign in character, from the previous uterine tumour. He had considered " congenital lung adenoma " along with other possibilities but ruled it out. His grounds for doing so are not wholly convincing : certainly there are several points of similarity between this case and those described or quoted by Hutchison (1952) as examples of pulmonary adenomatosis. A further case is described by Willis (1953) wherein a few well-defined nodules were found in the lungs of a woman aged 58, who died from extensive pelvic growth of a spindle-cell sarcoma, regarded as recurrent growth, following the removal a few years earlier of " fibroids " which had not been examined microscopically. Despite metastases in the iliac nodes and peritoneal cavity, the structure of the lung nodules was benign, consisting of " well-differentiated epithelial acini lined by cubical or low columnar cells, set in abundant smooth-muscular and fibrous tissue ". The conclusion reached by Willis was that the nodules were " benign " metastases from a uterine adenomyoma which had later undergone sarcomatous change.

There are thus 4 reported instances of tissue of endometrial type being found within the thorax, but of these only two are examples of endometriosis. In both, the lesion lay, not within the lung substance, but upon the pleura ; and, as already noted, the pleura is just the situation within the thorax where endometrial tissue is most likely to appear if cœlomic epithelial metaplasia is possible at all. The reported occurrence of cyclical hæmoptysis, in the absence of lesions such as tuberculosis or bronchiectasis which might be the source of co-menstrual bleeding, implies that endometrium can become established within the lung ; but in such cases endometrium in the lung seems never to have been demonstrated. Even if it were demonstrated in an occasional case, the question of its origin, by metaplasia or metastasis, would remain unsettled. The occurrence of intra-uterine adenomyosis or of pelvic peritoneal endometriosis does not mean that endometrial tissue can be spread by the blood stream, although it is reasonable to expect that it might, and if vascular spread does occur, one would expect the lung to be the commonest site for the appearance of metastatic deposits. No such cases have been reported.

In the light of this analysis it seems unlikely that the decidual tissue in the present case owed its origin to deposition of uterine

endometrium before the current pregnancy. That it arose by metaplasia is at least theoretically possible, since it lay immediately beneath the pleura, but again the supporting evidence is slender. There are thus no convincing grounds for supporting either of these possibilities as the explanation of the present case.

The third possibility, the transfer of decidua from the placental site, recalls the known occurrence of transportation of trophoblast to the lungs. For more than 50 years it has been generally accepted that during pregnancy there is a constant passage of fragments of trophoblast from the placenta to the lungs, though complete proof is lacking. Metastasis of decidua is another matter. Those who have studied the phenomenon of trophoblastic transportation, for example Schmorl (1893), who first described the occurrence, and Ceelen (1931), who discussed cellular embolism of the lung in great detail, make no mention of decidual tissue within the lungs, and a study of the literature has failed to reveal any record of its occurrence. In a communication on toxæmia of pregnancy, Schneider (1950) includes a diagram showing how decidual tissue could gain access to the maternal circulation as a result of retroplacental hæmorrhage, but there is no mention of decidual tissue having been identified in the lungs of such cases. However, since trophoblastic lung embolism almost certainly does occur, it would seem that escape of tissue from the placenta to the lungs is anatomically possible ; and this is probably the best reason for preferring the third possibility.

It will be noted that the decidua in the present case is not lying within a blood vessel, which suggests that it had not arrived in the lung during parturition ; nor is there any surrounding tissue reaction such as would indicate that a vessel large enough to have contained this decidual mass had been eroded and destroyed. It is concluded, therefore, that the tissue, if it did come from the uterus, must have arrived in the lung as a single cell or as a few cells, which, impacted in a capillary vessel, had multiplied with a slowness and benignity such that no unusual tissue response was aroused in the neighbourhood. The presence of the mitotic figure supports the view that cellular multiplication was taking place. How long the growing mass had taken to reach its present size can only be guessed.

Summary

A small focus of decidual tissue was found within the substance of the lung in a woman aged 26, who died 4 hours after delivery of a mature infant. The evidence bearing on its possible sources of origin is discussed and the conclusion is reached that the most likely explanation of the occurrence was transportation of a cell or cells from the maternal part of the placenta to the lung, where the transplant grew slowly.

I am most grateful to Professor A. C. Lendrum for much helpful criticism during the preparation of this report, and to Professor R. J. Kellar, Department

of Obstetrics and Gynæcology, and Dr R. F. Ogilvie, Department of Pathology, Royal Infirmary, Edinburgh, for access to the clinical and necropsy records of the patient.

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"HEXAMETHONIUM LUNG"

By
W. WALLACE PARK and F. J. COCKERSOLE

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"HEXAMETHONIUM LUNG"

Report of a Case Associated with Pregnancy

BY

W. WALLACE PARK, M.B., Ch.B.

AND

F. J. COCKERSOLE, M.R.C.O.G., M.M.S.A.

From the Department of Obstetrics and Gynaecology, Kingston Hospital, Kingston-upon-Thames and the Department of Pathology, Queen's College (University of St. Andrews), Dundee

IN recent years the use of hypotensive drugs has attracted increasing attention. A number of such agents are now widely used in the treatment of hypertensive disease associated with pregnancy.

The present case is reported to show that such therapy may not always be free of danger to the mother, and to draw attention to an unusual fibrosis occurring in the lungs of some cases under treatment with drugs of the hexamethonium series.

The condition was first described in 1954 by Doniach, Morrison and Steiner in the lungs of 3 out of 54 patients undergoing treatment with hexamethonium bromide for hypertensive disease. Two of these died, one after 7 months, the other after 12 months of treatment. The third patient, 2 years after the start of therapy, was able to resume work. All 3 patients had shown radiological evidence of pulmonary oedema ("bat's wing" or "butterfly" shadowing) at some time during their illness. The lungs of the 2 fatal cases showed at necropsy wide areas of translucent appearance and firm, rubbery consistency, and, histologically, fibrinous pulmonary oedema with widespread patchy fibrosis. Similar lesions were seen by Morrow, Schroeder and Perry (1953) in 5 out of 37 patients who died during or shortly after the cessation of therapy, in a total series of 258 patients treated with a combined hydrazinophthalazine and hexamethonium regime. How many of the 37 fatal cases came to necropsy is not stated. The lesion in their cases, designated "interstitial pneumonia", may have been the same as that described by Doniach *et al.* but no pathological details are included in the report. A rather similar example is described by Robillard *et al.* (1955) of a patient who died in uraemic coma, the lungs showing fluid exudate and "early fibrosis" in the interstitial tissue but no fibrin or fibrous tissue within the alveoli.

A further instance of this condition, occurring during pregnancy and characterized by prominent intra-alveolar fibrin and fibrous tissue, is now reported.

CLINICAL DATA

The patient, aged 37, was expecting her eighth child. She had previously been delivered normally of 7 living infants at term, whose birth weights ranged between 7½ pounds (3·30 Kg.) and 8 pounds (3·63 Kg.). Hyperemesis gravidarum in varying degree occurred early in each pregnancy. Following the fourth pregnancy there was an attack of "phlebitis".

The sixth pregnancy is the first for which accurate details are available. Labour was induced surgically at term, and was followed by the delivery of a 7 pound 9 ounce (3·43 Kg.) male infant, after a 4-hour labour. Thrombophlebitis affecting the deep veins of the right leg was diagnosed on the seventh day after delivery. There was no hypertension noted at any time during this pregnancy or in the puerperium.

Early in the seventh pregnancy, in 1949, the patient was admitted to hospital with excessive vomiting. The blood pressure was 160/100 and remained raised despite rest. Renal function tests at this time showed normal results. Albuminuria developed at 36 weeks and labour was again induced surgically. A male infant of 7 pounds 4 ounces (3·2 Kg.) was delivered, after a 2-hour labour the same day. Two months after delivery the blood pressure was 150/96 and a trace of albumen was present in the urine.

The patient is said to have had an attack of pneumonia following this pregnancy but we have been unable to obtain any details about this illness.

The patient came under our care in January, 1952 when

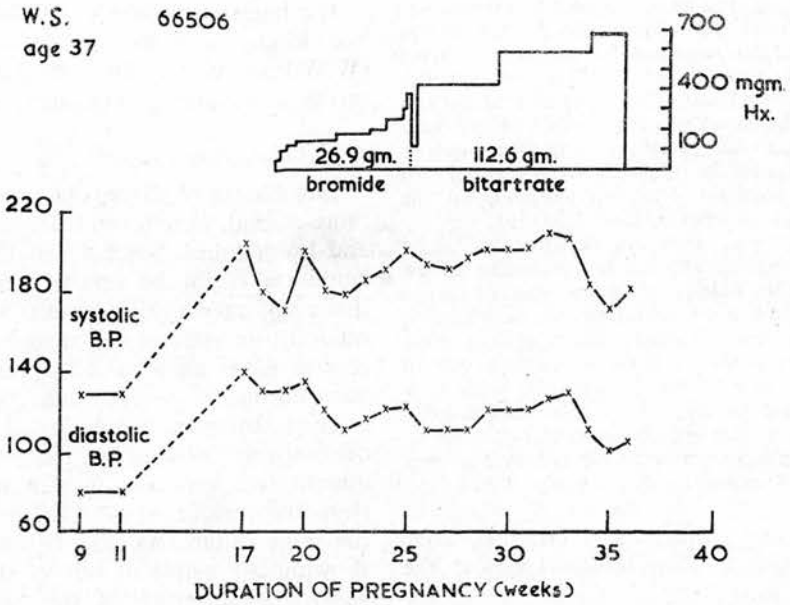

FIG. 1

The chart shows the fluctuations in blood pressure and the dosage of hexamethonium. The blood pressure was maintained at levels around 180/110 only by a steady increase in dosage.

she was 8-weeks pregnant. She was again suffering from hyperemesis gravidarum, which, although necessitating admission to hospital, responded quickly to isolation, sedation and rest. The blood pressure was 128/80. At 16 weeks the blood pressure was found to be 200/130 and a trace of albumen was detected in the urine. The patient was re-admitted to hospital where she stayed for the remainder of the pregnancy. Renal function tests showed considerable impairment of function. The blood urea was 48 mg. per cent and the urea clearance 25 per cent of normal. An intravenous pyelogram showed delayed excretion of dye but the diurnal variation of urinary specific gravity was between 1,004 and 1,020. The optic fundi showed narrowing of the vessels and possibly early papilloedema.

Treatment with hexamethonium bromide was started. The dosage used, and the behaviour of the blood pressure are shown in Figure 1. The blood pressure readings showed marked irregular daily variations but the progressive increase in the dose of hexamethonium salt was needed to keep the blood pressure down to an average level of 180/110. Hexamethonium bitartrate was substituted for the bromide salt to overcome the depressant effects of the latter.

The uterus increased steadily in size, although it was always considered that the foetus was small in relation to the calculated period of gestation. The patient's general condition remained satisfactory, except that at the 20th week (11th September, 1952) a slightly cyanotic appearance was noted, which was however transient.

By the 35th week there was some tachypnoea and 4 days later the patient felt and looked unwell. She complained of lower thoracic pain on deep inspiration, and slight cyanosis was again apparent. There were signs in the chest suggesting right lower lobe consolidation. Clinical examination and an electrocardiographic tracing failed to show any evidence of left ventricular failure. The following day the patient's condition was worse; cyanosis and dyspnoea were marked, and slight ankle oedema appeared.

The administration of hexamethonium was discontinued. Oxygen was given intermittently, chemotherapy was instituted, and Digoxin 0·25 mg. 8-hourly, was given. Twenty-four hours later the patient's condition showed some improvement, but signs of consolidation were now detected at the left base. The patient's temperature was not raised at any stage of her illness.

In so far as a firm diagnosis could be made, it was considered that the condition present was some obscure pulmonary complication, possibly infarction, with intrapulmonary thrombosis. This conclusion is interesting in view of the later findings.

Labour commenced spontaneously after a further 24 hours, and was followed 9 hours later by the rapid and easy delivery of a living female infant weighing 2 pounds 10 ounces (1·19 Kg.). The placenta was delivered normally 5 minutes later with a loss of 4 ounces (114 ml.). Labour had been easy and undisturbing to the mother whose general condition was considered to be unaltered.

The baby was limp at birth, and only gasping respira-

tion was established. The infant survived for 80 minutes.

Following delivery the mother's blood pressure was 136/78. Her condition remained unchanged for 8 hours but subsequently deteriorated. She became comatose and cyanosed. Death occurred 14 hours after delivery.

An X-ray of the thorax was taken 3 days before death (Fig. 2). Owing to the severity of the illness only a "portable" film could be obtained. We are grateful to Dr. James H. Smitham, Kingston Hospital, for the following remarks on this film (24th May, 1955):

"The main things which are apparent are some enlargement of the left ventricle and unfolding of the aorta. There is also widespread patchy consolidation in the right lung which is central rather than peripheral in distribution and there is a small quantity of fluid at the right base. There is also, I think, a small quantity of fluid in the left base in the costo-phrenic angle. The appearances would do very well for pulmonary oedema, of the type seen in incipient left ventricular failure.

"So far as I can make out the appearances here are very similar to those described by Doniach *et al.* (1954)."

At the necropsy performed by Dr. J. C. Lees, Kingston Hospital, Kingston-on-Thames, the main findings were:

Heart. Enlargement of moderate degree due to left ventricular hypertrophy.

Kidneys. A moderate amount of shrinkage, with scarring: some appearances rather suggestive of early cortical necrosis. Microscopically there is evidence of chronic pyelonephritis and moderately advanced arteriolar nephrosclerosis. Cortical tubules show advanced necrosis but it is difficult to know how much this is due to post-mortem autolysis.

Respiratory System. Right pleural cavity contained 600 ml. of clear greenish fluid.

Right lung: apart from a small area at the apex and a narrow band along the costophrenic margin, the lung substance was of an abnormally firm consistency with a rather dry cut surface exuding little air or fluid on pressure. No pus was seen. Some areas of haemorrhage were present, up to 3 cm. in diameter and not always abutting on the pleural surface. No ante-mortem thrombus was found in the pulmonary arterial tree.

Left lung: the upper half of the upper lobe was of normal consistency. The rest of the upper lobe and the whole of the lower lobe showed appearances similar to those of the right lung.

Macroscopic appearances suggested that the relative solidity and dryness of the lungs was due to a rather gelatinous oedema and patchy fine fibrosis.

The lungs were incised and placed in fixative, and kindly sent by Dr. Lees to one of us (W.W.P.) in view of his interest in other changes in the lungs during pregnancy.

Histology of the Lungs

Two blocks of tissue, one peripheral and one more central, were taken from each of the upper and lower lobes. Since it was thought that the condition might be one of massive placental tissue infarction, the blocks were chosen at random: no attempt was made, for example, to choose those areas which appeared to be the most fibrous.

The histological findings in all the sections are qualitatively essentially the same; there is quantitative variation in that not all sections show the various types of tissue abnormality to the same extent. As may be seen in Figure 3, showing the whole of one of the sections, the general architecture of the lung is severely deranged. This is due to the co-existence of areas of haemorrhage, oedema in various stages of coagulation, organizing exudate, fibrosis, collapse and compensatory emphysema. Tissue density tends to be greater centrally than beneath the pleura, but, taking the sections as a whole, subpleural fibrosis was commonly seen. There is no tendency for any particular form of tissue abnormality to be located predominantly in any particular zone of the lung.

Haemorrhage. This is present over many relatively large areas. It is recent haemorrhage, filling alveoli and alveolar ducts. Alveolar walls in these areas retain their normal staining properties, and obliteration of architecture characteristic of old infarction has not occurred. Haemosiderosis is not seen in any area.

Oedema. Even in the few small areas where pulmonary architecture is otherwise normal, oedema is seen. One of the more oedematous areas is shown in Figure 4. The oedema has the familiar appearance of a thin, smooth coagulum broken up by bubbles of air. Such oedema is of recent, perhaps terminal, origin. Exudation of longer standing is signified by the formation of hyaline or "asphyxial" membranes lining alveoli and alveolar ducts (Fig. 5). The staining reactions of these membranes show that fibrin formation is occurring in some places. Intra-

alveolar exudate is also prominent, and also shows partial conversion into fibrin. A further stage in the process—or so we interpret it—is evident organization of the fibrinous exudate and the appearance therein of young fibrous tissue. This is shown in Figure 6. Alveolar walls can still be discerned, and many alveoli contain fibrous tissue; the dark areas mingled with the fibrous tissue indicate fibrin which has not yet been absorbed. Ultimately patches of diffuse fibrosis are produced (Fig. 7). The fibrous tissue is young and cellular: dense collagen formation has not occurred. The features of Figure 8 show that this fibrosis is not an interstitial fibrosis: the elastic tissue pattern of the alveolar walls is well maintained, and the walls themselves are not greatly thickened. It is true that apparent alveolar wall thickening is seen in many places, as for example, in the upper left area of Figure 4. Appropriate staining, however, shows that this kind of appearance is almost always produced by collapse of alveoli and coalescence of their walls. In other places alveolar walls are truly thickened, but by exuded fluid and macrophages. Genuine interstitial fibrosis is minimal. Cuboidal metaplasia of the alveolar "epithelium" is rarely seen. Many alveoli, however, are filled with relatively large cells which may represent a desquamated lining although some at least, from their particulate content, appear to be macrophages.

Discussion

The abnormalities in this patient's lungs were many. They included homogenous proteinous exudate: hyaline membrane converted in part to fibrinous coagulum: pure fibrinous coagulum: fibrinous coagulum converted in part to fibrous tissue: and fibrous tissue, patchy in distribution and cellular in character. All but the first of these findings denote fibrinous precipitation in, and organization of, a pulmonary exudate of high protein content. The final result, seen in many of the sections, is occupation of the alveoli and related fine air passages by a still cellular, not markedly collagenous, fibrous tissue. This is a patchy development, not a true carnification of the lung.

The patient's story of a vague illness, possibly pneumonia, 4 years before the final illness, raises the question whether the abnormalities now seen in the lung may not be sequelae of that illness. This seems improbable, for, of the changes seen, all but the areas of fibrosis are clearly of recent origin. These areas of fibrosis have a structure which is almost indistinguishable from that sometimes seen in unresolved pneumonia but, in our experience, only when the patient has died in the third or fourth week with evidence of infection still manifest. The intra-alveolar fibrous tissue shows little or no retraction from the alveolar walls, and the alveolar pattern is on the whole well preserved—features which further confirm the view that this fibrosis is not the sequel of a pneumonia 4 years earlier.

The interpretations of the histological appearances must take note of the co-existence in the sections of apparently recent exudation and of varying degrees of resolution and organization. These might be interpreted as the result of a single massive exudation with variation from place to place in the efficiency of the processes of resolution and organization. Such an idea is certainly quite contrary to the generally accepted view, and to our own experience; and further, a single outpouring of fluid of this degree would surely have proved immediately lethal. It seems reasonable, therefore, to interpret the appearances, including the fibrin formation and fibrosis, as reactions of the lung to repeated sublethal episodes of fluid exudation of high protein content.

The mechanism causing such episodes of highly proteinous pulmonary oedema, with formation of fibrin and fibrous tissue in the alveoli, in the non-infected lung is uncertain. Widespread fibrin casts were seen by Lendrum, Scott and Park (1950) in the alveolar ducts and alveoli of patients with clinically manifest heart failure due to rheumatic and to hypertensive disease. It would seem clear, therefore, that, without defining the term more closely, "cardiac failure" is at least a contributory factor in the production of this kind of pulmonary oedema. Intermittent heart failure, but of the left side of the heart, was thought by Doniach *et al.* to be the cause of the oedema in their hexamethonium treated cases, but doubt has been expressed by Altschule (1954) whether failure of the left ventricle alone ever occurs: there is

certainly no convincing evidence from experimental procedures that it ever does. However, so long as the question remains undecided, it seems reasonable to argue that, since the myocardium of the left ventricle may undergo a pure or isolated hypertrophy, it may also undergo a pure or isolated failure. It does not follow, however, that isolated failure of the left ventricle is in fact the upset that precedes pulmonary oedema, at least of the type and degree under discussion. Cameron (1948) considers that ". . . no more than a transitory dissociation of output from the ventricles is conceivable, for just as soon as the pulmonary vessels become engorged automatic regulation of cardiac function occurs with compensation of back pressure". Similar views are expressed by Altschule. It may be wise, therefore, to go no farther meantime than say that certain acute cardiac dysfunctions may be associated with intrapulmonary exudation, and that the exudate may on occasion contain fibrinogen.

The formation of fibrin in non-infected exudates within the lung has attracted increasing attention within recent years. As well as appearing in the cases of cardiac failure just mentioned, and in the hexamethonium-treated cases of Doniach *et al.*, it has been described in cases of uraemia by Doniach (1947, with earlier references) and by Hopps and Wissler (1955), the last-named workers finding it in 62 per cent of a series of 107 uraemic patients, and in occasional examples of the Hamman-Rich syndrome (Pokorny and Hellwig, 1955).

It is probable that all cases of uraemia, apart from the acute recoverable forms, are complicated to some extent by cardiac failure. Therefore, even when clinically inconspicuous, cardiac failure may partly explain the formation of a pulmonary exudate, and thus of intra-alveolar fibrin, in uraemic cases. Fibrin within the alveoli is, however, too frequent a finding in cases of uraemia to be satisfactorily explained on this basis alone—especially when the degree of failure may be minimal. Therefore, some further factor, associated maybe with the abnormal biochemistry of the blood, is probably present, a factor that increases capillary permeability: fibrin casts thus occur in association with a degree of cardiac failure that is less than the degree of failure that causes these casts when the pulmonary capillaries are healthy. This may also be in part the reason why non-infected fibrin casts are seen relatively more frequently in uraemic cases than in any other type of case: only patients with lesser degrees of cardiac failure survive long enough for fibrin to form and be present in sufficient quantity to be discovered in the few random blocks taken at routine necropsy. However, if this explanation be true, it is difficult to understand why diffuse fibrosis is so rare in uraemic lungs.

The later history of patients showing intrapulmonary fibrin casts is rarely known—because of the seriousness of the causal condition. However, it seems probable that, in the hexamethonium-treated cases at least, therapy allows a sufficient prolongation of life for a later stage of development to be seen than would otherwise be possible. Whatever be the explanation, the end-result is an appearance quite unlike that in the Hamman-Rich syndrome with its interstitial fibrosis and thickening of alveolar walls. There is no interstitial fibrosis in our case, and we find it hard to believe either that the lungs did pass through an initial stage of interstitial fibrosis or that they could progress to such a state with the passage of time, despite the views of Peabody and Peabody (1954) that the histology of hexamethonium lungs resembles that of the Hamman-Rich syndrome.

The fibrin casts in uraemic lungs may show some evidence of organization but this is nearly always small in amount and inconspicuous: diffuse fibrosis is rarely, if ever, seen. This may indicate either that organization is at an early stage or that it is inefficient and slow to start. Since many patients may live in a state of uraemia for some weeks or months, we suspect that inefficient organization is the true explanation. The discrepancy between the extensive organization and fibrosis in hexamethonium lungs and its paucity in uraemic lungs is puzzling and, so far as we know, unexplained.

Fibrin in any situation is ultimately removed by lysis. In infected exudates this is achieved, perhaps exclusively so, by leucocytic enzymes. In non-infected exudates it seems necessary to ascribe the disappearance of fibrin to soluble fibrinolysins present in plasma or tissue fluid.

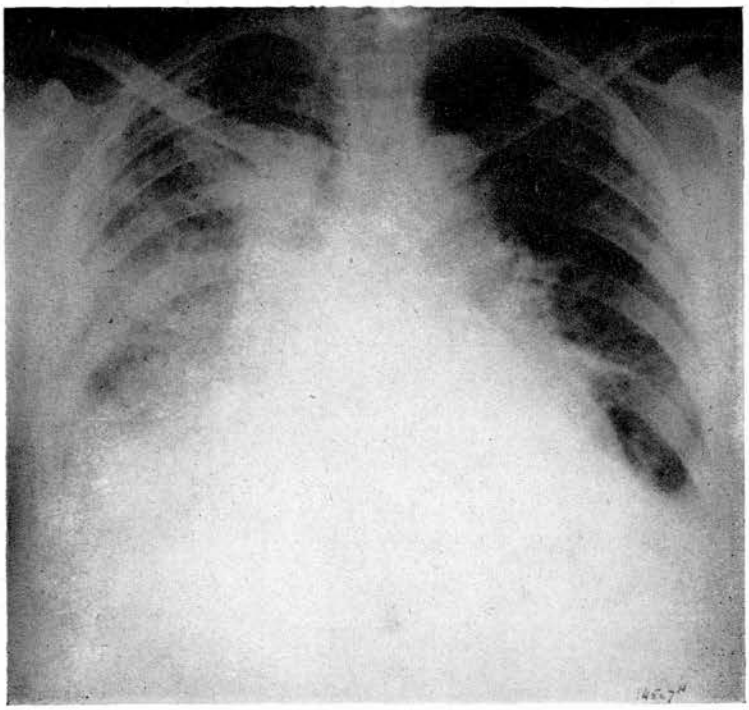

FIG. 2
A film of the chest taken 3 days before death. (See text.)

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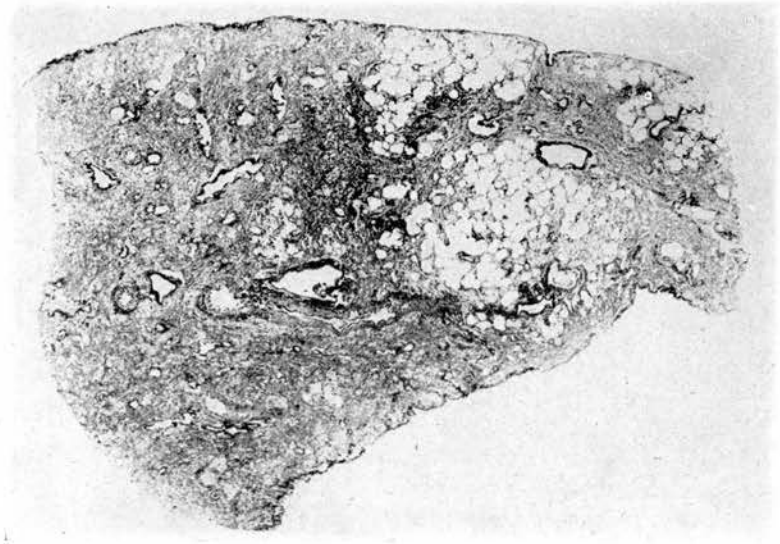

FIG. 3

The texture of the lung is very uneven. Areas of increased density due to organizing oedema and fibrosis contrast prominently with areas of compensatory emphysema. Picro-Mallory. ×4.

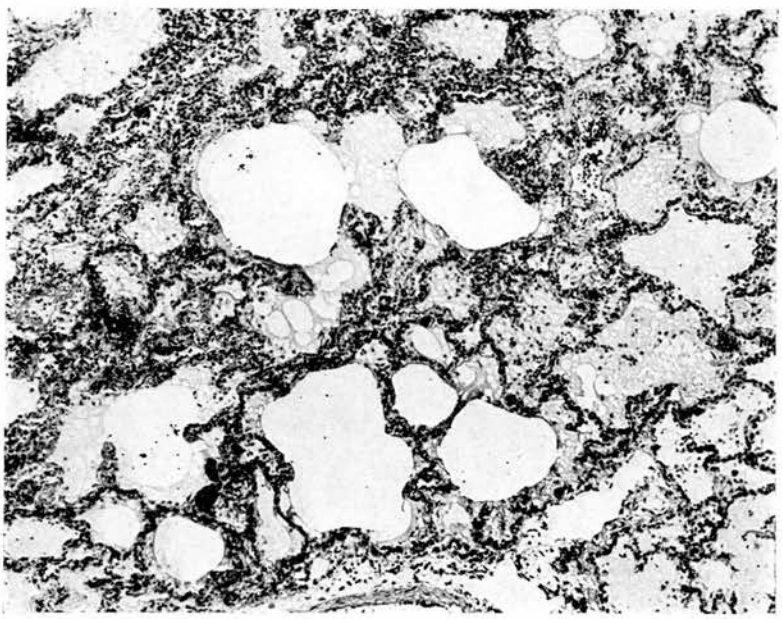

FIG. 4

An area of oedema, probably agonal: neither fibrin nor organization can be seen. The alveolar walls show no undue thickening. Areas of apparent alveolar wall thickening in the upper part of the field are produced by collapse and coalescence of alveoli. Haematoxylin and eosin. ×64.

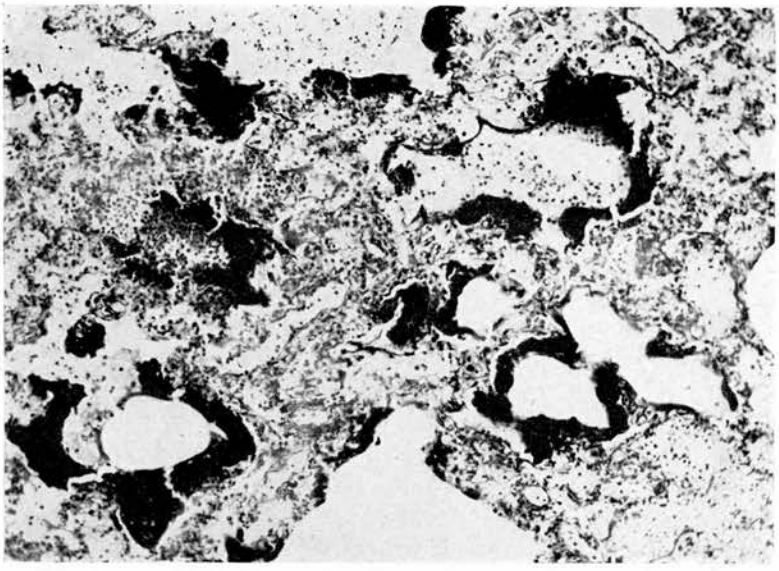

FIG. 5

Membrane formation in alveolar ducts and alveoli. The membranes, frequently of great thickness, are mainly serous coagula. They stain a deep blue with the picro-Mallory stain but, at high magnification, show occasional strands of red-staining fibrinous material in the deeper layers. Picro-Mallory. Minus blue filter. ×98.

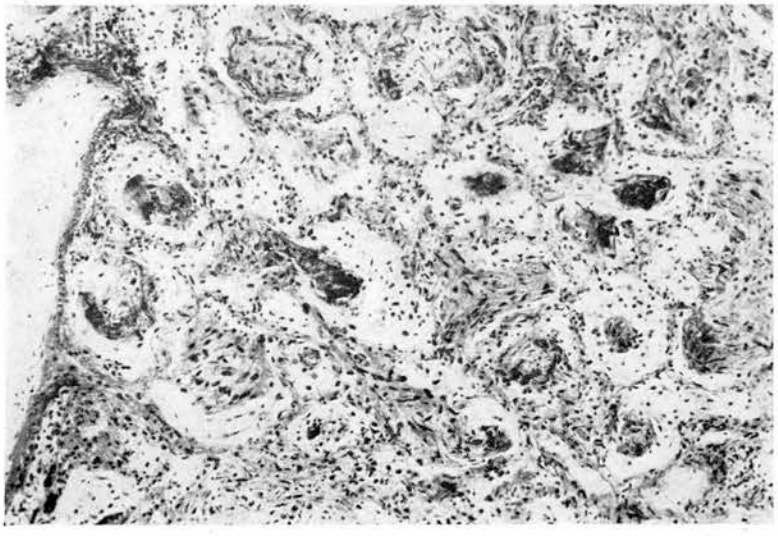

FIG. 6

A field from a zone of organization. The alveolar pattern is still recognizable. Many of the alveoli contain a mixture of fibrin (black) and cellular fibrous tissue. Picro-Mallory. Minus red filter. ×100.

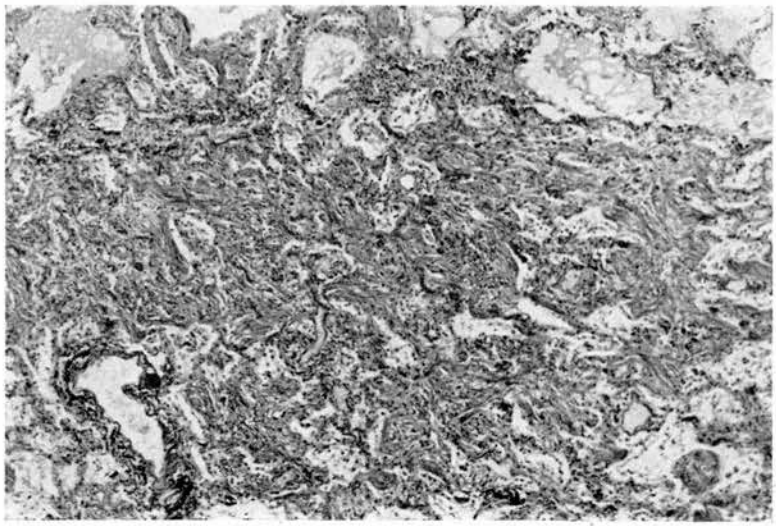

FIG. 7

An area of diffuse fine fibrosis. The fibrous tissue is cellular: dense collagen formation has not yet taken place. van Gieson. ×60.

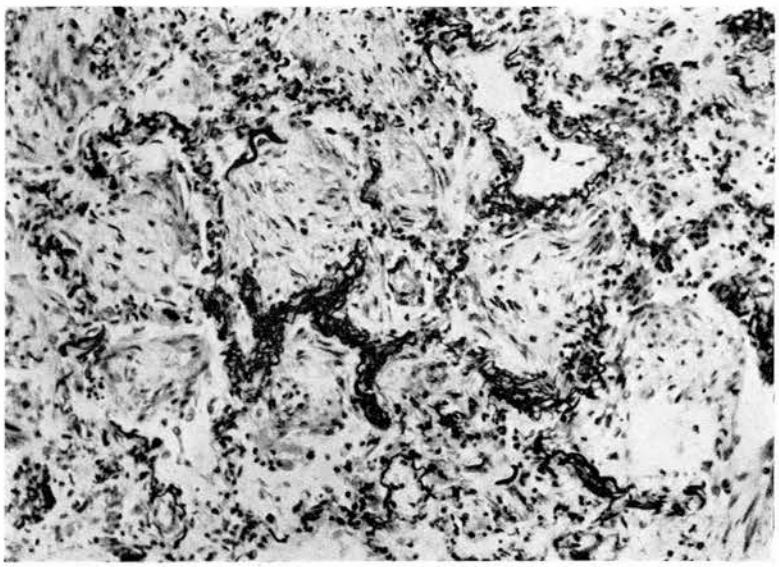

FIG. 8

Elastic tissue staining shows that alveolar architecture has been relatively well maintained despite the diffuse fibrosis. Also, there is no evidence of a significant degree of interstitial fibrosis. Weigert's elastica, haemalum and light green. ×161.

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Of the factors controlling fibrinolysis in the absence of leucocytes little is known. It is almost certainly a highly complex process, probably as complex as that of fibrin-formation itself, and it would not be surprising if at times it became deranged. If fibrinolysis in the lung is inadequate or fails altogether, subsequent fibrosis appears to be inevitable, though once again it has to be admitted that knowledge of the physico-chemical processes determining the occurrence or non-occurrence of fibrosis is still very limited. Of the factors which might conceivably influence the onset and speed of fibrinolysis the age of the fibrin, that is, the length of time it has lain in the alveoli, cannot be admitted as relevant, since the age of the fibrin is itself a function of fibrinolysis. There may, however, be different types of fibrin. Whether the fibrin of the pathologist, produced as it is by widely different diseases, always has exactly the same constitution and properties in all circumstances may be doubted. It would be surprising if it were always identical with the pure fibrin of the haematologist, prepared from purified fibrinogen and thrombin. The fact that two forms of purified fibrin clot, one soluble and the other insoluble in urea, have been shown to exist (Lorand, 1950) goes some way to support these speculations, as does the observation of Sandritter and Bergerhof (1954) that four morphologically distinct types of fibrin can be identified in necropsy tissues. Differences in the constitution of fibrin, which might perhaps be better written "fibrin", may well be the explanation of such unusual features as the curious resistance to lysis and organization shown by the fibrin in uraemic pulmonary exudates, and the relative rapidity and extent of organization in "hexamethonium lung".

The possibility that some direct toxic action of hexamethonium compounds is responsible for the pulmonary changes was mentioned by Morrow and by Doniach and their colleagues. Doniach *et al.* consider this unlikely, and recall that animal experiments carried out by other workers had provided no evidence to incriminate hexamethonium as such. However, the remarkable and specific action of alpha-naphthyl thiourea (ANTU), reminds us that the normal permeability of pulmonary capillaries can be dramatically increased by direct drug action (Richter, 1945). It is still too early, we feel, to absolve hexamethonium entirely from blame in this respect, rare though pulmonary complications in hexamethonium therapy may be. We have further considered whether the small size of the infant in our case, the prematurity of its birth and its short survival might also be in some way attributable to toxic drug action. This possibility cannot be excluded beyond doubt but we feel that the severity of the mother's illness is by itself an adequate explanation for these features of the case. Like Morris (1953), in his account of the use of hexamethonium in 10 cases of hypertension during pregnancy, we do not think that the drug had any influence on the course of labour.

The hexamethonium lung poses two questions —how does the highly proteinous oedema arise, and why is organization and fibrosis so prominent? We have briefly discussed both matters. It seems reasonable to associate the attacks of pulmonary oedema with episodes of cardiac failure which, because of the nature of the disease, is likely to be a hypertensive and therefore a left ventricular failure. The precise way in which a failing left ventricle favours the development of pulmonary oedema is not, so far as we can assess the evidence, fully understood. Some factor, such as anoxia, which directly impairs capillary permeability, is probably required in addition to dissociation of output between the ventricles: opinions vary as to the existence and degree of such a dissociation of output. It is, we feel, too early to exclude the possibility that hexamethonium itself may have a damaging effect on pulmonary capillaries. The intra-alveolar fibrosis, never prominent in untreated hypertensive cases, may occur because these patients survive repeated episodes of near-lethal pulmonary oedema, and with each there is a consequent organization. Other factors may, however, be involved, such as differences in the type of fibrin, differences in the rate and efficiency of fibrinolysis, and in the speed of onset of organization.

Summary

The case is reported of a woman of 37, treated with hexamethonium compounds for

severe hypertension during her 8th pregnancy. She died after the birth of a live infant, in the 36th week. Treatment with hexamethonium drugs had been continuous, in increasing dosage, from the 17th week. Severe, ultimately fatal, respiratory disease developed during the 35th week. Necropsy showed nephrosclerosis, hypertrophy of the left ventricle, and a state of "solid oedema" and widespread fine fibrosis throughout both lungs. Microscopically the condition was one of non-infected, fibrinous, pulmonary oedema with organization and areas of fibrosis. The possible mechanism of development of the lesion is discussed.

We wish to thank Mr. J. V. O'Sullivan for permission to publish this case, and our thanks are also due to him and to Professor A. C. Lendrum for many helpful comments during the preparation of this report. We are indebted to Dr. J. C. Lees for the necropsy findings, to Dr. J. H. Smitham for the X-ray report, and to Mr. J. W. Corkhill for assistance with the photomicrography.

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