Papers and Originals

Specializations of the Syncytium of the Human Chorion

W. J. HAMILTON,* M.D., D.SC., F.R.C.O.G., F.R.S.E.D.; J. D. BOYD,† M.A., M.D., D.SC., F.R.C.O.G.

[WITH SPECIAL PLATE]

Brit. med. J., 1966, 1, 1501-1506

The biological interest of the mammalian placenta as the intermediary between two organisms has caused it to receive extensive attention from embryologists and physiologists. Obstetricians and pathologists have also contributed much information on the human placenta, and there is a vast literature on its general topography and histological structure (Snoeck, 1958; Wilkin, 1965). Moreover, in recent years electron microscopy has provided information on the "fine- or ultra-structure of the human placenta which has necessitated a reassessment of the nature and functional mechanism of the membrane barrier it interposes between mother and foetus (Boyd and Hughes, 1954; Wislocki and Dempsey, 1955; Bargmann and Knoop, 1959; Hashimoto *et al.*, 1960; Panigel and Anh, 1963; Lister, 1963, 1964; Boyd and Hamilton, 1966a). Current developments of increasingly reliable and more carefully assessed histochemical methods, and their use in placental investigations, are also contributing significantly to our understanding of the organ (Wislocki and Padykula, 1961; Velardo and Rosa, 1963; Wachstein *et al.*, 1963; Curzen, 1964; Hagerman, 1964).

Notwithstanding the excessive literature on the human placenta, however, and the wide contemporary interest in its investigation, great uncertainty still persists on many of its structural features. There are several reasons for this uncertainty. In the first place it cannot be emphasized too strongly that the human placenta is very different from those of the usual laboratory animals; hence, in the explanation of the human organ, comparative studies have not been as rewarding as might have been expected. Again, many of the investigations in man have been made on limited regions only of separated placentae, usually at or near full-term. As a consequence knowledge of the *in situ* topography of the organ and of its normal regional variations is imprecise. For example, completely convincing accounts are not yet available of such important aspects of the placenta as the arterial supply to, and venous drainage from, the intervillous space or the exact arrangement and branching of the chorionic villous stems. Elsewhere, from studies based on extensive material of *in situ* and separated specimens of all gestational ages, we have given detailed consideration to some of these problems (Hamilton and Boyd, 1951, 1960; Boyd and Hamilton, 1960, 1966b).

The present contribution is concerned with an aspect of the organ to which surprisingly little attention has been given—namely, the remarkable regional variations in structure shown by the trophoblastic syncytium, that highly specialized membrane which covers the surfaces of the chorionic villi and lines the intervillous space. We will not discuss the peripheral

syncytium, on which there are conflicting opinions (Boyd and Hamilton, 1960; Schramm, 1962; Park, 1965), nor, since they are essentially cytotrophoblastic in nature, the villous nodules, so well described by Meyer (1921).

Structural Variations of Trophoblastic Syncytium

The syncytium is almost certainly derived from the cytotrophoblast, which in the villi, constitutes what is usually known as Langhans's layer. Evidence from a number of sources indicates that individual cytotrophoblastic cells fuse to produce the multinucleate syncytium (Enders, 1965; Boyd and Hamilton, 1966a). Moreover, in at least some areas of villous growth there is a continuous accretion of such cells into the syncytium throughout pregnancy.

The chorionic villi are of course the essential elements of the foetal placenta. They can be classified into a number of categories—main-stem villi (trunci chorii), branching villi (rami and ramuli chorii), and the free, or terminal, villi. The last-named are continuously augmented in number throughout gestation. In early stages of their differentiation all the villi are covered with syncytium, which encloses a continuous Langhans's layer of cytotrophoblast. In the last half of pregnancy in many regions, especially in the large and older-established trunci and rami, Langhans's layer becomes interrupted (Special Plate, Fig. 19) and discontinuous. In the smaller villi, however, many of the cytotrophoblastic cells persist to the end of pregnancy, and undoubtedly provide later additions to the villous syncytium (Wislocki and Bennett, 1943; Hamilton *et al.*, 1962; Strauss, 1964).

The trophoblastic syncytium is one of the most important of the histological elements that intervene between the maternal and foetal blood-streams; as such, it constitutes part of the so-called "placental barrier." From the method of its origin, and its detailed structure, both morphological and histochemical, the syncytium can no longer be considered to function as a simple semipermeable membrane. In mammals generally highly specialized mechanisms evolved to aid in the transfer of certain substances from the maternal organism to the foetus are now known. In the human placenta such specializations are manifested by the syncytium in its surface microvilli (see Special Plate, Fig. 19), its mitochondria, and its complicated vesicular structure; the picture presented in electron micrographs is very different from the traditional interpretation of the syncytium as a simple membrane. Indeed, there is now much evidence showing that the syncytium is concerned in the active transfer of many substances which cross it. The syncytium does become thinned during the course of pregnancy, and this fact has been widely stated to account, in part at least, for the increase in placental per-

* Professor of Anatomy, University of London, at Charing Cross Hospital Medical School.

† Professor of Anatomy, University of Cambridge.

meability as pregnancy advances (Hamilton and Boyd, 1950; Hagerman and Villee, 1960; Hamilton *et al.*, 1962). But in some areas the syncytium is involved in the production of morphological specializations which do not appear to be adaptations merely for transfer and which are the prime subject of this communication.

Types of Specialized Regions

The specialized regions have been described in different ways and with different terms by those placentalogists who, over the years, have directed attention to them. Thus those areas in which there is an aggregation of syncytial nuclei have been variously called syncytial sprouts, syncytial buds, syncytial knots, nuclear clumps, and proliferation nodes (Getzowa and Sadovsky, 1950; Alvarez *et al.*, 1964; Fox, 1965). In addition, however, there are stretches of thinned syncytium from which nuclei are absent; these regions, following Bremer (1916), are usually called epithelial plates. Our own observations have led us to the opinion that there are at least four types of specialization of the trophoblastic syncytium of the chorionic villi (see Diagram). These are:

1. Syncytial sprouts—projections from the syncytial surface into the intervillous space.
2. Syncytial buds (stromal trophoblastic buds of Boyd and Hamilton, 1964)—projections into the stroma of the villi.
3. Epithelial plates.
4. Syncytial clumps or knots—thickened areas of the syncytium, often adjacent to the epithelial plates, in which nuclei are massed or grouped together.

1. Syncytial Sprouts

Once the chorionic villi have been established as the dominant feature of placental structure, small surface elevations, the initial syncytial sprouts (Diagram, 1a), become apparent on them. These sprouts project into the intervillous

space; they usually possess a central concentration of clumped syncytial nuclei, and their attachment region is often constricted in a stalk-like manner (Special Plate, Fig. 1). At such a stage of their development all the syncytial sprouts appear to be identical; their subsequent history, however, seems clearly to indicate that there are in fact two varieties of them. There are, firstly, those sprouts which represent no more than the initial phase in the development of a free villus (Diagram 1a). As development proceeds such a purely syncytial structure will acquire, by extension from the

Schematic diagram to show possible syncytial derivatives of a chorionic villus. 1a, Early syncytial sprout. 1b, Later stage in the development of a syncytial sprout, commencing invagination by cytotrophoblast. 1c, Fully established small chorionic villous branch with stromal core and capillary. IIa, Pedunculated syncytial sprout. IIb, Liberated syncytial sprout in intervillous space. IIIa, An early stage in the development of a stromal trophoblastic bud. IIIb, A stromal trophoblastic bud separated from the surface and situated in the interior of villus. IV, Epithelial plate with underlying capillary. V, Syncytial knot or clump.

LEGENDS TO SPECIAL PLATE

FIG. 1.—Photomicrograph of a section of a syncytial sprout from a fourth-month placenta (foetus, 113 mm.). The sprout shows nuclear clumping; note the absence of stromal tissue. ($\times 1,000$.)

FIG. 2.—Photomicrograph of a section of another syncytial sprout from the same placenta as in Fig. 1. Note invasion of the sprout by stromal tissue. ($\times 600$.)

FIG. 3.—Photomicrograph of a section of a small chorionic villus from a seventh-month placenta (foetus, 230 mm.). The dense stroma shows numerous capillaries. ($\times 520$.)

FIG. 4.—Photomicrograph of a section of syncytial elevation on a small chorionic villus from a fourth-month placenta. This may be a stage in the production of a free sprout. ($\times 1,000$.)

FIG. 5.—Photomicrograph of a section of another attached syncytial sprout from the placenta illustrated in Fig. 4. ($\times 1,000$.)

FIG. 6.—Photomicrograph of a section of a syncytial sprout from a fifth-month placenta (foetus, 120 mm.). The sprout is constricted at its attachment and may be in the process of separating to become free in the intervillous space. ($\times 1,000$.)

FIG. 7.—Photomicrograph of a section of a placenta of the fourth week (somite embryo) showing two syncytial sprouts free in the intervillous space—one having apparently normal, the other pyknotic, nuclei. ($\times 750$.)

FIG. 8.—Photomicrograph showing a separated syncytial sprout in an endometrial vein (from the same specimen as Fig. 7). ($\times 130$.)

FIG. 9.—Photomicrograph from a placenta of the second month (embryo, 20 mm.) showing two syncytial sprouts in a myometrial vein. ($\times 130$.)

FIG. 10.—Photomicrograph showing an enlargement of one of the syncytial sprouts illustrated in Fig. 9. ($\times 780$.)

FIG. 11.—Photomicrograph of a portion of a villous stem showing a number of stromal trophoblastic buds. From a fourth-month placenta (foetus, 113 mm.) ($\times 65$.)

FIG. 12.—Photomicrograph of a section through a portion of a chorionic villus from a third-month placenta (foetus, 70 mm.) showing a stromal trophoblastic bud approximated to the endothelium of a foetal blood-vessel. ($\times 520$.)

FIG. 13.—Photomicrograph showing syncytial sprouts and portions of villi in a myometrial vein from a pregnant uterus of the fifth month (foetus, 140 mm.). ($\times 63$.)

FIG. 14.—Photomicrograph of a section through a stromal trophoblastic bud in a fourth-month placenta (embryo, 113 mm.). There is syncytium in the interior and cytotrophoblast in the periphery of the bud. ($\times 770$.)

FIG. 15.—Photomicrograph through a stromal trophoblastic bud undergoing cystic dilatation, from a fourth-month placenta (foetus, 97 mm.). ($\times 770$.)

FIG. 16.—Photomicrograph of portion of a full-term placenta showing fusion of villi by syncytial clumps. ($\times 400$.)

FIG. 17.—Photomicrograph of a small villus from a full-term placenta to show an epithelial plate with an underlying capillary and clumping of the adjacent syncytial nuclei. ($\times 1,500$.)

FIG. 18.—Transverse section of a terminal villus to show two epithelial plates and adjacent areas of clumped syncytial nuclei in a full-term placenta. ($\times 1,000$.)

FIG. 19.—Electron micrograph of a portion of a villus from a full-term placenta to show an epithelial plate with an underlying capillary containing foetal corpuscles. A maternal erythrocyte is seen in the intervillous space adjacent to the thinned syncytium of the plate which possesses a well-developed "brush border" of microvilli. ($\times 4,200$.)

FIG. 20.—Electron micrograph of a portion of a free syncytial sprout from a second-month placenta (embryo, 20 mm.). Note presence of microvilli. ($\times 9,000$.)

FIG. 21.—Electron micrograph of a portion of a free syncytial sprout from the placenta containing the sprout illustrated in Fig. 20. Note absence of microvilli. ($\times 6,000$.)

W. J. HAMILTON AND J. D. BOYD: SYNCYTIIUM OF THE HUMAN CHORION

W. J. HAMILTON AND J. D. BOYD: SYNCYTIIUM OF THE HUMAN CHORION

W. J. HAMILTON AND J. D. BOYD: SYNCYTIIUM OF THE HUMAN CHORION

adjacent Langhans's layer, an incipient cytotrophoblastic lining (Diagram Ib). In due course cells from the stroma of the villus, to the surface of which the sprout is attached, invade the central axis to form a core for the sprout (Special Plate, Fig. 2). There may even be some contribution to the core by differentiation of Langhans's cells. Vascularization of this core completes the process of what in effect is the production of a new villous branch (Diagram, Ic, and Special Plate, Fig. 3). Briefly, then, many of the syncytial sprouts are no more than stages in the formation of new (free or terminal) chorionic villi. Their method of development is much the same throughout gestation, though the later-produced villi are more slender and delicate.

The other variety of syncytial sprouts, though they arise in precisely the same fashion and appear to have the same structure as the first variety, have a quite different fate. Unlike incipient villi, however, the sprouts of this second type acquire neither cytotrophoblastic layer nor stromal core (Special Plate, Figs. 4–6). On the other hand, the stalk of attachment joining them to the villous system becomes increasingly attenuated (Diagram, IIa) and eventually ruptures, so that the sprout itself becomes a small spherical or ovoid mass of syncytium of up to 500 μ or more in diameter floating freely in the intervillous space (Special Plate, Fig. 7).

There is, to our knowledge, no information indicating what factors determine the fate of an early attached syncytial sprout. Some free villi begin to be apparent as branches of the villous trunks in late pre-somite and early somite stages, but they do not become obtrusive components of the placenta until much later in development. On the other hand, isolated masses of syncytium lying quite freely in the early intervillous space or in the lumina of uterine glands in the region of implantation are regularly found after the 13th or 14th day of development (Hamilton and Boyd, 1960). Such isolated syncytium may be of cytotrophoblastic shell origin (Boyd and Hamilton, 1960) and consequently not derived from the sprouts. By the mid-somite period (21st to 26th days, fertilization age), however, sprouts are found projecting from the surface of the chorionic villi into the intervillous space.

Although many of these sprouts are undoubtedly stages in villous development, some of them, as serial sections clearly demonstrate, are free in the intervillous space. Indeed, we have material demonstrating that in such stages some of the free sprouts have already entered the maternal circulation. Fig. 8 (Special Plate) shows such a sprout in the endometrial vein of a uterus which contained an 8-somite embryo. Ortmann (1938) has also figured a sprout in such a situation in another specimen of about the same stage. Such free syncytial sprouts can be found regularly in endometrial and myometrial veins of all subsequent gestational stages (Special Plate, Figs. 9 and 10); they have also been isolated from blood taken from uterine veins and the inferior vena cava of pregnant women in later stages of pregnancy up to and including full-term (Thomas *et al.*, 1959; Iklé, 1961, 1964). In spite of careful examination we have not been able to identify syncytial sprouts in the lymphatic vessels of sectioned uteri. The free syncytial sprouts in the intervillous space often show signs of degeneration, especially pyknosis (Special Plate, Fig. 7). Often, however, they are well preserved, and, in electron micrographs (Special Plate, Fig. 20), show an extremely well developed brush border of microvilli; the latter, however, may be absent (Special Plate, Fig. 21).

2. Syncytial Buds

Recently, under the term "stromal trophoblastic buds," we described (Boyd and Hamilton, 1964) certain projections from the deep aspect of the villous syncytium into the underlying stroma (Special Plate, Figs. 11, 12, 14, and 15). Many

of these projections become completely separated from the surface syncytium; all stages of such separation have been observed. Alvarez *et al.* (1964) have also described similar syncytial projections under the term "syncytial globules." It has recently come to our notice that Ishizaki (1960) had in fact described what would appear to have been similar proliferations in the stroma of the villi and called them "orphan bodies." It would seem that Ishizaki regarded them as pathological in nature and associated with placentalitis. We, however, have found them so constantly that we consider it unlikely that they are the result of pathological change. Wilkin (1965) has recently verified the existence of such buds which he called "*bourgeons trophoblastiques à l'intérieur du stroma villositaire*."

In our experience the syncytial stromal buds, which can be anything up to 500 μ in diameter, possess an outer covering of cytotrophoblast which represents the part of Langhans's layer invaginated into the villous stroma by inwardly projecting syncytium (Special Plate, Fig. 14). In their interior the stromal buds often show degenerative changes, especially nuclear pyknosis (Special Plate, Fig. 15). Moreover, not infrequently material with the staining reactions of so-called fibrinoid is found within the buds—a fact perhaps of some significance in relation to the origin of placental fibrinoid.

3. Epithelial Plates

Epithelial plates are areas of the syncytium, devoid of an underlying Langhans's layer, which have become extremely thin and from which the nuclei are absent (Special Plate, Figs. 17–19). Typically an epithelial plate overlies a stromal capillary, which may cause the thinned syncytium to bulge into the intervillous space. In such a region only five structural elements are interposed between the maternal and foetal blood-streams: the syncytium itself, the syncytial basement membrane, the stromal connective tissue, the vascular basement membrane, and the capillary endothelium. In the thicker syncytium adjacent to the epithelial plates the nuclei are often clumped to form the so-called syncytial knots (see below). It would seem that the nuclei have been displaced from the region of the plate, either by their own active migration or as the result of pressure from the underlying capillary, and have aggregated in the region of the knot. Shanklin (1958) has suggested that it may be lysis of the nuclei which accounts for their absence in the plates, but this suggestion does not explain the nuclear clumping. Fox (1965) states that the knot formation is due to proliferation of the syncytial nuclei, but we have never found convincing evidence for mitotic activity in them.

The epithelial plates themselves first become obvious in the second half of pregnancy (Getzowa and Sadosky, 1950), becoming more numerous with advancing gestation. Since their first description by Bremer (1916) the function of the epithelial plates has been discussed by a number of investigators (Wislocki and Bennett, 1943; Hörmann, 1951, 1953; Snoeck, 1958; Amstutz, 1960; Boyd and Hamilton, 1966c). It is generally agreed that they are probably of considerable importance in placental exchange. Bremer himself believed that they were primarily concerned with foetal excretion. Most investigators, however, consider the plates to be regions in which much of the passive transfer of substances of low molecular weight—for example, gases and water—takes place.

4. Syncytial Clumps or Knots

Syncytial clumps or knots are limited areas of the syncytium with clumped nuclei, found for the most part in the terminal villi, where they are situated mainly adjacent to the epithelial plates (Special Plate, Fig. 17). A review of the

literature on them has been given by Fox (1965). The syncytial knots have also been referred to as syncytial sprouts. There is, however, little justification for the use of the latter term in this connexion, since the history of the knots is quite different from that of either of the varieties of sprouts described earlier. The term "syncytial nuclear clumps" might be more appropriate for the knots, but even with this designation a terminological difficulty persists, for many regional syncytial thickenings with aggregated nuclei cannot initially be classified as knots or clumps or sprouts; full identification can be decided only by their subsequent fate.

Hörmann (1953) has suggested that syncytial-knot formation represents an attempt to protect the delicate epithelial plates by forming bridges between adjacent villi. That such connexions are found between villi is well established (Hamilton and Boyd, 1951; and Special Plate, Fig. 16). Our data confirm Fox's statement (1965) that the knots increase in number during gestation. In post-mature placentae the number of knots is yet further augmented; Fox has suggested that this increase may be the result of retrogressive changes in the villi. Wilkin (1965) has described and illustrated a larger number of syncytial knots (which he calls *amas syncytial*) on villi adjacent to regions which he identifies as chronic infarcts. Some of our own material also shows equivalent appearances, but we have not regarded such syncytial knots as precisely the same as those under consideration here, since they are not associated with epithelial plates. As with the syncytial sprouts, subsequent investigation may demonstrate that there are two varieties of so-called syncytial knots.

No convincing explanation has yet been provided for the function, if any, of the syncytial knots. A major factor in the production of some of them, as Fox has indicated, may be a diminution in the circulation of blood in the foetal villi; such an explanation, however, cannot be given for those knots closely associated with the epithelial plates, for the latter are intimately related to foetal capillaries. Increase in the number of syncytial knots has also been reported in placentae from patients with pre-eclamptic toxæmia (Sauramo, 1951; Burstein *et al.*, 1957; Hertig, 1960; Becker and Bleyl, 1961; Merrill, 1963; Kubli and Budliger, 1963).

Discussion

The causal processes underlying the development of the mammalian placenta are ill-understood, and we are unable to comment effectively on the mechanisms concerned in the production of the differentiations of the trophoblastic syncytium considered above. Nevertheless, we feel justified in commenting further on some aspects of the possible significance of the syncytial sprouts and the stromal buds. No further reference will be made to the epithelial plates; being, it would seem, functional adaptations concerned with transfer mechanisms between the foetal and maternal circulations, they are essentially part of a subject too large to come within our present intention.

Remarkable in its method of origin, its micro- and ultra-structure, and its functional activities, the syncytial trophoblast must be considered a highly specialized living tissue. Its special nature is also perhaps indicated by the fact that there is, at least normally, no effective maternal homograft reaction to its presence. In general, highly specialized cells or tissues represent definitive states; they do not usually give origin to new structures without in the process undergoing a preliminary reversion, or dedifferentiation, to a simpler type. In the syncytial trophoblast, however, we can find no trace of such dedifferentiation during the production of the sprouts, the buds, or the knots described in this contribution.

Virchow (1853, 1862) first clearly identified the chorionic villi as foetal elements bathed in maternal blood, and, later,

Langhans (1882) described the dual nature of their covering epithelium. It was not, however, until 1893 that Schmorl first indicated that portions of the villous system can become detached from the placenta and pass into the maternal circulation; he based his suggestion on the finding of multinucleate cytoplasmic fragments, which he regarded as placental in origin, in the small pulmonary vessels of women who had died from eclampsia. On the basis of histological and post-mortem findings many subsequent investigators, especially Veit (1905), have described the frequent separation of trophoblastic fragments, in the form of syncytial sprouts or even portions of villi, into the intervillous space, whence they pass by way of the maternal vessels to the lungs. Indeed, more recent investigations (Thomas *et al.*, 1959; Douglas *et al.*, 1959; Thomas, 1961) have demonstrated the regular presence of syncytial sprouts in the blood of the uterine veins and the inferior vena cava of living women during pregnancy. These findings have been confirmed by Iklé (1961, 1964), who, using the Herbeuval (1960) isolation method, estimated that, per day, there is an inflow rate of approximately 100,000 trophoblast "cells" (sprouts) into the maternal circulation. These trophoblastic sprouts have to be distinguished from maternal megakaryocytes (Minot, 1922), atypical haemoblastic cells, and osteoclasts (Alexander and Spriggs, 1960). Like the sprouts, the megakaryocytes and osteoclasts are multinucleate; they do not, however, possess a brush border.

So far as we are aware (and notwithstanding the statement by Griffiths and Salisbury, 1965) trophoblastic sprouts have never been found in the maternal peripheral circulation but only in vessels between the uterus and lungs. We have found no record of their passage into the systemic arterial system. Batson (1940, 1942, 1957) has stressed the role of the vertebral veins in the spread of pyæmic and malignant emboli from the pelvis to the head region. There is no evidence suggesting dissemination of the syncytial sprouts by this route, though there seems to be no inherent reason why some should not do so. As indicated above, we have found no evidence to suggest that such syncytial sprouts can be disseminated by way of the lymphatic system. The transport of malignant emboli to the lungs, where they form metastases, in cases of primary uterine choriocarcinoma and other malignant conditions is, of course, only too well known. Whether the normal passage of trophoblastic sprouts to, and settlement in, the maternal lungs can also be regarded as a metastatic process seems to us to be a moot point.

Griffiths and Salisbury (1965), in their monograph on circulating cancer cells, state that by definition no benign tumour can metastasize; they conclude (rather tautologically) that "neoplastic cells found in the blood-stream must be deemed to be malignant. It is possible for benign cells from various tissues to escape into the blood, but these cells are unable to multiply and produce metastases." The trophoblastic syncytial sprouts of normal pregnancy not only do not seem to multiply in the maternal lungs but they must be rapidly destroyed in the pulmonary arterioles and capillaries, which otherwise, if Iklé's enumeration is correct, would be extensively infarcted by them. Park (1965) states that the deported syncytium elicits no significant accumulation of inflammatory cells, granulation tissue, or fibrin in the lungs but quietly disappears by lysis. Tao (1964) has shown that in tissue cultures mixtures of autologous embryonic lung and trophoblastic "cells" exhibit complete compatibility, unlike such mixtures of trophoblast and autologous liver. In normal pregnancy the sprouts are, of course, liberated freely into the intervillous space whence passage to the uterine veins is direct. In malignant moles and choriocarcinoma, however, the emboli arise, as in other neoplastic conditions, through the passage of malignant tissue into the blood-stream by intravasation or by rupture of the wall of a vein in relation to the original tumour.

Villous Deportation

As indicated above, it is possible that even in normal pregnancies actual portions of chorionic villi may enter the maternal circulation. As early as 1856 Virchow thought that this process might occur, and Veit (1905) gave a detailed account of what he called villous transport (*Zottendeportation*). Park (1954, 1959) and Attwood and Park (1961) have discussed and given further descriptions of villous deportation. We ourselves (Hamilton and Boyd, 1951, 1960) have frequently observed chorionic villi herniated into the mouths of uterine veins communicating with the intervillous space; on occasion we have also observed villi in uterine veins remote from the intervillous space (Special Plate, Fig. 13). Recently Cameron and Park (1965) have even recorded the occasional presence of decidual tissue within the lungs and have drawn attention to other examples of such deportation (as they interpret the phenomenon) in the literature. In comparison with the transport of syncytial sprouts, villous deportation would appear to be of infrequent occurrence. Perhaps a villus is only deported when there has been what Attwood and Park (1961) have called undue "placental commotion"—for example, it has been found in association with amniotic embolism. Owing to the greater size of villous emboli when compared with syncytial sprouts, pulmonary infarction could be expected to be observed more frequently with the former than with the latter.

It is difficult to find a functional interpretation for villous deportation; the process must surely be regarded as essentially accidental. The transportation of syncytial sprouts into the maternal veins, however, seems to be a normal physiological occurrence. It may, of course, be what Iklé has called a physiological desquamation of syncytium without other functional significance. Again, as suggested by Thomas *et al.* (1959), substances liberated from the sprouts or arising as a result of their destruction in the lungs could conceivably damp down the production of antibodies by the maternal organism and thus explain the absence of a homograft reaction to the placenta. Or hormones may be liberated from the sprouts and explain, in part, the endocrine activity of the organ. Iklé has further suggested that, by the liberation of thrombokinas, the sprouts may influence blood coagulation during pregnancy. It must be admitted that none of these explanations on present evidence is very convincing; nevertheless, whatever their indeterminate function may be, the syncytial sprouts constitute a very remarkable biological phenomenon. We find it difficult to accept as completely purposeless their regular production during normal human pregnancy and their subsequent liberation into the maternal blood-stream.

An explanation of the functional significance of the ectopic trophoblastic material found in the connective-tissue cores of many placental villi throughout pregnancy, and for which we (Boyd and Hamilton, 1964) suggested the name "stromal trophoblastic buds" is also not readily forthcoming. By their breakdown the buds may liberate hormones which have an influence on the foetus. It is also possible that the buds, or at least their syncytial contents, can make their way through the endothelium into the foetal blood-vessels and from thence pass into the foetus. Salvaggio *et al.* (1960) have alleged that trophoblastic syncytium is often found in umbilical-cord blood at the time of delivery; mobilization of the stromal buds could provide an explanation for their findings. It must be pointed out, however, that Iklé (1961) was unable to find any trophoblastic material in the cord blood of 10 newborns. We ourselves have never found a stromal bud passing through the endothelium of a foetal vessel. We have, however, observed close contact between buds and the stromal vessels (Special Plate, Fig. 12) and on a number of occasions have observed and figured (Boyd and Hamilton, 1964) free masses of syn-

cytium in such vessels without, however, being able to convince ourselves that such appearances are not artifacts.

If future investigations demonstrate the reality of syncytial trophoblast material in the foetal vessels of undamaged placentae there may lie in this fact an explanation for the occasional occurrence of choriocarcinoma simultaneously in mother and foetus (Emery, 1952; Kay and Reed, 1953; Buckell and Owen, 1954; Mercer *et al.*, 1958) or of apparently primary instances of the condition in the foetus (Boyd, unpublished case). Embolic plugs of trophoblastic stromal buds in the foetal blood-vessels could also explain some of those congenital abnormalities which appear to be the result of obliteration of the blood supply to a region or organ (Boyd and Hamilton, 1964).

Summary

An account is given of certain specializations shown by the human chorionic villous syncytium. These include:

1. Syncytial sprouts—projections from the villous surface into the intervillous space; some of these sprouts develop into villous branches, others separate and pass into the maternal circulation.
2. Syncytial buds—projections from the villous covering into the stroma of the villi; these buds frequently separate from their origins to become free in the stroma, whence they may conceivably pass into foetal blood-vessels and, thence, to the foetus.
3. Epithelial plates—attenuated regions of the syncytial trophoblast; they possibly possess a special function in placental transport.
4. Syncytial nuclear clumps—thickened areas of syncytium, often adjacent to the epithelial plates, in which the nuclei are grouped together. The possible significance of these nuclear masses is discussed.

These different types of syncytial specializations are illustrated, and it is indicated how little is known about factors influencing the development of these specializations.

We wish to express our thanks to Messrs J. A. F. Fozzard, E. J. Park, J. W. Cash, R. H. Watts, K. W. Thurley, J. F. Crane, A. Campbell, and G. Oakes for photographic and technical assistance. We are also indebted to Mr. W. Simons for help with German literature.

REFERENCES

- Alexander, R. F., and Spriggs, A. I. (1960). *J. clin. Path.*, **13**, 414.
 Alvarez, H., De Bejar, R., Aladjem, S., Alvarez Santin, C., Remedio, M. R., and Sica Blanco, Y. (1964). *Cuarto Congr. Urug. Ginecol.*, **1**, 190.
 Amstutz, E. (1960). *Acta anat. (Basel)*, **42**, 12.
 Attwood, H. D., and Park, W. W. (1961). *J. Obstet. Gynaec. Brit. Cwlth.*, **68**, 611.
 Bargmann, W., and Knoop, A. (1959). *Z. Zellforsch.*, **50**, 472.
 Batson, O. V. (1940). *Ann. Surg.*, **112**, 138.
 — (1942). *Ann. intern. Med.*, **16**, 38.
 — (1957). *Amer. J. Roentgenol.*, **78**, 195.
 Becker, V., and Bleyl, U. (1961). *Virchows Arch. path. Anat.*, **334**, 516.
 Boyd, J. D., and Hamilton, W. J. (1960). *J. Obstet. Gynaec. Brit. Emp.*, **67**, 208.
 — (1964). *Ibid.*, **71**, 1.
 — (1966a). *J. Anat. (Lond.)*. In press.
 — (1966b). *Z. Zellforsch.*, **69**, 613.
 — (1966c). In preparation.
 — and Hughes, A. F. W. (1954). *J. Anat. (Lond.)*, **88**, 356.
 Bremer, J. L. (1916). *Amer. J. Anat.*, **19**, 179.
 Buckell, E. W. C., and Owen, T. K. (1954). *J. Obstet. Gynaec. Brit. Emp.*, **61**, 329.
 Burstein, R., Blumenthal, H. T., and Soule, S. D. (1957). *Amer. J. Obstet. Gynec.*, **74**, 85.
 Cameron, H. M., and Park, W. W. (1965). *J. Obstet. Gynaec. Brit. Cwlth.*, **72**, 748.
 Curzen, P. (1964). *Ibid.*, **71**, 388.
 Douglas, G. W., Thomas, L., Carr, M., Cullen, N. M., and Morris, R. (1959). *Amer. J. Obstet. Gynec.*, **78**, 960.
 Emery, J. L. (1952). *J. Path. Bact.*, **64**, 735.
 Enders, A. C. (1965). *Obstet. and Gynec.*, **25**, 378.

- Fox, H. (1965). *J. Obstet. Gynaec. Brit. Cwlth*, **72**, 347.
- Getzowa, S., and Sadovsky, A. (1950). *J. Obstet. Gynaec. Brit. Emp.*, **57**, 388.
- Griffiths, J. D., and Salisbury, A. J. (1965). *Circulating Cancer Cells*. Thomas, Springfield, Illinois.
- Hagerman, D. D. (1964). *Fed. Proc.*, **23**, 785.
- and Villee, C. A. (1960). *Physiol. Rev.*, **40**, 313.
- Hamilton, W. J., and Boyd, J. D. (1950). *Modern Trends in Obstetrics and Gynaecology*, edited by K. Bowes, p. 114. Butterworth, London.
- (1951). *Proc. roy. Soc. Med.*, **44**, 489.
- (1960). *J. Anat. (Lond.)*, **94**, 297.
- and Mossman, H. W. (1962). *Human Embryology*, 3rd ed. Heffer, Cambridge.
- Hashimoto, M., Kosaka, M., Shimoyama, T., Hirasawa, T., Komori, A., Kawasaki, T. and Akashi, K. (1960). *J. Jap. obstet. gynaec. Soc. (eng.)*, **7**, 122.
- Herbeuval, R. and H. (1960). *C.R. Acad. Sci. (Paris)*, **250**, 3070.
- Herzig, A. T. (1960). In *Placenta and Foetal Membranes*, edited by C. A. Villee, p. 109. Williams and Wilkins, Baltimore.
- Hörmann, G. (1951). *Arch. Gynäk.*, **181**, 29.
- (1953). *Ibid.*, **184**, 109.
- Iklé, F. A. (1961). *Schweiz. med. Wschr.*, **91**, 943.
- (1964). *Bull. Schweiz. Akad. med. Wiss.*, **20**, 62.
- Ishizaki, Y. (1960). *Obstet. and Gynec.*, **15**, 602.
- Kay, S., and Reed, W. G. (1953). *Amer. J. Path.*, **29**, 555.
- Kubli, F., and Budliger, H. (1963). *Geburtsh. u. Frauenheilk.*, **23**, 37.
- Langhans, T. (1882). In *Fests. f. Henle Beitr. Anat. Embryol.*, **69**.
- Lister, Ursula M. (1963). *J. Obstet. Gynaec. Brit. Cwlth*, **70**, 766.
- (1964). *Ibid.*, **71**, 21.
- Mercer, R. D., Lammert, A. C., Anderson, R., and Hazard, J. B. (1958). *J. Amer. med. Ass.*, **166**, 482.
- Merrill, J. A. (1963). *Clin. Obstet. Gynec.*, **6**, 96.
- Meyer, A. W. (1921). *Contr. Embryol. Carneg. Instn.*, **12**, 327.
- Minot, G. R. (1922). *J. exp. Med.*, **36**, 1.
- Örtmann, R. (1938). *Z. Anat. Entwickl.-Gesch.*, **108**, 427.
- Panigel, M., and Anh, J. N. (1963). *C.R. Acad. Sci. (Paris)*, **257**, 3669.
- Park, W. W. (1954). *J. Path. Bact.*, **67**, 563.
- (1959). In *Modern Trends in Pathology*, edited by D. H. Collins, p. 180. Butterworth, London.
- (1965). *The Early Conceptus, Normal and Abnormal*, p. 74. Livingstone, Edinburgh.
- Salvaggio, A. T., Nigogosyan, G., and Mack, H. C. (1960). *Amer. J. Obstet. Gynec.*, **80**, 1013.
- Sauramo, H. (1951). *Ann. Chir. Gynaec. Fenn.*, **40**, 164.
- Schmorl, G. (1893). *Pathologische-anatomische Untersuchungen über Puerperal-Eklampsie*. Vogel, Leipzig.
- Schramm, B. (1962). *Gynec. et Obstet.*, **61**, 423.
- Shanklin, D. R. (1958). *Obstet. and Gynec.*, **11**, 129.
- Snoeck, J. (1958). *Le Placenta Humain*. Masson, Paris.
- Strauss, F. (1964). *Fortschr. Geburtsh. Gynäk.*, **17**, 3.
- Tao, T. W. (1964). *Exp. Cell Res.*, **36**, 275.
- Thomas, L. (1961). In *1st International Conference Congenital Malformations*, p. 230. Lippincott, Philadelphia.
- Douglas, G. W., and Carr, M. C. (1959). *Trans. Ass. Amer. Phycns*, **72**, 140.
- Veit, J. (1905). *Die Verschleppung der Chorionzotten (Zottendeportation). Ein Beitrag zur geburtshilflichen Physiologie und Pathologie*. Bergmann, Wiesbaden.
- Velardo, J. T., and Rosa, C. G. (1963). *Handbuch der Histochemie*, **7/iii**, 1. Fischer, Stuttgart.
- Virchow, R. (1853). *Verh. phys.-med. Ges. Würzb.*, **4**, 370.
- (1856). *Gesammelte Abhandlungen zur wissenschaftlichen Medicin*. Meidinger, Frankfurt.
- (1862). *Ibid.*, 2nd ed. Grote, Hamm.
- Wachstein, M., Meagher, J. G., and Ortiz, J. (1963). *Amer. J. Obstet. Gynec.*, **87**, 13.
- Wilkin, P. (1965). *Pathologie du Placenta*. Masson, Paris.
- Wislocki, G. B., and Bennett, H. S. (1943). *Amer. J. Anat.*, **73**, 335.
- and Dempsey, E. W. (1955). *Anat. Rec.*, **123**, 133.
- and Padykula, Helen A. (1961). In *Sex and Internal Secretions*, edited by W. C. Young, 3rd ed., p. 883. Williams and Wilkins, Baltimore.

Lung Cancer and Bronchitis in Northern Ireland, 1960-2

GEOFFREY DEAN,* M.D., F.R.C.P.

Brit. med. J., 1966, **1**, 1506-1514

This paper summarizes the results of a retrospective epidemiological study of men and women who died of lung cancer or bronchitis during the years 1960-2 in Northern Ireland. The purpose of the study was to obtain information about the extent of the associations with lung cancer and bronchitis of smoking habits, area of residence, occupation, social class, month of birth, morning cough three or more years before death, illnesses during the last 10 years of life, and the incidence of cancer and bronchitis among parents, brothers, or sisters of those who died from lung cancer or bronchitis. Northern Ireland was chosen as the area to be studied, since the objective was to cover so far as was possible all the men and women aged 35 or more who had died of lung cancer or bronchitis during a recent period in a moderately large area of the United Kingdom. In this study 93% coverage was obtained.

Through the courtesy of the Registrar-General a list was obtained, for confidential use in the investigation, of all Northern Ireland residents aged 35 years or more who were recorded in the Register of Deaths as having died of lung cancer or bronchitis in Northern Ireland during 1960, 1961, and 1962. For each of these subjects a "control" was selected, who was the next person in the Register of Deaths of the same sex in the same five-year age group, who last resided in the same type of area, and who died of a non-respiratory illness. Personal interviews were then sought with the relatives of all those on the lists by trained women interviewers of the Health Surveys Unit of AGB Research Ltd. during January-July 1964. During 1960-2 873 male and 167 female residents aged 35 or more had died of lung cancer, and 1,262 males and 630 females

had died of bronchitis, in Northern Ireland. Including controls, this gave a total of 5,864 interviews to be carried out.

For the purposes of the present study Northern Ireland was divided into six areas, consisting of Inner Belfast, Outer Belfast, environs of Belfast, urban districts, small towns, and truly rural districts. Inner Belfast was the central part of Belfast County Borough containing approximately half of the County Borough's population: this area had already been defined in work carried out by the Department of Social and Preventive Medicine of the Queen's University of Belfast. Outer Belfast comprised the remainder of Belfast C.B. The Census Office had already coded lung cancer and bronchitis deaths by these areas. The environs of Belfast comprised Newtownabbey Urban District plus the townlands of Castlereagh, Hillsborough, and Lisburn Rural Districts. Urban districts consisted of Londonderry C.B., all Municipal Boroughs, and all urban districts except Newtownabbey U.D. Small towns consisted of 19 towns and villages containing 50 or more houses, having no legally defined boundaries, and with a population of at least 1,000. Truly rural districts were the remainder of Northern Ireland. The population in each type of area is given in Tables IV and V.

The results of the interviews were summarized by the Health Surveys Unit of AGB Research. Most of the tables in this paper were calculated by this unit and are taken from a detailed report on the results of the survey (Wicken, 1966). The comments in the present paper and the organization and planning of the study are, of course, my personal responsibility.

The lung cancer and bronchitis mortality rates among adults (male and female) aged 35 or more in Northern Ireland during the years 1960-2 are given in Table I.

* Senior Physician, Eastern Cape Provincial Hospital, Port Elizabeth, South Africa.