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The Placental Lesions in Congenital Syphilis

A Study of Six Cases

P. Walter[1], P. Blot[2], and B. Ivanoff[3]

[1] Department of Pathology, [3] Department of Biology, Centre International de Recherches Médicales de Franceville, Franceville, Gabon, Africa
[2] Department of Obstetrics and Gynaecology, Hôpital Provincial de Franceville, Franceville

Summary. Placentas from six mothers with serological tests suggestive of recent syphilitic infection and whose babies were suspected of being or proven to be infected by *Treponema pallidum* are described. One placenta from this series was large, bulky and pale, while the other 5 were without remarkable gross features. In all cases, the associated histological lesions were 1) hypercellular areas in the terminal and stem villi and 2) a focal peri- and/or intravillous polymorphonuclear concentration with or without necrosis. The former change which was the most frequent was characterized by an apparent increase of villous stromal cells, ultrastructurally indentified as mesenchymal cells and Hofbauer cells. In addition, numerous fetal monocytes were found in the villous vascular lumina. The findings described here and in the literature suggest that congenital syphilis is associated with a spectrum of placental changes. We believe that these changes depend on the immunological reaction of the fetus. According to the sequence of events described in untreated patients, we distinguish two morphological phases: 1) an inductive phase without placental changes and 2) a reactive phase characterized by a predominantly lymphocytic inflammatory infiltration of the villi, followed by a reaction of mononuclear phagocytes.

Key words: Syphilis congenital – Placental morphology – Villitis

Congenital syphilis is the consequence of transplacental passage of *Treponema pallidum* from an infected mother. The incidence of congenital syphilis correlates most closely with the incidence of primary or secondary syphilis in women (Kaufman et al. 1977). Although syphilis is a reportable disease in most developed countries, cases of congenital syphilis are rarely recorded.

Offprint requests to: P. Walter, Institut d'Anatomie Pathologique, 1, place de l'Hôpital, B.P. 247/R6, F-67006 Strasbourg Cedex Fránce

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During the fiscal year of 1977, 463 cases of congenital syphilis were reported in the United States (U.S., Department of Health, Education and Welfare 1978). As only about 50% of the cases of syphilis in women living in developed countries are discovered (Felton 1973), this figure must be interpreted as a low estimate of the true incidence of congenital syphilis in the U.S.

Furthermore, Kaufman et al. (1977) reported that syphilitic infection of the newborn is overlooked in 80% of the cases in the U.S., mostly because clinical experience with this disease is scarce and serological diagnostic criteria are lacking. For instance, the latest fluorescent treponemal antibody absorption (FTA-ABS) test for the detection of antitreponemal antibody of fetal origin (IgM) is not satisfactory for routine use (Kaufman et al. 1974) and is of questionable specificity (Reimer et al. 1975). Therefore, placental examination could be of great importance in determining whether a congenital syphilitic infection should be suspected (Taber and Feigin 1979).

Early reports on the placental lesions in congenital syphilis (McCord 1934; Dorman and Sayun 1937; Whipple and Dunham 1938) occurred at a time when the most common placental modifications were not delineated and it is therefore doubtful that the changes described were entirely related to syphilis (Benirschke and Driscoll 1967). The first reliable morphological data were reported by Hörmann (1954), and more recently Russell and Altshuler (1974) and Braunstein (1978) noted a triad of histological changes in the placentas in cases of congenital syphilis.

This report concerns the changes found in 6 placentas (one monochorial, diamniotic) obtained from 6 women with serological tests suggestive of recent syphilitic infection. The aim of our study was to provide by both histological and ultrastructural investigation further insights into the pathology of this apparently increasing (Antal 1976) but yet poorly documented disease. Further, we attempt to place these findings in the perspective of current knowledge of the course of syphilitic infection.

Materials and Methods

The 6 placentas of this study were from a group of 79 placentas with villitis selected from a series of 920 specimens collected during a 1 year period at the Obstetrics Department of the Hôpital Provincial de Franceville (Gabon, Africa). The placentas were examined and specimens of cord blood and blood from each mother taken at the time of parturition were tested at the Centre International de Recherches Médicales de Franceville (C.I.R.M.F.).

Clinical Data

Reliable clinical data were scarce, and in all but one case *T. pallidum* infection was detected by serological screening at the time of delivery. As the date of the last menstrual period was usually lacking, term was assessed by means of the usual clinical scoring system and by placental morphology.

Serological Tests

Serum from blood samples taken at the time of parturition from all women with villitis in their placenta ($n=79$) were screened for syphilis by the microhaemagglutination-*Treponema pallidum* (MHA-TP) test. The positive cases were further tested by a fluorescent treponemal

antibody absorption (FTA-ABS) test. The results of the quantitative MHA-TP test were compared with those from prenatal and/or postnatal maternal blood, when available, in order to detect a change in titers. Cord blood from 5 of the 7 babies born to women with serological findings suggestive of recent syphilitic infection was screened by both MHA-TP and FTA-ABS tests. Blood samples obtained from three of these babies later in infancy were also tested by MHA-TP tests.

Placentas

Placentas previously fixed in 10% buffered formalin were trimmed of blood clots and membranes and weighed after sectioning the cord about 3 cm from its placental insertion. Five to fifteen paraffin blocks were prepared from each placenta: one with membranes and a cord slice and the others with full-thickness slices of the organ. Histological sections from each block were stained with hematoxylin and eosin (H&E), periodic acid of Schiff (PAS) and the Warthin-Starry stain for spirochetes. Tissue for electron microscopy was obtained from cases 5 and 6. The small samples were fixed immediately after delivery in 4% buffered glutaraldehyde. The tissue was post-fixed in osmium tetraoxyde and embedded in araldite. Ultrathin sections were stained with lead citrate and uranyl acetate and examined with a Siemens Elmiskop 102 transmission electron microscope (TEM).

Results

Serological and Clinical Findings

The serological tests were suggestive of a recent syphilitic infection in 6 women. None had been treated for syphilis before or during pregnancy. Blood samples from each of these 6 women were positive for both MHA-TP and FTA-ABS tests at the time of parturition. The results of the quantitative MHA-TP test are recorded in Table 1. The women from case 5 had obvious maculopapular and pustular skin lesions, while no clinical signs were noted in the 5 others.

Table 1. Titers of the microhaemagglutination *Treponema pallidum* (MHA-TP) tests in both mothers and babies

Case number	Mother M Child C	Prenetal (months)	Birth	Postnatal (months)
1	M	n.a.	1/2,560	n.a.
	C		macerated	
2	M	n.a.	1/2,560	1/2,560 (11°)
	C		—	0
3	M	n.a.	1/5,120	1/5,120 (10°)
	Ca		1/1,280	1/5,120 (10°)
	Cb		1/320	1/5,120 (10°)
4	M	1/1,280 (5°)	1/2,560	n.a.
	C		1/1,280	n.a.
5	M	1/5,120 (2°)	1/1,280	n.a.
	C		1/5,120	n.a.
6	M	1/1,280 (6°)	1/1,280	n.a.
	C		1/320	

n.a.: not available

Table 2. Congenital syphilis: Clinical features of the babies and essential morphological data of the placentas

Case number	Assessed gestational age (weeks)	Offspring		Placenta			
		Clinical features at birth	Birth weight	Weight	Large hypercellular villi	Necrotizing villitis	Vascularitis
1	38	Still born, macerated	–	520 g	a	c	c
2	40	–	2,160 g	400 g	b	c	d
3a	36	–	2,410 g	220 g	b	c	d
b		–	2,010 g				
4	40	–	2,820 g	500 g	b	c	c
5	40	Bullous palmo plantar lesions	2,350 g	450 g	b	c	d
6	33	Still-born, skin lesions and hepatomegaly	–	490 g	a	c	c

a present in each microscopic field (× 10)
b present in each histological section
c less than one per histological section
d absent

The consequences of maternal syphilitic infection in the fetus were of varying severity. Case 1 and 6 delivered still-born infants (Table 2). The offspring from the former was macerated, no autopsy could be performed; the fetus from the latter had vesicular skin lesions and hepatomegaly and a liver biopsy was obtained. The baby from case 5 had typical cutaneous palmo-plantar bullous lesions, while those from cases 2, 3 (twin a and b) and 4 were free of clinical signs at birth and later in infancy (2, 3 a–b). Spirochetes were identified in three cases, either in cutaneous lesions of the infant at birth (cases 5 and 6) or in placenta (case 4). Cord blood obtained from five newborns (cases 3 a–b, 4, 5 and 6) was positive for both MHA-TP and FTA-ABS tests. Titers of the quantitative MHA-TP test in infants are also recorded on Table 1. The assessed gestational age and the birth-weights are given in Table 2.

Placental Morphology

Gross Features. The placental weight and other outstanding morphological features are given in Table 2. The placenta from case 1 had an unusual pale pink color and was thicker than normal (7 cm) and relatively heavy (520 g). Also the placenta from case 6 had a high weight for the assessed gestational age (Table 2). The weight of the other placentas ranged from 220 g to 500 g and their colour was normal.

Histology. The placentas from the 6 cases had a combination of lesions which were distinct from those observed in the rest of the group of placentas with villitis from which they were selected. Some of these lesions were common to all 6 placentas of our series, while others were not (Table 2). The common placental changes involved both the terminal villi and the stem villi. These changes were diffuse in case 1 (Fig. 1) and less extensive in the other 5 cases (Fig. 2).

The villi involved were larger than normal (Fig. 1), but their syncytiotrophoblast had a normal appearance relative to the gestational age (Fig. 3). The outstanding morphological changes involved the stroma which appeared hypercellular but of a loose texture (Fig. 3). Two kinds of cells were distinguished in the stroma of these villi. One had a poorly defined cytoplasm and long, irregular, seemingly anastomotic projections (Fig. 3); the other was usually found in spaces delimited by the former (Fig. 4). The latter was characterized by a globular and sometimes round cytoplasm containing a round or irregular shaped nucleus with marginated chromatin (Fig. 3) and an inconspicuous nucleolus. Few narrow vessels were recognizable in the stroma of these villi and the peripheral vasculo-syncytial membranes appeared relatively reduced (Fig. 3). Some stem villi showed similar but focal stromal changes (Figs. 1 and 4), while others were normal (Figs. 1). In some villi, either normal or with such changes, a variable degree of thickening of the trophoblastic basement membrane was observed. These villous changes were distinguishable from the hydropic villi which were found in some placentas (cases 5 and 6). The latter were large and the vascularisation was poorly developed, but the stroma was not hypercellular. Also, stromal cells had a scant, often elongated or bizarre shaped cytoplasm and the nucleus contained dense chromatin.

The hypercellular stromal changes of terminal and stem villi were associated with other lesions. Focal (necrotizing) villitis, although present in each placenta was uncommon (Table 2). This villitis consisted of either or both intra- and perivillous polymorphonuclear concentration with stromal and/or syncytiotrophoblastic necrosis. In case 4, multinucleated giant cells were associated with perivillous leucocyte concentrations (Fig. 5). The necrotizing villitis was associated in two cases (3 and 5) with dense stromal collagenous changes in some terminal villi. Spirochetes were found in atypical or fragmented form in several placental sections from case 4. Rare lymphocytes were identified in the stem villi with vascularitis. These changes were scarce and present only in three cases (cases 1, 4 and 6). No remarkable feature was noted in the decidua basalis and focal lymphocyte infiltration was a common finding in the collected placentas ($n=79$). Chorioamniotitis was present in cases 1, 2, 4 and 6. The lesions in the monochorial, diamniotic twin placenta had no remarkable qualitative or topographical features. Except for case 1, the other five placentas had a regular architecture with a large proportion of villi of normal structure and diameter for the assessed gestational age (Fig. 2).

Ultrastructure. Placental tissue obtained from cases 5 and 6 and processed for transmission electron microscopy contained normal and atypical large

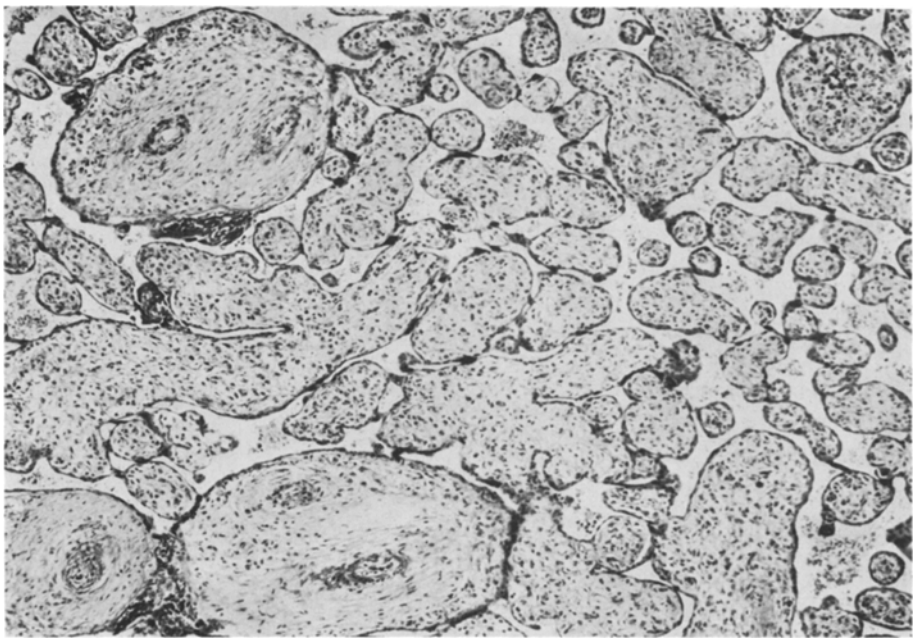

Fig. 1. Placenta at term (case 1) with large and hypercellular terminal villi. Hypercellular areas are present at the periphery of several stem villi. The syncytiotrophoblastic layer is flattered. HE × 100

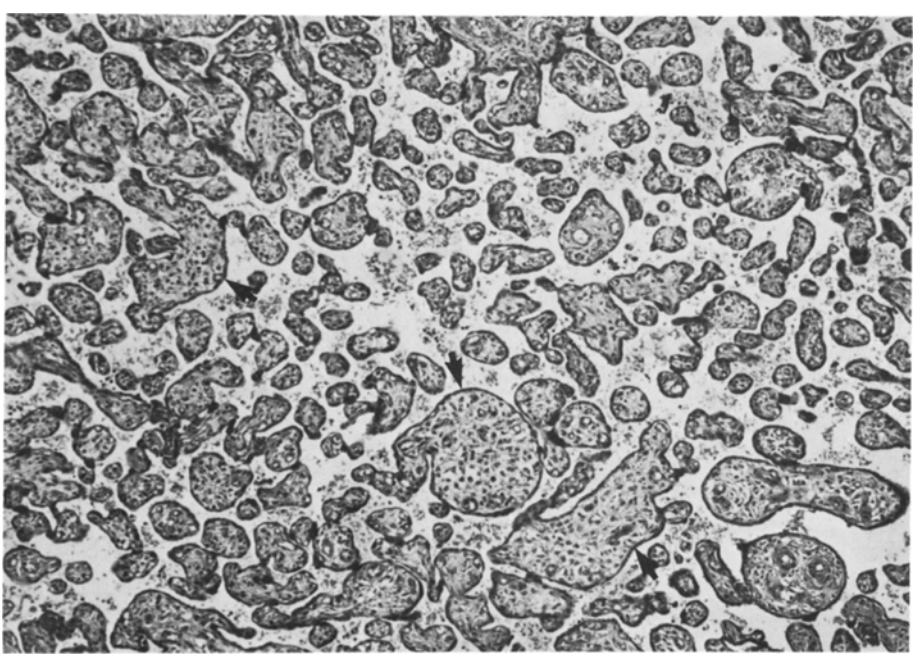

Fig. 2. Placenta at term (case 4) with numerous normal and a few large hypercellular terminal villi (*arrows*). The stromal texture of the latter is looser than that of the former. HE × 100

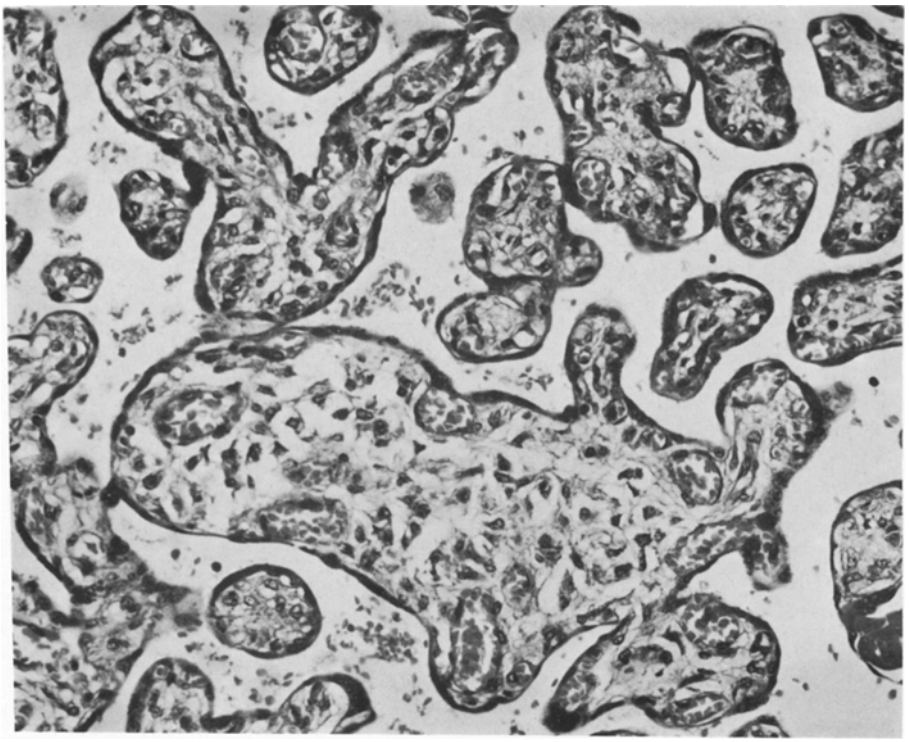

Fig. 3. Placenta at term (case 4) with an enlarged and hypercellular terminal villus. The cytoplasm of the stromal cells is not easily distinguishable but seems to have anastomotic cytoplasmic elongations delimiting empty spaces. The central villous vascular system is poorly developped. The syncytiotrophoblastic layer is normal. HE × 330

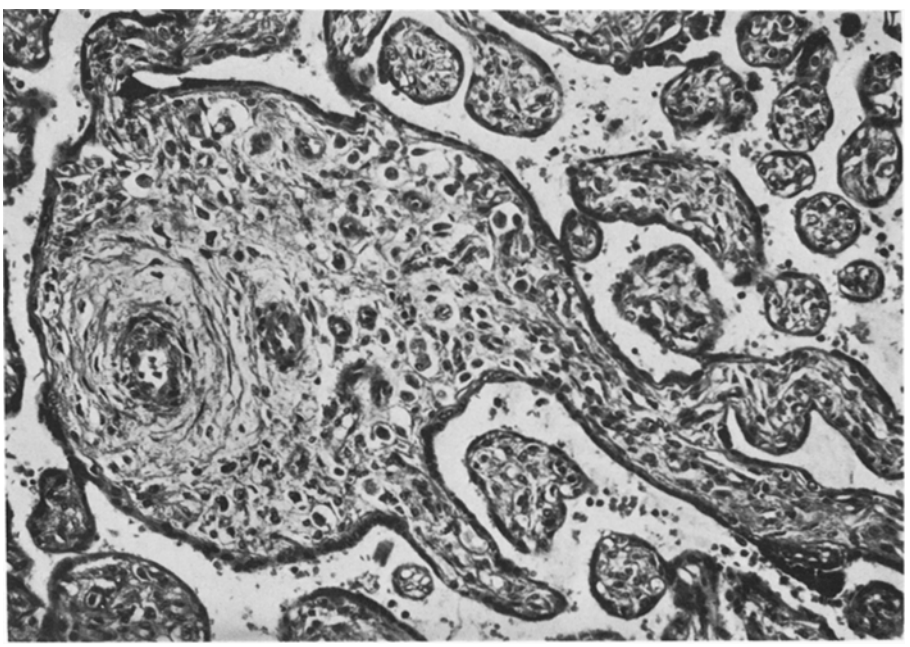

Fig. 4. Tertiary stem villi branching into terminal villi. Two kinds of cells are distinguishable in the hypercellular stroma: a globular round one located in vacuole-like spaces and one more numerous located in the intervening connective tissue. Both large vessels are normal in structure (Case 5). HE × 330

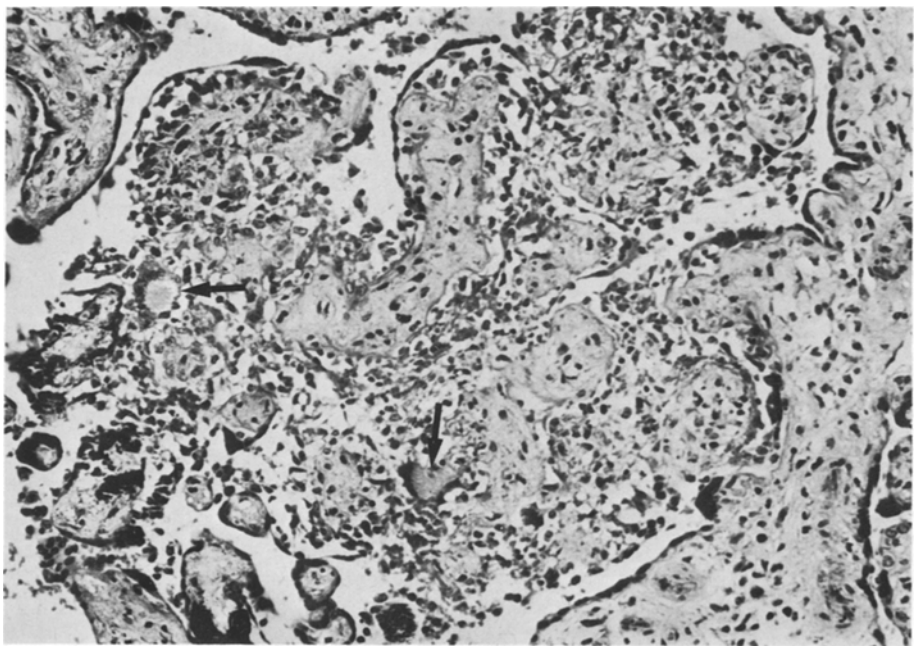

Fig. 5. Villitis with a predominant perivillous polymorphonuclear concentration and partial villous necrosis (case 4). Two multinucleated giant cells (*arrows*) can be distinguished in the inflammatory infiltrate. HE × 330

hypercellular villi, but none of the other occasionally associated lesions. The villi of normal diameter had no distinctive ultrastructural feature except for a focal homogeneous thickening of the trophoblastic basement membrane. The large villi were covered by a syncytiotrophoblast without major changes (Fig. 6). In some parts, the syncytium contained large empty vacuoles. The cytotrophoblast was without modification.

The most important changes were restricted to the stroma which appeared loose in texture (with scanty collagen bundles) but rich in cells (Fig. 6). The cells were elongated or had irregular, often stellate, shapes with peripheral cytoplasmic projections. The cytoplasm was moderately dense and contained small mitochondria and profiles of smooth endoplasmic reticulum. Such mesenchymal cells were sometimes united by long and slender cytoplasmic projections, delimiting areas often containing another type of cell. The latter had the features of Hofbauer cells with peripheral projections, intracytoplasmic vacuoles and dense granules (Fig. 7). Usually the stromal spaces delimited by the mesenchymal cells and containing Hofbauer-like cells were free of connective tissue or any other structures. The villous core contained rare, small central and few larger peripheral vessels with normal structure. Fetal monocytes were noted with unusual frequency in the lumina of these vessels. No spirochetes were found in the villi or the intervillous spaces.

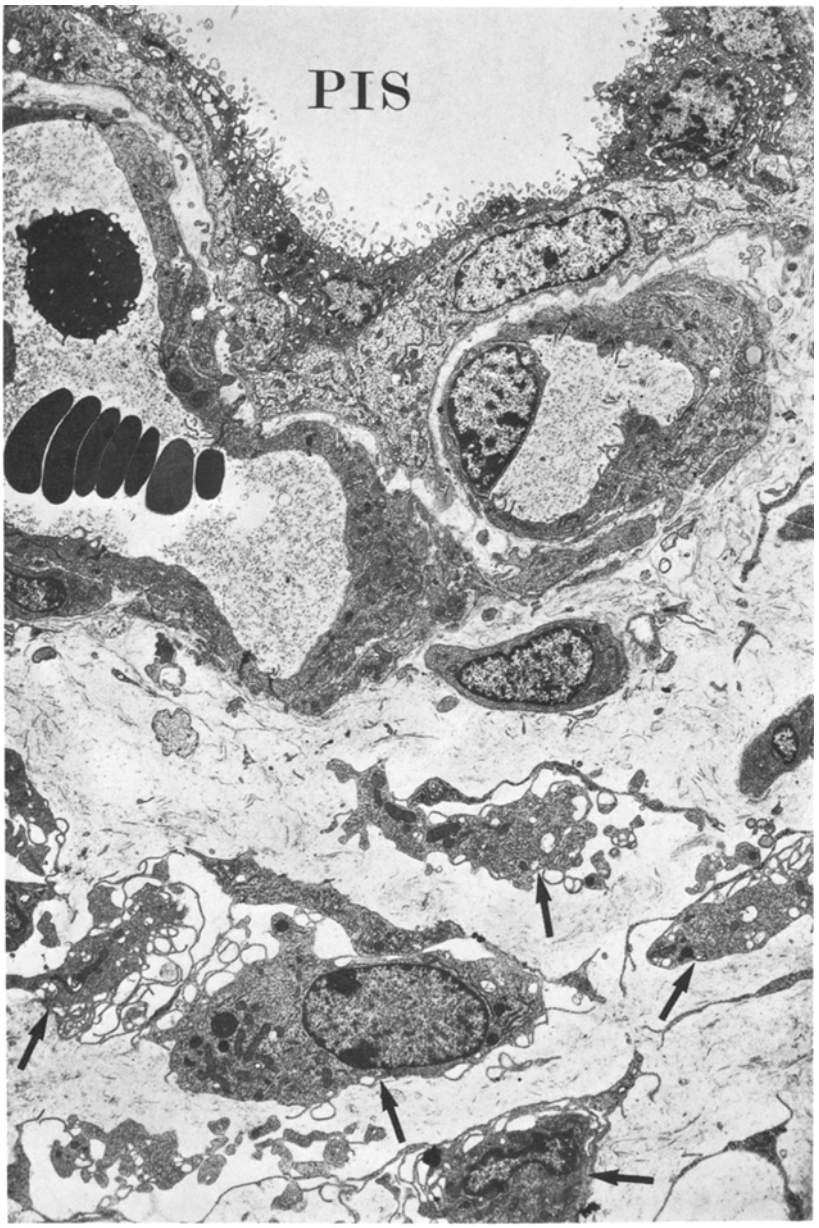

Fig. 6. TEM micrograph from a term placenta (case 5). The syncytiotrophoblast, the cytotrophoblast and the basal lamina are normal. The walls of the villous peripheral vessels are well structured. The villous stroma has loose texture and there is an apparent excess of Hofbauer cells (*arrows*). *PIS:* Placental intervillous spaces. × 6,000

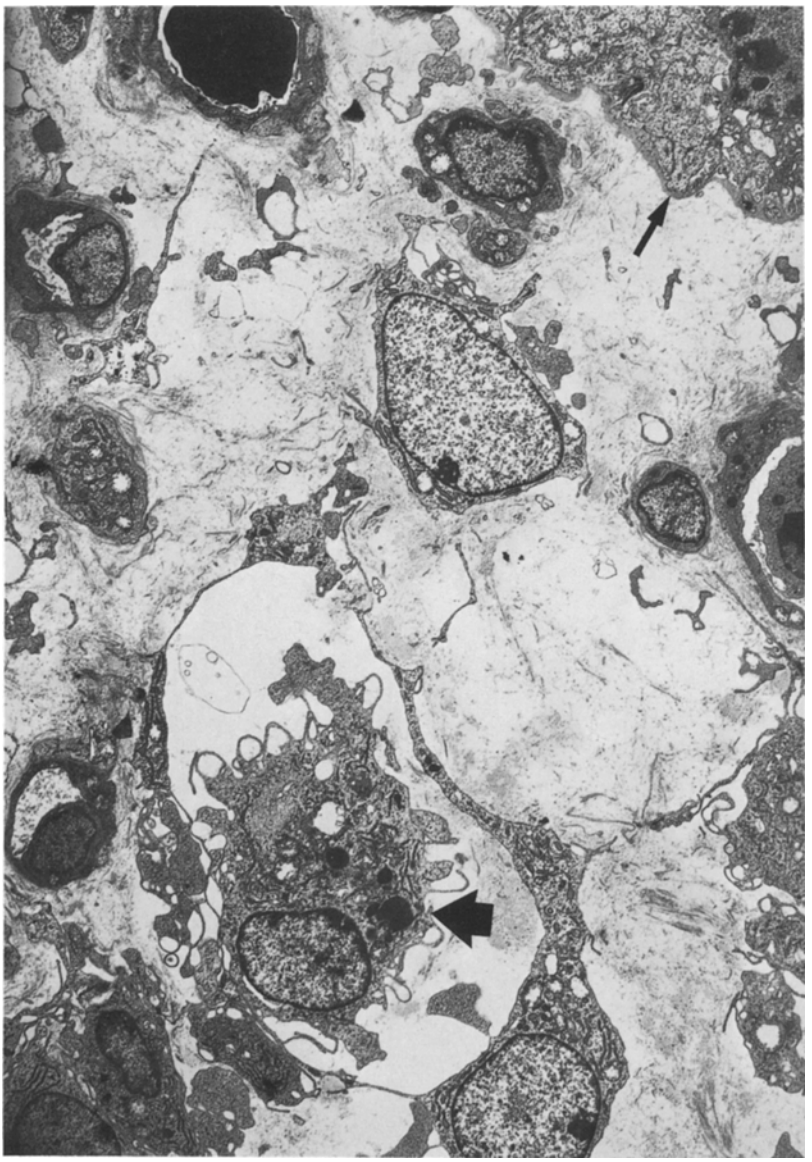

Fig. 7. TEM micrograph from a large hypercellular villus from a term placenta (case 5). The syncytiotrophoblastic layer is at the right upper corner (*arrow*). The mesenchymal cells with long, slender, cytoplasmic projections compartmentalize the stroma. A Hofbauer cell (*large arrow*) is enclosed in one such compartment. Small, well structured vessels and few collagen bundles are present in the stroma. × 6,000

Discussion

Congenital syphilis will continue to occur as long as infectious syphilis exists among adults of child bearing age. Statistics from the World Health Organization have drawn attention to the seemingly increasing trend of

syphilis almost everywhere in the world (Antal 1976). Studies indicate that syphilis remains highly prevalent in Africa (Harris 1975). The six cases from our series were collected in an African equatorial region. Since reliable clinical data were lacking in all but one case, the diagnosis of syphilis was based on serological treponemal tests. Although none of the treponemal tests distinguishes between syphilis and other treponematoses, the former was highly probable in cases 1, 2 and 3, and definitively established in cases 4, 5 and 6 by identification of spirochetes. Moreover, yaw and bejel, the treponematoses still present in certain areas in Africa, have been virtually eliminated in Gabon (WHO Wkly Epidem. Rec. 1981).

The increase of syphilis in almost all parts of the world has stimulated interest in this ancient disease. Considerable information has accumulated in recent years concerning different aspects of host immunity and, particularly, cell mediated immunity in syphilis (Pavia et al. 1978). Also, more precise insights into the mechanism of syphilitic infection in the fetus have been obtained. Silverstein (1962) suggested that the placental lesions and fetal disease in congenital syphilis may be determined by fetal immunological reaction and may, therefore, not occur before the immunological system has begun to develop in the fetus. More recently, Harter and Benirschke (1976) provided support for this hypothesis in localizing *T. pallidum* in tissues of fetuses of 9 and 10 weeks without associated histological inflammatory reaction.

In congenital syphilis, the placenta has classically been considered to be large, bulky and pale (Hörmann 1954). However, these macroscopic features were found in only one case from the present series (Case 1). The enlargement of this placenta correlates with extensive histological villous changes and was associated with prenatal fetal death. Furthermore, from the present and previously reported series (Hörmann 1954; Russell and Altshuler 1974) it appears that placental enlargement was associated with perinatal fetal death in about 50% (11/21) of such cases.

The outstanding histological feature in each of our six observations was the presence of large hypercellular villi in variable proportions (Fig. 1). These villi were characterized by a loose, poorly vascularized stroma with numerous mesenchymal and Hofbauer-like cells. Whether these lesions correspond to the oedematous villi described by Hörmann (1954) or to the immature villi with increased cellularity noted by Russell and Altshuler (1974) could not been ascertained. Almost all the villi of the placenta with peculiar macroscopic features (Case 1) were involved by these changes (Fig. 1). The pale pink color of this placenta can be related to both the poorly developed villous vascular system and the reduction in width of the intervillous spaces. In addition to the apparent stromal cell hyperplasia, numerous fetal monocytes were present in villous vascular lumina. It is noteworthy that Karayalcin et al. (1977) found a monocytic haematological reaction in 9 infants with congenital syphilis. The function of the monocytes in congenital syphilis remains unclear, but they may be involved in the fetal cell-mediated immune response. Several features suggested that these villous changes were related to a reactive, presumably inflammatory, process: 1) the changes involved a variable number of terminal villi and

stem villi (focally) while the remaining placental structures were normal, 2) Hofbauer cells, which seemed to be increased in number, are thought to belong to the mononuclear phagocyte system and are, therefore, primarily involved in inflammatory or immunological reactions (Wood 1980), and 3) the associated reaction of fetal monocytes which belong also to the mononuclear phagocyte system may also be inflammatory or immunological in origin.

The large hypercellular villi were associated with focal peri-and/or intravillous polymorphonuclear concentration combined with syncytiotrophoblastic and/or stromal necrosis. In one case, villitis with multinucleated giant cells was observed (Fig. 5); similar findings were reported by Russell and Altshuler (1974). Contrary to previous reports (Hormann 1954; Russell and Altshuler 1974; Braunstein 1978), vascularitis was rather uncommon in the placentas from our series (Table 2). Also, while villous lymphocyte and/or plasmocyte infiltration was a common feature in the several reports in the literature, it was lacking in our material.

The comparison of the morphological features as described by Hörmann (1954), Russell and Altshuler (1974), Braunstein (1978) and in the present series suggests that in congenital syphilis, the placenta is involved in a spectrum of histological lesions. We believe that the changing pattern of the placental lesions may follow the sequence of events observed during the course of unmodified experimental syphilitic infection in the testis of rabbits (Baker-Zander and Sell 1980) or in untreated adult human *T. pallidum* infection (Turner and Hollander 1957). The latter is characterized by 3 successive stages: 1) an inductive phase without host immune response, but with exponential increase in the number of infecting organisms, 2) a reactive phase manifested by lymphocyte infiltration, followed by an infiltration of mononuclear phagocytes (macrophages) and 3) a stage of latency which corresponds to a state of immunity with persistence of the infecting organisms.

During the fetal inductive phase which, in cases of early intrauterine infection, may be prolonged until the fetus has begun to become immunologically competent, no inflammatory reaction occurs in the placenta or in any other part of the conceptus, as noted by Harter and Benirschke (1976). The villous inflammatory infiltrate, with either a predominantly lymphoplasmocytic infiltration or a mononuclear phagocyte cell (Hofbauer cell and monocyte) reaction, may correspond to the fetal reactive phase. Clinically, it seems that conditions similar to the latency phase, characterized by the persistence of the infecting organisms and a late appearance of symptoms, may occur in a fetus with syphilis. Unfortunately nothing is yet known about the chronology of immunological events in the fetus infected with *T. pallidum*.

In investigation of general immunological function, there is some evidence that the development of the immune system seems to be adequate for antibody synthesis by the 15–16 week, i.e. placental lesions may not occur before the fourth month, an assumption largely confirmed by both early and more recent reports (McCord 1934; Harter and Benirschke 1976; Hager

1978). Little is known, on the other hand, about the development of the mononuclear phagocyte system in fetuses (Stiehm 1975; Loke 1978; Marshall 1979).

The various patterns of placental lesions in congenital syphilis, which we assume to be essentially determined by the fetal immune response, cannot be viewed as specific to *T. pallidum* infection. In fact, we observed rare large hypercellular villi in 3 placentas with villitis of unknown non syphilitic aetiology and lympho-plasmocytic infiltration of the villi is common in cytomegalovirus infection (Benirschke et al. 1974). However, the findings described here and in the most recent literature suggest that congenital syphilis should be suspected when placentas are involved by inflammatory lesions of both types: 1) reactive characterized by villitis with either a lympho-plasmocytic infiltration or Hofbauer cell and fetal monocytic hyperplasia and 2) necrotizing villitis with a peri- and/or intravillous polymorphonuclear concentration.

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