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Embolic Trophoblast in Peripheral Circulation During Pregnancy.* (26502)

BENJAMIN L. TOY AND LUKE G. TEDESCHI (Introduced by C. G. Tedeschi)

Department of Laboratories and Research, Framingham Union Hospital, Framingham, Mass., and Departments of Pathology and Surgery, Massachusetts Memorial Hospitals, Boston

Pulmonary embolism by trophoblastic fragments during pregnancy was first demonstrated by Schmorl(1), and is now considered a commonplace finding in normal gestation. Park(2), as well as Bardawil and Toy (3) have implied that one may anticipate uncomplicated trophoblastic embolism to the lungs in roughly half of all seemingly physiological pregnancies. The fate of ectopic trophoblasts has aroused particular interest as a possible factor in the genesis of choriocarcinoma. Experiments such as those by Park(2) have suggested a destiny no more threatening than ultimate degeneration and disappearance from the host.

Until recently, free trophoblastic embolism has been observed only in the pulmonary capillaries. Douglas *et al.*(4) recently reported isolation of syncytial masses at time of Caesarean section from the veins of the broad ligament in 8 of 13 cases, the ovarian veins of one patient, and the inferior vena cava in 3 samples from an unstated number of cases out of a total of 33 explored. Attempts to isolate trophoblasts from the antecubital vein failed to reveal positive results. The desirability of a statistical perspective on the problem of trophoblastic embolism and its analysis has induced the authors to submit their results of a similar survey.

Materials and methods. Blood samples were drawn from a total of 155 patients in various stages of pregnancy, 10 of whom were in active labor at time of sampling. Specimens were obtained in all cases from the antecubital vein and in 22 of these patients blood was also secured from the placental site during Caesarean section. Ten smears and a serially sectioned cell block were examined in each of the first 130 cases; 5 smears were evaluated in each of the remaining 25 cases. The latter included 5 samples from the placental site.

Early attempts to apply the method of Sandberg and Moore(5) yielded unsatisfactory results. The majority of samples have been processed according to the technic of Malmgren and his group(6) as later modified by Long and his colleagues(7). Heparinized blood is centrifuged and the cellular sediment treated with streptolysin O to destroy erythrocytes and polymorphonuclear leukocytes. The remaining cellular debris is concentrated by centrifugation and smeared out on slides for staining by the Papanicolaou technic.

All slides were scanned systematically with a mechanical stage; all positive or equivocal cell forms were marked and restudied until classified.

Results. In no case was a cell remotely resembling ectopic trophoblasts retrieved from the antecubital vein of a pregnant patient. Occasional bizarre forms were observed but rejected as blood cell debris upon close examination. In 3 cases, all sampled at

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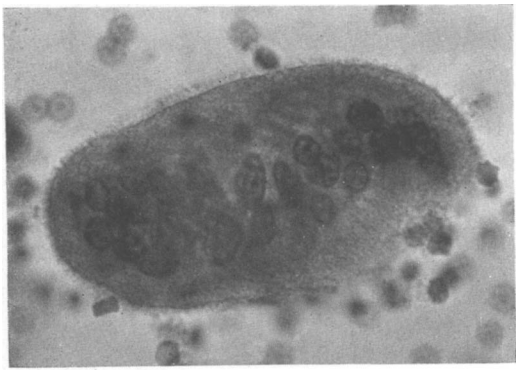

FIG. 1. Embolic syncytial trophoblast recovered from placental site at time of Caesarean section. This syncytial knot exhibits typical multinucleate pattern, peripheral brush border, and abscissional zone. Operation performed because of pelvic disproportion and toxemia. (F.U.H. Case No. 154988.)

the placental site, questionable multinucleate debris was isolated, but distinction between partially disintegrated syncytium and fortuitously coalescent lymphocytic flotsam was not possible.

In a fourth case, a single syncytial embolus was isolated from the placental site (Fig. 1). This cell, evidently a detached knot, was completely consistent with syncytial trophoblast by the usual histological criteria. This patient FUH #154988, a 29-year-old Gravida II Para I, came to Caesarean section because of pelvic disproportion and toxemia.

Discussion. The clearcut identification of embolic trophoblast *ex situ* presents a challenge to even the most experienced observer, particularly in evaluation of severely autolysed remnants. The ubiquitous megakaryocyte, first described as a frequent impactus in the pulmonary capillaries by Aschoff(8), is easily distinguished from trophoblast except in poorly preserved specimens. The isolation of Langhans cells, however, is much more difficult; except in metastatic mole or choriocarcinoma, it is practically impossible to identify them cytologically as emboli, and published reports of cytotrophoblastic embolism must be evaluated with extreme caution. In the more than one thousand slides of the Boston Lying-in Hospital series reported earlier(3), not one definite Langhans cell was found although many hundreds of syncytial emboli were identified. The blood samples examined in the present series yielded a variety of bizarre cellular elements, but none was felt to warrant identification as trophoblast.

The demonstrations by Douglas and his group(4) are wholly consistent with syncytium, and are valuable documentation of a previously assumed but uncharted stage along the route from chorion to lung. Our own experience in sampling the peripheral circulation has confirmed our *a priori* impression of the near futility of small and random samples in attempting to trap circulatory emboli which occur infrequently and inconstantly. Whether uterine commotion, a classically postulated agent in setting trophoblastic emboli adrift in the maternal circulation, may explain the greater yield in the Douglas series is a matter of speculation.

The absence of trophoblastic cells from antecubital specimens in either study is significant. Most workers have assumed almost total trapping of embolic matter in the pulmonary capillaries. While the possibility of passage through the lung may not be excluded, the phenomenon remains wholly undocumented. Animal studies reported elsewhere(3) have suggested virtually complete filtration of trophoblastic emboli in the lung; follow-up experiments planned in this laboratory will attempt a review under more stringent conditions. Granted the occasional passage of a trophoblastic fragment through the pulmonary capillaries, it is hardly necessary to stress the extreme unlikelihood of retrieving such a seldom traveler with a random venipuncture.

Summary. A total of 155 blood samples from the peripheral circulation of patients in varying stages of pregnancy have been screened for embolic trophoblastic cells by one of the standard technics for segregation of circulating cancer cells. A single syncytial embolus has been found in a specimen from the placental site at time of section; all other samples have been negative. Statistical and technical difficulties are discussed briefly.

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Relation of the Mecholyl Test to Catecholamine Excretion.* (26503)

ARNOLD G. BLUMBERG AND HARRY GOLDENBERG
(With technical assistance of Daniel L. White)
Departments of Internal Medicine and Biochemistry, Hillside Hospital, Glen Oaks, N. Y.

The mecholyl (methacholine) test has been proposed as a measure of sympathetic tone (1). Funkenstein(2) postulated that the differences in reactivity of the systolic blood pressure in human subjects to injection of mecholyl was related to the relative excretion of epinephrine and norepinephrine. He suggested that those subjects whose blood pressures returned rapidly to the base line after injection of mecholyl had reacted by producing more norepinephrine; in contrast, those whose blood pressures stayed low for a long period were assumed to produce more epinephrine in response to stress. Elmadjian (3) studied urinary excretion of epinephrine and norepinephrine and was able to correlate the mecholyl area with the excretion of norepinephrine but not with epinephrine. Manger(4) studied the blood level of epinephrine and norepinephrine and could demonstrate no change in these levels with injection of mecholyl. Since we have been able to standardize the procedure and interpretation of the mecholyl test(5), it seemed appropriate to reinvestigate the relationship between the urinary excretion of the active catecholamines and mecholyl area.

Methods. The mecholyl test was carried out as outlined previously(5). Subjects were patients at Hillside Hospital, a voluntary psychiatric institution. They were seen early in their hospital stay, and were not receiving specific medication at the time of study. In all, 48 patients were studied. Each was tested under basal conditions. A urine sample was collected prior to the test. The patient then rested for at least a half-hour during which time his blood pressure was automatically recorded at intervals of one minute by a recording sphygmomanometer. When the pressure was noted to be steady, an injection of 1 cc of mecholyl (10 mg) was given subcutaneously. The change in pressure was recorded over the next 20 minutes. A urine sample was then collected. The mecholyl area was determined by plotting systolic pressure *vs.* time in minutes on graph paper (10 squares/cm) and measuring the area enclosed by means of a compensating polar planimeter. The area was corrected for the basal blood pressure as previously described.

For control purposes, the mecholyl test procedure was repeated in 10 selected patients using 1 cc of normal saline (subcutaneous) instead of mecholyl. Blood pressure areas and urine analyses were conducted as for the standard test.

Chemical analyses. Urine specimens (25-50 cc) were analyzed for epinephrine and norepinephrine by the fluorometric method of von Euler and Floding(6). Creatinine content was determined simultaneously, and catecholamine output calculated as μg/g creatinine.

Observations. In the 10 control studies in which saline alone was injected (Table I), there was relatively little change in blood pressure as manifested by areas generally

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