LATENT CHORIOCARCINOMA

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Latency, the concealed retention of potentially or actually malignant cells in a dormant state over a long period of time, is a curious and important phenomenon which has been observed in numerous types of malignant tumors. Because of the foreign nature of the cells of the placental chorion, and the presumably easy establishment of the date of their origin in the body, latent choriocarcinoma has attracted particular attention. Series of such cases have been collected by Outerbridge (1) and others, with several instances of latent periods of over five years. Dorr and Cutler (2) record an example with an apparent interval of thirty years between the last known pregnancy and the discovery of the tumor at the age of seventy.

The latent period in choriocarcinoma is accepted as indicating the time of existence of the retained placental chorion before the first appearance of symptoms of malignant development. The end-point is usually reasonably determinable, but the beginning depends in nearly all cases upon the establishment of the date either of the last pregnancy or of the menopause. Because of the inherent uncertainty of such dates, except in instances of artificial termination of fertility, e.g., hysterectomy or bilateral oophorectomy, the validity of many reported latencies is open to question.

Hitschmann (3) in his monograph on chorionic tumors (1928) goes so far as to cast doubt upon the whole subject of their latency, mentioning as sources of error, first, the possibility of unnoticed or deliberately concealed pregnancy occurring within the supposed latent period, and second, the ease of mistaking the amenorrhea of an unrecognized pregnancy for that of the menopause. He also shows the fallacy of regarding the cases occurring after fifty as having been necessarily latent, by pointing out the known frequency of both normal and molar gestations after that age.

The accumulated data cannot, however, be discredited in such wholesale fashion, since the existence of latency in choriocarcinoma is well established by the occurrence of a few cases in which the above sources of error are clearly excluded. Such a case is that of Krössing, quoted by Vineberg (4), in which choriocarcinoma was found in the uterus over three years after bilateral oophorectomy and five and one-half years after the original mole. Another instance is that reported by Cary (5), with recurrence three years after hysterectomy. The case of Dorr and Cutler (2) also seems unquestionably valid to the extent of at least ten to fifteen years, inasmuch as the tumor did not appear until the age of seventy. The possibility of teratomatous origin must be considered in this and other cases, but is improbable in view of the intrauterine location of the tumor.

To the small group of cases in which proof of latency is apparently conclusive, we add another.
A white woman, thirty-two years old, entered the White Memorial Hospital on May 19, 1936, complaining of persistent productive cough, with hemoptysis, for five months; pain in the right chest, dyspnea, weakness, and weight loss, for one month.

The medical history included an appendectomy in 1927; dilation and curettage on three occasions, for which no dates were given, and hysterectomy for dysmenorrhea in 1929. The patient was said to have had one pregnancy, with a normal delivery in 1924, and no abortions.

After autopsy had disclosed the unexpected nature of the tumor, the following additional information was obtained. Curettement for apparent abortion of a two months' pregnancy, in September 1927, yielded material described as a hydatidiform mole. No embryo was found. Curettement was repeated, apparently within a few days, and the remainder of the mole was removed. It was said that "pathological examination revealed no malignancy." The patient continued to have excessive vaginal bleeding and lower abdominal pain, and a third curettage was done in January 1928, but the findings were not reported. Pelvic examinations showed slight and variable enlargement of the uterus and adnexal regions. The right ovary was said to be palpable on one occasion. The patient seemed otherwise well, and gained weight during this period.

Hysterectomy, including removal of the cervix and at least one fallopian tube, was performed Nov. 18, 1929. Whether the other tube and the right ovary were removed at that time or at the previous "appendectomy," is not known. The uterus and tube were submitted to a pathologist, Dr. R. M. Choisser, of Washington, D. C., who found no evidence of tumor in the material. The original microscopic sections, which we were able to obtain, show an essentially normal fallopian tube and myometrium, with endometrium in a late follicular phase, and slight chronic cervicitis.

We are indebted to Dr. J. Norman Kimble, Takoma Park, Maryland, for his assistance in the tracing of the patient's history.
Following the operation the patient’s symptoms were relieved, and she remained apparently well until, after six years, the present illness commenced.

**Examination:** Positive physical findings were a general anemic pallor, evidence of moderate weight loss, and an area of dullness and decreased breath sounds below the right scapula. As roentgenographic examination suggested a neoplasm of the mid-section of the right lung, bronchoscopy was done, revealing a granulating mass in the lateral wall of the right main bronchus. Biopsy showed principally necrotic material, but groups of large, dark-staining nuclei were suggestive of a malignant tumor.

**Course:** With the tentative diagnosis of bronchogenic carcinoma, six weeks of deep roentgen irradiation was given, followed by an exploratory thoracotomy at the Hospital of the Good Samaritan, July 24, 1936. This disclosed a large mass occupying the upper half of the lower lobe of the right lung. Because of extension of the tumor into the mediastinum, pneumonectomy was not attempted. The patient failed steadily, and died Sept. 28, 1936, nine months after the onset of symptoms.

**Autopsy Findings:** The thoracotomy incision had healed well, with reunion of the severed costal cartilages. The right pleural cavity was obliterated by dense adhesions; the left pleural cavity was free.

Filling most of the mid-portion of the right lung was a huge rounded mass of red, hemorrhagic, friable tissue, with advanced central necrosis. Spherical tumors of similar appearance but much smaller size were scattered through the rest of both lungs. The intervening pulmonary tissue was edematous, and the right lung showed considerable pneumonitis and atelectasis.

Tumor was found elsewhere only in the mediastinal lymph nodes, and as a solitary 6 cm. sphere in the upper pole of the right kidney. There was no evidence of a mediastinal teratoma.

Except for the atrophic left ovary, which was adherent to the sigmoid colon, the internal genitalia were absent. No suggestion of tumor could be found in the pelvis or in any of the abdominal or pelvic lymph nodes.

**Microscopic Findings:** Sections from the tumors in the lungs and kidney show vascular, hemorrhagic, and extensively necrotic tissue composed of cells of two types. Sheets of apparently individual cells, with large vesicular nuclei, prominent nucleoli, and numerous mitotic figures, are bordered intermittently by elongated giant cells. These latter consist of eosinophilic masses of cytoplasm containing central irregular clumps of densely staining nuclei. This appears typical of choriocarcinoma, with the characteristic syncytium and Langhans cells.

**Friedman Test:** This procedure was not thought of until the discovery of the choriocarcinoma microscopically. Purified aqueous extracts both of the tumor tissue and of the formalin in which it had been fixed for about twenty-four hours gave a definitely positive Friedman reaction.

**DISCUSSION**

Questions of theoretical and practical interest arise regarding the location and nature of the chorionic tissue during the latent period, the source and time of its derivation, and the possible effects of hormonal secretion by the latent chorion.

It seems clear from both clinical and pathological findings that the final development of the tumor began in the right lung, with secondary dissemination to the other lung, the lymph nodes, and the kidney.

The original source of the chorionic tissue seems undoubtedly to have been the vesicular mole, which represented the patient’s last known pregnancy. The time at which this tissue was transported from the uterus to the lung, and the character of the transported tissue, whether benign or malignant, are debatable.

Placental chorion and portions of villi are frequently deported to the lungs
in normal pregnancy, but especially in the presence of vesicular mole (Schmorl, 6, quoted by Novak; Schmauch, 7). Schmorl also stated that while the deported chorionic elements from normal placentae show no tendency to proliferate, those from moles give evidence of growth after their distant lodgment.

In view of these considerations it appears plausible that simple pulmonary embolism of benign molar tissue occurred during the original curettements, with change to malignancy only in the last stage of the patient’s history.

The principal alternative explanation is that the chorionepithelioma developed simultaneously with the mole and metastasized to the lung as a malignant tumor. Then, after the primary growth was completely removed from the uterus by curettement, the malignant deposit in the lung was held in a mysterious restraint during the period of latency. Such simultaneous development of mole and chorionepithelioma is a possibility, as shown by Mathieu (8). The failure of the metastatic lesion to continue immediate malignant development is also possible, if one accepts the reported instances of apparent regression and disappearance of chorionepitheliomatous metastases after removal of the primary tumor (Corrêa, 9; Fredrikson, 10).

A comparison of these two concepts—late malignant change and restraint

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**Figs. 2 and 3. Choriocarcinoma in Lung**

In Fig. 2 (left), × 250, note the multiple deeply stained nuclei and distinct cytoplasm of the syncytial cells, as well as the uniform size and rounded shape of the smaller Langhans cells.

In Fig. 3 (right), × 200, the multinucleated cells near the open blood channel are the syncytial cells. The Langhans cells have distinct lightly stained nuclei. The presence of the two cell types is the essential characteristic of this type of tumor.
of tissue already malignant—suggests the idea that their difference may be more apparent than real, depending largely on the meaning of the term "malignant."

Another possible, but less probable, course of events is that a portion of the mole was retained in the uterus and gave rise to a choriocarcinoma which metastasized at the time of or preceding the hysterectomy. The negative pathological findings in the material from this operation, and the patient's apparent general well-being, both before and after the surgery, make this explanation unlikely.

A final point for discussion is the cause of the patient's symptoms of pelvic pain and menorrhagia, with variable enlargement of the adnexal structures. Since these persisted to the time of hysterectomy, when no tumor was found, they cannot reasonably be explained as the local signs of a malignant growth. The idea suggests itself that these symptoms and findings were the effects of an interference with the ovarian cycle by the small amounts of gonadotropic hormone secreted from the latent chorion. According to this view the removal of the internal genitalia and the probable early atrophy of the remaining ovary relieved the symptoms by eliminating the responsive tissues.

**Summary**

A case is reported illustrating the possibility of deportation and long survival of tissue from a hydatidiform mole. Complete hysterectomy two years after the mole, and six years before the appearance of the choriocarcinoma, provides unusual proof of a genuine period of latency in this type of tumor.

**References**