Experimental Production of Endometrial Polyps in the Guinea Pig*

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Under the term endometrial polyps is grouped a variety of tumors of polypoid structure which are attached to the inner uterine wall by pedicles of variable length and thickness. Although their histologic characteristics differ greatly, the most common variety has a tissue structure similar to that of the surrounding endometrium. The polyps may be single or multiple; small, or large enough to occlude the uterine lumen. In the human, sloughing of the tip in the pedunculated variety may be the cause of persistent hemorrhage (1, 2).

Endometrial polyps in laboratory and domestic animals occur rarely and apparently have not been produced experimentally in any animal.

During an investigation on the embryo-endometrial interrelationship at the time of implantation in the guinea pig (3), it was found that endometrial polyps could be produced if small inert objects were implanted just below the epithelium of the endometrium at any time between the second and seventh days after ovulation. Therefore, an investigation was undertaken to determine: (1) the frequency of occurrence of endometrial polyps in the normal guinea pig; (2) the time during the reproductive cycle that polyps could be produced by the techniques to be described; (3) whether polyps could be induced to develop in all regions of the endometrium; and, (4) the ultimate fate of the polyps.

MATERIALS AND METHODS

The data presented here were obtained from 157 sexually mature female guinea pigs. The animals were maintained on a ration of oats, hay, green vegetables, and water. The events in the female reproductive cycle were timed from the onset of the animal's willingness to mate as determined, either by placing the female with a vigorous male at hourly intervals, or the animal's response to manual manipulation as described by Young, Dempsey, and Myers (4). In the experimental animals the endometrial polyps were induced in the following manner: Perfectly round glass or paraffin beads, 50 μ to 75 μ in diameter, were prepared according to the method described elsewhere (3). The paraffin beads were sterilized before use by repeatedly rinsing them in 70 per cent alcohol and sterile distilled water; the glass beads were boiled in distilled water. A single bead was inserted into the end of a number 27 hypodermic needle which had been ground very short and to a fine point. A stylet was fitted into the bore of the needle so that a single bead could be pushed from it after the end of the needle had been placed in position in the endometrium. Using aseptic technique the cornua were exposed separately by incisions made through the axial muscles of the back. The needle was inserted into the uterus by directing it from the surface toward the lumen as carefully as possible so that there would be only minimal tissue damage. Attempts were made to place the beads just below the epithelium lining the lumen. Because of the blind method of inserting the beads they could not always be placed in the desired position. However, a sufficient number of beads were inserted so that at least some beads were located in all regions of the endometrium from the antimesometrial to the mesometrial areas (Fig. 1). The animals into which beads had been implanted between the second and seventh days were killed for examination between the twelfth and sixteenth days after the onset of heat. Those in which beads were implanted after the seventh day were examined toward the end of the reproductive cycle or during the succeeding cycle.

In the guinea pig the vaginal orifice becomes occluded by the growth of a thin vaginal membrane several days after the end of heat. The vaginal membrane of each experimental animal was examined daily in order to detect the possible presence of blood behind this membrane, thus indicating the presence of a bleeding polyp.

As controls, sham operations were performed including the insertion of the needle into the uterus but without the deposition of a bead. If at the time of killing, polyps, or subepithelial beads which had not induced polyps were found, the tissues were removed, fixed in Bouin's fluid and prepared for histologic examination in the usual manner.

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**OBSERVATIONS**

*Frequency of occurrence of endometrial polyps in the normal guinea pig.*—Small endometrial polyps were observed in only 3 per cent of 200 cornua of normally mated and unmated females in all stages of the reproductive cycle. This survey was made in conjunction with another investigation in which the entire luminal surface of the endometrium was carefully examined with a binocular dissecting microscope (5). The polypoid outgrowths found in these normal animals ranged in length from 1 to 3 mm. One such polyp is shown in Figure 2. It appeared as a small outgrowth from the region of the antimesometrium and was attached to it by a rather broad base. The histologic characteristics of these polyps vary. Some were composed of a connective tissue core completely covered by either a simple or a stratified layer of epithelium. In general they contained the same histologic components as that of the underlying endometrial stroma (Fig. 8). Several of the polyps were devoid of a covering epithelium and were composed of cells which appeared similar to those of the subepithelial stroma. Even though the number of polyps observed in normal animals is small there is no significant difference in the frequency of their occurrence in pregnant and non-pregnant animals. From the observations made it may be concluded that endometrial polyps in the normal guinea pig occur rarely and do not grow to a large size.

*Experimentally induced polyps.*—The site of formation in the cornua and the time in the reproductive cycle that endometrial polyps could be produced was investigated in 57 animals. It was observed that polyps could be induced to develop, by the method described, between the second and seventh days after the onset of heat. A total of 35 endometrial polyps was observed in 38 of the 57 cornua into which beads had been implanted. Polyps could be produced most consistently from beads implanted near the apex of the antimesometrium on the fifth and sixth days after ovulation. No polyps developed from beads implanted between the eighth day and the onset of the succeeding heat period.

As mentioned earlier the control experiment consisted of sham operations on the opposite cornu into which the needle, used for implanting the beads, was inserted through the uterine wall in the same manner as if a bead were to be deposited. In no instance did a polyp develop as the result of this procedure.

Typical examples of the experimentally induced endometrial polyps in both the fresh and fixed condition are shown in Figures 4 through 8. All of these polyps were removed from females in which beads had been implanted on either the fifth or sixth day and the animals killed on the twelfth day of the same cycle. The majority of polyps were attached to the endometrium by a narrow base and invariably originated within the area of the apex of the antimesometrium. The rate of development of the polyps varied considerably. It is possible that the differences in size were dependent upon the extent of stimulation on the endometrium at the time the bead was inserted. In the majority of cases the distal end of the polyp was bulbous in appearance (Figs. 4 and 6) although occasionally the body of the polyp was wider than its distal end (Fig. 8).

When polyps were examined in the fresh condition, a high degree of vascularity was noted. In most instances the base of the polyp was composed almost entirely of large blood vessels; the body and bulbous end, at this stage of development, ordinarily appeared either red and hemorrhagic or black and gangrenous (Figs. 4, 6, and 7). Necrosis and sloughing of the bulbous tip of the polyps was responsible for intrauterine hemorrhages in approximately 30 per cent of the cornua containing these growths.
FIG. 2.—Whole mount of a portion of a fresh uterus slit open along the mesometrial border. This specimen was removed from a normal guinea pig killed on the 6th day of the reproductive cycle. Arrow points out the polyp situated within the apex of the antimesometrium. ×7.

FIG. 3.—Longitudinal section through an endometrial polyp removed from a normal guinea pig on the 5th day of the cycle. Hematoxylin and eosin. ×450.

Figs. 4 through 8.—Typical examples of experimentally induced endometrial polyps. In each case the uterus was slit open along the mesometrial border. The cornua in Figures 4 and 6 had been fixed in Bouin's fluid; those in Figures 5, 7, and 8 were photographed while fresh. ×7.

FIG. 9.—Histologic section through an endometrial polyp which had been removed from one of the experimental animals. Note the dilated capillaries. Hematoxylin and eosin. ×450.
The histologic characteristics of the polyps varied somewhat depending upon the extent of involvement of the endometrium during the growth of the polyp and on the amount of hemorrhage into the stroma. Every polyp in the experimental group was completely covered by a layer of epithelium. Near the base of each polyp this epithelium was ordinarily cuboidal and stratified but as the polyp increased in length the superficial epithelium became much flattened. In the actively growing polyps the stroma consisted of closely packed cells with large vesicular nuclei. The cytoplasm was dense and stained quite basophilic when compared to areas of the endometrium not immediately involved (Figs. 9 and 10). During the early stages of development the stroma contained a rich capillary bed which was almost sinusoidal in nature (Fig. 9). Mitotic figures were infrequent except within the endothelium of the blood vessels. The histologic picture of the polyps in general simulated closely that seen in a decidual response initiated by an implanting ovum. As already mentioned hemorrhages were frequently seen within the stroma especially in the more distal portion. These hemorrhages were associated with a rapid necrosis and sloughing of the tissue and in certain instances were the site of uterine bleeding.

The very localized origin of the polyps may be seen in Figures 10 and 12. The base of the rather large polyp shown in Figure 12 was composed almost entirely of blood vessels. It is of interest that the stroma underlying the base of most of the polyps retained, more or less, its normal histologic characteristics (Figs. 10 and 12). In Figure 12 there is considerable hemorrhage in the entire peripheral areas and when examined in the fresh state the entire polyp appeared gangrenous. When sectioned the central area, although free from hemorrhage, nevertheless showed that the majority of cells were undergoing cytolysis.

If more than the most superficial stroma of the endometrium was involved in polyp formation the deeper glands were incorporated within its base. They hypertrophied and became cystic (Figs. 11 and 15). At times, in addition to the dilated glands within the base of the polyp, other cystic glands were found immediately surrounding the point of origin.

The location of the bead in relation to the polyp varied considerably. In the majority of instances it was located within the stroma distal to the base (Figs. 10 and 12). If, on the other hand, the bead originally lodged in the deeper layers of the endometrium it remained at the site of implantation and was not incorporated in the polyp as it developed.

The polyps ordinarily underwent cytolysis rapidly after the twelfth day of the cycle and had completely lost contact with the endometrium by the time of the onset of the succeeding heat period. The polyps were not resorbed but became detached at the base and came to lie free within the uterine lumen. In several instances they had partially passed through the cervix and in one case the elongated, whitish remnant was pulled from the vagina during the succeeding heat period (Fig. 14). Histologically the degenerating polyps appeared as meshworks of connective tissue fibers enclosing the remains of the cytolyzing cells (Fig. 13).

It is of interest that by employing the technique described, polyps could be induced only within the area of a few millimeters of the apex of the antimesometrium (Fig. 1), and only in response to beads implanted between the second and seventh days of the cycle. Figure 16 is a section of a cornu in which two beads had been implanted in the area of the apex of the antimesometrium on the tenth day and the animal killed for examination on the nineteenth day. There was no evidence of polyp formation, nor was there any visible disturbance of the endometrium as the result of the needle track. It is an interesting correlation that the antimesometrial area is the usual site of implantation in the guinea pig, also, as indicated by these experiments, this is the only area that can be stimulated to produce polyps.

DISCUSSION

There is no absolute etiological factor which has been shown to be the cause of endometrial polyp formation. It has been suggested that the immediate cause of the hyperplasia may be due to an excessive stimulation of the endometrium with estrogen. This is probably the best explanation of the cases of polyoid hypertrophy as described in the human (6, 7). Others have indicated that localized inflammatory changes may cause endometrial hyperplasia in a circumscribed area which eventually results in polyp formation (9). It seems likely that localized stimulation of the endometrium during the corpus luteum phase of the cycle in the human would also result in polyoid growths similar to those described in the guinea pig. It can only be conjectured whether after they had formed they would persist or slough off at the end of the cycle.

With the exception of the human, endometrial polyps occur only rarely in mammals. In the latter they ordinarily do not reach a significant size, nor have they been demonstrated to be the cause of persistent hemorrhage.

In consideration of the time in the reproductive cycle that endometrial polyps can be induced in
the guinea pig; their histologic characteristics, and the length of time during which they persist, it is believed that these polyps represent abortive decidual reactions in a localized area. They have several characteristics however, which are ordinarily not seen in a decidua induced by the usual experimental means (8). In the first place their localized origin with the minimal disturbance of the underlying stroma emphasizes the potentials of growth of the more superficial layers of the endometrium. Secondly, when the deeper layers become involved and the glands of the stratum basalis were included in the growth, they hypertrophied and became cystic. It is interesting that the passage of the needle without deposition of a bead failed to induce polyps in any region of the endometrium, irrespective of the time in the reproductive cycle that it was inserted. On the other hand, the presence of a small bead, deposited with the same needle and located in the apex of the antimesometrium, invariably induced a polyp, if inserted in the proper time of the cycle. Thus if a polyp is to be induced at all there must be, either a greater initial stimulus, or the stimulus must exert its influence over a longer span of time. It is known that the stimulus necessary to induce a decidual reaction varies from species to species and need not be specific (9, 10). Of particular interest is the regional variation in the sensitivity of the endometrium to the specific stimuli used here. To date there is no specific histologic or cytologic information which would give as a clue to the meaning of this regional difference.

Examination of the sites of normal implantation (11, 12) and the experimental reversal of the mesometrial-antimesometrial axis in the rat (15) indicate that in the majority of animals at least, there is a definite polarity with respect to the ovum-endometrial interrelationship. It is important to investigate the role of each in the determination of this polarity.

SUMMARY

1. Endometrial polyps occur rarely in the normal guinea pig and do not grow to a large size.
2. Polyps may be experimentally induced by inserting small inert objects into the immediate subepithelial stroma of the endometrium in the antimesometrial area between the second and seventh days of the reproductive cycle.
3. The polyps thus produced resemble localized deciduomata to some extent. They differ from other deciduomata in that hemorrhages frequently occur into the stroma of the polyps. Necrosis and sloughing of the tips of the polyps resulted in uterine bleeding in 30 per cent of the polyps examined.

REFERENCES
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