Effect of Electroshock and Electronarcosis on Intraocular Ovarian and Endometrial Transplants.* (20271)

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Women receiving electroshock (ES) and electronarcosis (EN), frequently have a temporary suspension of menstruation during and following intensive treatment(1). For this no adequate explanation has been offered. Treatments given a week apart do not have this effect. Clarification of these facts may aid our understanding of what takes place during electroconvulsive treatment(ECT).

Various reports have appeared indicating that electrical current application to animals resulted in hypophyseal stimulation(2-6). Marshall and Verney(7) reported that electrical currents applied to the head of rabbits can induce ovulation. This does not occur when the stalk of the pituitary is severed. That EN affects hypophyseal activity is indicated in the studies of Ellis and Wiersma(3) reporting hypertrophy of the thyroid, gonads, and adrenals.

Method. We removed the ovaries of rabbits and transplanted them to the anterior chamber of the eye. This makes it possible to follow ovarian developments and since the ovary is severed from its normal nerve connections, we can be certain of the hormonal nature of the stimulation of the ovaries by ECT. Endometrium was also introduced into the eye to serve as easily observable target tissue for the transplanted ovary. Twenty-eight adult female Dutch rabbits, averaging 4½ months of age, were studied in 4 groups. Prior to and during experimentation the animals were kept in individual cages to prevent pseudopregnancy. They were maintained at a temperature of 70°F, and were fed standard rabbit pellets. Water was given *ad libitum*. All 28 animals received intraocular ovarian implants, and 22 animals in addition received endometrial transplants, after the method of Benjamin, Belt, and Krichesky(8). The animals were castrated to obtain tissues for transplantation. Moreover, we observed that removal of the ovaries was necessary in order that pituitary hormones would reach the transplant. This differential absorption of endogenous hormone by the target gland *in situ* has been previously described(9). One ovary in each case was preserved in Bouin's fluid, as was also a uterine sample (subtotal hysterectomy), for later histological examinations. Frequent observations and drawings were made of the transplants. Occasional photographs were taken. At the conclusion of each series, the animals were sacrificed by intravenous injection of air. We fixed tissues (intraocular transplants, adrenals, pituitary, thyroid, and uterus) in Bouin's fluid and prepared them for later histological studies.

Treatment procedure. ES was induced with 60-cycle sinusoidal current applied to the head according to a procedure outlined for use with rabbits(10,11). The onset was of the glissando type(12). Since we were using a smaller breed of rabbit we employed an initial current of less intensity (40-45 ma) for 30 seconds during which the complete seizure pattern was "tripped" as indicated by the development of a strong extensor stretch. The current was cut at 30 seconds, and the grand mal seizure was ended with vigorous clonic contractions which in some cases were followed by strong walking movements. Respiration was resumed 30-40 seconds after the beginning of the extensor stretch as with human beings. EN diverges from ES after the first 30 seconds when the current instead of

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The ECT equipment used in this study is a standard treatment apparatus manufactured by the Electronicraft Company, Los Angeles, Calif. and specifically calibrated to allow for control of minute amounts of current.

being cut is dropped to 5 ma. Respiration, however, is resumed within 30-40 seconds after the beginning of the extensor stretch as with ES treatment. Then the current is raised to a point compatible with a quiet narcosis marked by good muscle tone, salivation, and a minimum of stridor so that there is deep regular breathing. The total duration of the EN treatment in this experiment was limited arbitrarily to 5 minutes. With few exceptions, upon termination of EN treatment the rabbit righted itself instantaneously with no cataleptic symptoms appearing. This is in direct contrast to the slow awakening in the ES-treated animals which pass through an intermediate stage of catalepsia.

Preliminary experiments. Preliminary experimentation with 12 animals suggested the following conclusions: 1. Both ES and EN treatment caused growth of the transplanted tissues. 2. ES-treated animals, however, would appear to require about twice as many treatments before growth was observed. 3. In non-castrates, no stimulation of ovarian transplants occurred following treatments; although transplanted endometrium responded. Furthermore, upon direct observation of the animals the ovaries and uteri showed evidence of stimulation.

Experiment. As a check upon these findings 16 additional animals were castrated and received intraocular transplants. After one week all 16 had viable implants. By the 17th day after castration and implantation we could see no evidence of growth. On the 18th day we applied EN to 8 animals, ES to 3, and did not treat the other 5. The treatment schedule approximated that given to human patients: one was given each day the first 7 days with the remainder spaced about every other day for a total of 12 treatments. Six of the EN-treated animals showed growth after 2 treatments and two required 3. Growth continued throughout the rest of the experiment. Two of the ES-treated animals showed growth after 6 treatments; one required 7 treatments. No growth was observed in the controls throughout the experiment.

Microscopic observations. Effect of EN on intraocular transplants. The ovaries at the time of transplantation were immature (translucent, small, few follicles with antra), and the uterus *in situ* was still infantile. Fifty-nine of the 62 transplants in all the EN-treated animals (including the 8 preliminary animals) remained viable. Definite hyperemia and activity were observable after the third EN treatment in 2 of the EN animals and after the second treatment in 6 of the animals. Occasionally bleeding into the anterior chamber was noted immediately following treatment. More frequently, in the ovar-

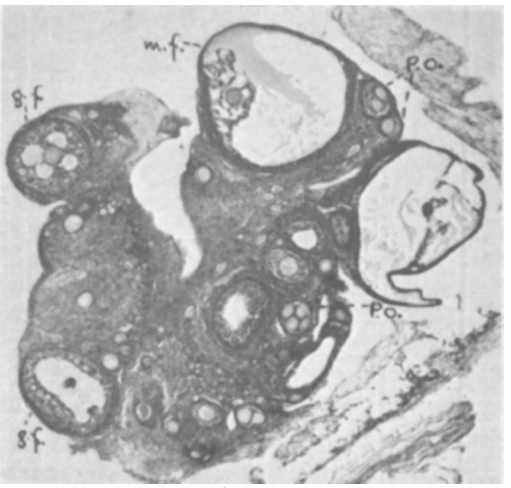

FIG. 1. Ovarian intraocular transplant of rabbit EN-8. Note growing follicles (g.f.) of varying sizes; polyova (P.O.) with definite nuclei; mature follicle (m.f.); numerous primary follicles; and some atretic follicles. No luteal tissue is present. H. and E. × 30.

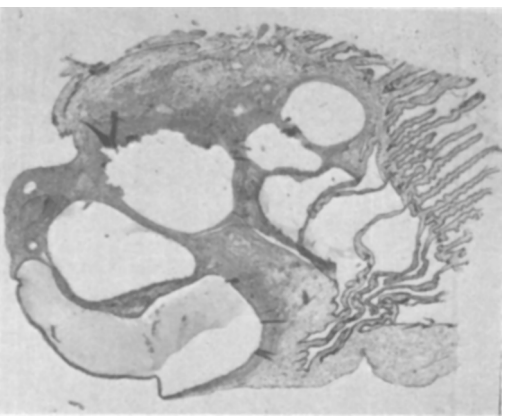

FIG. 2. Ovarian intraocular transplant of rabbit EN-4. Observe marked cystic dilation of follicles, compression of granulosa cell layers, cloudiness of follicular fluid when present, and extravasated blood. H. and E. × 15.

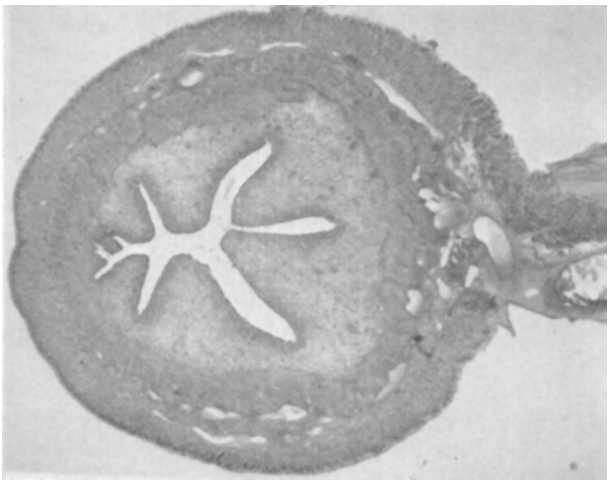

FIG. 3. Cross section of uterus of rabbit EN-1 removed at necropsy following 12 EN R_x, showing a typical estrus or proliferative condition. H. and E. × 30.

ian transplants, *blutpuncta* were seen. As a general rule, growth once initiated continued as treatments progressed. Vesicular follicles appeared and increased both in size and in number. Histological sections of ovarian transplants indicate definite stimulation and growth (Fig. 1, 2). Two patterns, or degrees of response, appeared. In one (Fig. 1), highly activated transplants include follicles in all stages of development from primordial to mature follicles. Strikingly, many multiple follicles occur. Inasmuch as polyovular follicles are not a common occurrence in the non-stimulated rabbit ovary, an excessive hypophyseal discharge of gonadotropins might have disrupted the complicated histogenic interrelationship described by Dawson(13) as existing between the germinal epithelium, oovocytes, and the initial layer of follicular cells. In the other pattern (Fig. 2), cystic follicles characteristic of a hyperstimulated ovary predominate.

Secretory activity of the intraocular ovarian transplants is evident in the appearance of the uterine tissue, both *in situ* and in the eye. Typical estrogen effects—glands with straight lumina, edematous stroma particularly in the deeper layers, well developed muscularis and serosa, and hyperemia throughout—are illustrated in a specimen removed at necropsy following 12 EN treatments (Fig. 3). The intraocular endometrium increase in area and hyperemia synchronously with the activation of the intraocular ovarian tissue(4). The proliferative property of endometrium is shown in the invasion of adjacent eye tissues by the epithelium as it covers the surface of the entire transplants and extends onto the iridial tissues(5). Frequently, it appears to undergo a metaplasia, as described by Allen and Priest(14), to a type resembling tubal epithelium. Luteinization, although infrequently

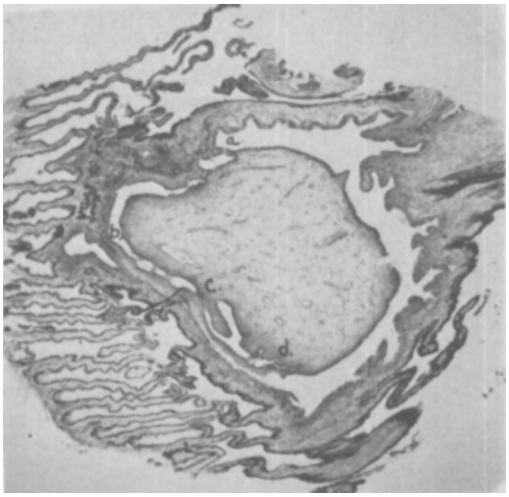

FIG. 4. Endometrial intraocular transplant of rabbit EN-5 (see Fig. 2). Size, organization, stromal nuclei dispersion, and extensive vascularization attest to estrogen stimulation of the transplant (compare with control, Fig. 7). Note complete coverage of transplant by the epithelium and its proliferation onto adjacent eye tissues at a, b, c, and d. H. and E. × 23.

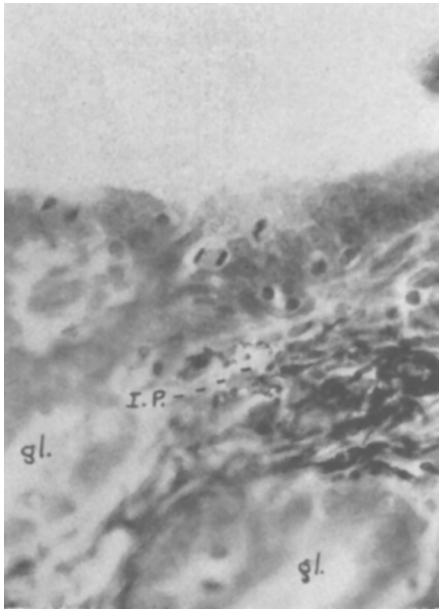

FIG. 5. High power of *c* in Fig. 4. Mitoses evident. Note hyperplasia, forming gland-like structures (gl.) in the iris tissue. Iridial pigment is present at I.P. H. and E. × 487.

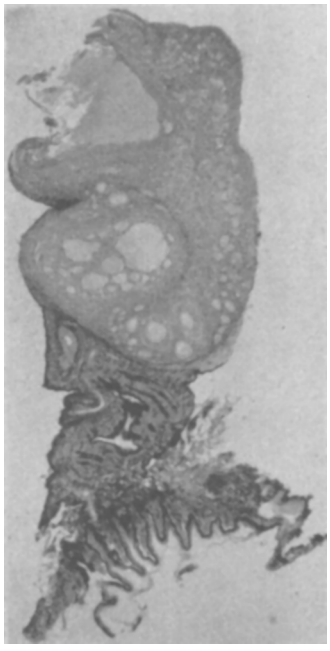

FIG. 6. Ovarian intraocular transplant of rabbit ES-1. Note numerous follicles, majority devoid of follicular cells, and many atretic follicles in early stages of development. H. and E. × 30.

observed, was seen only as very small clusters of polyhedral lipochrome cells, scattered occasionally through the ovarian stroma.

Effect of ES on intraocular transplants. The number studied (6, including the preliminary studies) was small, yet several interesting facts were noted. It was apparent that twice the number of ES treatments are necessary to activate the intraocular transplants as are required when EN treatment is used. Once initiated, the growth seemed to follow a slower rate and the transplants developed hyperemia more slowly. Ovarian intraocular tissue in such animals consisted chiefly of primordial follicles (Fig. 6), and only a few follicles showed antra development. In those animals in which growth approached that in the EN rabbits, the ovarian transplants became grossly cystic at the time of the 9th or 10th treatment. This would be followed by a definite decrease in hyperemia, and by the time of necropsy (3 days after final treatment) atrophy had occurred. Why these transplants behaved differently from those observed in the EN animals poses an interesting question and invites further study.

Intraocular transplants of non-treated animals. This group, in direct contrast to either of the other two, showed either typical castration atrophy of the endometrial intraocular

FIG. 7. Endometrial intraocular transplant of rabbit C-3 (control, receiving no shock R_x). Note disorganized, avascular, and slightly developed endometrium typical of a castrate. H. and E. × 30.

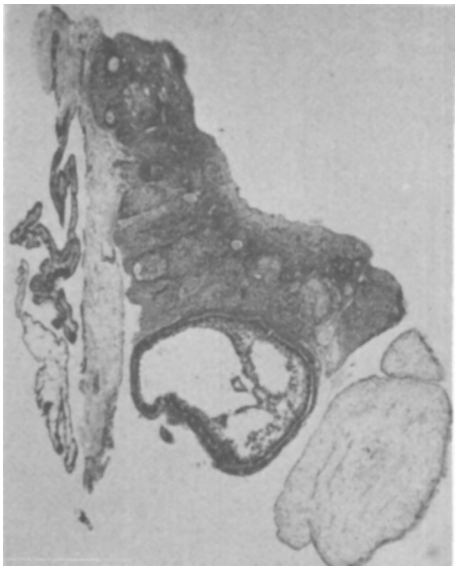

FIG. 8. Ovarian intraocular transplant of same animal (Fig. 7). Transplant is relatively small and consists chiefly of solidly packed stroma. Follicles present, other than the one Graafian, are very small or are undergoing atresia. H. and E. × 30.

transplants (Fig. 7) and ovarian transplants which contained solidly packed stroma and few follicles (Fig. 8) or endometrial transplants just barely maintained, displaying no progressive growth. In the latter, the accompanying ovarian transplants manifested little physiological activity, and the uteri *in situ* were slightly motile at necropsy; otherwise the uteri were smaller, avascular and completely flaccid.

Summary and conclusions. 1. Intraocular ovarian transplants of gonadectomized rabbits subjected to ECT show follicular stimulation. Twice as many ES treatments were required as EN to obtain growth. Follicles were observed in all stages of development, including both maturing and cystic. Hemorrhagic follicles occurred frequently but terminated in follicular atresia rather than ovulatory corpora lutea. The experimental animals gave good evidence of estrogen production by the ovarian intraocular transplants in the proliferative condition of both the endometrial transplants and the uteri *in situ*. (No attempt was made to exclude possible adrenal cortical activity.) This was in direct contrast to the lack of activation and even atrophy of transplants (and uteri *in situ*) in similarly prepared but non-treated controls. 2. It is known that menstruation may be prevented by maintenance of high estrogen levels. This sometimes occurs in the presence of cystic ovarian follicles as well as during continued administration of estrogens. 3. Continued follicular growth with resultant maintenance of high estrogen secretion may result from stimulation of the hypothalamic-pituitary neuro-humeral pathways by the electric current. Such a "constant estrus" condition might account for the interruption of the cyclic activity in women receiving ECT, as well as its resumption as treatments are spaced farther apart.

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