the MLC test and typing. Cells of dizygotic twins did not stimulate, but typed differently with respect to 10 of 29 antiserums. Leukocyte chimerism in these twins might account for nonstimulation in MLC tests. Bach and Uchida have studied a pair of chimeric human twins whose cells did not stimulate (*6a*). In a study of the donors and recipients of kidney transplants [(done retrospectively) in the Denver program (*7*)] there were several combinations in which cells from the donor failed to stimulate cells from the recipient in one-way cultures although typing of donor and recipient shows clear antigenic differences. In these cases, possible changes in the immunological status of kidney recipients on long-continued immunosuppressive therapy must be considered.

It is suggested that the locus which controls MLC reactivity and in which are included most of the genes controlling the antigens we have measured is the major histocompatibility locus in man. Dausset, Ivanyi, and Ivanyi (*8*) have grouped a series of leukocyte antigens into a single system which they called Hu-1. They also found (*8*) that MLC reactivity was correlated to some extent with incompatibility for at least one of four antigenic factors in the Hu-1 system. Since, in all likelihood, we are measuring some of the same factors which Dausset *et al.* have included in the Hu-1 system, it seems appropriate that the locus be called Hu-1. This locus includes antigens of the Du-1 system (*2*).

This locus may be the major histocompatibility locus for the following reason: (i) In all other species studied there has been one major histocompatibility locus. (ii) Silvers (*9*) has shown that in rats, two strains differing at the major locus will stimulate in MLC. Members of two strains that are compatible at the major locus but that differ by multiple minor loci incompatibilities—with the time of skin-graft rejection being comparable to those of the major incompatibilities—do not stimulate in mixed cultures. (iii) The 8- to 14-day survival of skin grafts between individuals incompatible at Hu-1 (*3, 4*) is comparable to major locus incompatibilities in other species, whereas the time of survival of skin grafts for Hu-1 compatible siblings (15 to 42 days) is not consistent with an H-2 locus difference. In species which have been best characterized, incompatibility at the major locus usually leads to graft rejection within 8 to 13 days, whereas differences at only minor loci can lead to graft rejection in more prolonged periods of time (*10*). (iv) Survival of kidney homografts in individuals who are compatible at Hu-1 seems better (*11*) than that in Hu-1 incompatible siblings. The former group has maintained good function without any steroid therapy, whereas individuals in the latter group have all needed supplemental steroid therapy to maintain good function.

It is unlikely that all the antigens determined by Hu-1 have been identified. In MLC tests cells may respond to antigens that the available antiserums would miss. Antibodies of new specificity could be prepared by reciprocal immunization of siblings whose leukocytes type alike but who mutually stimulate.

The importance of obtaining a complete representation of the Hu-1 locus is considerable both for genetic studies and for matching donors and recipients in a transplantation program.

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29 March 1967

Intrauterine Devices: Effects on Ultrastructure of Human Endometrium

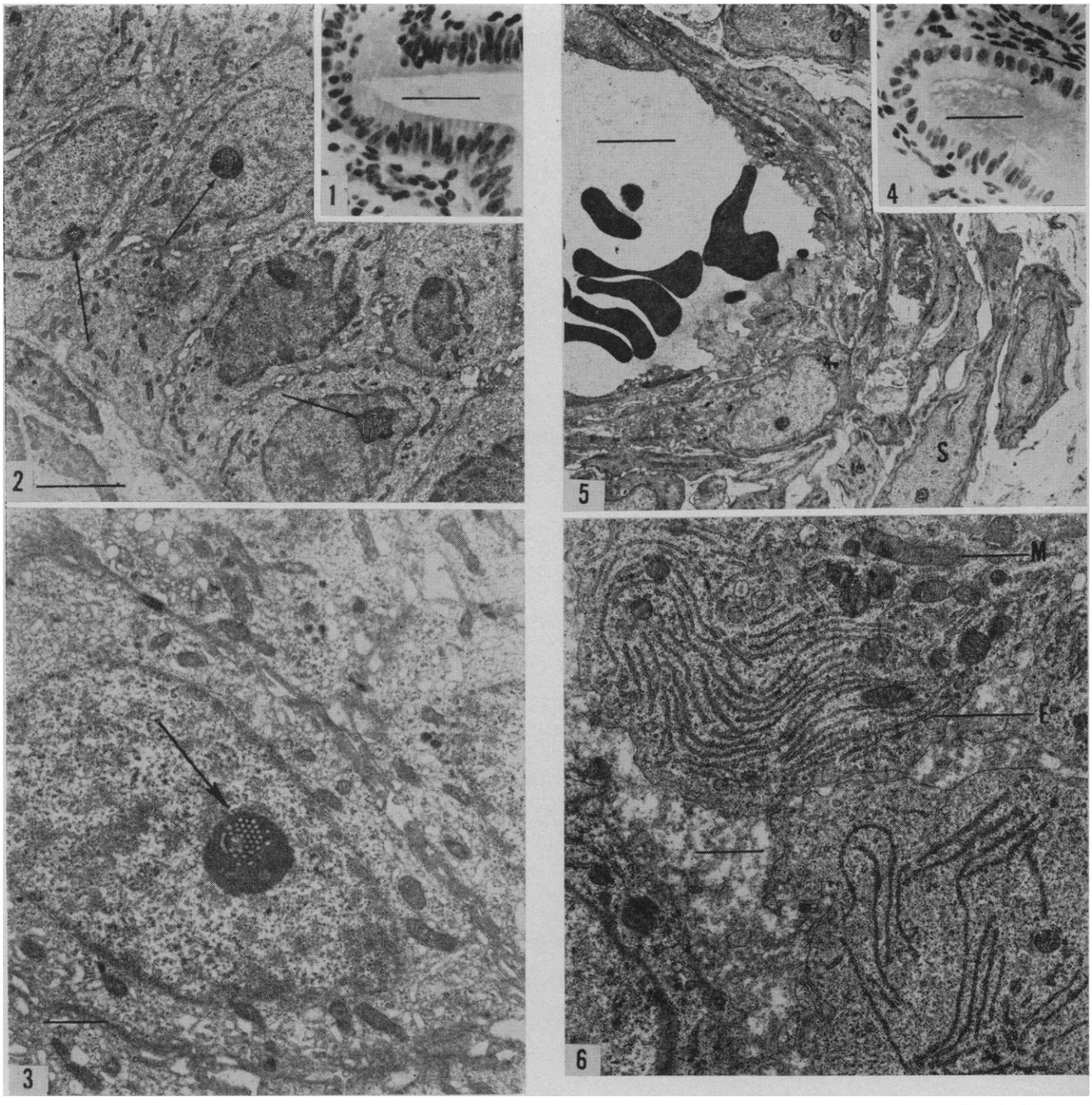
Abstract. *The human endometrium, studied with the electron microscope, undergoes asynchronous and premature cyclic development in response to intrauterine contraceptive devices. Typical nucleolar channel systems and other cellular characteristics of the normal secretory phase appear before ovulation, and decidualization occurs several days prematurely. Disturbance of the synchrony of ovular and endometrial development may be a mechanism of contraceptive action of these devices.*

Reactions of the endometrium to intrauterine foreign bodies vary widely even in closely related species (*1*). For the morphologic response in women to be ascertained, direct studies of the human endometrium are required. The commonly used plastic intrauterine contraceptive devices (IUD's) cause neither interference with transport of spermatozoa (*2*) nor significant chronic infection (*3*), but histological examination of the endometrium in contact with the IUD suggests that there is an alteration of cyclic pattern (*4*). My report of the ultrastructural changes in the human endometrium discloses premature maturation and asynchronous development of epithelium and stroma. The appearance, in the proliferative phase, of ultrastructural features previously described only in association with ovulation or exogenously administered hormones suggests an alteration in endometrial maturation. This effect may represent one mechanism of contraceptive action of the devices.

Endometrial biopsies obtained 6 weeks after insertion of the Lippes loop were repeated at semiannual intervals for periods of up to 3 years; 168 specimens obtained from 51 women were dated according to established histological criteria (*5*) before electron microscopy was performed. Specimens from the immediate vicinity of the loop showed transient inflammation, telangiectasia, and slight fibrosis. Other parts of the endometrium appeared normal histologically. The ultrastructure of each specimen was compared with that of its control (*6*), which was obtained by endometrial biopsy of the same patient before insertion of the device.

Specimens of proliferative endometrium resembled the controls in that an

ultrastructural pattern consistent with growth and endogenous metabolism was maintained and large glycoprotein granules were formed by the time of ovulation. However, a well-developed nucleolar channel system (NCS) was found in 20 percent of the preovulatory endometria (Figs. 1–3). This structure, never reported for normal proliferative endometria, has been considered indicative of ovulation (*7*) or of exogenously administered estrogen and progesterone (*8*). The NCS was more commonly found in experimental secretory endometria than in the controls during the first 3 days after ovulation, and it disappeared from the experimental specimens about 2 days earlier in the cycle. In both control and experimental endometria the NCS was confined to epithelial nuclei. Its structure



Figs. 1–6. Fig. 1. Histological section of normal proliferative endometrium. Line represents 50 μ ($\times$ 248). Fig. 2. Electron micrograph of endometrium shown in Fig. 1. Three nucleolar channel systems (arrows) are seen in proliferative epithelium. Line represents 4 μ ($\times$ 3550). Fig. 3. Higher magnification of nucleolar structure (arrow) showing amorphous matrix and tubular channels in cross section. Line represents 1 μ ($\times$ 10,650). Fig. 4. Histological section of normal endometrium about 5 days after ovulation. Line represents 50 μ ($\times$ 248). Fig. 5. Electron micrograph of endometrium (at day 19 or 20) shown in Fig. 4 with premature perivascular cuff of stromal cells (*S*). Line represents 4 μ ($\times$ 3195). Fig. 6. Higher magnification of stromal cells of endometrium shown in Fig. 5. Endoplasmic reticulum (*E*) and large mitochondria (*M*) are prominent. Line represents 1 μ ($\times$ 10,650).

was identical to that described in normal secretory endometrium (*9*), comprising an amorphous matrix, dense granules, and a series of tubular channels. The NCS connected the perinuclear space with channels of endoplasmic reticulum, providing a means for direct nucleocytoplasmic exchange. Additional, less obvious postovulatory characteristics were found in the experimental proliferative specimens.

Secretory endometria showed histologic and ultrastructural evidence of a premature decidual reaction. In about 25 percent of specimens taken after ovulation a perivascular cuff of stromal cells and an unusually well-developed endoplasmic reticulum were found by day 19 or 20 (Figs. 4–6). In a few specimens a pattern of broad cellular contact between stromal cells, similar to that in the decidua, was found as early as the late proliferative phase, particularly in association with prominence of the NCS's. In the experimental series, large mitochondria were more common at the end of the proliferative phase and shortly after ovulation, but no consistent change was observed in Golgi bodies or microtubules or in the distribution of secretory granules. All alterations in endometrial pattern suggested that there was premature maturation; the ultrastructure of the experimental specimens was similar to that of normal controls from several days later in the cycle. These ultrastructural changes affected the entire endometrium of the corpus, except for the portion in contact with the device, where direct results of pressure were obvious. The asynchrony, furthermore, often affected stroma more than epithelium, creating a pattern resembling that produced by certain oral progestational agents.

Although the relation of ovarian steroids to the development of the NCS, which presumably accompanies synthesis of nucleic acids, is ill-defined, the interaction of hormones, nucleic acids, and proteins in uterine metabolism is under intensive study (*10*). Upon which of these factors the IUD exerts a primary effect is not yet clear, but the premature and asynchronous maturation of the human endometrium must affect the precise correlation with ovular development. In macaques, furthermore, the intrauterine device increased the rapidity of tubal transfer of ova in animals treated with gonadotropins to induce superovulation (*11*). The premature appearance of ova in the endometrial cavity is another factor that may disturb the precise synchrony required for normal implantation.

These electron microscopic studies suggest that the IUD creates an environment unfavorable for blastocystic attachment. The mechanism of action, which is primarily contraceptive rather than abortifacient, makes the device a more generally acceptable means of control of fertility.

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5 May 1967

Temperature Compensation in Short-Duration Time-Measurement by an Intertidal Amphipod

Abstract. *The duration of the swimming response of an intertidal amphipod to increases in hydrostatic pressure apparently serves to measure the timing of wave uprush on the beach. Experiments have demonstrated that this response to a standard pressure-increase stimulus varies in duration only slightly with temperature over the range from 10° to 28°C, with estimated* Q_{10} *values of 1.3 to 1.5. Relative insensitivity to temperature, such as here described, seems to be an essential component of biological time-measuring systems (including endogenous circadian, tidal, and lunar rhythms) that are ecologically keyed to the timing of temperature-independent environmental factors.*

One of the most unusual properties of circadian rhythms, and a feature that has been extensively studied experimentally, is the relative insensitivity of these time-measuring systems to environmental temperature. While Q_{10} values (*1*) ranging between 2 and 3 are very commonly observed in other biological systems at cellular, tissue, and whole-organism levels, the Q_{10}'s of steady-state, free-running circadian rhythms of both plants and poikilothermous animals usually differ very little from 1.0, with extreme values from different organisms lying between about 0.9 and 1.2.

As Pittendrigh has emphasized (*2*), this relative independence of temperature is of obvious selective advantage; if the internal rhythmicity is to serve the organism as a time-measuring system in an ecologically useful way, relative insensitivity to temperature must be achieved in some manner. This requirement, that a physiological time-measuring system must correspond over a wide range of temperatures to geophysical, temperature-independent time-measurement, applies not only to circadian rhythms but also to endogenous tidal rhythms, as well as to lunar rhythms with fortnightly and monthly recurrence. At time scales appreciably shorter than these long-period endogenous rhythms (biological time-measurement on the order of milliseconds to minutes), however, there is usually far less reason to expect temperature compensation of the time-measuring process because there is seldom direct ecological significance to the absolute duration of time measured.

A clear exception to this generalization is the response of the intertidal amphipod *Synchelidium* sp. to the small increases in hydrostatic pressure associated with waves on the beach. The duration of the animals' intense swim-