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cases, i.e., about half. In reasonably controlled similar circumstances, sperm were found in none of 30 cases fitted with a Lippes loop. More inflammatory cells were found in the washings from the Lippes loop patients as compared with the control population.

Thus, it really does seem that tubal sperm are not as available in the tubes of patients wearing an IUD as compared with the tubes of patients without IUDs.

Once again, this finding cannot be as absolute as this series would suggest, for ectopic pregnancies do occur and the number of IUD observations in the entire world is probably no more than 50. Furthermore, some studies found some sperm in IUD wearers (e.g., Am. J. Obstet. Gynecol. *94:* 114, 1966).

Nevertheless, at the moment, it does appear as if the IUD, whatever else it does, somehow or other reduces the number of sperm available in the fallopian tube.—Ed.)

Estradiol Implants for Conception Control

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Oral contraceptives are the most effective means of controlling conception, but many are adversely affected by them. For women over 35 years of age, the use of oral contraceptives is especially hazardous.

It has been shown that four pellets of 17β-estradiol (25 mg each), implanted subcutaneously at 6-month intervals, can provide excellent control. The authors applied this method in step-down fashion, reducing the number of pellets every 6 months (four, three, two, one). Oral progestogen was given for 7 to 10 days each month to induce orderly periods of uterine withdrawal bleeding.

The pellets were implanted in the abdomen, 1 inch above, and parallel to, Poupart's ligament. A total of 490 sexually active women of reproductive age, 60 per cent of whom were under 35 years of age, participated in the study; 410 returned for three pellets, 351 for two pellets, and 295 stayed on the full course. Most of the women in the latter group continued at the one-pellet level every 6 months for a period ranging from 1 to 8 years. The study encompassed 18,480 cycles, or 1540 woman years.

Because of a belief that continuous administration of estrogen is conducive to endometrial cancer, the authors evaluated 294 endometria. None of these revealed malignant change.

Hysterectomy was performed in 78 women. The indications for it were abnormal uterine bleeding, adenomatous hyperplasia, enlarged ovary, and a desire for permanent control of conception.

Computerized statistical scattergrams for triglycerides, cholesterol, weight, glucose, and blood pressure revealed only slight overall mean change. Coagulation studies were done on 11 patients at random, and no marked changes in antithrombin III were seen. In a battery of tests, levels of factor VIII were raised, but no increase in platelet adhesiveness was found. Prothrombin time, partial thromboplastin time, platelet count, fibrinogen, and factors II, VIII, and X were within normal range for the authors' laboratory.

Seven women experienced bouts of menorrhagia. The abnormal bleeding was readily stopped by the administration of two tablets of oral progestogen every 2 hours until bleeding was arrested. Retention of water was not an infrequent complaint, and in some instances a diuretic and potassium were prescribed. The condition usually cleared up promptly.

There were six pregnancies among the 490 women of the series. Two of these should be discounted, since one apparently occurred before the pellets were implanted, and the other occurred a few days thereafter. The corrected Pearl index of four pregnancies during 1540

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woman years was 0.273. This compared favorably with the rate for other contraceptive methods. Future conception was not compromised by the pellet method.

The authors studied the levels of estrone and estradiol in 32 women who were on the one-pellet-only regimen for 1 to 7 years. The levels of these hormones remained within normal physiological range.

Women who experienced nausea, depression, and other untoward effects while on oral contraceptives usually found that such reactions were rarely noticed after implantation of pellets. No instance of galactorrhea, pulmonary or cerebral embolus, or endometrial cancer has been encountered in the subjects thus far.

Pellet implants proved to be a worthwhile alternative for those women who could not tolerate oral contraceptives. The regimen was particularly welcome to women over 35 years of age, since many physicians refuse to prescribe oral contraceptives for them.

The systemic absorption of estrogen from implants, rather than through the gastrointestinal tract, and immediate clearance through the liver, may be the explanation for decreased interference with clotting mechanisms, triglycerides, cholesterol metabolism, and glucose. Further studies are indicated to learn whether the use of a natural estrogen (E_2) induces less metabolic derangement than do the synthetic estrogens (ethinyl estradiol and mestranol).

(I have voiced my concerns about estrogen pellet implantations on several occasions and, therefore, hesitate to do it again. However, in the past 6 months, two papers have appeared on pellet administration as a mode of estrogen therapy, both in the American Journal of Obstetrics and Gynecology and a communiqué from the ACOG Committee on Gynecological Practices has circulated the results of a questionnaire regarding the use of estrogen pellets. Therefore, it seems timely to discuss once more the pros and cons of this practice.

Estrogen pellet therapy has been used for a number of years, usually as a rapid and simple way to control or prevent estrogen withdrawal symptoms following operative castration and hysterectomy. The reasons for adopting this therapeutic approach were the ease of administration, the efficiency of the absorption, and the gradual decrease of estrogen stimulation achieved. The gradual diminution and withdrawal over a period of 6 months or a year was frequently associated with a satisfactory clinical control involving no further necessity for medication. However, it was immediately recognized that there was a wide individual variability in the clinical response among patients. This was assumed to be related to the difference in absorption. In the past 10 years, several publications have appeared which address this point. Hunter et al. (J. Obstet. Gynaecol. Br. Commonw. *80:* 827, 1973) reported clinical and laboratory evidence of effective estradiol serum levels among 34 of 42 women who received 100-mg pellets of estradiol at operation (hysterectomy and bilateral salpingo-oopherectomy). Twenty-three of these women showed an effect up to 15 months postoperatively, whereas 11 continued to have increased serum estrogen levels between 16 months and 2 years. In 1978, a report of serum E_2 levels in eight women having 50-mg E_2 implants (two estradiol pellets of 25 mg each) showed the mean increase in estradiol to be 136 pg/ml and serum estrone 64.8 pg/ml. These levels persisted for 76 days and the clinical effects were observed from 6 months to 1 year. The mean levels, of over 150 pg/ml of estradiol and 100 pg/ml of estrone, are above those usually seen in the early follicular phase of the menstrual cycle and, therefore, must be considered in the high unopposed estrogen range. Lobo et al. recently (Am. J. Obstet. Gynecol. *138:* 714, 1980) reported the serum values after pellet implantation of 25 mg of estradiol in 22 oophorectomized, hysterectomized women. There was a relatively wide range of absorption during the first week from a low of about 30 pg/ml to a high of approximately 145 pg/ml. Following this, the levels then ranged between 30 and 122 pg/ml. These levels gradually fell but by the sixth month were still above the 20 pg/ml value seen in the castrate control patients. Clinical symptoms of these patients were also indicative of some variability of absorption. The

authors speculate that the wide variability among individuals in relation to serum estrogen levels is perhaps related to subcutaneous body fat. Nezhat et al. in the article abstracted above also report serum E_2 values on a group of women receiving one 25-mg pellet implant every 6 months. Although relatively few women were sampled again, a substantial variation was seen; however, the values for estradiol ranged between 150 and 250 pg/ml, whereas those for estrone were about 50 to 120 pg/ml, again in the lower range for midcycle values. The quotation from a previous paper is "that estradiol and estrone were sustained at high physiologic levels on the descending-dose regime." It would seem from the above studies that for the first 2 years on this regime the dosages achieved are extremely high indeed.

We must assume that the reason for this high descending-dose regime is to inhibit the hypothalamic-pituitary axis and suppress ovarian function sufficiently to prevent a rebound. I would have thought that this would have been accomplished. I was surprised that there were two pregnancies after patients had begun the one pellet every 6 months regime.

Although I personally do not choose pellet implantation, I can see the advantage for the postoperative patient who has had a hysterectomy and bilateral salpingo-oopherectomy. A single implant lasting 6 months or a year only may be acceptable therapy but not repeated implants. In addition to the relatively unpredictable absorption from individual to individual, the major objection which I have is the difficulty in discontinuing the dosage in the event of adverse reactions or of changing circumstances which make the drug administration deleterious. This might be development of hypertension, some chronic illness, or diabetes. If, in fact, it is desirable to bypass the liver, which it may well be, vaginal administration (also subject to variable absorption but very efficient) can be used. To advocate this type of high dosage continuous estrogen therapy is troublesome. The clinical problems with this can be surmised by the numbers of patients who had hysterectomies, 78. This seems to me to be a high incidence among women under the age of 44. Seventeen were in conjunction with repair operations, nine for descensus, and three for pelvic inflammatory disease. Thus, 29 of the 78 operations may have been unrelated to the estrogen administration. The remaining 49 perhaps might have been related in some way to the estrogen administration. Look the indications over and decide for yourself. In addition to this, 17 biopsies were taken for bleeding indications. The administration of the progestational drug which has been advised with pellet implantation has been changed from 5 to 7 days to 10 days and now sometimes to 14 days indicating that there is a problem. If one must add this amount of progestational drug in addition to the pellet implantation every 6 months, I see no advantage in this form of contraception, although a great deal of weight is given to the effect of bypassing the liver. Lobo et al., who also emphasized this advantage, found that there were greatly increased levels of triglycerides in three older women and cautioned that careful monitoring of patients with hypertension or overt diabetes is necessary.

The biopsy studies are not completely reassuring, although almost half of the patients, 243 of 490, had endometrial sampling. This includes the 78 patients who underwent hysterectomy. Fifty-seven biopsy specimens showed some type of hyperplasia. Only 37 were rebiopsied. In the paper, it is stated that one patient with adenomatous hyperplasia elected to have a hysterectomy. One wonders if the nine patients who had a hysterectomy for bleeding also had hyperplastic patterns? There seem to be some patients who had a hyperplastic pattern who had no repeat biopsy. Unless endometrial sampling is performed routinely on all patients, preferrably every year, but certainly in this study at the end of the 2-year descending dose regime, it is impossible to know what the pathological risk factor is. The addition of a progestational drug is not sufficient to allay concern *re* endometrial growth patterns. Now, after 10 years, the au-

thors are advocating progestational drugs to be given for 10 to 14 days occasionally. Although 10 to 14 days of an antimitotic agent (progestational drug) is certainly more efficient than 5 to 7 days. It is still not the equivalent to the unopposed estrogen levels in the normal cycle which are in the area reported after pellet implantation only in the 5 days prior to the midcycle LH surge.

It is fallacy, as has been repeatedly stated, to believe that a regular bleeding phase can be equated to complete endometrial shedding. Equally, the endometrium that does not bleed cannot be equated to an unstimulated estrogenic pattern.

In brief, I am "agin" it. This therapy should not be used in any woman who has a uterus, as with these serum estrogen levels some women are sure to get into trouble. Even if it is only one woman in 500 or 1000, that is one too many. In addition to consideration of endometrial cancer risks, neither of the recent articles concerning administration of estrogen pellets has addressed the question of breast disease. I realize that there is no hard evidence as yet that estrogen is associated with the risk of breast tumors, however, the breast is an estrogen target tissue. Therefore, it is theoretically at risk. There is some evidence that, if estrogen is an "associated carcinogen," it may be 20 years between exposure and development of disease. with these unknown factors, the old admonition "as little therapy as necessary to accomplish the goal" is certainly to be considered. Estradiol pellet therapy does not meet this criterion.—Ed.)

Cytologic Evidence of the Association of Condylomatous Lesions with Dysplastic and Neoplastic Changes in the Uterine Cervix

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The viral etiology of the genital wart, condyloma acuminatum, seems to be firmly documented. An increasing number of reports on the malignant transformation of condyloma acuminatum has appeared in the literature during recent years. At the same time, condylomatous lesions, including the newly discovered types, have been shown to be associated with epithelial dysplasias and neoplasias of the uterine cervix in a remarkably high percentage of cases. Based on these findings and on the results of epidemiological studies, a hypothesis has been advanced that the virus found in the genital warts may be involved in the etiology of human genital cancer.

The present study was made to assess the cytological patterns characteristic of condyloma in smears derived from histologically verified dysplastic and neoplastic cervical lesions. The purpose of the work was to search for further evidence regarding the hypothesis that condylomatous lesions of the cervix are closely related to cervical squamous carcinoma. The smears included in the study were obtained from 272 women (aged 30, 35, 40, 45, and 50 years) with histologically verified severe dysplasia (71 cases), carcinoma *in situ* (129 cases), or invasive squamous carcinoma (72 cases) of the uterine cervix.

The presence of the following cytological parameters, regarded as manifestations of condyloma virus infection of the genital tract, was noted: dyskeratotic superficial cells in sheets or singly scattered, koilocytic cells, binucleated cells with either large or small nuclei, and multi-