EFFECTS OF CLOMIPHENE CITRATE* ON ENDOMETRIAL HYPERPLASIA IN THE PREMENOPAUSAL FEMALE

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Clomiphene was administered continuously in a dose of 100 to 200 mg daily for 16 to 18 months to 6 patients (5 approaching menopause and one postmenopausal) having endometrial hyperplasia with a presenting complaint of irregular and profuse bleeding. After cessation of clomiphene therapy the results were atypical secretory endometrium—2 patients; normal menstrual cycles —3 patients; spontaneous menopause—one patient. The therapeutic effects of clomiphene are temporary. If the ovary maintains its potential for follicular maturation and ovulation, a secretory phase will be induced in the endometrium which lasts 6 to 8 weeks. Endometrial atrophy then will develop and remain unchanged as long as therapy is continued. The major side effects of clomiphene are hot flashes and ovarian cysts.

PROLONGED PERIODS OF ANOVULATION OCCUR frequently in the premenopausal female probably as a result of the inability of the aging ovary to respond to usual and sequential gonadotropic stimulation. Prolonged and unopposed estrogen in adequate quantity usually results in cystic and adenomatous hyperplasia of the endometrium. Atypical adenomatous hyperplasia (carcinoma in situ) also may occur in premenopausal females but specific cause for this morphologic variation is unknown.

An association between endometrial hyperplasia and subsequent carcinoma has been noted in the human since 1904 but considerable variance of opinion still exists regarding histogenesis, hormonal interplay and prophylaxis. A fair summation of the data seems to be that, in *predisposed* individuals, the unopposed action of estrogenic substances for considerable periods of time will result in endometrial adenomatous hyperplasia, carcinoma in situ and, occasionally, carcinoma.[13] Recent studies have suggested an endocrine correlation in patients with endometrial carcinoma because of the high incidence of prolonged anovulation, dysfunctional uterine bleeding and infertility in these patients.[5] A suggested method of prophylaxis against this progressive "unrest" of the endometrial epithelium had been to secure ovulation, menstruation and pregnancy.[4] Prior to 1960 this goal was not possible because substances which effected ovulation in the human female were not available.

Detailed studies by Kistner[9, 10] on 9 patients in 1959 and 1962 demonstrated that synthetic progestagens produced marked changes in the glands and stroma of endometrium classified as carcinoma in situ. Profound gland atrophy and decidual conversion of stroma were constant findings following prolonged therapy with these compounds. Cystically dilated and adenomatous glands retained their basic configuration but the epithelial cells appeared secretorily exhausted with a low cuboidal inactive pattern.

Since these original observations, 23 patients with cystic and adenomatous hyperplasia and 8 patients with carcinoma in situ have been treated with various synthetic progestational compounds. All patients in this group were menopausal or postmenopausal. Glandular and stromal atrophy was produced in all patients subsequent to treatment. Nine patients with adenomatous hyperplasia and 4 patients with carcinoma in situ were treated by hysterectomy at the conclusion of initial therapy to study the endometrium completely. In 5 of these 13 patients residual hyperplasia was evident but with specific progestational effect. Fourteen patients with adenomatous hyperplasia and 4 with carcinoma in situ have been followed for 3 to 7 years by sequential curettage as the only therapeutic measure subse-

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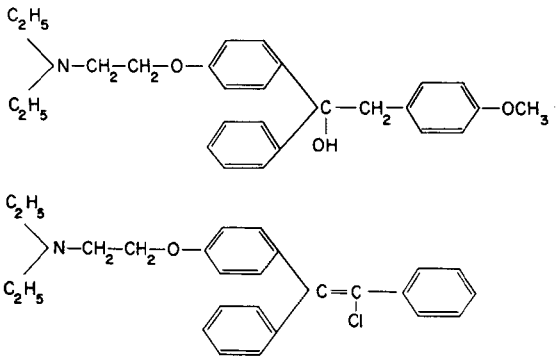

FIG. 1. Structural formulas of MER-25, 1-6p-2-diethylaminoethoethoxyphenyl-1-phenyl-2-p-methoxyphenylethanol (above) and MRL-41, 1-[p-(β-diethylaminoethoxy)phenyl]-1,2 diphenyl-2-chlorathylene (Clomid) below.

quent to progestin therapy. In no instance has invasive carcinoma occurred.[18]

Kaufman and associates reported in 1959 that endometrial hyperplasia of varying degrees could be reversed by ovarian wedge resection in patients with Stein-Leventhal syndrome, presumably by the subsequent cyclic action of endogenous progesterone.[6] Another method for the induction of ovulation in patients with this syndrome was reported in 1959 by Kistner and Smith[12] using a nonsteroidal estrogen antagonist, MER-25* (Fig. 1).

They reported ovulation in 4 patients with Stein-Leventhal syndrome following the administration of this substance. Each of these patients had associated endometrial hyperplasia. Three of these patients subsequently became pregnant and none has had a recurrence of hyperplasia in a follow-up period of more than 5 years. The fourth, not married but having a diagnosis of early invasive endometrial carcinoma, has been followed for 7 years without a recurrence of endometrial atypia (as determined by sequential curettage) since ovulation was established regularly. Kistner since has reported similar results using clomiphene citrate instead of MER-25.[8]

Although clomiphene citrate may exert its primary effect on the ovary to effect an increase in the secretion of estrogenic substances,[16, 17] there is also evidence that it has antiestrogenic properties in its effects on the endrometrium and breasts.[15]

This is a report of the results of clomiphene citrate given constantly for 6 to 18 months to premenopausal women with endometrial hyperplasia. The purpose of the investigation was to observe morphologic changes in the glands and stroma during such therapy. Wall and associates have reported the results of treatment of 2 postmenopausal patients with clomiphene citrate.[19] They noted reversal of hyperplasia in one patient and disappearance of adenocarcinoma in another. Charles et al.[1] treated 6 patients with endometrial hyperplasia and produced normal ovulatory cycles in all. Three patients, however, were under the age of 40 years. Whitelaw[20] has reported the treatment of 5 patients whose curettage specimen showed endometrial hyperplasia. Each of these patients had been treated by frequent uterine curettage without relief of recurrent bleeding. Ovulation was induced in all except 3 of 28 treatment cycles and irregular bleeding was controlled. The patients treated by Whitelaw were also under age 40.

MATERIAL AND METHODS

The group studied consisted of 4 women whose curettage specimen prior to treatment showed atypical adenomatous hyperplasia and 2 patients with cystic hyperplasia of the endometrium. One of the latter patients had a large fibroid uterus but surgery was contraindicated because of medical complications. The patients varied in age from 39 to 51. The precise dose schedule and length of therapy is outlined in Table 1. The endometrium was sampled frequently during therapy by endometrial biopsy or curettage. The length of treatment varied from 6 to 18 months. Hysterectomy was done in 2 patients at the conclusion of treatment and the endometrium studied by the method previously described.[9] The patients were seen originally because of excessive and irregular anovulatory bleeding although in one (patient 3) the bleeding was classified as being postmenopausal. The diagnosis in each case was made by a thorough uterine curettage performed by the senior author. Clomiphene therapy was administered constantly in a daily dose varying between 100 to 200 mg.

CASE REPORTS

Case 3 (FHW-22609). This patient is a 51-year-old white female whose chief complaint was that of irregular bleeding and staining of 6-month duration. The menopause had occurred 3 years previously at the age of 48; during the interval between 1948 and 1960

* William S. Merrell Co., Cincinnati, Ohio (withdrawn).

TABLE 1.

Name and number	Age	Pathology and clinical diagnosis	Dose schedule	Length of therapy/ effect	Post-treatment biopsies of endometrium	Side effects	Follow-up
1. E.T. FHW-78736	46	Adenomatous hyperplasia; hypermenorrhea	100 mg./d. started 11/18/61	6 mos./ amenorrheic during Rx	4 wks. Rx: atypical secretory; 12 wks.: no tissue; 6 mos.: no tissue	Ovarian cyst after 3rd mo.	Resumed regular periods 3 mos. after stopping Rx; biopsy May 1964: 16-day secretory
2. S.M. FHW-75329	39	Adenomatous hyperplasia; hypermenorrhea	150 mg./d. started 8/29/60	10 mos./ amenorrheic during Rx	8 wks. Rx: atrophic; 7 mos. Rx: prolif. without activity; 10 mos. Rx: atrophic	Ovarian cyst after 3rd mo.	Resumed regular periods 1 mo. after stopping Rx; regular periods in 1963–64
3. Q.S. FHW-22609	51	Adenomatous hyperplasia; postmenopausal bleeding	100–200 mg./ d. started 6/28/61; no treatment for 5 mos.; 200 mg./d. started 11/20/61	8 mos./ amenorrheic 11 mos./ occ. staining	8 mos. Rx: atypical with progesterone effect; hyperplasia recurred; 11 mos. Rx: inactive endometrium with few mitoses	Hot flashes	Hyperplasia recurred again after 2nd course of Rx; course of Depo-Provera prior to hysterectomy
4. M.M. FHW-14588	49	Adenomatous hyperplasia; hypermenorrhea	100 mg./d. started 6/19/61	7 mos./ amenorrheic during Rx	3 mos. Rx: inactive; 7 mos. Rx: proliferative without activity	Hot flashes	Resumed normal periods 2 mos. after stopping Rx; biopsy in May '62; prolif. vag. hyst. July '62 for prolapse; endometrium prolif.
5. J.McD. FHW-72371	44	Cystic hyperplasia; hypermenorrhea and large fib. uterus	100 mg./d. started 10/17/60; no treatment for 4 mos.; 150 mg./d. started 8/14/61	6 mos./no treatment for 4 mos.; 12 mos./ amenorrheic during Rx	3 mos. Rx: inactive prolif. 6 mos. Rx. (D & C) inactive endometrium 2nd course of Rx 2 mos. Rx: prolif. with little activity; 12 mos. Rx: (D & C): inactive prolif.	Hot flashes; tired feeling	Slight staining after D & C in Dec. 1963; no bleeding from Feb. to May 1964
6. M.S. FHW-70773	45	Cystic hyperplasia; dysfunctional bleeding; mastodynia and chr. cystic mastitis	100 mg./d. started 6/5/61; 150 mg./d. on 8/28/61	6 mos./ amenorrheic during Rx; secretory endometrium after 3 mo.; atrophic after 6 mo.	3 mos. Rx: inactive endometrium	Hot flashes	Periods resumed 3 mos. after Rx. stopped; then treated with progestin cycles x 3 mos.; periods normal in 1964

no bleeding had occurred. The patient was seen first in the out-patient department of the Free Hospital for Women in 1936 because of irregular uterine bleeding. An endometrial biopsy performed at that time was classified as "endometrial dysplasia." The endometrial biopsy which was performed at the time of her visit to the out-patient department in March 1960 (Fig. 2) was interpreted as cystic and adenomatous hyperplasia (S-60-3067). A dilatation and curettage was advised but the patient did not return until August 1960.

A dilatation and curettage performed on August 15, 1960 revealed a copious amount of tissue (Fig. 3) upon which a diagnosis of cystic and adenomatous hyperplasia was made (S-60-3159). Because of this diagnosis clomiphene citrate was initiated in a dose of 100 mg daily beginning on October 10, 1960. Patient next was seen on November 7; at that time an endometrial biopsy was performed (Fig. 4) which was read as "cystic and adenomatous hyperplasia with tubal metaplasia and dilated blood vessels" (S-60-4200). Following this the amount of bleeding gradually diminished and the patient noted only minimal staining dur-

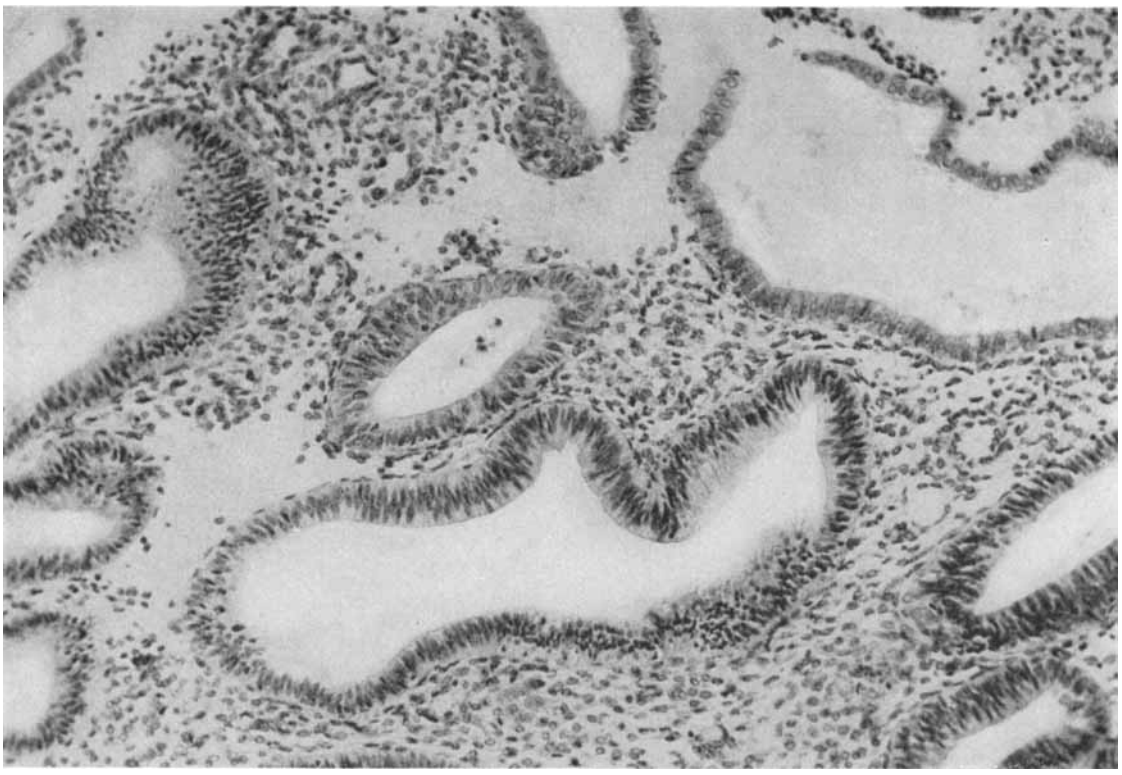

FIG. 2. Patient 3 in Table 1. Portion of endometrical biopsy showing cystic and adenomatous hyperplasia (FHW-S-60-3067; ×200).

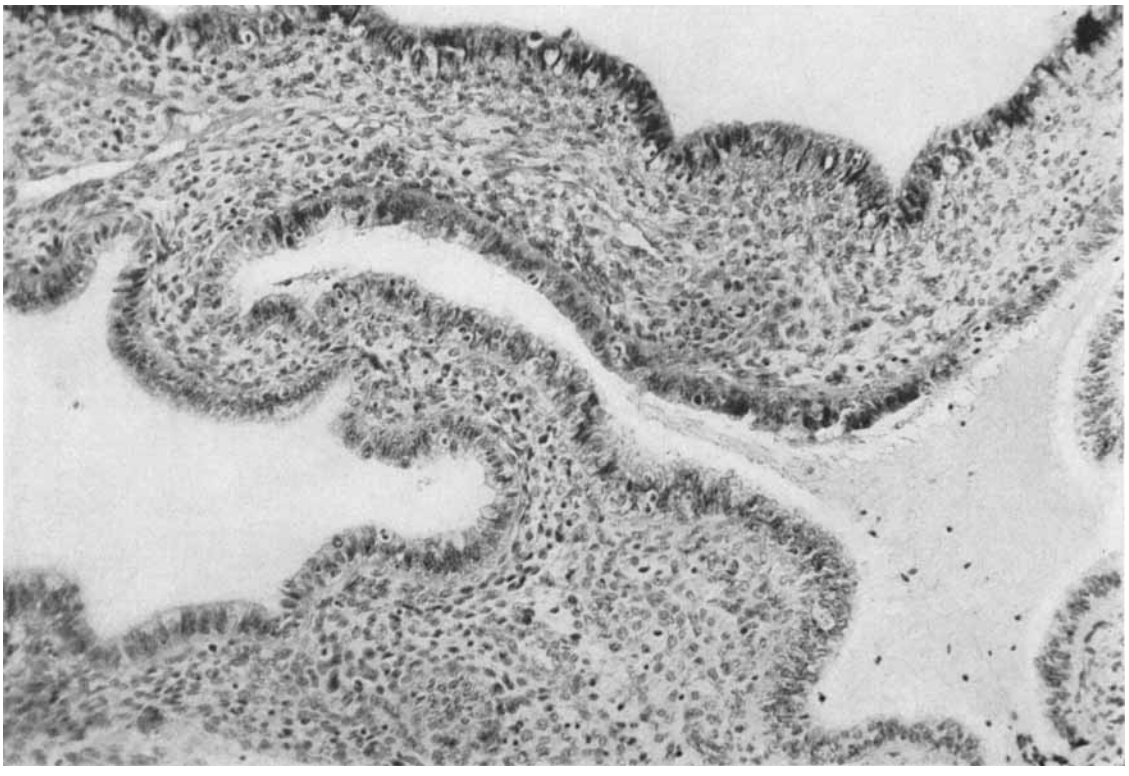

FIG. 3. Patient 3 in Table 1. Curettage specimen showing cystic and adenomatous hyperplasia (FHW-S-60-3159; ×200).

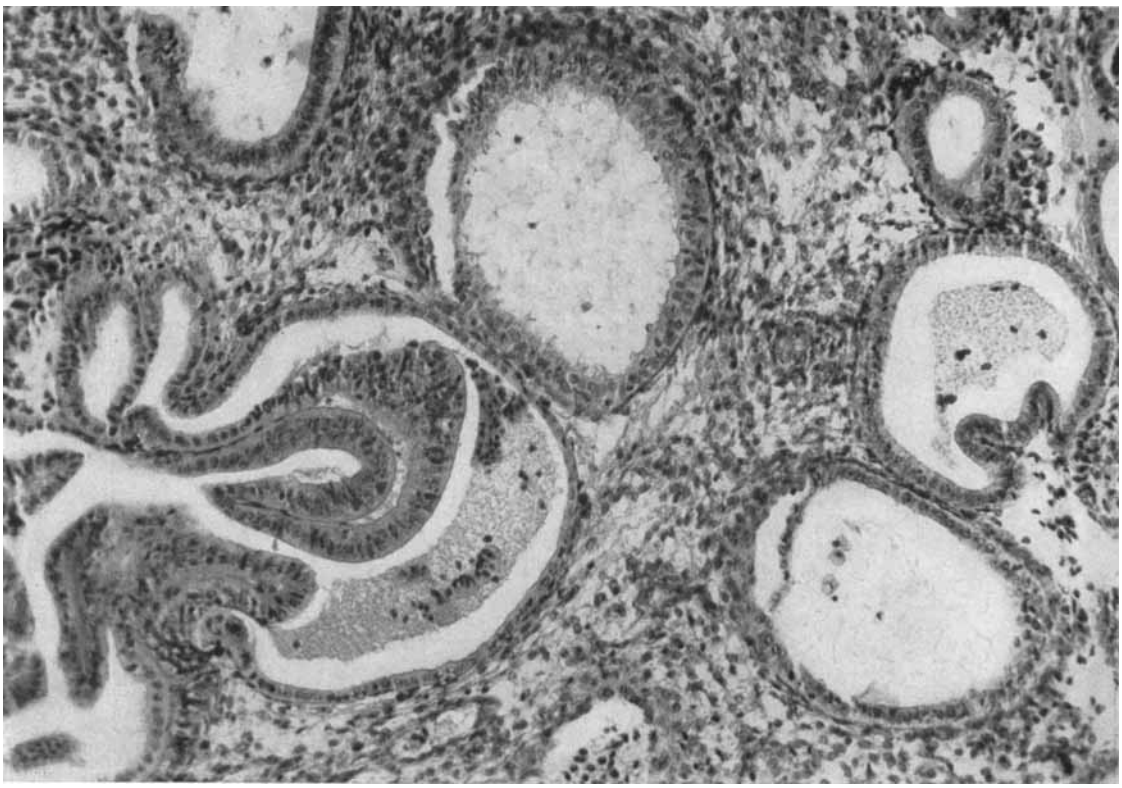

FIG. 4. Patient 3 in Table 1. Endometrial biopsy specimen obtained after 4 weeks of Clomid therapy (100 mg. daily). The gland in top center shows tubal metaplasia but also slight evidence of secretory activity (FHW-S-60-4200; ×200).

ing the next 4 weeks. On November 20 another endometrial biopsy was performed which again was interpreted as "cystic and adenomatous hyperplasia" (S-60-4386). When the patient next was seen on December 19, neither further bleeding nor side effects were noted.

At the time of the next visit, January 16, 1961, there had been no recurrence of bleeding and an endometrial biopsy at this time revealed slight cystic and adenomatous hyperplasia, lowering of the epithelium and more basal nuclei (S-61-153). Clomiphene citrate was continued in a dose of 100 mg daily and at the time of the next visit, February 13, the patient complained of rather severe hot flashes. An endometrial biopsy done on this date revealed atypical proliferative endometrium with slightly dilated but irregular glands with low columnar epithelium (S-61-508). Vaginal cytology for hormonal effect performed on March 20 revealed a marked diminution in the cornification index as compared with the pretreatment examination. On March 20 the dose of Clomid* was increased to 150 mg daily. The hot flashes continued and, when the patient next was seen, April 17, the vaginal smear was compatible with that during menopause.

At the time of the next visit, May 15, the patient had noted very slight staining for the previous 2 weeks and therefore the dose of Clomid was increased to 200 mg daily. This dose was continued until June 28 at which time therapy was discontinued and the patient was admitted to the hospital for a follow-up curettage. At this time only fragments of endometrium could be obtained. These were interpreted as "atypical endometrium with silghtly dilated glands showing low columnar epithelium and stroma with evidence of progesterone effect and hemosiderosis" (S-61-2151) (Fig. 5). This concluded 8 months of continuous therapy during which time the patient had received 33.5 Gm of clomiphene.

During the period of therapy, particularly after February 13, the patient noted excessive hot flashes which continued until the medication was discontinued. A control FSH was more than 5 but less than 15 mouse units. Follow-up determinations of FSH on March 20, 1961 were more than 50, less than 96 mouse units and on April 17 the same determination was obtained.

During the next 3 months no therapy was

* Clomiphene citrate, William S. Merrell Company, Cincinnati, Ohio.

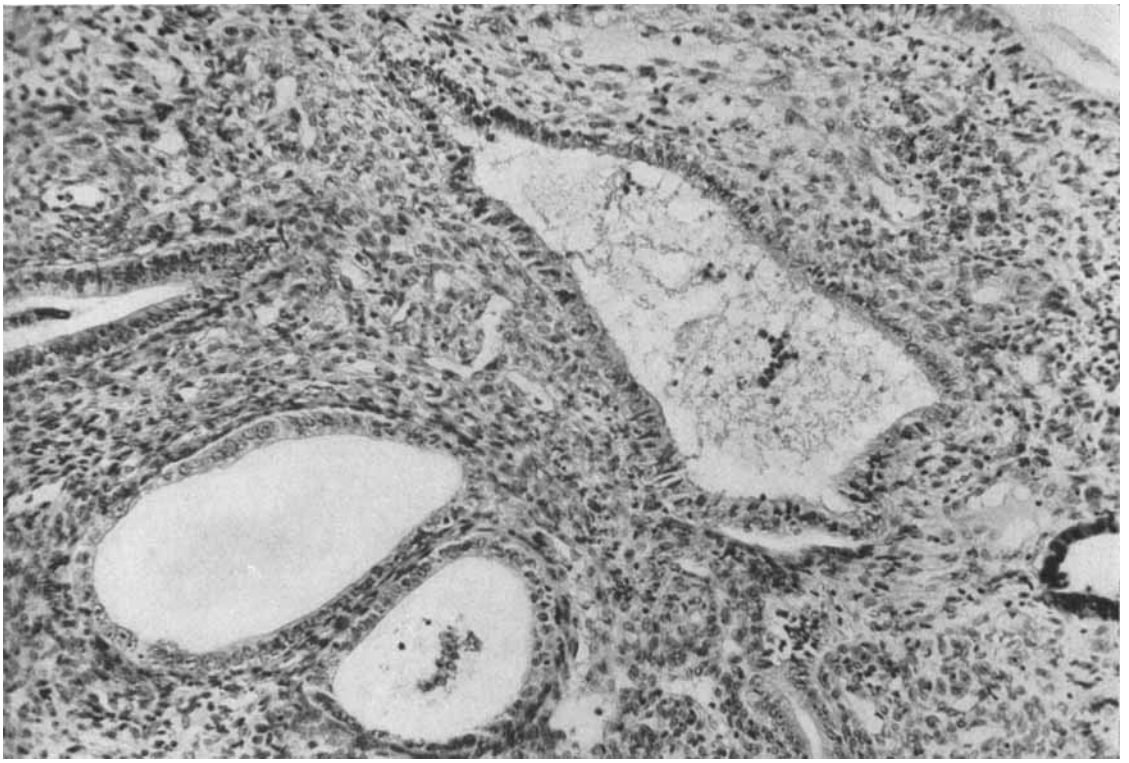

FIG. 5. Patient 3 in Table 1. Curettage specimen obtained after 8 months of continuous Clomid therapy. It demonstrates an atypical endometrium with slightly dilated glands with low columnar epithelium and stroma with evidence of progesterone effect and hemosiderosis (FHW-S-61-2151; ×200).

given and the patient noted continuous staining daily after the curettage in June. On September 19 she had a very heavy flow which lasted 4 days. She was seen in the out-patient department on September 25, 1961 and an endometrial biopsy performed at this time (Fig. 6) revealed "cystic and adenomatous hyperplasia" (S-61-3168). Since the hyperplastic endometrium had recurred during the 3 months the patient was not receiving treatment with Clomid, it was decided to restart treatment at this time. Therefore, on September 25, 1961 she was restarted on a dose of 100 mg daily. She was seen one month later and on November 23 another endometrial biopsy was performed, which at this time showed "cystic and adenomatous hyperplasia with low columnar epithelium" (S-61-3810). At this time the dosage of Clomid was increased to 200 mg daily. The next visit occurred on December 15, at which time the patient complained of daily staining until December 5 but no staining or bleeding after that time. She had noted recurrent hot flashes and insomnia. An endometrial biopsy obtained at this time revealed "atypical endometrium with a few cystically dilated glands; low inactive endometrium with very few mitoses" (S-61-3810) (Fig. 7). The dose of 200 mg daily was continued; a follow-up endometrial biopsy on January 15, 1962 showed "proliferative endometrium with minimal hyperplasia" and one on March 29 revealed "cystic hyperplasia with endometritis." Another endometrial biopsy on June 11 showed "focal adenomatous hyperplasia with minimal anaplasia." Clomid was continued in a daily dose of 200 mg and then was discontinued on September 11, 1962.

Following the discontinuance of therapy the patient was relatively asymptomatic but did have intermittent staining during December 1962 and January of 1963. On February 14, 1963 the patient was re-admitted to the hospital for a follow-up uterine curettage. The tissue removed at this time showed "cystic hyperplasia with squamous, tubal metaplasia and stromal sinusoidal thrombosis" (S-63-686). Because of the recurrence of hyperplasia at this time, the patient was then treated with Depo-Provera* for 12 weeks, following which a complete hysterectomy and bilateral salpingo-oophorectomy were performed. The pathology report on the excised uterus was "chronic endometritis with atypical atrophic endometrium with decidua and extensive stromal breakdown; adenomyosis with decidual reaction; degeneration" (S-63-2492).

* Medroxyprogesterone acetate, The Upjohn Company, Kalamazoo, Mich.

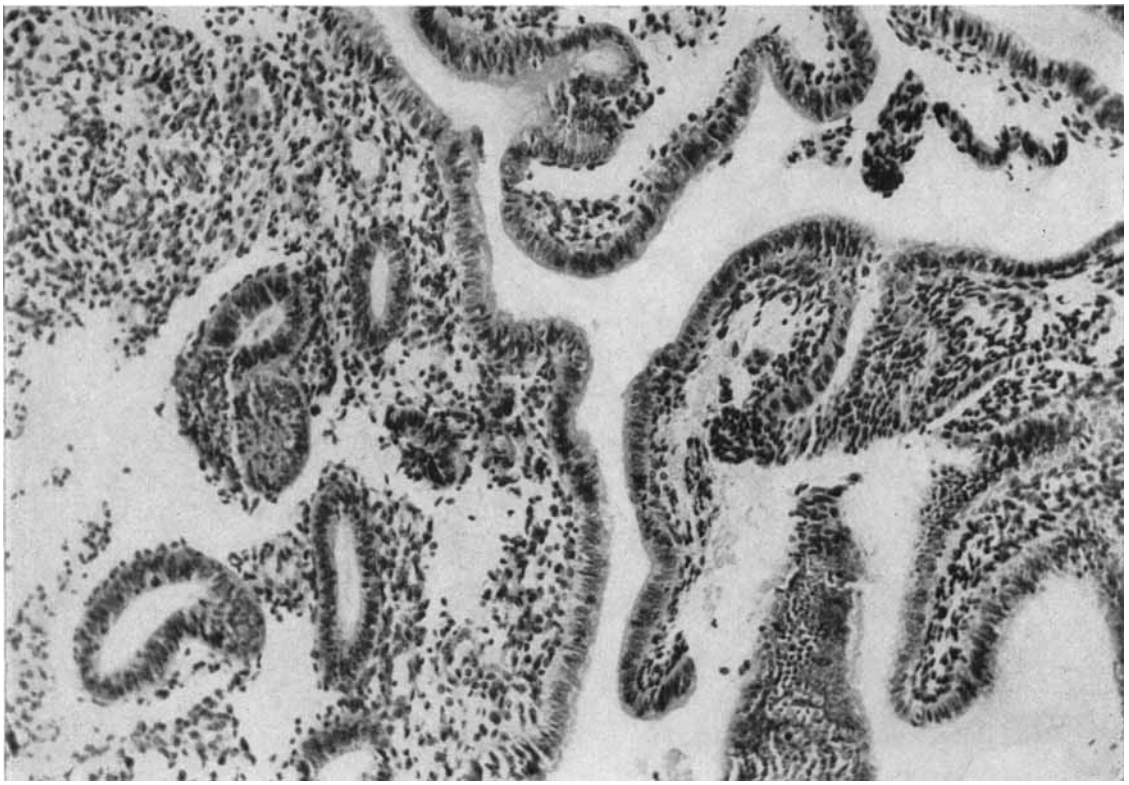

FIG. 6. Patient 3 in Table 1. Recurrent endometrical hyperplasia after an episode of recurrent bleeding in September 1961 after 3 months without Clomid therapy (FHW-S-61-3168; ×200).

Case 5. This patient is a 44-year-old white female whose chief complaint was that of polymenorrhea of 6-month duration. She first was seen in the out-patient department of the Free Hospital for Women on June 26, 1959 because of this complaint. She gave a past history of having had a total colectomy for ulcerative colitis in 1957. This operation was complicated by pulmonary infarction on the ninth postoperative day. Pelvic examination revealed a large fibroid uterus approximately 10 × 10 × 6 cm. On September 3, 1959 a uterine curettage was performed (Fig. 8) which revealed proliferative endometrium with cystic hyperplasia (S-59-3711). The patient first was treated with artificial cycles using norethynodrel with mestranol from October 1959 until Febuary 1960, during which time she had normal withdrawal flows. An endometrial biopsy done on April 25, 1960 showed only proliferative endometrium (S-60-1721).

In April 1960 she had recurrent irregular and profuse flowing and Clomid was started on April 25. From April 25, 1960 until February 2, 1961 100 mg was administered daily. During this time she was completely amenorrheic except for an episode of bleeding on December 16, 1960, approximately one month after she had run out of pills. She restarted Clomid on January 16, 1961 and had no further bleeding. An endometrial biopsy performed on February 13 (S-61-509) showed inactive proliferative endometrium. Another endometrial biopsy was performed on March 16 but the quantity of tissue removed was not sufficient for adequate diagnosis. On April 13, one year after initiation of therapy with Clomid, a thorough uterine curettage was performed. The endometrium at this time was "inactive" (S-61-1170) (Fig. 9). Clomiphene citrate was discontinued at this time.

The patient next was seen on August 14, 1961 because of recurrent hypermenorrhea. Clomid was started again, this time in a dose of 50 mg daily. The hypermenorrhea again was controlled and the patient had not had any bleeding when next seen on October 9. An endometrial biopsy which was done at this time showed "proliferative endometrium without activity." Clomid was continued in this same dose, 50 mg daily, until August 1962, one year of therapy after restarting. An interval endometrial biopsy in February 1962 revealed "proliferative endometrium with little activity" (S-62-452). The patient next was seen on November 5, 1962, three months after discontinuing Clomid. She had no complaints and there was no bleeding at that time.

The patient next was seen on November 4,

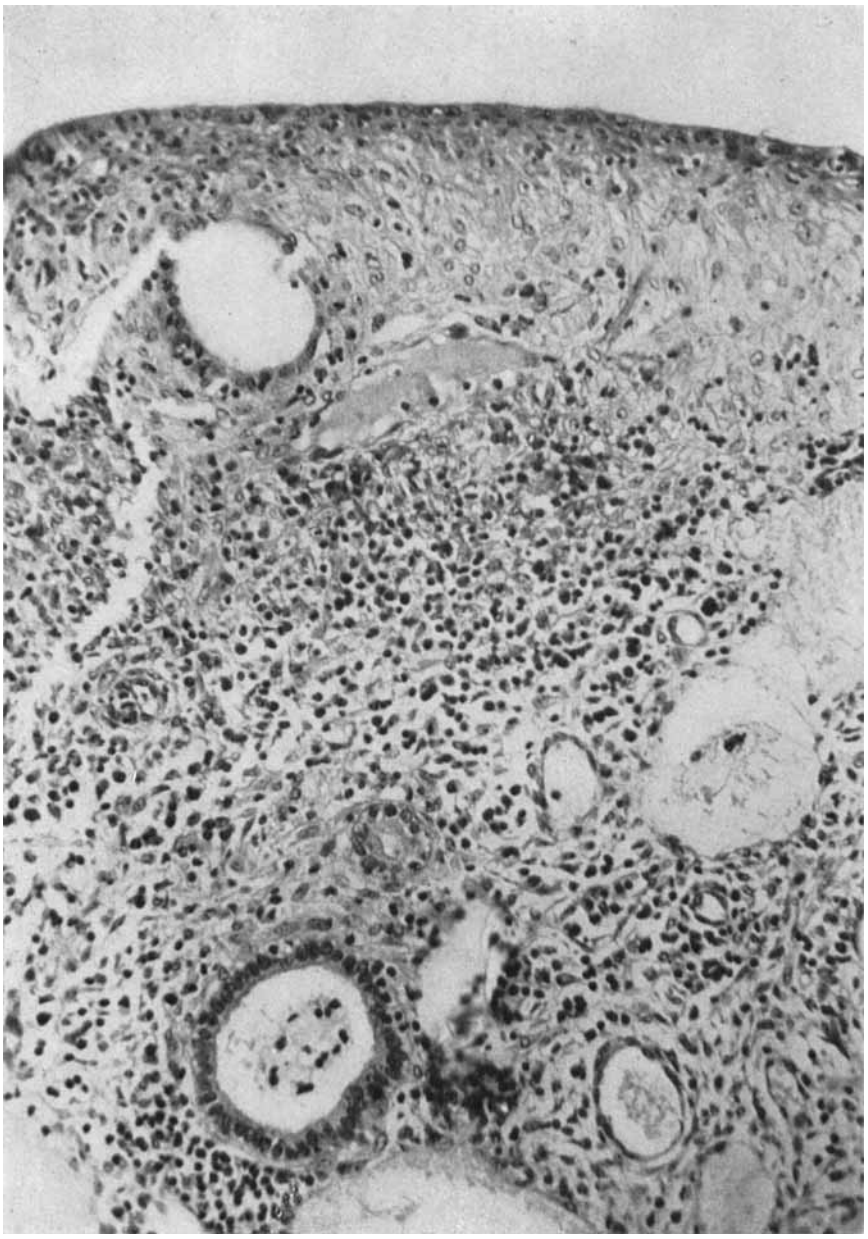

FIG. 7. Patient 3 in Table 1. Biopsy specimen after second course of Clomid. Patient had received 100 mg. daily from September 25, 1961 for 12 weeks when this tissue was obtained. Note atypical endometrium with inactive glands, surface decidua and inflammatory cells in the stroma (FHW-S-61-3810; ×200).

1963, stating that she had had just a little staining in November 1962 and very slight staining in March, July and October 1963. Examination at this time revealed a quite small uterus with no evidence of a fibroid.

The patient was admitted to the hospital again on December 11, 1963 for a follow-up curettage. Examination under anesthesia revealed an anterior uterus of normal size, measuring approximately 7 × 5 × 3 cm. There was no evidence of a leiomyoma. A thorough curettage was performed but the curettings were scant and histologically showed "slight proliferative activity" (S-63-5463) (Fig. 10). The patient next was seen in the clinic on January 21, 1964, at which time she stated that minimal irregular spotting had occurred since the time of curettage. No further treatment was administered at this time. The only side effects noted during the 2 courses of therapy were in March 1961, at which time the patient complained of tiredness, weakness and some hot flashes. Again in October 1961 she complained of tiredness.

The last follow-up visit occurred in November 1965, at which time the patient had no complaints and apparently had entered spontaneous menopause. There had been no bleeding since her last visit and on pelvic examination the uterus was almost normal size.

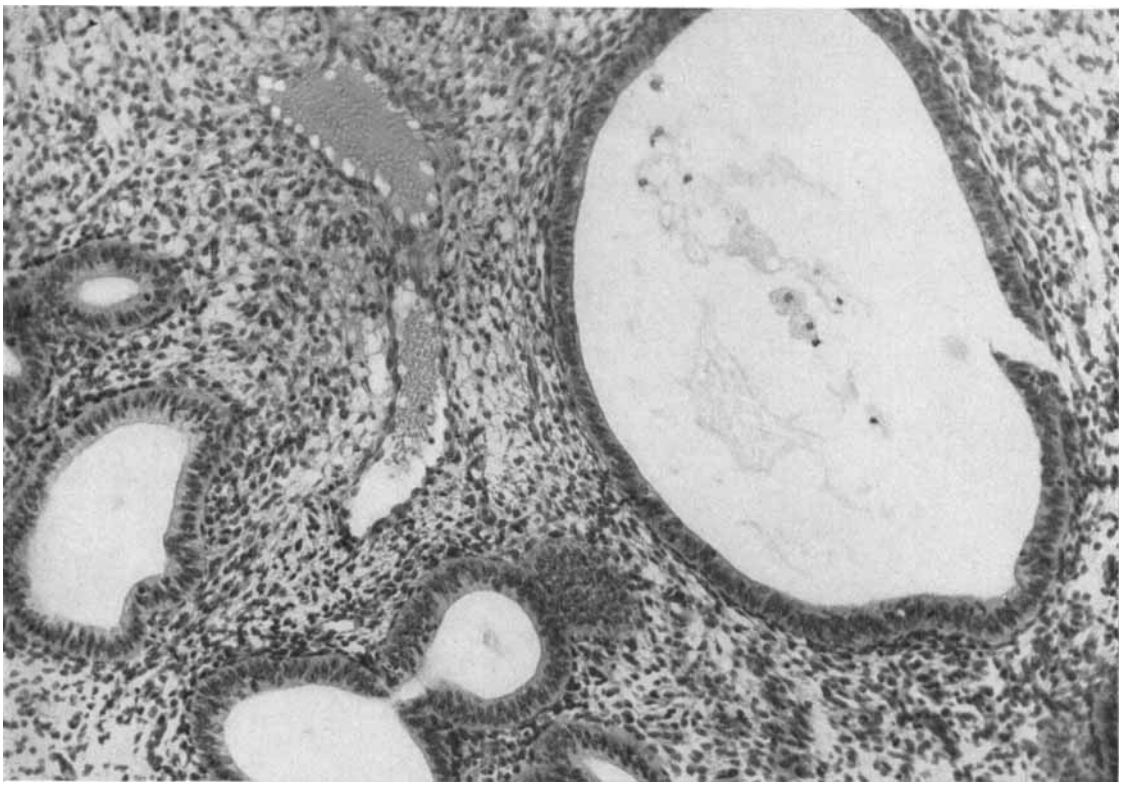

FIG. 8. Patient 5 in Table 1. Curettage specimen obtained from a 44-year-old patient with a large fibroid uterus. It shows basically proliferative endometrium with cystic hyperplasia (FHW-S-59-3711; ×200).

RESULTS

Patients 1 (Mrs. E.T., age 46) and 2 (Mrs. S.M., age 39) were treated for 6 and 7 months, respectively, and in each case the endometrium was converted from that of cystic and adenomatous hyperplasia to an "atrophic" pattern. Patient 1 began to ovulate and menstruate subsequent to the cessation of clomiphene therapy and a biopsy performed in May 1964 revealed normal 16-day secretory endometrium. Patient 2 also resumed regular menstrual periods subsequent to termination of therapy and an endometrial biopsy in October, 1964 revealed normal "menstrual" endometrium. In both of these patients the hyperplasia developed subsequent to 8 to 10 months of anovulation. In each patient clomiphene therapy produced endometrial atrophy: ovulation and menstruation occurred subsequent to termination of therapy.

Patient 3 (Mrs. Q.S., age 51) was treated on 2 separate occasions. The original curettage produced voluminous tissue which was classified as cystic and adenomatous hyperplasia. After the first course of therapy of 8 months duration the endometrium was noted to be "atypical with progesterone effect." Subsequent to therapy the patient noted recurrent abnormal bleeding and an endometrial biopsy done 3 months later again demonstrated cystic and adenomatous hyperplasia. The second course of therapy extended over 10 months and at the end of this time the endometrium obtained by curettage was classified as "inactive with few mitoses." Nine months after cessation of clomiphene therapy recurrent uterine bleeding occurred and a hysterectomy was performed.

Clomiphene treatment was administered for 7 months to patient 4, (Mrs. M.M., age 49) and resulted in a reversion of hyperplasia to an inactive proliferative endometrium. However, a vaginal hysterectomy was performed 6 months after the cessation of therapy because of prolapse and slight irregular bleeding.

The temporary effect of clomiphene is illustrated clearly in patients 3 and 4 since the irregular bleeding re-occurred 9 and 6 months after therapy had been concluded.

Patient 5 (Mrs. J. McD., age 44) had a large fibroid uterus and cystic endometrial hyperplasia in 1959 and was treated with clomiphene on 2 occasions during 1961 and 1962

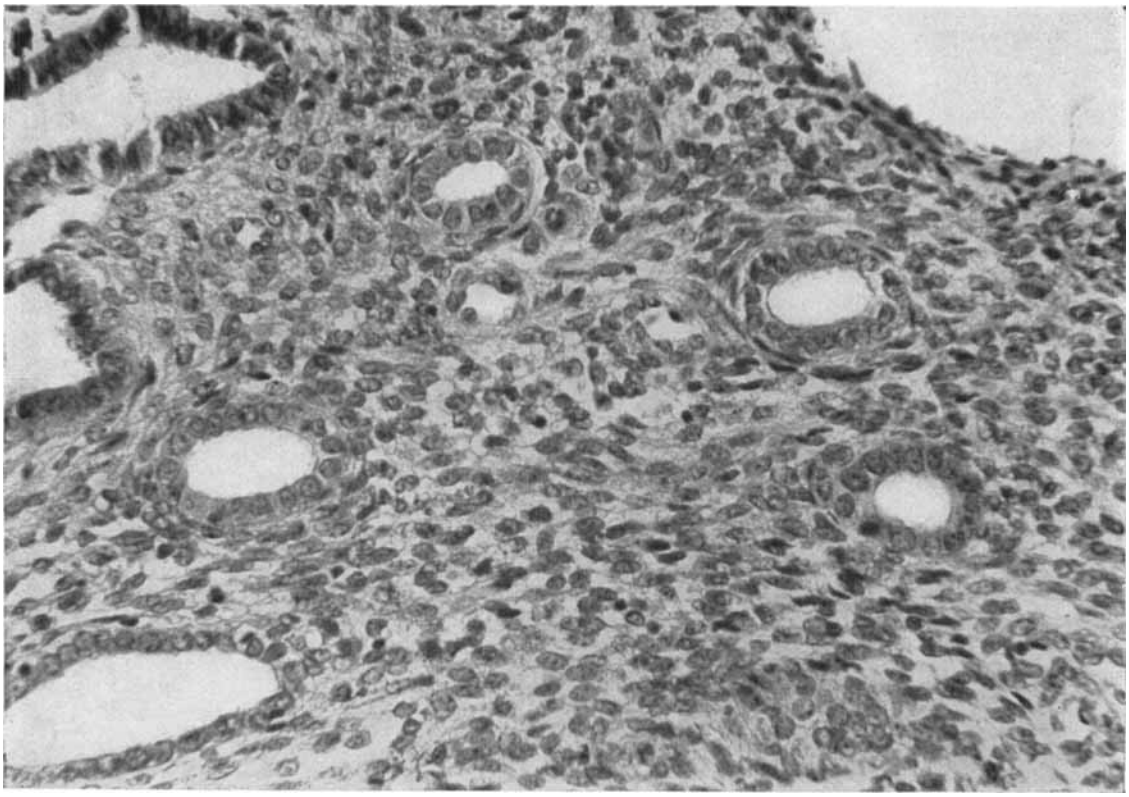

FIG. 9. Patient 5 in Table 1. Curettage specimen obtained after one year of Clomid. No bleeding had occurred during the therapy except when the patient discontinued Clomid temporarily. This pattern was interpreted as "inactive endometrium" (FHW-S-61-1170; ×200).

for a total treatment period of 18 months. A previous total colectomy and postoperative pulmonary embolism contra-indicated hysterectomy. Subsequent to therapy the patient entered spontaneous menopause and another curettage in December 1963 revealed only scant curettings and no leiomyomata.

Patient 6 (Mrs. M.S., age 45) was treated with clomiphene for 6 months because of a combination of cystic endometrial hyperplasia and recurrent mastodynia and fibrocystic disease of the breast. Her endometrium was converted from "hyperplasia" to "inactive" during the first 3 months of therapy. Clomiphene was continued for another 3 months during which time no further bleeding occurred. Normal menses began 3 months after cessation of therapy and again became irregular within 4 months. This was controlled by artificial cycles with synthetic progestins for 3 months. Subsequent spontaneous menstrual periods occurred in 1964 and a biopsy in December 1964 revealed 22-day secretory endometrium.

The side effects are listed in Table 1 and include the development of ovarian cysts in 2 patients and hot flashes in 4 patients. These vasomotor symptoms occurred in the 4 patients in whom ovarian cysts did not develop after prolonged therapy.

DISCUSSION

Although the specific morphologic changes preceding carcinoma of the endometrium are not documented adequately, suggestive evidence has been advanced by Hertig and Sommers to indicate that adenomatous hyperplasia precedes carcinoma.[5] Several prospective experiments have indicated, however, that adenomatous hyperplasia does not always proceed relentlessly towards unequivocal carcinoma and that it is, at present, impossible to predict which hyperplasia will and which will not develop a malignant potential.[3, 7] Gusberg has stated that approximately 12% of patients having this lesion subsequently develop invasive carcinoma of the endometrium if no treatment except curettage is performed.[2, 3]

The relationship of estrogenic substances to the development of endometrial hyperplasia is clear.[2] The relationship of these same substances to invasive carcinoma is clouded by assumptions based on individual case reports, retrospective reasoning and uncontrolled ex-

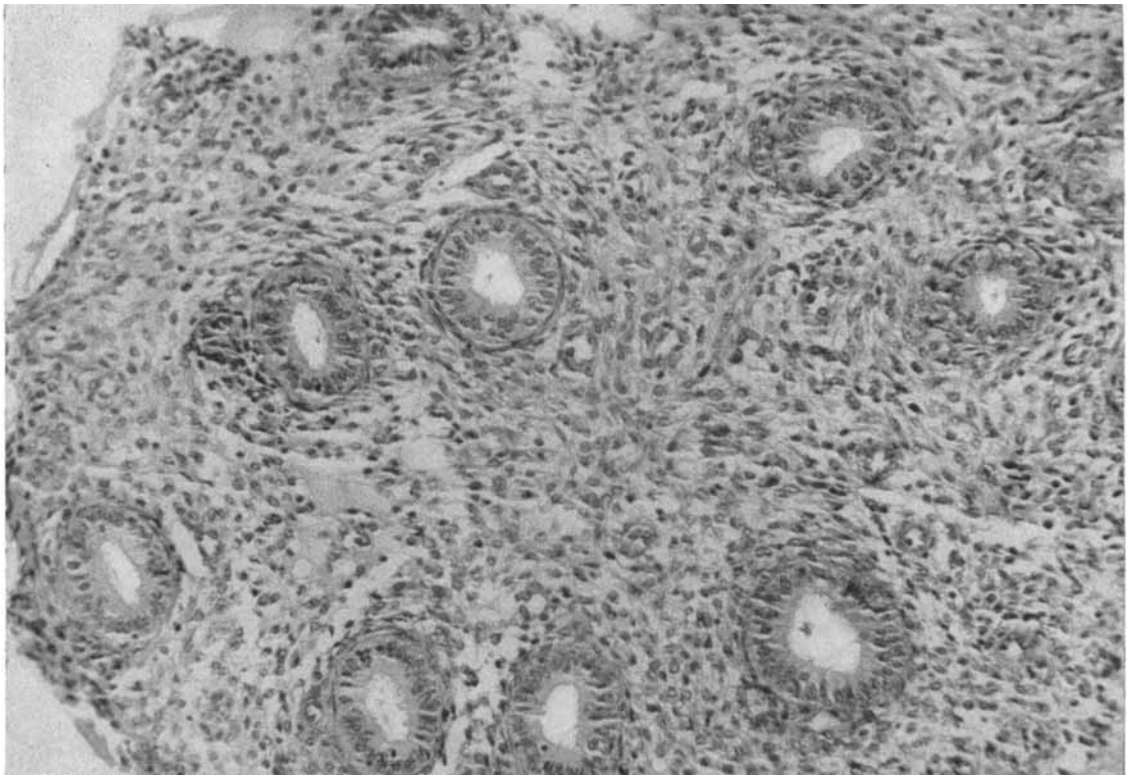

FIG. 10. Patient 5 in Table 1. Curettage specimen obtained in December 1963 showing only slight proliferative activity. Clomid had been discontinued in April 1961 at the time of curettage noted in Figure 9. Recurrent bleeding occurred in August 1961 and Clomid was restarted at that time and was continued for one year, being discontinued in August 1962. Slight staining occurred in March, July and October 1963. This curettage was obtained 16 months after Clomid had been discontinued. In 1964 the patient entered spontaneous menopause and no further bleeding has occurred as of November 10, 1965 (FHW-S-63-5463).

perimentation. Several years ago we produced varying degrees of endometrial hyperplasia and anaplasia in young normally menstruating human females by the administration of an estrogen for 45 to 100 days.[11] After the exogenous estrogen was discontinued and subsequent ovulation intervened, all patients had normal endometrium as determined by biopsy.

Clomiphene citrate products an ovulatory response in approximately 75% of patients who have been anovulatory on the basis of abnormal pituitary or ovarian function. The observations to date suggest that clomiphene exerts its effect by direct stimulation of the pituitary gland or possibly as a hypothalamic regulator. Other evidence suggests that clomiphene may act also on the ovary, the endometrium or other peripheral sites by substituting for estrogen in the normal binding sites.

Although the patient most likely to benefit from a therapeutic regimen with clomiphene is the young female with a problem of irregular or absent ovulation, it also should be remembered that endometrial hyperplasia frequently occurs in women approaching the menopause as a result of constant estrogen stimulation over a rather long period of time. The induction of ovulation in these patients is not desirable nor has it been shown to be a common occurrence following clomiphene in this age group. We previously have reported our results in the treatment of 11 patients in the age group 16 through 26 whose endometrium was classified as hyperplastic or "anaplastic."[8, 14] Apparent ovulation was obtained in 41 of 44 treatment cycles and the post-treatment biopsy showed normal secretory pattern in each instance.

CONCLUSIONS

Although precise evidence of ovulation is not available in the 6 patients observed in this study, atypical secretory endometrium was noted by biopsy in 2 patients. This change may have resulted from progesterone secreted by a corpus luteum or from luteinized theca cells of a follicle cyst. The finding of atrophic endometrium may be explained on the known anti-estrogenic property of the compound.

Three patients reverted to normal menstrual

cycles after cessation of clomiphene therapy and, as of January 1965, had normal secretory endometrium by biopsy. Although it is possible that each of these patients would have had spontaneous return of normal menses, it is more probable that each would have been treated by hysterectomy because of the combination of hypermenorrhea and endometrial hyperplasia.

The therapeutic effects of clomiphene are temporary as evidenced by the return of bleeding 6 to 9 months after cessation of therapy. If the ovary maintains its potential for follicular maturation and ovulation, a secretory phase will be induced in the endometrium which lasts 6 to 8 weeks. Endometrial atrophy then will develop and remain unchanged as long as therapy is continued. The latter effect of "estrogen antagonism" has been documented adequately by observations showing negation of cervical mucus patterns and vaginal cornification in human subjects.

The major side effects noted subsequent to the administration of clomiphene were hot flashes in 4 patients and ovarian cysts in 2 patients. Such cystic enlargement is perhaps the most convincing evidence indicating that clomiphene is capable of stimulating ovarian secretory activity in the human female. Microscopic study of the cysts and the associated endometrium has indicated that these structures are indeed of functional nature.

Although the changes described in this report were produced in patients near or after the menopause, they should not be interpreted as cures. The endometrial hyperplastia returned in the one postmenopausal patient after therapy had been discontinued. Both ovaries showed cortical stromal hyperplasia—a possible source of estrogen. The use of a compound such as clomiphene seems to be of value in premenopausal patients who are known to have irregular ovulation prior to complete cessation of menstruation. During this time a few patients will develop hyperplasia or carcinoma in situ as a result of, or coincident with, constant estrogen stimulation. If the ovary is still reactive to pituitary gonadotropins, therapy probably is accomplished best by short cycles of 3 to 5 days rather than risk the development of ovarian cysts. Cyclic ovulation and menstruation for 4 to 6 months will usually eliminate the hyperplastic process. If ovulation cannot be induced, advantage may be taken of the anti-estrogenic effect of clomiphene without risking the possibility of cystic enlargement of the ovary. In these patients the compound may be given constantly for 6 to 18 months to produce atrophy of a previously hyperplastic endometrium.

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