PREMENARCHAL CLIMACTERIC

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When climacteric symptoms occur in women, they usually appear between the ages of 40 and 50. They are occasionally seen in women past 60, are quite uncommon before 30 and rare before 20. In almost all cases climacteric symptoms are antedated by relatively normal menstrual periods.

Climacteric symptoms appearing before the menarche are very rare. Albright[1] has used the term *premenarchal menopause praecox* in referring to cases of primary amenorrhea with little or no breast development and persistently positive tests for urinary gonadotrophins. However, similar cases which we have encountered and patients with primary amenorrhea in general do not have menopausal symptoms. In the case reported here climacteric symptoms appeared before the onset of the menses and at an age when puberal changes are not ordinarily complete. In addition to the primary amenorrhea there were typical signs of moderately severe prepuberal primary ovarian deficiency.

CASE REPORT

An unmarried white woman, aged 21, was seen on October 29, 1942 with the complaint of frontal headache of fifteen years' duration. The headaches occurred almost every day over periods of two to three weeks. They were never bilateral but were associated with nausea. Mild diplopia was present but was associated with close work only.

The patient had never menstruated. Since the age of 15 she had experienced hot flashes typical of ovarian deficiency, which spread upward over the neck and head and lasted a few minutes several times daily. They were always more pronounced when she was under nervous tension or had a headache. Libido was minimal. She was extremely emotional and irritable and had poor endurance. There were no other symptoms of pituitary or hypothalamic dysfunction.

The family history was irrelevant. She had occasional attacks of tonsillitis and had mumps at the age of 8.

Physical examination revealed the following significant findings:

Weight—114 pounds (51.8 kg.)
Height—66¼ inches (165.6 cm.)
Span (arms extended)—68¾ inches (171.8 cm.)
Symphysial height—36¼ inches (90.6 cm.)

The hair on the arms and forearms and the axillary and pubic hair was finer and straighter than usual but approximated normal in amount. No breast tissue was palpable, and the nipples and areolae were pale and infantile. The labia were flat and underdeveloped. The vagina admitted one finger, and the vaginal wall showed only slight rugosity. By palpation the uterus was estimated to be one-third normal size.

Stained vaginal smear was typical of severe follicular deficiency. The vaginal cells were chiefly rounded and relatively small. There were very few leukocytes. The smear did not show purely round deep cells as is typical of castrate smears.

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The blood count was normal except for 78 per cent (12 Gm.) hemoglobin. Blood cholesterol was 124 mg. per 100 cc., and blood calcium 10.5 mg. per 100 cc. Basal metabolic rate was plus 2. The curve of a single dose 100 Gm. oral glucose tolerance test was as follows:

Hours	Fasting	½	1	2	3	4
Blood sugar (mg./100 cc.)	110	127	48	48	41	74
Urine sugar	0	-	0		0	

In spite of this evidence no symptoms of hypoglycemia were noted. Urinalysis was normal, and Wassermann reaction of the blood was negative.

Roentgenographic studies of the skull revealed a normal sella turcica with some demineralization of the bone. Epiphyseal age was calculated to be about 20 years, the epiphyseal line at the distal ends of the radius having failed to close completely.

The optic fundi were normal. In the visual field examination the patient called green "pink." The visual field for red was severely constricted.

Bioassay for gonadotrophic hormone in a 24 hour urine specimen showed average rat ovarian weight of 83 mg. and average uterine weight of 78 mg. as compared with an average ovarian weight in uninjected controls of 18 mg. and average uterine weight of 21 mg. Urinary 17-ketosteroid determination done on an unfractionated extract showed 6.2 mg. per 24 hours. Estrogen assay showed less than 10 rat units per 24 hours.

On November 11, 1942 the patient was started on 1 mg. daily of stilbestrol dipropionate orally in courses of twenty-five days. After two weeks of therapy she felt well, was more energetic, and had no headaches. She complained of some soreness of the nipples, and her breasts were noticeably larger. On the twenty-eighth and twenty-ninth days of treatment intramuscular injections of progesterone in doses of 5 mg. were given. Four days after withdrawal of therapy the patient had her first menstrual flow, which was scant and lasted for two days. Further treatment with subsequent uterine bleeding is shown in the treatment schedule and in figure 1.

GONADOTROPHIC HORMONE ASSAYS

Rat Test

Test Animals	BEFORE TREATMENT	AFTER TREATMENT	
	12-1-42	10-21-43	1-18-44
	mg.	mg.	mg.
Ovarian weight. . . .	83	16	19
Uterine weight. . . .	73	19	11
Uninjected Control Animals			
Ovarian weight. . . .	18	26	19
Uterine weight. . . .	21	38	26

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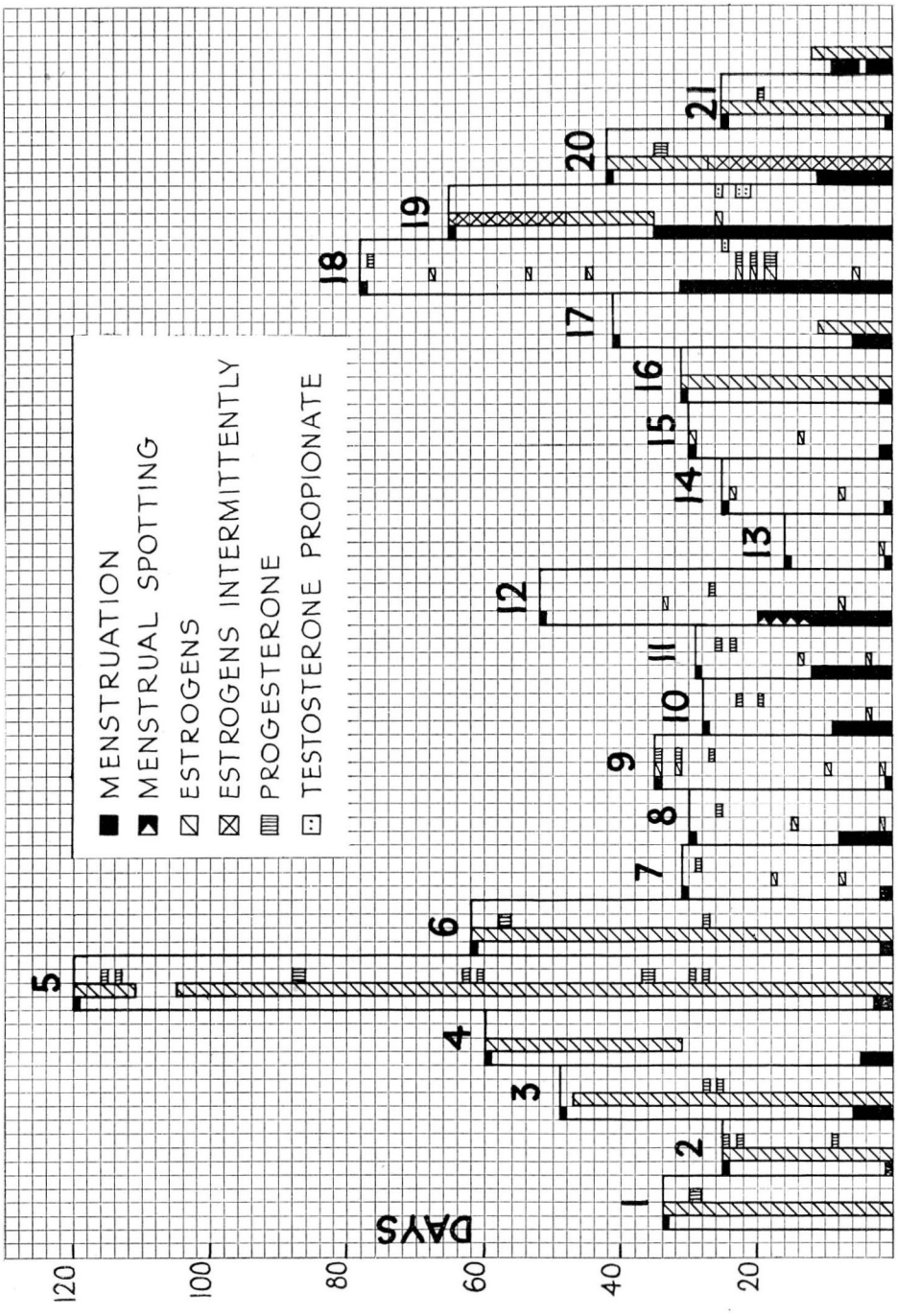

Fig. 1. Menstrual cycles are represented by numbered columns. The solid block at the top of each column represents onset of uterine bleeding, which is continued at the bottom of the succeeding column. Columns 5 and 6 are represented as one cycle, although

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TREATMENT SCHEDULE

Cycle	Date	Medication	Daily dose	Route of administration	Duration days	RESPONSE: Vaginal smear	RESPONSE	Cycle	Date	Medication	Daily dose	Route of administration	Duration days	RESPONSE: Vaginal smear	RESPONSE
1	11–11–42	Stilbestrol dipropionate	1 mg.	Oral	13	4 plus	No headaches or hot flashes. Rested and energetic	5	6– 2–43	Estradiol benzoate	2000R.U.	I.M.			Much gastrointestinal disturbance.
										Progesterone	5 mg.	I.M.			
	11–24–42	Stilbestrol dipropionate	1 mg.	Oral	22		Good energy. Breasts enlarging.			Monomethyl stilbestrol	10 mg.	Oral	16		
									6– 3–43	Estradiol benzoate	2000R.U.	I.M.			
	12– 9–42	Progesterone	5 mg.	I.M.						Progesterone	5 mg.	I.M.			
	12–10–42	Progesterone	5 mg.	I.M.					6–18–43	Ethyl hexane	15 mg.	Oral	8	3 plus	
	12–14–42								6–26–43	Ethyl hexane	20 mg.	Oral	20	3 plus	Feels fine.
2	12–16–42	Stilbestrol dipropionate	1 mg.	Oral	7		Headaches last only 2 hr. now. Hair coarser. Breasts correspond with puberal development of 12 yr. Nipples are growing. Axillary and pubic hair increasing. Vagina is larger, a speculum can now be inserted. Uterine length 6 cm.			Progesterone	5 mg.	I.M.			
									6–28–43	Progesterone	5 mg.	I.M.			
									7–16–43	Ethyl hexane	30 mg.	Oral	8		
	12–23–42	Stilbestrol dipropionate	2 mg.	Oral	14	Almost			7–22–43	Progesterone	5 mg.	I.M.			
		Estradiol benzoate	2000R.U.	I.M.		4 plus			7–23–43	Progesterone	5 mg.	I.M.			
									7–24–43	Monomethyl stilbestrol	18 mg.	Oral	16	3-4 plus	
									8–16–43	Ethyl hexane	30 mg.	Oral	5	3 plus	
									8–19–43	Progesterone	5 mg.	I.M.			
									8–21–43	Progesterone	5 mg.	I.M.		2 plus	Headaches and hot flashes.
										Monomethyl stilbestrol	18 mg.	Oral	18		
									8–25–43						
	1– 6–43	Stilbestrol dipropionate	3 mg.	Oral	15	4 plus	No headaches. Feels fine.	6	9– 8–43	Stilbestrol dipropionate	1 mg.	Oral	14	2-3 plus	Feels fine. Few headaches. No hot flashes.
		Progesterone	5 mg.	I.M.						Estradiol benzoate	2000R.U.	I.M.			
	1– 8–43	Progesterone	5 mg.	I.M.					9–22–43	Stilbestrol dipropionate	2 mg.	Oral	13	2 plus	Feels fine.
										Progesterone	5 mg.	I.M.			
3	1–21–43	Stilbestrol dipropionate	3 mg.	Oral	13	About			10– 5–43	Stilbestrol dipropionate	3 mg.	Oral	16	Premenstrual type	Occasional headaches. Feels fine generally.
		Estradiol benzoate	2000R.U.	I.M.		4 plus	Breasts larger. Axillary and pubic hair more profuse. Vagina larger with more rugosity.		10–21–43	Stilbestrol dipropionate	3 mg.	Oral	12	4 plus	Occasional headaches. Feels fine.
										Progesterone	5 mg.	I.M.			
	2– 3–43	Stilbestrol dipropionate	3 mg.	Oral	21	Under			10–22–43	Progesterone	5 mg.	I.M.			
		Progesterone	5 mg.	I.M.		4 plus			10–25–43						
	2– 5–43	Progesterone	5 mg.	I.M.				7	11– 2–43	Stilbestrol dipalmitate	5 mg.	I.M.		2-3 plus	10 days later, feels fine, symptom free.
	2–26–43														
4	3–30–43	Patient has not received medication for 34 days. Has felt let down. Frequent headaches and bowel movements. Vaginal smear castrate with some red blood cells.							11–12–43	Stilbestrol dipalmitate	5 mg.	I.M.		4 plus	11 days later, feels fine.
									11–23–43	Progesterone	10 mg.	I.M.			
	3–30–43	Ethinyl estradiol	0.20 mg.	Oral	13				11–25–43						
		Estradiol benzoate	2000R.U.	I.M.				8	11–27–43	Stilbestrol dipalmitate	5 mg.	I.M.			
	4–12–43	Ethinyl estradiol	0.20 mg.	Oral	10	3-4 plus	Feels quite well.		12–10–43	Stilbestrol dipalmitate	5 mg.	I.M.			
	4–22–43	Ethyl hexane	15 mg.	Oral	9	3 plus	No nausea. Has a headache.		12–21–43	Progesterone	10 mg.	I.M.			
	4–26–43								12–25–43						
5	5– 1–43	Ethyl hexane	15 mg.	Oral	12		Feels fine.	9	12–27–43	Stilbestrol dipalmitate	5 mg.	I.M.		3 plus	8 days later, looks and feels well.
	5–12–43	Ethyl hexane	15 mg.	Oral	9	4 plus	Severe headaches.		1– 4–44	Stilbestrol dipalmitate	5 mg.	I.M.			5 days later, headaches.
	5–22–43	Ethyl hexane	15 mg.	Oral	11	2-3 plus	Feels headachy and miserable.		1–21–44	Progesterone	10 mg.	I.M.			
									1–26–44	Estradiol benzoate	4000R.U.	I.M.			
	5–25–43	Progesterone	5 mg.	I.M.						Progesterone	5 mg.	I.M.			
	5–27–43	Progesterone	5 mg.	I.M.					1–29–44	Estradiol benzoate	4000R.U.	I.M.			
										Progesterone	5 mg.	I.M.			

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TREATMENT SCHEDULE — Continued

Cycle	Date	Medication	Daily dose	Route of administration	Duration days	RESPONSE: Vaginal smear	RESPONSE:	Cycle	Date	Medication	Daily dose	Route of administration	Duration days	RESPONSE: Vaginal smear	RESPONSE:
10	2- 2-44	Stilbestrol dipalmitate.	10 mg.	I.M.		3 plus	16 days later, feels fine.	18	10-28-44	Estradiol benzoate....	6000R.U.	I.M.			
	2-18-44	Progesterone.....	5 mg.	I.M.						Progesterone.....	10 mg.	I.M.			
	2-21-44	Progesterone.....	5 mg.	I.M.			7 days later, feels miserable. Nervous, headaches, cramps.		10-30-44	Estradiol benzoate....	6000R.U.	I.M.			
										Progesterone.....	10 mg.	I.M.			
	2-26-44								11- 1-44	Testosterone propionate.....	50 mg.	I.M.			After bleeding a month, stopped on 11-4-44.
11	3- 1-44	Stilbestrol dipalmitate.	10 mg.	I.M.		About 3 plus 4 days later			11-21-44	Stilbestrol dipalmitate.	20 mg.	I.M.		2-3 plus	9 days later, headaches returned, irritable. No hot flashes.
	3-11-44	Monomethyl stilbestrol	12.5 mg.	I.M.											
	3-21-44	Progesterone.....	10 mg.	I.M.											
	3-23-44	Progesterone.....	10 mg.	I.M.					11-30-44	Stilbestrol dipalmitate.	10 mg.	I.M.		3 plus	14 days later, feels better, fewer headaches.
	3-26-44														
12	4- 3-44	Monomethyl stilbestrol	25 mg.	I.M.		2 plus 19 days later			12-14-44	Stilbestrol dipalmitate.	10 mg.	I.M.			
									12-23-44	Progesterone.....	10 mg.	I.M.			
	4-22-44	Progesterone.....	10 mg.	I.M.		2-3 plus 22 days later			12-24-44						
								19	1-15-45	Testosterone propionate.....	25 mg.	I.M.			
	4-29-44	Monomethyl stilbestrol	25 mg.	I.M.					1-16-45	Testosterone propionate.....	25 mg.	I.M.			
	5-17-44														
13	5-19-44	Monomethyl stilbestrol	30 mg.	I.M.			17 days later, headaches for 2 days before bleeding.		1-19-45	Testosterous propionate.....	25 mg.	I.M.			
										Estradiol benzoate....	1000R.U.	I.M.			
	6- 2-44								1-29-45	Monomethyl stilbestrol	25 mg.	I.M.		3 plus	
14	6-10-44	Monomethyl stilbestrol	20 mg.	I.M.						Diethyl stilbestrol....	2 mg.	Oral		12 days later	
	6-26-44	Monomethyl stilbestrol	50 mg.	I.M.		Blood	15 days ater, feels fine. No headaches or hot flashes.		2-10-45	Diethyl stilbestrol....	2 mg.	Oral	Irregularly for 43 days	2-3 plus	44 days later, feeling fine. No headaches or hot flashes. Uterus still not normal size.
	6-27-44														
15	7-11-44	Monomethyl stilbestrol	25 mg.	I.M.		3 plus 10 days later			2-27-45						
	7-27-44	Ethinyl estradiol.....	0.05 mg.	Oral	49	2-3 plus	Head aches and nervous. No hot flashes.	20	3-26-45	Diethyl stilbestrol....	2 mg.	Oral	30	2-3 plus	No headaches or hot flashes.
									4- 2-45	Estradiol benzoate....	6000R.U.	I.M.			
16										Progesterone.....	5 mg.	I.M.			
	8-27-44									Stilbestrol unguent...	2 mg.	Topical	(appli	ed to bre	asts daily)
17	9- 7-44	Stilbestrol dipalmitate.	15 mg.	I.M.		Severely deficient	36 days later, head aches and nervous. No hot flashes. Uterus larger.		4- 3-45	Estradiol benzoate....	6000R.U.	I.M.			
										Progesterone.....	5 mg.	I.M.			
	10- 7-44								4-10-45						
18	10-13-44	Stilbestrol dipalmitate.	15 mg.	I.M.				21	4-25-45	Diethyl stilbestrol....	2 mg.	Oral	21	3 plus	Headaches and hot flashes recently.
	10-25-44	Estradiol benzoate....	2000R.U.	I.M.					4-30-45	Estradiol benzoate....	6000R.U.				
		Progesterone.....	10 mg.	I.M.						Progesterone.....	5 mg.				
	10-26-44	Estradiol benzoate....	2000R.U.	I.M.					5- 5-45						
		Progesterone.....	10 mg.	I.M.					5-17-45	Hydroxy-phenyl hexane.....	9 mg.	Oral	18		

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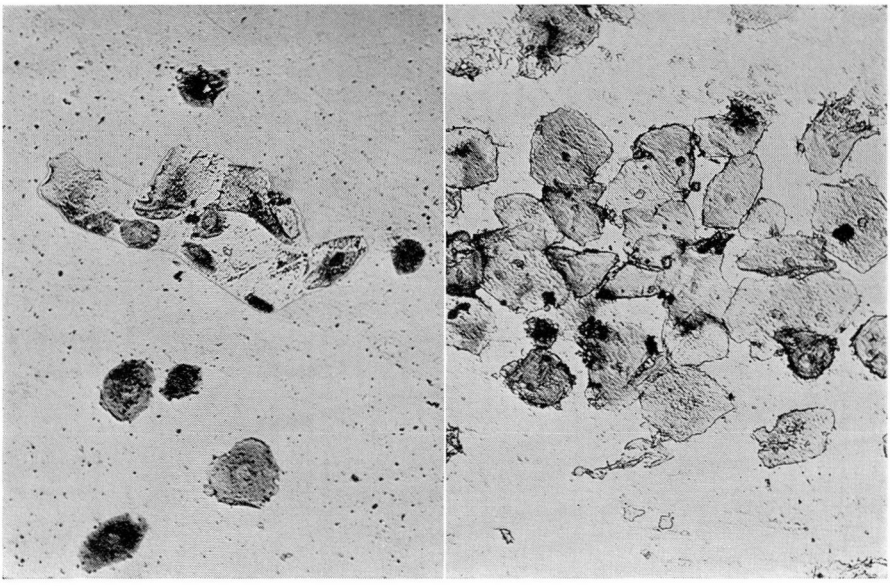
COMMENT

Anatomic changes were relatively rapid at first but later were less noticeable, although doses of estrogens were larger. After two months of treatment she had no hot flashes and only occasional headaches, which were very mild and lasted not more than an hour or two. Her irritability disappeared, energy and endurance increased, and she gained 15 pounds. Breast size became average normal for approximately 11 to 12 years of age, and the nipples enlarged and darkened. There was some increase in axillary and pubic hair. The vagina had developed, and a slight discharge was present. An almost complete estrogenic response was demonstrated by the vaginal smear (fig. 2a and b). A speculum could be inserted, and the uterine canal measured 6 cm.



a. *b.*

FIG. 2. a. Vaginal smear before treatment. b. Relatively complete vaginal smear response (Jan. 21, 1943). (x 125)

After over thirty months of treatment little anatomic change appeared to be taking place (fig. 3a and b). The patient usually felt in the best of health, was cheerful, energetic, and free from symptoms except for slight headache, which usually occurred before a period of bleeding. The breasts were 9 cm. in diameter and could be called normal for age 13. The nipples were small, and the nipples and areolae became very

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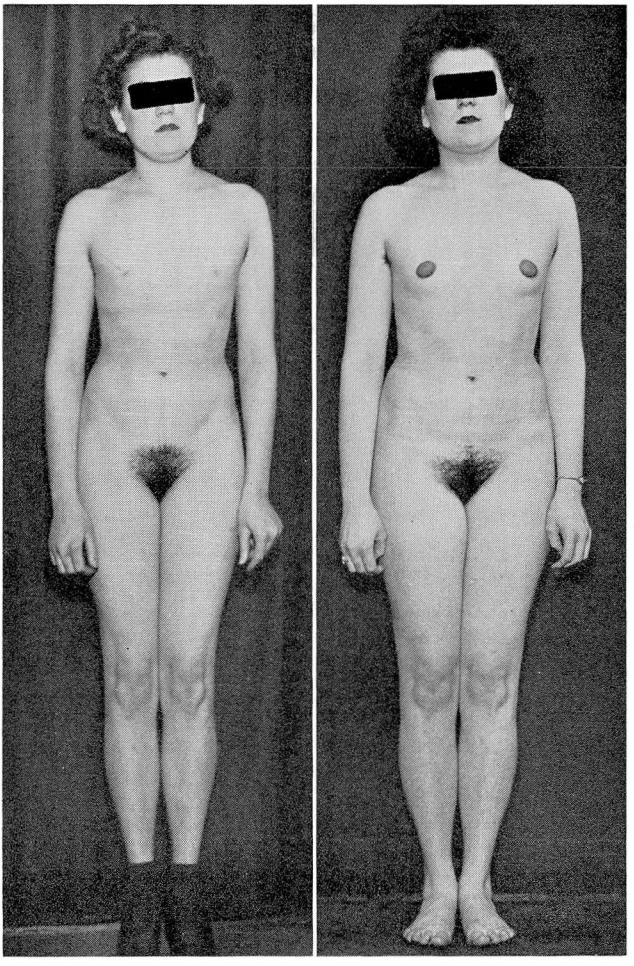
dark brown. Axillary and pubic hair was normal in amount but straighter than average. The labia were underdeveloped, and the clitoris was very small. The vagina was normal in size, the cervix small normal; the fundus was normal on palpation; and the uterine canal measured over 7 cm. in length. Recently an endometrial biopsy on the first day of menstrual bleeding showed a somewhat atypical proliferative (follicular) type of endometrium consistent with changes usually seen early in the cycle.



a. *b.*

Fig. 3. a. Nov. 11, 1942. Relatively normal amount of pubic hair. b. April 2, 1945. Note increase in size of breasts and increase in size and color of areolae.

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A considerable array of various estrogens was used in therapy. All were effective, but the dose range varied greatly. The most active from the standpoint of dosage was ethinyl estradiol. This drug given orally in doses of 0.20 mg. daily gave complete symptomatic control and almost a full estrogenic vaginal response. Diethyl stilbestrol in doses of 2.0 mg. per day gave complete symptomatic response but 3.0 mg. was required daily to produce normal vaginal smears. Stilbestrol dipropionate orally in doses of 1.0 mg. a day gave complete symptomatic and vaginal response during the first few weeks. This was not tried later. The dose requirement of all estrogens appeared to rise somewhat during the course of treatment. Ethyl hexane (2,4-di-[parahydroxyphenyl]-3-ethyl hexane) (Benzestrol, formerly Octofollin) gave complete symptomatic response with 20 mg. daily doses, but vaginal smear response was incomplete on a dose of 30 mg. Complete symptomatic response was obtained with hydroxy-phenyl hexane (Hexestrol) with 9.0 mg. per day. Monomethyl stilbestrol ($\alpha\alpha$ diethyl 4 hydroxy 4 methoxystilbene) (Monomestrol) was given intramuscularly on four occasions in doses of 25, 25, 30, and 50 mg. Symptoms recurred in about two weeks after each injection, at which times the vaginal smears were deficient. Intramuscular injections of 5 to 10 mg. of stilbestrol dipalmitate controlled symptoms for more than eleven and more than sixteen days respectively associated with almost complete control of the vaginal smears.

By using moderate doses of estrogen followed by small doses of progesterone and withdrawal, uterine bleeding was brought about repeatedly at intervals which were usually predicted with only fair accuracy. The greatest tendency for bleeding to occur during estrogen therapy and for it to be unduly prolonged followed relatively large injections (15 to 20 mg.) of stilbestrol dipalmitate or monomethyl stilbestrol.

SUMMARY

A case of prepuberal primary ovarian failure with climacteric symptoms is reported. The response of the patient to treatment has been outlined for a period of over thirty months, and some of the observations as to relative effectiveness of various estrogens noted.

REFERENCES

1. Albright, F., Smith, P., and Fraser, R.: A syndrome characterized by primary ovarian insufficiency and decreased stature. Am. J. M. Sc. **204**:625 (November) 1942.

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