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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<sup>1</sup> 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 Placed memory	Fasting	$\frac{1}{2}$	1	2	3	4
(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.

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

### GONADOTROPHIC HORMONE ASSAYS

Rat Test



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RESPONSE		Much gastrointesti- nal disturbance.		Feels fine.				Headaches and hot flashes.	Feels fine. Few head- aches. No hot	reasones. Feels fine.	Occasional head- aches. Feels fine	generatiy. Occasional head- aches, Feels fine.	10 davs later. feels	fine, symptom free. 11 days later, feels fine.		8 days later, looks and feels well. 5 days later, head- aches.
H	Vaginal smear			3 plus 3 plus			3-4 plus 3 plus	2 plus	2-3 plus	2 plus	Premen- strual	4 plus	2-3 nhis	4 plus		3 plus
Dura-	tion days	ç T	97	8 20 8	æ	6	16 5	18	14	13	16	12			<u> </u>	
Boute of	adminis- tration	I.M.	I.M.	Oral	LUN UN	I.M.	Oral Oral	I.M. Oral	Oral I.M.	Oral I.M.	Oral	Oral I.M.	T M	I.M. I.M.	I.M. I.M. I.M.	WWWWWW
	Daily dose	2000R.U. 5 mg.	2000R.U.	20 mg.	o mg. 30 mg.		18 mg. 30 mg.	õmg. õmg. 18mg.	1 mg. 2000R.U.	ž mg. ž mg.	3 mg.	3 mg.	o ma	5 mg. 10 mg.	5 mg. 5 mg. 10 mg.	5 mg. 5 mg. 10 mg. 6 00 R.U. 5 mg. 5 mg.
	Medication	Estradiol benzoate Progesterone	Estradiol benzoate	Ethyl hexane Ethyl hexane Ethyl hexane	Progesterone Progesterone	Progesterone	Monomethyl stilbestrol Ethyl hexane	Progesterone. Progesterone. Monomethyl stilbestrol	Stilbestrol dipropionate Estradiol benzoate	Stilbestroldipropionate Proresterone	Stilbestrol dipropionate	Stilbestrol dipropionate Progesterone	Lrugesterone	Stilbestrol dipalmitate. Progesterone.	Stilbestrol dipálmitate. Stilbestrol dipalmitate. Progesterone.	Stilbestrol dipalmitate. Stilbestrol dipalmitate. Frogesterone Fostatiol benzoate Frogesterone Frogesterone
	Date	6- 2-43	6- 3-43	6-18-43 6-26-43	6-28-43 7-16-43	7-22-43	7-24-43 8-16-43	8-19-43 8-21-43	8-25-43 9- $8-43$	9-22-43	10- 5-43	10-21-43	10-25-43 10-25-43	11-12-43 11-23-43	11-25-43 11-27-43 12-10-43 12-21-43	12-25-48 12-27-43 1-4-44 1-26-44 1-26-44 1-29-44
	Cycle	ŝ							9				-	•	∞	6
ESPONSE		No headaches or hot flashes.	Kested and energetic Good energy. Breasts	entarging.	Headaches last only	coarser. Breasts cor- respond with puberal	development of 12 yr. Nipples are grow-	ing. Axillary and pu- bic hair increasing. Vagina is larger, a	speculum can now be inserted. Uterine length 6 cm. No beodeches Feels	fine.	Reaats larvar Avil-	more profuse. Vag-	rugosity.	lown. Frequent head- ne red blood cells.	Feels quite well. No nausea. Has a	readacite. Feels fine. Severe headaches. Feels headachy and miserable.
B	Vaginal smear	4 plus				Almost 4 plus	•		4 nlue		About	9 4	Under 4 plus	las felt let te with so	3-4 plus 3 plus	4 plus 2-3 plus
Dure-	tion	13	22		2	14			ž	2	13		21	days. H r castra	10 10 10 10	13 19 11
Route of	adminis- tration	Oral	Oral	I.M. I.M.	Oral	Oral L.M.			Oral	I.M.	Oral		Oral I.M. I.M.	ion for 34 ginal smea	Oral Oral Oral	Oral Oral Oral I.M.
	Daily dose	1 mg.	1 mg.	5 mg. 5 mg.	1 mg.	2 mg. 2000R.U.		- -	3 mg	5 BG	3 mg.		or o	d medicat ments. Va	0.20 mg. 2000R.U. 0.20 mg. 15 mg.	15 mg. 15 mg. 15 mg. 5 mg.
	Medication	Stilbestroldipropionate	Stilbestroldipropionate	Progesterone	Stilbestrol dipropionate	Stilbestrol dipropionate Estradiol benzoate			Stilhestroldinronionate	Progesterone	Stilbestrol dipropionate Fistradici honzoate		Stilbestrol dipropionate Progesterone	Patient has not receive aches and bowel moven	Ethinyl estradiol Estradiol benzoate Ethinyl estradiol Ethyl hexane.	Ethyl hexane Ebyy hexane Ethyl hexane Progesterone Progesterone
	Date	11-11-42	11-24-42	12 - 9 - 42 12 - 10 - 42	12-14-42	12-23-42			1- 8-43	1-8-43	1-21-43		2- 3-43 2- 5-43	2-26-43 3-30-43	3-30-43 4-12-43 4-22-43	$\begin{array}{c} 4-26-43\\ 5-11-43\\ 5-12-43\\ 5-22-43\\ 5-27-43\\ 5-27-43\end{array}$
-	Cycle	-			2				87		3			4		n.

TREATMENT SCHEDULE

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SPONSE			fter bleeding a onth. stopped on	-4-44. davs later, head-	thes returned, irri- ble. No hot flashes. days later, feels	thes, tewer neau-				·	l days later, feeling ie. No headaches	still not normal re.	o headaches or hot whes.	(-11 - F	s dauy)	eadaches and hot	SHEEL LCCCHULY.	
RE	Vaginal smear		Ā	2-3 plus 9	3 plus 14	58			-	o pius 12 days later	2-3 plus 44	n si cis	2-3 plus N		ed to bre ast	3 plus H	¥ 	
	tion										Irregu- larly	days	30		(appu	21		18
Routant	adminis- tration	I.M. I.M. I.M.	I.M.	I.M.	I.M.	I.M. I.M.	 I.M.	LM.	I.M.	0ral	Oral		Oral	IN.	I.M. I.M.	Oral		Oral
	D'aily dose	6000R.U. 10 mg. 6000R.U. 10 mg.	50 mg.	20 mg.	10 mg.	10 mg. 10 mg.	25 mg.	25 m <i>e</i> .	25 mg. 1000R.U.	20 mg.	2 mg.		2 mg.	6000R.U. 5 mg.	6000R.U. 5 mg.	2 mg.	6000R.U. 5 mg.	9 me.
	Medication	Estradiol benzoate Progesterone Estradiol benzoate	ate	Stilbestrol dipalmitate.	Stilbestrol dipalmitate.	Stilbestrol dipalmitate. Progesterone	Testosterone propion- ate	Testosterone propion- ate	Testosterous propion- ate Estradiol benzoate	Monometry 15 tubestrol	Diethyl stilbestrol		Diethyl stilbestrol	Estradiol benzoate Progesterone	Estradiol benzoate	Diethyl stilbestróf	Estradiol benzoate	Hydroxy-phenyl hexane
	Date	10-28-44 10-30-44	#F-1 -11	11-21-44	11-30-44	12-14-44 12-23-44	12-24-44 1-15-45	1-16-45	1-19-45	CT-67-1	2-10-45	1 1 1	2-21-40 3-26-45	4- 2-45	4-3-45	4-10-45 4-25-45	4-30-45	5- 5-45 5-17-45
	Cycle	18			•		19						80			21		
RESPONSE		16 days later, feels fine. 7 days later, feels miserable. Nervous,	incautacines, cramps.						17 days later, head- aches for 2 days be- fore bleeding.	15 davs ater feels	fine. No headaches or hot flashes.		Head aches and ner- vous. No hot flashes.		36 days later, head aches and nervous.	No not nashes. Uter- us larger.		
H	Vaginal smear	3 plus		About 3 plus	4 days later	2 plus 19 days later	22 days 22 days later			Blood		3 plus 10 days	later 2-3 plus		Severely deficient		,	
	tion days								i				49					
Routeof	adminis- tration	I.M. I.M.		I.M.	I.M. I.M.	I.M.	1.M.	I.M.	I.M.	LM.		I.M.	Oral		I.M.	Ĩ	I.M.	I.W.
	Daily dose	10 mg. 5 mg. 5 mg.		10 mg.	12.5 mg. 10 mg. 10 mg.	25 mg.	10 mg.	25 mg.	30 mg.	20 mg. 50 mg.	0	25 mg.	0.05 mg.		15 mg.		15 mg. 2000R.U	10 mg. 2000R.U. 10 mg.
	Medication	Stilbestrol dipalmitate. Progesterone		Stilbestrol dipalmitate.	Monomethyl stilbestrol Progesterone	Monomethyl stilbestrol	Frogesterone	Monomethyl stilbestrol	Monomethylstilbestrol	Monomethyl stilbestrol Monomethyl stilbestrol		Monomethyl stilbestrol	Ethinyl estradiol		Stilbestrol dipalmitate.		Stilbestrol dipalmitate. Estradiol benzoate	Progesterone Estradiol benzoate Progesterone
	Date	$\begin{array}{c} 2-& 2-44\\ 2-18-44\\ 2-21-44\end{array}$	2-26-44	3- 1-44	3-11-44 3-21-44 3-23-44	4-3-44	4-22-44	4-29-44 5-17-44	5-19-44	0- 2-44 6-10-44 6-26-44		7-11-44	7-27-44		8-2/-44 9- 7-44	10 7 44	10-13-44 10-25-44	10-26-44
	Cycle	10		11		12			0 51 51	14		15		16	11		18	

TREATMENT SCHEDULE -- Continued

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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.



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 public 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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