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Cyproterone acetate in treatment of precocious puberty

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Kauli, R., Pertzelan, A., Prager-Lewin, R., Grünebaum, M., and Laron, Z. (1976). *Archives of Disease in Childhood*, **51**, 202. **Cyproterone acetate in treatment of precocious puberty.** Twenty-nine children (23 girls, 6 boys) with precocious puberty were treated with cyproterone acetate for various periods of time ranging from 6 months to 3 years 4 months. They received an oral dose ranging from 70–150 mg/m^2 per day, or an intramuscular depot injection once a fortnight or once a month at a dose ranging from 107–230 mg/m^2. Both forms of therapy were found to suppress the signs of sexual maturation, but the oral form proved to be superior. Only the younger patients with a bone age under 11 years showed a beneficial effect upon linear growth and bone maturation. No side effects were noted, but additional advantageous effects upon behaviour and sociability were.

It is concluded that at present cyproterone acetate by mouth is the drug of choice in the treatment of precocious puberty. The treatment should be initiated as early as possible to attain maximum benefit.

The treatment of precocious puberty constitutes a difficult therapeutic challenge. A number of drugs, mainly progestational agents, have been tried in an attempt to find an agent which will stop the progression of sexual maturation and prevent the premature closing of the bony epiphyses by inhibiting the gonadotrophin secretion (Richie and Crawford, 1958; Greenblat *et al.*, 1958). Medroxyprogesterone acetate has been widely used since 1962 (Kupperman and Epstein, 1962; Hahn, Hayles, and Albert, 1964; Laron and Rumney, 1965; Kaplan, Ling, and Irani, 1968; Cloutier and Hayles, 1970; David, Bovier-Lapierre, and Sempé, 1972). Other compounds used include chlormadinone acetate (Menking *et al.*, 1971) and danazol (Greenblatt *et al.*, 1971), but none of these has given completely satisfactory results.

In 1964, Neumann and Hamada introduced a new drug, cyproterone acetate (1, 2 alpha methylene-6chloro-4, 6, pregnadiene-17-alpha-ol-3, 20-dione-17-alpha acetate; Androcur or SH-714, Schering Co., Berlin), which had been shown to possess antiandrogenic and antigonadotrophic properties in experimental animals (Neumann and Hamada 1964; Johnson and Naqvi, 1969). Reports of clinical trials with cyproterone acetate in the treatment of precocious puberty in a total of 38 children have been published recently (Helge *et al.*, 1969; Ludeseher, Rameis, and Gleispach, 1969; Bossi, Zurbrugg, and Joss, 1973; Rager *et al.*, 1973; Werder *et al.*, 1974).

The present report summarizes our experience with cyproterone acetate in 29 children with precocious puberty treated since 1967.

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Material and methods

Twenty-nine children (23 girls, 6 boys) with true central precocious puberty were studied. (Clinical data are presented in Table I.) All were treated with cyproterone acetate for various periods from January 1967 to May 1974. Only those patients who had been treated for at least 6 months and who have been under continuous follow-up were included.

A diagnosis of precocious puberty was made when signs of sexual maturation had appeared before the age of 8 years in girls and before the age of 9½ years in boys, or when signs of puberty had appeared close to the normal limits for age but had progressed at a very fast rate resulting in a pubertal stage far advanced beyond the chronological age of the child.

When considering possible therapy with cyproterone acetate, we took into account the age of the patient, the degree of bone age advancement and of pubertal signs, and the psychological implications resulting from the sexual precocity. Before starting therapy, and at regular

TABLE I

Linear growth and bone maturation in patients with precocious puberty before and during therapy with cyproterone acetate

Case no.	Sex	First pubertal signs	Duration therapy (oral & IM)	Before initiation of therapy					At last examination on therapy				
				CA	BA	Height	HA	Subscapular skinfold thickness	CA	BA	Height	HA	Subscapular skinfold thickness
		(yr) (m)	(yr) (m)	(yr) (m)	(yr) (m)	(cm)	(yr) (m)	(mm)	(yr) (m)	(yr) (m)	(cm)	(yr) (m)	(mm)
1	F	2 6	2	3 2	3 9	101	4 1*	6	5 3	6 6	119·5	6 10*	5
2	F	3	3 3	3 11	11	111·5	5 7*	9	8 2	14	130	8 10*	13
3	F	2 6	3 4	4 1	11	128	8 9	20	8 3	13 6	147·3	11 7	14
4	F	2 3	10	7 2	13 3	144·2	11 3	17	8	13 6	148	11 7	17
5	F	6 6	1 9	7 6	11 2	135·5	9 8	20	9 6	13	146·4	11 6	15
6	F	7 6	1 2	7 11	10 2	143	11	19	9 1	11	151	12 3	8
7	F	5	1 7	8 5	10	138·4	10 3	9	10 1	12	152·3	12 3	15
8	F	7 6	1	8 7	11 3	144	11*	13	9 6	13	148	11 10	19
9	F	8 3	6	8 10	11 6	153·2	12 3	15	9 4	13	155·8	13	22
10	F	4 5	1 4	9 1	12 3	153	12 6	17	10 5	13	160·2	14 2	20
11	F	8	9	9 1	12	150	12	23	9 11	13	153	12 6	24
12	F	9 6	6	9 6	13 6	141	10 9*	22	10	14	143	11*	22
13	F	7	1 6	9 6	11	143·8	11*	4	11 1	13	153·6	12 6*	5
14	F	7	3 4	9 8	13	141	10 9	26	13	14 6	147	11 5	28
15	F	8 6	2 1	9 10	13 3	145·2	11 3*	12	12	14 6	148	12*	9
16	F	8 6	1 3	9 10	11	143·3	11	17	11 1	13	150·4	12 1	6
17	F	7 6	1 2	10 4	12	137·4	19 1*	9	11 6	12 6	143	11*	9
18	F	7	1 6	11	13	143·2	11*	12	12 6	14	146·3	11 7*	18
19	F	7 6	2 7	11 4	13 6	141·1	10 9*	16	14 3	16	144·8	11 3*	13
20	F	9 6	6	11 6	12	140·4	10 9*	8	12	13 6	141·7	11*	8
21	F	8	1 7	11 10	14 3	142·6	11	16	13 5	15	145·1	11 4	16
22	F	10	10	12	14 6	147·3	11 9	8	12 10	15 6	148·7	11 11	16
23	F	10	3	12 4	13	131·2	9 1*	17	15 2	15 6	136·1	9 9*	24
24	M	9	1	8 3	12 6	132·1	9	3	9 4	13 6	138·8	10 4	12
25	M	9	1 6	10 2	15	148·5	12 2	16	11 9	16 6	150·3	12 7	26
26	M	9	6	11 5	13 6	139·8	10 7	9	11 10	13 6	146·7	11 10	8
27	M	10	1 10	11 6	16	164·4	14 6*	20	13 3	17	168	15*	28
28	M	7 6	1 2	12 4	15 6	152·2	12 10*	8	13 6	17 6	153·8	13*	10
29	M	10	10	12 8	16	142·6	11 2	11	13 10	17	143·7	11 3*	15

*Familial short stature. CA, chronological age; BA, bone age; HA, height age; IM, intramuscular.

intervals during cyproterone acetate therapy, the patients were given a complete clinical examination, with complete blood count, urine analysis, and chemical analysis of the blood, including urea, electrolytes, and liver functions tests; skull *x*-rays, EEG, neurological and ophthalmological examinations. Urinary 17-ketosteroids, 17-hydroxysteroids, pregnanetriol, oestrogens, and gonadotrophins were determined. In a number of patients plasma luteinizing (LH) and follicle stimulating hormones before and during LH-RH stimulation were also determined. These results are reported elsewhere (Kauli *et al.*, 1975).

Pubertal signs were rated according to a scoring system developed in our institute (Laron and Dickerman, 1976). Testicular volume was measured using the Prader orchidometer (Prader, 1966; Zilka and Laron, 1969). Bone age was estimated according to the *Atlas* of Greulich and Pyle (1955). Urinary gonadotrophins were measured by bioassay using a modification of Albert's method (Albert, 1955) until 1971, and by radioimmunoassay thereafter. Plasma LH was measured according to Midgley (1966).

Initially cyproterone acetate was available only in tablet form. The oral dose ranged from 70–150 mg/m^2 per day in two to three divided doses. In 1971 the drug became available in a form suitable for injection, which was given a trial in 11 girls and 2 boys; intramuscular depot injections were given once every 2–4 weeks, at a dose ranging from 107–230 mg/m^2 per injection. Because of the largely unsatisfactory response (see Results), all of these patients were changed to oral treatment, with the exception of Case 20, who proved uncooperative and in whom treatment was stopped after 6 months.

Results

The overall results of the treatment with cyproterone acetate are presented in Tables I and II.

Clinical signs. Both forms of cyproterone acetate proved to be effective in slowing the progression of the clinical signs of puberty, but results of the oral therapy were so clearly superior to those of the depot injections that the injections were discontinued.

Breast size was arrested in 17 of the 22 girls on oral therapy and decreased in the other 5, while of

TABLE II

Effect of treatment with cyproterone acetate orally or intramuscularly (IM) on signs of sexual maturation in patients with precocious puberty

	Disappeared		Decreased		Advance arrested		Further advance	
	Oral	IM	Oral	IM	Oral	IM	Oral	IM
Girls								
Breast size			5		17	5		6
Vulval redness and discharge	10		12	1		9		1
Menses*	17	3				5		1 (menarche)
Axillary hair	2		6		11	9		
Pubic hair	1		3		18	11		
Acne	3		13			5		1
Behavioural disorders	2		3					
Total no. treated	22	11	22	11	22	11	22	11
Boys								
Testicular volume			3		3	2		
Penis enlargement					4		2	2
Ejaculation	4							2
Axillary hair					6	2		
Pubic hair			1		5	2		
Acne			4		1	1		
Behavioural disorders			3	1				
Total no. treated	6	2	6	2	6	2	6	2

*Menstruation was present in only 17 girls.

the 11 on depot injections only 5 showed an arrest and the other 6 showed further increase in size. Testicular volume decreased in 3 of the 6 boys on oral therapy and was arrested in the other 3. 2 boys on depot injections showed an arrest of volume. Vulval redness and discharge decreased in all of the 22 girls on oral therapy and later disappeared completely in 10. In 9 girls on depot injections who were examined no change was evident. In one the redness and discharge decreased, and in one it further increased.

Menstruation ceased completely in the 17 menstruating girls on oral therapy, but repression was largely unsatisfactory in the 8 menstruating girls receiving depot injections, even when the dose was increased to 160 mg/m^2. Case 13 menstruated for the first time while receiving injections. Penile growth was arrested in 4 of the 6 boys on oral therapy; it was unchanged in the other 2, but they were not taking medication regularly. There was no arrest of penile growth in the 2 boys on depot injections. The ejaculations present in 4 of the boys on oral therapy were suppressed, while in the 2 on depot injections they continued, and increased.

Both axillary and pubic hair growth remained unchanged in the children given depot injections. On oral therapy it decreased in a number of patients, and there was a complete disappearance of axillary hair in 2 girls and of pubic hair in one. Acne either decreased or disappeared in almost all of the patients on oral therapy, while in most of the patients on depot injections it remained unchanged.

Behaviour and emotional status. In 8 cases (5 girls, 3 boys) the parents reported that the children had become calmer and more sociable. An improvement in school achievement was reported in 2 children. Masturbation ceased in Case 25, who had previously exhibited an uncontrollable urge.

Laboratory data. There was evidence of decreased gonadotrophin secretion in most of these patients. The urinary excretion of gonadotrophins was suppressed and became undetectable in most patients. The basal plasma LH level was similar before and during therapy, but the peak responses of plasma LH on LH-RH stimulation were lower during therapy in most of the patients tested. Inhibited gonadotrophin secretion was more pronounced in those on oral therapy (Kauli *et al.*, 1975).

Vaginal smears were examined in only 5 of the girls before therapy was started and in 7 during therapy, the rest being unwilling to undergo this examination. There was a marked reduction in the number of cornified cells during the administration of cyproterone acetate, more so with the oral therapy than with the depot injections.

Linear growth and bone maturation (Table I). The effect of cyproterone acetate on these parameters could be evaluated only in 21 patients who were treated for at least one year. 13 of these patients received depot injections for periods ranging from 6 months to one year, but all (with the exception of Case 20, as noted previously) subsequently received the oral form of the drug for at least 6 months.

The height, height age, bone age, mean SD from the 50th centile height for age, and the bone age/chronological age ratio was calculated at the initiation of therapy and compared with those found during the last examination performed under therapy with cyproterone acetate. It was evident that the effect of therapy on growth depended on the age, the degree of bone maturation, and the stage of puberty at which therapy was started. Cyproterone acetate was more effective in decreasing the rate of bone maturation when therapy was started before a bone age of 11 years. This had a beneficial effect also on the linear growth. Here again it seemed that oral therapy was more effective than therapy with the depot preparation. The slowing of bone maturation induced by cyproterone acetate therapy in several individual cases is shown in Figs. 1 and 2. The actual linear growth for 2 of the youngest patients is shown in Fig. 3. It can be seen that the linear growth in both patients proceeds along the same centile and that the advancement of bone age is slowing down. For purposes of comparison, Fig. 4 presents the linear growth and the reflected bone age of 2 older patients who started therapy when their bone age was more advanced. In spite of the slowing effect on bone age advancement, growth velocity slowed down until an arrest of growth took place.

Body weight and skinfold thickness. With the exception of 3 patients who had shown a tendency towards obesity even before therapy was started, there was no excessive weight gain under therapy with cyproterone acetate and the linear weight curve continued along the same centile. There was no significant change in skinfold thickness (Table I).

Side effects. There were no complaints of side effects and no pathological findings in any of the routine blood and urine tests performed during therapy. An oral glucose tolerance test was performed in 18 patients, in 7 of them both on and off therapy. No glucose intolerance was found, but in some patients there was an increased output of insulin (these data will be published separately).

Discussion

The beneficial effect of cyproterone acetate therapy in precocious puberty previously reported

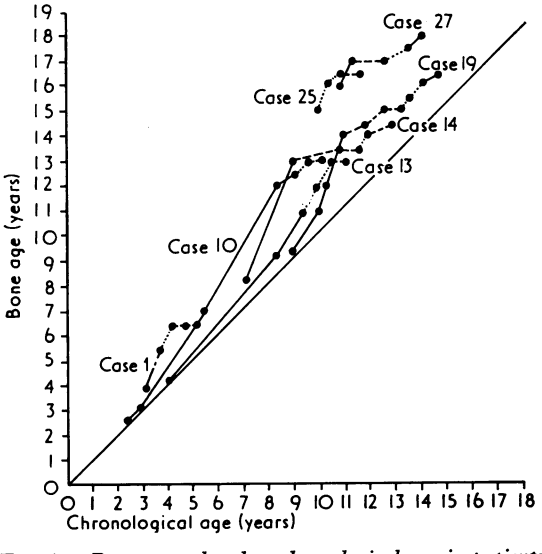

FIG. 1.—*Bone age related to chronological age in patients with precocious puberty treated with cyproterone acetate orally* (- - -) *and by depot intramuscularly* (. . .) *or untreated* (——).

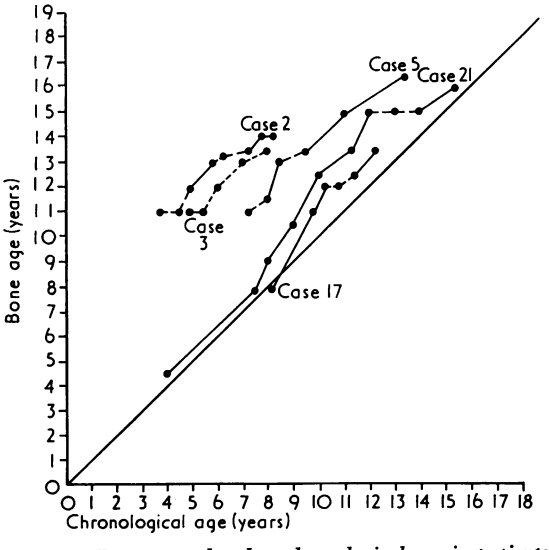

FIG. 2.—*Bone age related to chronological age in patients with precocious puberty treated with cyproterone acetate orally* (- - -) *or untreated* (——).

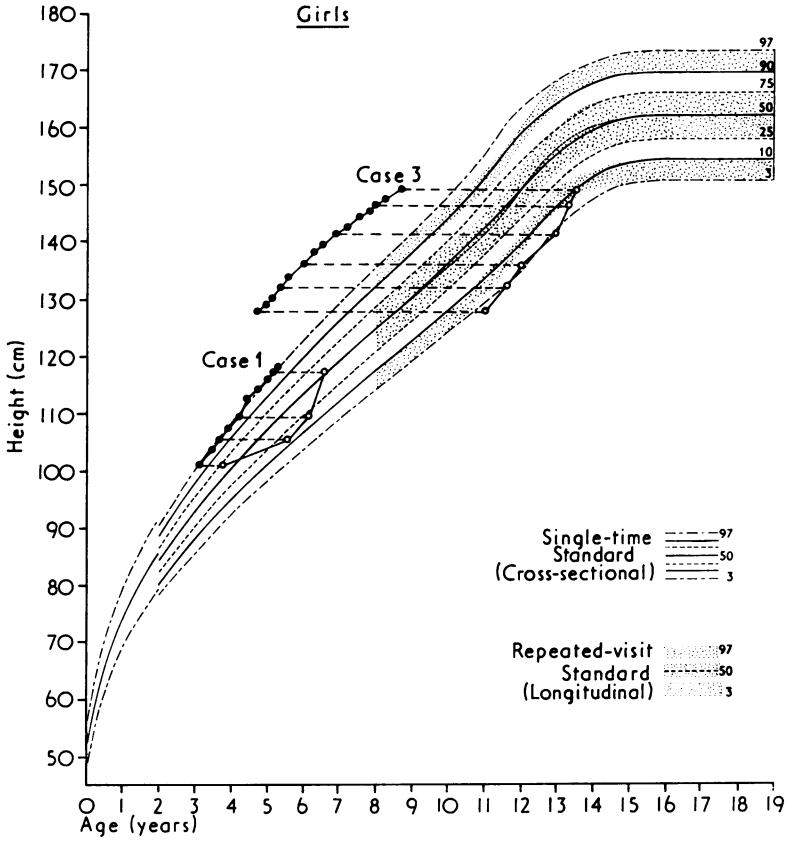

FIG. 3.—*Linear growth (●) of two girls with precocious puberty treated with cyproterone acetate. Although advanced bone age (○) is reflected on the growth chart, note that in these girls treatment was started while bone age was not too advanced (compare Fig. 4).*

by other workers in smaller series of patients has been confirmed in this study. We also found that the efficacy of the drug in slowing the advancement of puberty is much greater when it is given by mouth than by depot injections. The oral administration of a dose of 70–150 mg/m^2 clearly stopped the progression of the clinical signs of puberty. Measurements of the urinary gonadotrophins and plasma LH during LH-RH stimulation before and during therapy, showed that the drug suppressed pituitary gonadotrophin release. That fact partially explains the clinical effects on the signs of sexual development, though part is probably due to the peripheral antiandrogen effect.

These data also show a beneficial effect of the drug on linear growth and bone maturation in a considerable number of children. Like Bossi *et al.* (1973), we found a positive response only in younger patients with a bone age of less than 11 years. In these children growth continued on a parallel line with the normal centile and the bone age advancement was slowed, a finding not present in the children in whom bone age was already advanced beyond the age of 12 years when therapy was started. While it is difficult to calculate the total gain in linear growth, any gain achieved in these children, who would otherwise be stunted, can be considered beneficial.

Other advantages of cyproterone acetate treatment include a lessening of signs of aggression, restlessness, and masturbation in a number of patients who presented behaviour problems. Sociability and in some cases scholastic achievement improved notably. Its effect upon the intellect are the subject of a separate study (Galatzer *et al.*, 1976). In all cases there was a secondary

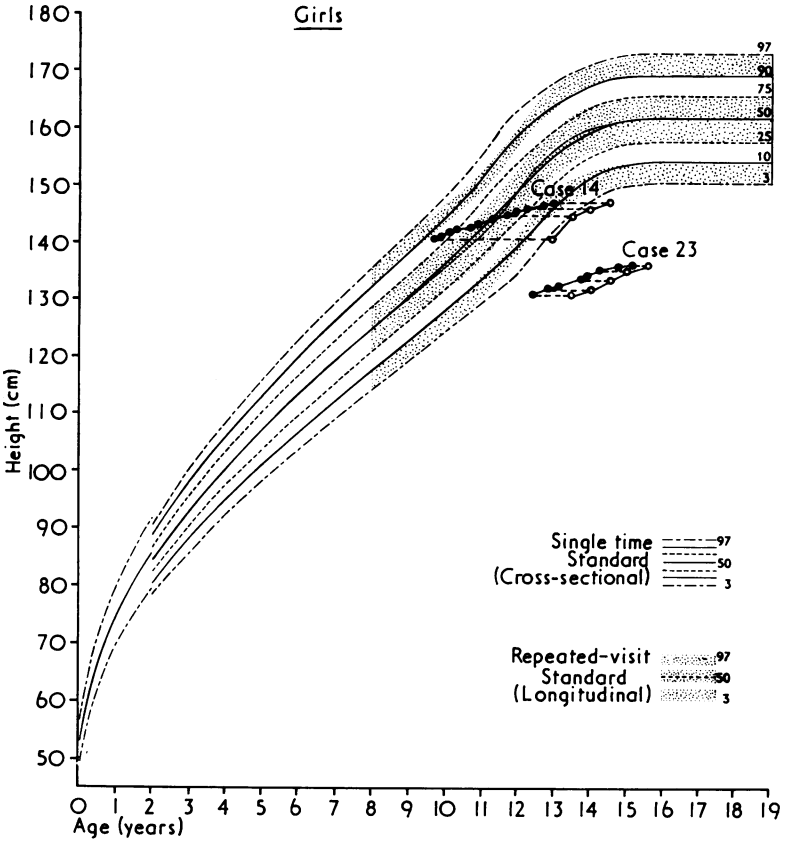

FIG. 4.—*Linear growth (●) of two girls with precocious puberty treated with cyproterone acetate. Treatment was started while the bone age (○) was over 13 years, and the results were less satisfactory than in the cases shown in Fig. 3.*

effect of a relaxation of anxiety and tension in the family environment. No side effects whatsoever were noted.

In conclusion, it seems that at present cyproterone acetate given orally is the drug of choice in the treatment of precocious puberty, but that to gain maximum benefit treatment must be started at an early stage of the disorder.

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