These patients may not have shown excessive growth during early childhood as observed by Aceto et al. (1966). After therapy was stopped, 2 cases showed the expected adrenal overactivity (high urinary 17KS). Treatment must, therefore, be continued.

The present management for all types of congenital adrenal hyperplasia was recently reviewed (Raiti and Newns, 1970). The criteria for diagnosis have not altered (Raiti and Newns, 1964).

Summary

Twenty-seven of 35 cases with the salt-losing type and all 10 with the simple virilizing type grew within the 3rd-97th centile for height. 8 of the salt-losers grew below the 3rd centile; all had received excessive cortisone, and all had delayed bone ages.

The total daily cortisone replacement dose should be based on the expected cortisol production rate for body size, and should not exceed twice this rate, which is 12 mg/m² per 24 hr. No difference in growth pattern was found when cortisone was given either in 2 or 3 equally divided doses. During the first two years of life, a minimum cortisone dose of 15 mg/day is recommended (in divided doses), even though this exceeds the calculated requirement.

Effect of Gonadotrophin Therapy on Testicular Volume and Sexual Development in Adolescent Boys with Hypogonadotropic Hypogonadism

Most of the recent reports on gonadotrophin therapy of eunuchoidism deal with its effect on adult hypogonadotropic males, with particular emphasis on the restoration of spermatogenesis. Studies of the adolescent age group, including serial measurements of testicular volume, are few (Johnsen, 1966; Lytton and Kase, 1966; Crooke, Davies, and Morris, 1968). This report was designed to evaluate the effect of human chorionic gonadotrophin (HCG), singly and in combination with human menopausal gonadotrophin (HMG), on testicular volume and on secondary sexual characteristics in a group of adolescent hypogonadotropic boys.

Patients and Methods

Six adolescent patients with hypogonadotropic hypogonadism were treated with HCG and HMG for periods ranging from 3 to 25 months. Endocrine evaluation revealed isolated gonadotrophin deficiency in 5 and associated insufficiency of ACTH, TSH, and GH in one patient (Case 6). All periodically underwent a complete physical examination which included body measurements and evaluation of sexual development. Testicular volume was estimated by means of an "orchiometer", i.e. a series of ellipsoids of known volume (Prader, 1966; Zilka and Laron, 1969). The diameter of the penis and its extended length were measured in millimetres with a slide caliper. Sexual hair was scored by arbitrary signs, and 6 stages were graded from — to ++. Skeletal age was estimated according to the Atlas of Greulich and Pyle (1960). Urinary 17-ketosteroids were assayed by the method of Peterson and Pierce (1960). Determination of urinary gonadotrophins in terms of mouse uterine units was performed by a modification of the method described by Albert (1955).

Treatment. HCG, given as a source of ICSH activity, was administered intramuscularly twice weekly. Case 1: 2000 IU/wk for 6½ mth; Case 2: 2000 IU/wk for 3 mth and 3000 IU/wk for 16 mth; Case 3: 1000-5000 IU/wk for 30 mth and 10,000 IU/wk for 7 mth; Case 4: 3000 IU/wk for 3 mth and 5000 IU/wk for 16 mth; Case 5: 5000 IU/wk for 15 mth; Case 6: 3000 IU/wk for 8 mth. HMG (Pergonal—500*), given as a source of FSH activity, will be referred to in terms of

*Pergonal-500: lyophilized HMG from human menopausal urine prepared by Instituto Farmacologico Serono, Rome, Italy, marketed in Israel by Ikapharm. One ampoule contains 75 IU FSH and 75 IU ICSH.
IU of FSH included in the preparation. It was administered intramuscularly 2 to 3 times a wk. Case 1: 150 IU/wk for 6½ mth; Case 2: 225 IU/wk for 3 mth; Case 3: 150 IU/wk for 7 mth; Case 4: 225 IU/wk for 8 mth; Case 5: 225 IU/wk for 7 mth; Case 6: 300 IU/wk for 4 mth. Timing and combination of HCG and HMG therapy can be seen in the Fig. Cases 1 to 5 received ultimately replacement therapy with Durasterone (R)-Teva (D)*. 250 mg intramuscularly every 2 to 4 weeks, or methyltestosterone (MT) orally 15 mg/day (Case 2). Case 6 received thyroxine replacement therapy at the time of the study.

* A long-acting testosterone preparation containing 20 mg testosterone propionate, 80 mg testosterone heptanoate, and 150 mg testosterone undecylate per ampoule.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>1 B.R.</th>
<th>2 A.I.</th>
<th>3 M.B.</th>
<th>4 H.M.</th>
<th>5 M.S.</th>
<th>6 E.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>158-4</td>
<td>161-5</td>
<td>151-9</td>
<td>158-8</td>
<td>178-5</td>
<td>166-5</td>
</tr>
<tr>
<td>HCG (IU/W)</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
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<td>300</td>
</tr>
<tr>
<td>Urine FSH (IU/24hr)</td>
<td>&lt;3</td>
<td>&lt;15</td>
<td>&lt;15</td>
<td>&lt;15</td>
<td>&lt;3</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Urine 17KS (mg/24hr)</td>
<td>73-81</td>
<td>26-31</td>
<td>3-8</td>
<td>70-91</td>
<td>87-29</td>
<td>6-32</td>
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<tr>
<td>Pubic hair</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Axillary hair</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Facial hair</td>
<td>F</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>F</td>
<td>+</td>
</tr>
<tr>
<td>Penis length (mm)</td>
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<td>57</td>
<td>68</td>
<td>50</td>
<td>74</td>
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<td>14</td>
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<td>19</td>
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<tr>
<td>Ejaculation</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Plasma FSH (ng/ml)</td>
<td>4-7</td>
<td>47</td>
<td>47</td>
<td>1-9</td>
<td>0-7</td>
<td>14</td>
</tr>
<tr>
<td>Plasma LH (ng/ml)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Testicular volume (ml)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Bone age</td>
<td>10-11</td>
<td>11-12</td>
<td>11-12</td>
<td>10-11</td>
<td>10-11</td>
<td>10-11</td>
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<tr>
<td>CA</td>
<td>6-7</td>
<td>7-8</td>
<td>7-8</td>
<td>7-8</td>
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<td>7-8</td>
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<tr>
<td>Chronological age</td>
<td>10-11</td>
<td>11-12</td>
<td>11-12</td>
<td>10-11</td>
<td>10-11</td>
<td>10-11</td>
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</tbody>
</table>

**Results and Comments**

Pertinent clinical and laboratory data, related to dosage of drugs and duration of treatment, are illustrated in the Fig.

Cases 2 to 6 received HCG alone over a period averaging 16.4 months (range 8–30 months). During this period the mean increase in testicular volume was 1.78 ml ($P = <0.05$).

During combined therapy of HCG and HMG received by all patients over periods ranging from 3 to 8 months (mean 5.9 month), the mean testicular volume increased by a further 1.1 ml ($P = <0.05$).

Comparison of the testicular volumes of Cases 1 to 6 before and at the end of the whole trial, i.e.

**Fig.**—Pertinent clinical and laboratory data* and treatment schedule in 6 patients with hypogonadal hypogonadism (Ht, height; BA, bone age; CA, chronological age; F, fuzz).

* Plasma FSH and LH values appearing in this figure are the subject of another study (Laron et al.—in preparation).
of spermatogenesis. Due and noted that of size (1966) dotrophin administration. An observed tendency in the post-treatment period. In all instances they remained below 1.5-3 mouse units/24 hr. The single value of 200 mouse units/24 hr detected during the combined trial in Case 4 was most probably due to urinary excretion of recently administered HMG (Morell, Crooke, and Butt, 1968), as his assay became negative after stopping treatment.

An obvious increase in sexual hair and penial size was noted under HCG and combined trial in all subjects. True increase in breast tissue was observed in Cases 1 and 5. Long-acting testosterone (Durasterone®) injections induced further progress in secondary sexual characteristics.

Ejaculations were reported by Cases 1, 3, and 4 while under gonadotrophin treatment and by Cases 2, 5, and 6 while receiving Durasterone® injections. Seminal fluid was available for examination in only one patient (Case 3) 14 months after cessation of HCG-HMG therapy; it revealed aspermia.

Bone age retardation in the pretreatment period averaged 4 years in 5 patients (Cases 1 to 5) and 1½ years in one patient (Case 6) who was on thyroxine replacement therapy. Progress in skeletal maturation was noted on subsequent examination but bone age/chronological age discrepancy remained essentially unchanged in the treatment period. This was also reported by Johnsen (1966).

The observed tendency towards increased 17-ketosteroid secretion under HCG and combined therapy is in keeping with previous reports (Crooke et al., 1968; Johnsen, 1966).

Testicular biopsy of Case 5 performed before the start of gonadotrophin therapy confirmed the diagnosis of hypogonadotropic hypogonadism. Biopsies of Cases 1, 3, 4, and 6 performed after 10 to 30 months of gonadotrophin treatment showed that, in spite of the increase in testicular size and secondary sexual signs, testicular histology remained in the prepubertal stage. Other investigators have observed an increase in testicular size upon gonadotrophin administration. Thus, Lytton and Kase (1966) investigated a eunuchoid adolescent with panhypopituitarism due to craniopharyngioma, and noted that HCG induced an increase in the size of the gonads and accelerated the early stages of spermatogenesis. A further increase in testicular size and maturation was achieved by the subsequent addition of HMG. Johnsen (1966) treated two hypogonadotrophic males aged 16 years 7 months and 22 years respectively with HCG and HMG, singly and in combination. HCG caused a noticeable increase in the testicular volume of one patient and some increase in the other. HMG alone had no effect on testicular size. The best results were achieved with combined therapy.

Similar results were reported by Crooke et al. (1968) who treated 6 eunuchoidal men with HCG and human pituitary FSH. Some of them showed an increase in testicular volume under HCG or FSH alone, but the most striking changes in testicular size, morphology, and function were obtained with combined therapy. These patients, however, comprised a heterogeneous group when compared with ours.

Due to the slow induction of secondary sexual characteristics by the gonadotrophins as shown by this investigation, and those of other authors, as well as the cost and inconvenience of the repeated injections, it seems to us that at present the treatment of choice of gonadotrophin insufficiency during puberty is the use of long-acting testosterone preparations.

Summary

The effect of treatment with human gonadotrophins was evaluated in 6 hypogonadotropic adolescent boys. Treatment was started at 15 to 19 years 10 months of age for periods ranging from 3 to 25 months. The dosage ranged from 1000 to 10,000 IU/week for HCG and from 150 to 300 IU/week for HMG. An increase in testicular volume during the course of HCG alone and especially during combined HCG-HMG therapy was registered. There was also an effect on the secondary sexual characteristics but little influence on bone maturation.

In view of the slow induction of secondary sexual characteristics and the cost and inconvenience of this treatment schedule, it seems inadvisable to use this therapeutic approach routinely.

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REFERENCES


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Late Infantile Metachromatic Leucodystrophy

Effect of Low Vitamin A Diet

Late infantile metachromatic leucodystrophy (MLD) is a genetically determined, generalized, sulphatide lipidosis, in which lipid metachromatic substances accumulate in the nervous system and other organs, due to a deficiency of the lysosomal enzyme, arylsulphatase A (Austin et al., 1964; Mehl and Jatzkewitz, 1965).

The disease is characterized by a slowly progressive course which has been divided into four stages according to the degree of motor handicap (Hagberg, 1963). The first symptoms and signs generally appear between 1 and 2 years in a previously normal child, and consist of hypotonia, unsteady gait, and valgus deformity of feet. The child gradually loses the ability to walk, sit, or crawl, and develops spasticity, with diminished or absent tendon reflexes, and may in addition show ataxia and tremor (stages I and II). Mental regression, hypertonic spasms, violent root pains, and total aphasia follow (stage III), and the child eventually dies between 3 and 6 years in a state of decerebrate rigidity, with cortical blindness and deafness (stage IV).

Attempts to alter the course of this disease by various therapeutic means have so far not met with any success. Because vitamin A is necessary for one of the metabolic steps in the synthesis of sulphatide (Sundaresan, 1966), Melchior and Clausen (1968) tried a vitamin A deficient diet in the treatment of a child with advanced MLD, but did not obtain any clinical improvement. We report a further case of MLD in which we tried a vitamin A deficient diet, with some apparent success.

Case Report

A girl presented at the age of 2½ years with delay in walking.

She was born normally at 37 weeks’ gestation weighing 2920 g. The neonatal period was normal. In the first year she reached her developmental milestones quite normally—she sat unsupported at 6 to 7 months and pulled herself to a standing position at 9 to 10 months—but did not achieve the ability to walk independently, and at the age of 2 years 3 months, she could just take two to three steps unsupported. Her intellectual development seemed quite normal. She could talk well, making sentences of 4 to 5 words.

On examination at that stage, the only abnormal findings were slight hypotonia, especially in relation to the knee joint which would go into recurvatum when weight was taken on them; absent knee and ankle jerks; and a convergent concomitant squint. The fundi were normal. Her intelligence was difficult to assess because of poor co-operation. Delayed motor development with possible laxity of ligaments around the knee joints was diagnosed and she was given a course of physiotherapy.

Three months later there was no obvious change but she was reluctant to walk unless supported. The hypotonia was more pronounced. The knee jerks were still absent. Ankle jerks and the plantar response were equivocal. She was irritable and readily distressed when examined.

Four months later she was described by her parents as being ‘ever so nervous’, trembling all the time, would not sit or stand, was uncooperative, and ‘not bothering to do anything’. The parents attributed to the arrival of the new sib. On examination, she was unable to maintain a sitting or standing position without support. It was noted that intermittently her right knee would hyperextend and the whole leg would go stiff. Because of definite weakness in her limbs at that stage, it was decided to do a muscle biopsy to exclude an underlying neuromuscular disorder.

On routine histological stain the quadriceps muscles showed no striking abnormality. There was an obvious variation in fibre size, falling into two populations, one about 30 μ in diameter and the other about 60 μ. However, on histochemical stains it was apparent that there was selective atrophy of type 1 fibres, and a denervation process was suspected. Motor nerve conduction velocity was then done and was very slow, confirming the presence of a peripheral neuropathy.

When assessed again six months later, there was an obvious deterioration in her condition. She was completely unresponsive and would not speak any words. She had difficulty in swallowing food and tended to choke. She was constantly grinding her
Effect of gonadotrophin therapy on testicular volume and sexual development in adolescent boys with hypogonadotrophic hypogonadism.

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