infection. Since Case 18 failed to respond adequately to either arginine alone or arginine with oestrogen priming, an insulin response test was performed, and she also failed to respond to this.

Discussion

The majority of subjects with chromosomal anomalies also have a disorder of growth. Tall stature in males with multiple X chromosome disorders, and short stature in subjects with the XO syndrome or autosomal aneuploidies are characteristic. No adequate explanation for these disorders of growth in subjects with chromosomal anomalies has been advanced. Plasma growth hormone has not been studied in these subjects except in a few patients with the XO and XXY syndromes (Frasier, 1967; Hillman and Colle, 1969; Lundberg and Wahlström, 1970) in whom the PGH responses were not different from those in normal control subjects.

In the present study all subjects with anomalies of the sex chromosomes had positive PGH responses (Table). It is of interest that among this group the 2 subjects who required more than one test for demonstration of a positive PGH response also had marked growth retardation (more than 2 SD below the mean).

Among the subjects with autosomal aneuploidy, 3 failed to respond adequately to the initial arginine stimulation test. Two of these (Cases 16 and 24) did exhibit adequate PGH responses when the test was repeated with oestrogen priming. In one case (Case 18), a 16·6-year-old female who had a height age of 3·4 years and mosaicism for a cell line with possible trisomy D, none of the 3 stimulation tests (arginine, arginine with oestrogen priming, insulin) resulted in an adequate response of 5 ng/ml above baseline. These results suggest an anomaly of growth hormone production in this patient which probably contributed to her dwarfism.

The average height of adult patients with Down's syndrome is approximately 151 cm for males and 141 cm for females (Penrose and Smith, 1966), both values being 3 SD below the mean height for normal subjects. The mean height of 50 adult male subjects with X chromosome anomalies (Klinefelter's syndrome) reported by Hambert (1966) was 180·3 cm ± 6·8 cm, which is nearly 1 SD above the mean height for normal adult males. Since the groups of subjects with Klinefelter's and Down's syndromes in our study had normal PGH responses, the characteristic short stature in subjects with Down's syndrome and the tall stature in males with multiple X chromosome anomalies are probably not related to anomalies of growth hormone production.

Summary

Twenty-six subjects with chromosomal anomalies were studied for responsiveness of plasma growth hormone levels to one or more stimuli (arginine, oestrogen priming followed by arginine, and insulin-induced hypoglycaemia). 4 of these subjects required more than one test to demonstrate a positive growth hormone response, and one subject failed to respond to any of 3 tests. It is concluded that the production of growth hormone in these patients is usually normal.

References


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Folic Acid Replacement in Folate-deficient Children on Anticonvulsants

Reynolds (1967) found that folic acid reversed the retarding effect of anticonvulsants in 22 out of 26 folate-deficient adult patients, and Neubauer (1970) noted a similar improvement in 28 out of 50 children. Reynolds (1967) also reported an in-
increase in fit frequency. Neither study was controlled. Because the increased energy, drive, and 'speed of cerebration' described by these authors would benefit children's education, we undertook a control trial of folic acid versus placebo in folate-deficient children attending a convulsion clinic. Simple reaction time and the numbers of hours slept were chosen as the objective measurements most likely to reflect the changes in behaviour noted by Reynolds and Neubauer. Fit frequency was also recorded.

**Patients and Methods**

We first measured the levels of serum folate (Ball and Giles, 1964), Hb concentration, and mean corpuscular volume in 39 children (25 boys and 14 girls) who had been taking anti-convulsant drugs for over 3 months. We compared their levels with those in 25 children (15 boys and 10 girls) of similar age who were not taking anti-convulsants; they were either outpatients or they had been admitted to hospital very recently.

Of the anti-convulsant group, 25 children had serum folate levels below 5 ng/ml. With their parents' permission, 19 of these entered a trial comparing an 8-week period of treatment with oral folic acid, 5 mg daily, with a similar period on placebo. The children were used as their own controls and the placebo was given first. The simple reaction time of those children able to cooperate with the test was estimated on 3 occasions during each treatment. They pressed a button in response to a light signal; we varied the period between signals by hand in a sequence derived from a table of random numbers and the reaction time was measured and displayed electronically. The parents kept records of the days on which fits occurred and the number of hours slept. Haematological data obtained while on placebo were compared with those in the second and eighth week on folic acid.

**Results**

The children taking anti-convulsant treatment had significantly lower serum folate levels than the children of the same age not taking these drugs (Table), but there was no significant difference in the Hb or mean corpuscular volume (P > 0.1).

**TABLE**

*Comparison of Serum Folate Levels in Children with and without Anti-Convulsant Treatment*

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Cases</th>
<th>Serum Folate &lt; median*</th>
<th>Serum Folate &gt; median*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsant</td>
<td>25</td>
<td>7</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td>No anticonvulsant</td>
<td>7</td>
<td>14</td>
<td>18</td>
<td>25</td>
</tr>
</tbody>
</table>

P = 0.01 (Fisher-Yates 2 × 2 contingency tables).

*Median serum folate level (all children) = 5 ng/ml.

Some children were included in the controlled trial whose serum folate levels were within the normal adult range for this laboratory (3–10 ng/ml) but the red cell folate levels (Dacie and Lewis, 1968) confirm that they were folate-deficient (Fig.1). There was a marked rise in serum and red cell folate levels within 9 days of taking folic acid (Fig.2). Though there was a significant rise in Hb concentration (P < 0.03), no variation was found in mean corpuscular volume, serum iron, or serum vitamin B12 (Matthews, 1962).

![Fig.—Red cell folate levels during placebo and folic acid administration: shaded area indicates the normal adult range for this laboratory.](http://adc.bmj.com/)

Up to 8 weeks after the introduction of folic acid there was no significant change in the reaction time of the 16 children able to cooperate with the test. Similarly there was no significant difference in the number of hours slept by the 16 children with completed records. Of the 18 children with completed records of days on which fits occurred, 9 were free of fits during the trial, and the number of days on which the other 9 had fits was not affected by folic acid. Two children complained of 'dizziness' while on folic acid but there was no such complaint while taking the placebo.

**Discussion**

Our preliminary survey confirms previous observations that anti-convulsant therapy is frequently associated with low serum folate levels in children (Dahlke and Mertens-Roesler, 1967; Neubauer, 1970).

The lack of behavioural response to folic acid replacement in this trial is in keeping with the findings of 3 double-blind trials in adults (Grant...
and Stores, 1970; Jensen and Olesen, 1970; Ralston, Snaith, and Hirley, 1970). It is unlikely that the differences between these results and those of Reynolds (1967) and Neubauer (1970) can be explained by shorter exposure to folic acid; Neubauer (1970) noticed mental improvement in younger children from 5 to 8 weeks after starting folic acid and the adults reported by Grant and Stores (1970) received folic acid for 6 months with no effect. We have now shown that normal levels of folate are achieved very rapidly in both the red cells and serum when folic acid is given to folate-deficient patients on anticonvulsants; these results taken together with the lack of behavioural response in the controlled trials suggests that, in this context, folic acid has little direct effect on mental function. The possibility remains that the very slow deterioration in mental performance noted in some epileptics might be related to chronic folic acid deficiency.

We also confirmed the results of the controlled trials in adults (Grant and Stores, 1970; Jensen and Olesen, 1970; Ralston et al., 1970) in not showing an increase in fits due to folic acid. Folic acid has undoubtedly provoked fits in some individuals (Chanarin et al., 1960; Reynolds, 1967), but this response seems unusual.

Summary

Significantly lower serum folate levels were found in 39 children taking anticonvulsant drugs than in 25 controls (P = 0.01). Because of reports of improved mental function after folic acid replacement in folate-deficient epileptics, 19 children entered a trial of folic acid versus placebo. There was no significant difference in simple reaction times, in numbers of hours slept, or in fit frequency. The increase in fits due to folic acid which has been reported seems to be an uncommon response to the vitamin.

We would like to thank Drs. G. F. A. Harding and P. M. Jeavons for help with this project; Mr. R. S. Easterby for advice about the electronic equipment which was kindly loaned by the University of Aston in Birmingham; and Macarthy's Laboratories for supplying folic acid and inert tablets through the agency of Mr. R. H. Leach, pharmacist, at the Children's Hospital.

References


Short Reports


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Trimethoprim/Sulphamethoxazole in Pertussis: Comparison with Tetracycline

Antibiotics, if given early in the disease, are moderately effective in reducing the frequency and severity of cough in pertussis (MRC Report, 1953). Tetracycline, chloramphenicol, and erythromycin have all been recommended (MRC Report, 1953; Christie, 1969; Bass et al., 1969).

Trimethoprim/sulphamethoxazole is a bactericidal combination active in vitro against Bordetella pertussis (Bushby, 1969), and it was considered that it might prove a suitable alternative agent in the treatment of pertussis. It was therefore decided to undertake a direct comparison between this agent and tetracycline, during a recent outbreak of the disease in Nigeria.

Materials and Methods

Patients were included in the trial if Bord. pertussis was isolated from the naso-pharynx, or if they had a typical 'whooping' cough, and a relative and absolute lymphocytosis. No account was taken of previous vaccination history. Patients accepted into the trial were randomly allocated to one of two treatment groups.

(a) Tetracycline group. Children under 2 years old were given 62.5 mg tetracycline 6-hourly, and older children 125 mg 6-hourly, for one week.

(b) Trimethoprim/sulphamethoxazole group. Children under 6 months old were given 20 mg trimethoprim with 100 mg sulphamethoxazole twice daily.