ABNORMAL URINARY ANDROSTERONE/ETIOCHOLANOLONE RATIO IN HYPOTHALAMIC DISTURBANCES IN MAN

By
Svend G. Johnsen

ABSTRACT

The urinary androsterone/etiocholanolone (A/E) ratio was determined in 233 normal subjects. Compared with these, a group of 28 cases of adiposo-genital dystrophy (a.-g. d.) in boys and men showed a very considerable increase in the A/E ratio. It is shown by analyses in 23 cases of primary testicular failure and male castration and in 17 cases of exogenous obesity that this change in a.-g. d. is not secondary to the main symptoms, i.e. obesity and hypogonadism; neither can it be explained on a thyroid basis. Studies of 2362 fractionated 17-KS-determinations performed in all kinds of endocrine disorders showed that an elevated A/E ratio is found in certain conditions all of which are of hypothalamic origin. Furthermore it was found that an elevated A/E ratio was present in verified organic damage of the hypothalamus. In a number of a.-g. d. cases the A/E ratio was followed up to 10 years through the puberal age. Usually the ratio remained unaffected by the great puberal rise in the excretion of A and E. In contrast to the others some patients showed a fall in the ratio during puberty and these usually showed satisfactory gonadal development. Determination of the A/E ratio before and after the administration of a large dose of testosterone propionate was done in 23 cases of hypothalamic dysfunction and in 22 other cases. The abnormal A/E ratios in hypothalamic cases were reproduced during the metabolism of exogenous testosterone, which shows that the abnormal ratios originate from an abnormal androgen metabolism and not from abnormal hormone production. The findings indicate that there is, in man, a central regulation of androgen metabolism in which the hypothalamus is involved. The diagnostic, pathogenetic and theoretical implications of the findings are discussed.
The major end-products of androgen metabolism in man are the stereoisomers androsterone (A) and etiocholanolone (E). These differ only in the orientation of the hydrogen atom at C-5, A being 5-α and E being 5-β. By the reduction of the double bond in either of the three principal human androgens, dehydro-epiandrosterone (DHA), testosterone and 4-androstenedione, A and E are formed in approximately equal quantities. Accordingly the ratio between A and E in the urine (A/E ratio) is usually close to unity (Gallagher et al. 1951; Brooksbank & Salokangas 1959; Jayle 1962; Baulieu & Mauvais-Jarvis 1964 b; Dorfman & Ungar 1965).

Gallagher and his co-workers have shown that the A/E ratio is dependent on the level of thyroid hormone (Bradlow et al. 1956; Hellman et al. 1959; Gallagher et al. 1960). In hyperthyroid states and after administration of tri-iodothyronine the relative proportion of A to E increases (high A/E ratio) without any change in their total amount. Conversely, a low A/E ratio is found in myxoedema. These abnormal spontaneous ratios in thyroid disorders remain unaltered in the metabolism of exogenous administered testosterone (as recently also confirmed by Skovsted et al. (1966)). Wilson & Schenker (1964) have shown that during long-term administration of large doses of corticosteroids the A/E ratio both from endogenous androgens and from exogenous testosterone is markedly lowered.

Large doses of corticosteroids and the level of thyroid hormone appear to be the only factors capable of influencing the A/E ratio derived from the metabolism of 11-deoxy-C19-steroids, and it is generally stated that the same ratio averaging approximately 1 is found in normal cases as well as in euthyroid patients (Dorfman & Ungar 1965).

In 1956, this department chose a method for fractionation of the urinary 17-ketosteroids for large scale routine tests (Johnsen 1956 a, b, c). In contrast to several other methods this procedure gives a clear-cut separation of A and E. We have found that an abnormally high A/E ratio is a frequent finding in the so-called adiposo-genital dystrophy (a.-g. d.). Subsequently the same finding was made in other endocrine disorders involving no change in the thyroid but showing a close relationship to hypothalamic dysfunction. We have also found that this metabolic abnormality can be induced by gross hypothalamic lesions and it would appear that the change persists once it has been induced. Finally, we have found by testosterone administration that the elevated A/E ratio is not caused by abnormal steroid hormone production but rather reflects a change in the metabolism of androgens.

To our knowledge these findings have not previously been reported.

METHODS

Fractionations of the urinary 17-KS were performed by the routine method described by Johnsen (1956 a, b, c). With reference to these papers a few points particularly
Table 1.
Determination of the A/E ratio in consecutive 24-h urine samples from 3 different subjects. A: normal male, 25 years old. B: normal male, 51 years old. C: female, 28 years old, during constant treatment with cortisone.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.14</td>
<td>0.56</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>1.11</td>
<td>0.62</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>1.41</td>
<td>0.56</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>1.26</td>
<td>0.54</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>0.90</td>
<td>0.57</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.56</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>1.08</td>
<td>0.55</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>1.24</td>
<td>0.53</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>1.14</td>
<td>0.93</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>1.38</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>1.21</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>1.26</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>mean</td>
<td>1.18</td>
<td>0.60</td>
<td>0.29</td>
</tr>
<tr>
<td>stand. dev.</td>
<td>0.15</td>
<td>0.13</td>
<td>0.07</td>
</tr>
</tbody>
</table>

relevant to this study should be mentioned. The method, while offering clear separation of A and E, does not yield entirely pure fractions. The E-fraction is contaminated with some non-specific colour. As judged from analyses of urines of totally hypophysectomized patients, this non-specificity of the E-fraction corresponds to less than 0.5 mg 17-KS per 24 hours, whilst for the A-fraction it is less than 0.05-0.1 mg. This error might tend to lower the A/E ratio value and thus minimize the abnormal findings presented. However, it would appear from the mean ratios found in normal subjects as compared with the findings in the literature that the error is insignificant. The consistency of the A/E ratio before and after testosterone administration excludes the theoretical possibility that contamination of the A-fraction with 9-androstenolone, formed from 11-oxy-17-KS, might account for some of the findings.

All 17-KS were measured with A as the standard disregarding the fact that the chromogenicity of E in the Zimmermann reaction is 10-15 per cent higher than that of A.

The day-to-day variation in the A/E ratio as determined by the method for 3 subjects showing different A/E levels is shown in Table 1. Repeated assays in patients are shown later.

Testosterone loading was performed by injecting intramuscularly testosterone propionate dissolved in oil in a dose of 2.5 mg per kg body weight. (This dose corresponds to 2.1 mg free testosterone per kg, i.e. 126 mg for a man weighing 60 kg). Beginning at the time of injection urine was collected for 2 × 24 hours.

MATERIAL

Clinical cases were studied by the investigator at the Male Hypogonadism Study...
Fig. 1.
The androsterone/etiocholanolone ratio (A/E) in 131 normal males aged 10–80 years. Ordinate: A/E ratio, log scale. Abscissa: age in years. The middle line connects the mean ratio of the age classes indicated. The area within the outer lines covers 95 per cent of the observations (mean ± 2 × stand. dev.).
Section. Some of the cases of intracerebral damage were studied by obtaining records from various departments.

A note on the concept a.-g. d. Observations made in boys and men diagnosed as cases of a.-g. d. constitute an important part of the study. The concept a.-g. d. has been extensively discussed and the concept widely rejected.

However, in extensive long-term studies (Johnsen 1956 d, 1957; cf. Johnsen 1962) it has been shown that in boys a condition of obesity with distinctive feminine characteristics combined with true hypogonadism does exist and is identical with the effect of anatomical damage of the hypothalamus (so-called Fröhlich’s syndrome). With regard to details about the existence of a.-g. d. in boys, its influence on the long-term sexual development and its existence in adult men, the reader is referred to the original studies.

As well as the clinical cases studied, 2300 routine analyses performed for several hospitals were screened. The diagnostic statements in this series are (with the exception of most of the hypogonadism cases and cases of organic brain lesion) preliminary observation diagnoses without any further verification.

Normal values for the A/E ratio were obtained from the fractionated 17-KS determinations in 112 men and 102 women published previously (Johnsen 1956 b).

RESULTS

1. The A/E ratio and its variation in normal subjects

In Fig. 1 the A/E ratios in 131 normal males aged 10–80 years have been plotted against age. The ratio is lowest before puberty (mean 0.65). From the age of 15–16 the ratio remains constant throughout life (a slight tendency to higher values in the youngest groups is insignificant). In 112 men aged 15–80 years the mean A/E ratio was 1.04. The range (mean ± 2 × stand. dev., as calculated from the log values showing a normal distribution) is 0.51–2.10. In 102 normal women aged 15–80 years the mean was 0.81, range 0.37–1.77. The difference between normal men and women is highly significant (P < 0.001). However, as compared with the normal individual variation and the magnitude of abnormalities shown below, the sex difference is small.

2. The occurrence of abnormally high A/E ratio in adiposo-genital dystrophy

It has been found that in the so-called a.-g. d. the chromatographic curve in the fractionated 17-KS frequently shows a strikingly low etiocholanolone-peak, as illustrated in Fig. 2.

In a preliminary study it was found that this change occurred in adults (Fig. 2 C) as well as before puberty (Fig. 2 E and F) and also with widely different levels of androgen excretion. An analysis of the first cases also showed that the relevant numerical expression of the finding is the A/E ratio rather than the excretion of E in absolute terms or expressed as per cent of the total 17-KS.

599
Fig. 3 shows the A/E ratio in 28 cases of diagnosed a.-g. d. in males aged 10–36 years. It is seen that the group differs very markedly from the normal, 27 of the 28 being above the normal mean and 14 (50 per cent) outside the normal range. Some patients showing lower »physiological age« than chronological age due to hypogonadism, should probably have been placed further to the left in the diagram. This would have increased the abnormality.

24 of the cases were in the age group 10–20 years (mean age 14.4 years). The 30 normal subjects of the same age (cf. Fig. 1) form an identical age group (mean age 14.5 years). The normal mean for the A/E ratio in this age is 0.86. The mean ratio of the patient group is 2.02 and 1.71 if the two ex-
tremely high values are omitted. In the latter case, the mean $\pm 2 \times \text{stand. dev.}$ is 0.73-4.04 and the difference between the normal subjects and the patients highly significant ($P < 0.001$; all calculations were made on log values).

As shown in Fig. 3 no major difference in the ratio is found in patients observed before and after puberty.

Finally it is evident from Fig. 3 that the cases of a.-g. d. do not form two different categories, i.e. those with normal and those with abnormal A/E ratios. The patients rather form a new group with a normal distribution, but all display a higher ratio than expected. This view is supported by the fact that no evident clinical differences were noted between patients with values outside or within the normal range.

3. Analysis of the causes of high A/E ratio in adiposo-genital dystrophy

Hyperthyroidism, the only established endogenous cause of elevation of the A/E ratio, is not present in a.-g. d. On the contrary, several investigators have previously observed hypothyroidism in this condition because of the low BMR usually found. In our series, PBI, cholesterol and other thyroid parameters have been consistently normal in a.-g. d. Thus any thyroid origin of the A/E abnormalities could a priori be ruled out.

There are no clinical signs of adrenal hyperfunction in a.-g. d. The excretion of 17-KGS and dehydroepiandrosterone is normal. Furthermore, other findings reported below exclude the possibility that the abnormal A/E ratio is related to the production of abnormal steroids.

---

**Fig. 2.**

Chromatographic curves of the fractionated 17-KS determination in typical cases of abnormal A/E ratio. A: Normal male, 22 years old. A/E ratio 0.9. B: Castrated male with obesity, 26 years. Low A and E level, but normal A/E ratio (0.7). C: 36 years old male with a.-g. d. Normal androgen level, but elevated A/E ratio (2.1).

D: Normal 11 years old boy. A/E ratio 0.6. E: 12 years old boy with severe a.-g. d. Very low E. A/E ratio 2.8. F: 11 years old boy with a.-g. d. following severe poliomyelitis with encephalitis. Very high A/E ratio (3.8).

G: 21 years old woman previously operated on for aneurysm of the internal carotid artery. After the operation permanent amenorrhoea and obesity (Fröhlich's syndrome). A/E ratio 3.7. H: 30 years old male with internal hydrocephalus following encephalitis, hypogonadism and »dyscrine» obesity. A/E ratio 2.3. I: 21 years old male who developed »dyscrine» obesity after operation for glioma occupying the lower part of the 3rd ventricle. A/E ratio 2.1. (Although high, the DHA value is not outside the normal range).

Note that abnormal A/E ratio occurs quite independently of the magnitude of A and E excretion.
The A/E ratio in 28 cases of a.-g. d. Ordinate: A/E ratio, log scale. Abscissa: age, years. Unbroken line and shaded area: Normal mean and normal limits, cf. Fig. 1.

Fig. 3.

The A/E ratio in testicular insufficiency. Black circles: 9 castrated criminals. Circle with cross: Castrated male with obesity secondary to castration. Open circles: 13 cases of primary testicular insufficiency. Cf. legend to Fig. 3.

Fig. 4.
The A/E ratio in 17 males with presumably «simple» obesity of exogenous origin. Cf. legend to Fig. 3.

The possibility remains that the elevated A/E ratio is secondary to one of the main symptoms of a.-g. d., i.e. hypogonadism or obesity.

Fig. 4 shows the A/E ratio found in 10 castrated sex criminals and in 13 cases of primary testicular insufficiency. In these groups the A/E ratio tends to be somewhat lower than in normal men. One of the castrates was also obese but displayed a low normal ratio (actual curve shown in Fig. 2 B).

In Fig. 5 the A/E ratio of 17 males with presumably «simple», «exogenous» obesity is shown. One case showed elevated A/E but there was no tendency towards elevation of the A/E in the group.

Thus, neither testicular insufficiency nor obesity per se induce elevation of the A/E ratio, and there was no explanation of the abnormal ratios on the basis of previously established findings.

This circumstance and the nature of a.-g. d. raised the hypothesis that hypothalamic dysfunction may in an unknown way bring about a change in the A/E. In order to investigate this possibility a large number of various endocrine cases were screened.

4. Screening of 2362 fractionated 17-KS determinations with regard to incidence of high A/E ratio in various diseases

During the period of investigation (one year) 2362 fractionated 17-KS determinations were performed for a large number of hospital departments. In 1490
an observation diagnosis was submitted with the sample allowing a rough characterization of the case. The overall incidence of A/E ratios over 2.0 was 11 per cent.

The incidence of A/E ratios over 2.0 in the various categories of disorders is seen in Table 2.

Samples showing abnormally high 17-KS excretion (hypercorticism, virilizing diseases, corticotrophin treated cases) have been separated from the remainder because a pathological steroid overproduction may cause a high A/E ratio for reasons other than those dealt with in this study.

In non-endocrine cases, the incidence of high ratios (2.9 per cent) is identical with the normal series (there might be a higher incidence in diseases of the liver but the number of cases is too small for evaluation).

In hypopituitarism and hypocorticism the incidence of high ratio is very low or nil, and it is of interest that the same applies to diabetes. As expected, a higher incidence was found in thyroid disorders (these cases were not followed up and the information supplied did not allow a differentiation between treated, untreated, hypo- or hyperthyroid cases).

Diseases which might have a relation to hypothalamic dysfunction have been collected in a separate group and here the incidence of A/E ratios over 2.0 is very much higher than in any other group. Extremely high frequencies of a high ratio are seen in a.-g. d. in adult men (69%) and in boys (27%) and also in organic brain lesion (38%) cf. below. The high incidence is furthermore seen in kryptogenetic infantilism. In a non-classified group of obesity in adults 24% had a high ratio. A specific diagnosis has not been made and most probably this group consisted of a number of atypical (»endocrine«) obesity cases since a hormone analysis was required. A mixed group of hypogonadal men and women also consisted of non-classified patients among whom there might have been cases of hypothalamic disorders. This accounts for the apparent discrepancy between Table 2 and the finding (cf. above) in fully examined patients that neither exogenous obesity nor primary testicular failure cause elevation of the ratio. Finally, a fairly high incidence of elevated ratios was found in »Cushing-like disease with hypercorticism«, which a.o. covers cases of hypothalamic obesity with gonadal affection in women, i.e. corresponding to a.-g. d. (cf. Bartels & Hjorth 1947).

The distribution of elevated A/E ratio in the absence of steroid overproduction among all kinds of endocrine cases shows that the change is specific and occurs in certain pathological conditions affecting hypothalamic centres.

5. *High A/E ratio in verified hypothalamic damage*

As seen in Table 2, high A/E ratio was seen in 11 cases with organic brain
Table 2.
The occurrence of elevated androsterone/etiocholanolone ratio (A/E ratio) in routine assays of fractionated 17-KS in the urine.

<table>
<thead>
<tr>
<th>Observation diagnosis</th>
<th>Number of analyses</th>
<th>No. with A/E ratio over 2.0</th>
<th>Per cent increased A/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>2362</td>
<td>243</td>
<td>10.3</td>
</tr>
<tr>
<td>Analyses without information or diagnosis</td>
<td>872</td>
<td>79</td>
<td>9.1</td>
</tr>
<tr>
<td>Rest</td>
<td>1490</td>
<td>164</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Diseases caused by pathological overproduction of steroids

<table>
<thead>
<tr>
<th>Disease Description</th>
<th>Number of Analyses</th>
<th>No. with A/E ratio over 2.0</th>
<th>Per cent increased A/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercorticism, all forms, + ACTH-treated</td>
<td>173</td>
<td>24</td>
<td>13.9</td>
</tr>
<tr>
<td>Virilizing disease in women</td>
<td>104</td>
<td>9</td>
<td>8.7</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>32</td>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>Total</td>
<td>309</td>
<td>37</td>
<td>12.0</td>
</tr>
</tbody>
</table>

Diseases with possible relation to hypothalamic dysfunction

<table>
<thead>
<tr>
<th>Disease Description</th>
<th>Number of Analyses</th>
<th>No. with A/E ratio over 2.0</th>
<th>Per cent increased A/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiposo-genital dystrophy in adult men</td>
<td>16</td>
<td>11</td>
<td>68.8</td>
</tr>
<tr>
<td>Organic brain lesion</td>
<td>29</td>
<td>11</td>
<td>37.9</td>
</tr>
<tr>
<td>Adiposo-genital dystrophy and other forms of obesity in children</td>
<td>118</td>
<td>32</td>
<td>27.1</td>
</tr>
<tr>
<td>Various cases of obesity in adults</td>
<td>38</td>
<td>9</td>
<td>23.7</td>
</tr>
<tr>
<td>Primary infantilism, cryptogenetic dwarfism in children</td>
<td>76</td>
<td>14</td>
<td>18.4</td>
</tr>
<tr>
<td>Hypogonadism in adults, mixed group</td>
<td>162</td>
<td>20</td>
<td>12.3</td>
</tr>
<tr>
<td>»Cushing-like disease« without hypercorticism</td>
<td>76</td>
<td>9</td>
<td>11.8</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>22</td>
<td>2</td>
<td>9.1</td>
</tr>
<tr>
<td>Total</td>
<td>537</td>
<td>108</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Other endocrine cases

<table>
<thead>
<tr>
<th>Disease Description</th>
<th>Number of Analyses</th>
<th>No. with A/E ratio over 2.0</th>
<th>Per cent increased A/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypopituitarism + hypophysectomized pts.</td>
<td>153</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Mb. Addisonii + adrenalectomized pts.</td>
<td>40</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>40</td>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>43</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other cases</td>
<td>8</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>Total</td>
<td>300</td>
<td>9</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Non-endocrine cases

<table>
<thead>
<tr>
<th>Disease Description</th>
<th>Number of Analyses</th>
<th>No. with A/E ratio over 2.0</th>
<th>Per cent increased A/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of kidney and circulatory system</td>
<td>39</td>
<td>2</td>
<td>5.1</td>
</tr>
<tr>
<td>Diseases of liver and digestive system</td>
<td>15</td>
<td>2</td>
<td>13.3</td>
</tr>
<tr>
<td>Malignant diseases</td>
<td>106</td>
<td>4</td>
<td>3.8</td>
</tr>
<tr>
<td>Diseases of bones, joints and muscles</td>
<td>64</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>Surgical gynaecological cases</td>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric cases</td>
<td>54</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other diseases</td>
<td>44</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>344</td>
<td>10</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Normal individuals

<table>
<thead>
<tr>
<th>Disease Description</th>
<th>Number of Analyses</th>
<th>No. with A/E ratio over 2.0</th>
<th>Per cent increased A/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series of normal men and women</td>
<td>236</td>
<td>7</td>
<td>3.0</td>
</tr>
</tbody>
</table>
lesion. By courtesy of a number of departments 10 of these cases could be examined from the records. The 10 cases comprise:

1) Boy, aged 10. From 8 years polyphagia and precocious puberty caused by glioma mesencephali and hypothalami. At 9 years of age unsuccessful operation in the hypotalamic region. A/E before operation 1.2, after operation 2.9. 2) Boy, aged 11, who developed feminine obesity after severe polioencephalitis. A/E 3.8 (chromatographic curve: Fig. 2 F). Later course showed severe hypogonadism (cf. Fig. 8). 3) Man, aged 20, with narcolepsy, dislocation of the lower end of the 3rd ventricle, and obesity. A/E 2.3. 4) Man, aged 21, operated for glioma at the lower end of the 3rd ventricle and with dyscrine obesity. A/E 2.1. (Curve Fig. 2 I). 5) Man, aged 30, with moderate internal hydrocephalus developed after encephalitis, dyscrine obesity and hypogonadism. A/E 2.4 (curve Fig. 2 H). 6) Man, aged 36, who developed obesity in connection with meningitis. A/E 2.5. 7) Woman, aged 21, operated for aneurysma of internal carotid artery. After operation she soon developed diabetes insipidus, obesity and amenorrhoea. A/E 3.7. (Curve Fig. 2 G). 8) Woman, aged 24, who had encephalitis with papillary oedema. 6 months later no cerebral complaints but obesity and slight hirsutism. Normal menstruation. A/E 2.3. 9) Woman, aged 37, with a history of previous encephalitis. Now complaining of fatigue and hypomenorrhea. No obesity. Electroencephalogram abnormal. A/E 3.0. 10) Woman, aged 64, with a tumour of the infundibulum hypophyseos, impaired vision and obesity. Operative removal of tumour with complete loss of hypophyseal stalk. A/E shortly after operation 2.5 and 3.0. Later severe hypopituitarism with disappearance of the A and E fractions.

In 4 of the 10 cases, specific hypothalamic symptoms developed after encephalitis. In 2 cases lesions affecting the lower end of the 3rd ventricle were demonstrated, and the last 4 patients had been operated on in the region of the hypothalamus.

The demonstration of hypothalamic damage in all these cases yields substantial evidence of the hypothalamic influence on the A/E ratio.

6. The course of the A/E ratio followed during puberal age in adiposo-genital dystrophy

It has been found that despite the very great rise in the urinary A and E during male puberty the A/E ratio usually remains fairly constant. This applies to normal ratios as well as to the high or high-normal A/E ratio in a.-g. d. Fig. 6 shows the excretion of A and E during puberty in a case of severe a.-g. d. (case No. 1 in Fig. 7). Despite a 8–9 fold rise in androgen excretion the abnormal A/E ratio remained unaltered.

This has been the usual finding. Fig. 7 shows the course of the A/E ratio during puberal age in 9 patients with a.-g. d. and 2 other hypogonadal males. These cases comprise (numbers referring to Fig. 7):

The urinary excretion of androsterone (A) and etiocholanolone (E) during the puberal age in a case of severe a.-g. d. (Case 1 in Fig. 7). Figures over bars indicate the A/E ratio. *) Value obtained during treatment with HMG and HCG. Note that the ratio has remained at the same abnormally high level despite a 8–9 fold rise in androgen excretion during the 5 years' period of observation.

The course of the A/E ratio during the puberal age in 9 cases of a.-g. d. (1–9), 1 case of hypogonadism of unknown origin (No.10) and 1 case of primary infantilism (No.11).

For description of cases see text.

unknown. 5: A.-g. d. Long-term course doubtful (virile, but gonadotrophins high). 6: A.-g. d., severe. Long-term course poor (persistent testicular hypo-

It is seen that the A/E ratio generally remains markedly unaffected by the great changes in the hormone levels occurring both in normal and abnormal puberty.

In a smaller number of a.-g. d. cases, a decreasing A/E ratio during puberty has been found. These are seen in Fig. 8, and comprise:


The difference in the prognosis of cases with unaltered and with decreasing A/E ratio is striking, although the pattern is not uniform. However, further analysis of the relationship between the level and the course of the A/E ratio and the severity and prognosis of the disease is outside the limit of this study.

Fig. 8.
The course of the A/E ratio during the puberal age in 6 cases of a.-g. d. showing decreasing ratios. For description of cases see text.
7. Reproduction of the abnormal A/E ratio in hypothalamic disorders during metabolism of exogenous testosterone

The fact that the abnormal A/E ratios found in hypothalamic disturbances usually persist unaltered during the great puberal change in androgen levels indicates that the cause of the abnormal ratios is rather a change in androgen metabolism than abnormal steroid hormone production. This was confirmed by the determination of the A/E ratio after the administration of large doses of testosterone propionate to some of the patients.

The dose of testosterone administered (2.1 mg per kg) showed in the first 24 hours after the injection, an increase in the excretion of A and E of usually 500–1300 per cent, the ratios thus reflecting almost exclusively the metabolites of the exogenous testosterone.

Fig. 9 shows the correlation between the A/E ratio before testosterone, and that in the first 24 hours after testosterone propionate injection in cases with hypothalamic dysfunction, cases with some other endocrine disorders and in normal subjects. It is seen that there is a fairly close relation between the spontaneous A/E ratio and the A/E ratio derived from exogenous testosterone in all conditions and at all A/E levels. In most cases, and particularly in hypothalamic cases, the ratios after testosterone are somewhat higher than before. In no hypothalamic case with a high spontaneous ratio was the A/E ratio derived from exogenous testosterone normal. On the contrary, in several cases of hypothalamic dysfunction with ratios in the upper normal range the ratios after testosterone were higher and even abnormal. Among the 23 hypothalamic patients in Fig. 9, 16 had a spontaneous A/E ratio below the upper normal limit; in 8 of these cases the ratio in one or both of the two periods after testosterone exceeded 2.0. As might have been expected, determination of the A/E ratio after testosterone injection allows of a further differentiation between normal subjects and patients with hypothalamic dysfunction.

In 11 normal subjects the mean recovery of the injected testosterone during the 48 hours of urine collection was 20.4 per cent in the A-fraction (range 11.1–26.3) and 19.8 per cent in the E-fraction (range 8.3–35.5). In 21 cases with hypothalamic dysfunction a mean of 17.2 per cent of the testosterone was recovered in the A-fraction (range 4.0–30.5) but only a mean of 8.0 per cent in the E-fraction (range 2.6–13.7). These findings show that the essential change in hypothalamic dysfunction is a decreased transformation of testosterone into the 5β-metabolite (E) without a compensatory increase in the transformation to the 5α-metabolite (A). This is in contrast to the findings in abnormal thyroid hormone levels which changes the A/E ratio without affecting the total recovery of testosterone in A + E (Hellman et al. 1959).

In normal subjects following a single intramuscular injection 80 per cent of urinary 17-KS metabolites from testosterone propionate appear within 48 hours (Hamburger et al. 1952), and a delayed testosterone metabolism interfering
The correlation between the A/E ratio before and during the first 24 hours after administration of a large dose of testosterone (2.1 mg per kg body weight). Black circles: 23 cases of hypothalamic dysfunction. Crossed circles: 10 cases of eunuchoidism, infantilism and exogenous obesity. White circles: 12 normal subjects or patients with non-endocrine disorders.

with 48 hour recoveries could not a priori be excluded in the group of patients. However, the excretions in the patients during the second 24-hour periods were usually much less than during the first periods as is the case in normal subjects. It should also be pointed out that delayed metabolism cannot account for a spontaneous, permanently increased A/E ratio.
DISCUSSION

The demonstration of a profound alteration in the androgen metabolism leading to elevation of the A/E ratio in hypothalamic dysfunction is a new finding. Apart from this department, few laboratories have used large scale routine tests for the fractionation of urinary 17-KS yielding a separation of A and E. This probably explains why the change has previously escaped notice. It is of interest that in a steroid study in children Gray et al. (1956) found a high A/E ratio in 3 cases of »adipose gynandristm« but these authors did not attribute any significance to the change.

It is at present not possible to explain the mechanism of the change. The finding of a high A/E ratio in a certain group of diseases which are associated with a hypothalamic dysfunction and also in cases of verified hypothalamic lesion, as well as the finding that an elevated ratio is not secondary to the main symptoms (either the obesity or the hypogonadism) of the conditions, and cannot be explained on a thyroid basis, indicate that the change is a direct hypothalamic effect. The A/E changes are seen whether or not the hypophysis is involved in the hypothalamic damage. Isolated hypopituitarism lowers the ratio (Johnsen 1956 c, cf. also Table 2).

It is interesting that James (1961), in Cushing's syndrome (without adrenal tumour), described a change in androgen metabolism going in the opposite direction (too much E as compared with A both spontaneously and after exogenous androstenedione). Cushing's disease with adrenal hyperplasia presumably originates from hyperfunctioning hypothalamic centres, whereas the syndromes dealt with in this study originate in hypothalamic hypofunction. It would appear that the metabolism of androgens is dependent on a central regulation via the hypothalamus but the mechanism is as yet obscure. The mechanism by which large doses of corticosteroids lower the A/E ratio (Wilson & Schenker 1964) is unknown but it is clear that this effect has nothing to do with the immediate adrenal suppressive effect of corticosteroids.

It is tempting to speculate on the pathogenetic significance of the change. Gallagher et al. (1960) have pointed out that metabolites of hormones may have independent physiologic functions different from the original substances from which they are derived. Thus, androsterone possesses a hypocholesteremic and possibly an increasing effect on oxygen consumption (a »thyromimetic« effect) (Hellman et al. 1959). Etiocholanolone is pyrogenic in man in doses comparable to the daily excretion (Kappas et al. 1957, 1958). There can be no question that the findings in this study indicate a greatly decreased production of etiocholanolone in hypothalamic dysfunction. Although androgen metabolites are quickly conjugated and excreted they may well have important physiological effects. Quite recently it was shown that both etiocholanolone (Bradlow et al. 1967) and androsterone (Fukushima et al. 1967) are in fact
biochemically active because they undergo series of oxidations and reductions of the oxygen at C-3 before they are conjugated and excreted. It seems clear that these substances have hitherto undisclosed metabolic functions and should not be regarded as «inert metabolites».

In the usual long-term course of a.-g. d. the obesity disappears or is greatly reduced in the puberal age (Johnsen 1956 d). This happens even when the abnormal A/E ratio, as is usually the case, remains unaltered. Although the obesity often returns 10–15 years later and the patients thus may be considered as «latent obese», it is difficult to believe that the obesity could be the result of abnormal steroid metabolism. The independence of the steroid changes and obesity is further indicated by the fact that we have found (unpublished results) elevated A/E ratios in hypothalamic syndromes which do not include obesity (some cases of primary infantilism). At this stage of our knowledge it might, however, be premature to exclude any influence of the change in androgen metabolism on the development of obesity.

The hypogonadism in severe cases of a.-g. d. (contrary to common belief) has a poor long-term prognosis. Despite the fact that the obesity often disappears and spontaneous puberty occurs the persistence of hypoplastic testes and poor fertility is the rule (Johnsen 1956 d, 1957). It is tempting to relate the persisting hypogonadism to the abnormal A/E ratio which most often also persists. The good gonadal development in most of the patients showing a fall in the ratio during the puberal age supports this view although the number of cases hardly allow definite conclusions about the relationship between ratio and prognosis. Finally it is noteworthy that in all the cases of hypothalamic syndromes which we have seen, the A/E changes (a.-g. d., primary infantilism, certain amenorrhea-cases, organic brain damage) have as their common feature an impaired gonadal function. It is, however, at present difficult to understand how an abnormal androgen metabolism can influence gonadal function unless we assume that steroid hormone metabolites play a role in the hypothalamic-hypophyseal-gonadal feed-back mechanisms. At this point it should be realized that the androgen metabolism in hypothalamic disease needs further study. The low recovery of testosterone in the sum of the A and E fractions points to the possibility that increased amounts of other metabolites, such as androstanediols (cf. Baulieu & Mauvais-Jarvis 1964 a) might be formed.

The diagnostic interest in the determination of the A/E ratio would appear to be significant, although there is a good deal of overlapping between normal and hypothalamic cases and presumably there is no simple relation between the magnitude of the A/E ratio and severity of disease. There are at present no direct methods for the demonstration of the function of the hypothalamic centres which influence gonadal function and thus the demonstration of a high or high-normal A/E ratio in a patient is a significant finding.

The diagnostic value of the A/E ratio is increased by assessing the ratio
after a suitable dose of exogenous testosterone. This is partly due to the fact that some androgen metabolites must be present in the urine in order to reflect the true ratio. With the analytical method used in this work, there is some non-specific material in the E-fraction (but very little, if any, in the A-fraction) which might lower the A/E ratio particularly in low-titre urines. It is difficult to evaluate whether these two factors fully explain the tendency to a somewhat higher A/E ratio after testosterone but there is no doubt that a differentiation between normal and pathological cases is improved by giving testosterone. Even in this case, however, there is considerable overlapping. Thus severe hypothalamic dysfunction can be seen with ratios in the upper normal range. On the other hand, high ratios without any symptoms or ratios below the normal mean with hypothalamic symptoms rarely occur, and the differential diagnosis between hypothalamic and hypophyseal hypofunction is further facilitated by the fact that the latter condition lowers the A/E ratio. It is an interesting question whether this decrease of the ratio in hypopituitarism, which even goes as far as complete disappearance of the A-fraction in total pituitary destruction, is the effect of »compensatory« hypothalamic hyperfunction (cf. low ratio in Cushing’s disease) and thus one more demonstration of the hypothalamic influence.

A final remark on the concept a.-g. d. should be added. Probably because of its old-fashioned and inadequate name the concept has become unpopular. The actual existence of hypogonadism in this condition and the parallelism between a.-g. d. and the effects of organic hypothalamic damage have, however, been demonstrated in large series of cases (cf. Johnsen 1956 d, 1957). Of interest in this connection is the finding in recent years of a hypothalamic control of gonadal function through gonadotrophin releasers. The demonstration in this study of the occurrence of the same specific endocrine change in organic hypothalamic lesion and in fat, feminine, hypogonadal boys and men is new evidence for the relevance and importance of the old concept a.-g. d.

ACKNOWLEDGEMENTS

Supported in part by the Ford Foundation.

Thanks are due to the Departments of Neurology, Neurosurgery and Psychiatry of Copenhagen University Hospital and the Department of Neurosurgery of Århus University Hospital for placing records of cases with organic brain damage at the author’s disposal.

REFERENCES


Received on October 11th, 1967.