believe this is a sign of impending death. Conversely the presence of a pulsatile midline echo in comatose patients is of favorable prognostic value.

Le Petit and his associates (4) have reported a series of 86 cases in which they observed on the cathode ray screen pulsations which could be cinematographically recorded. In our experience observation of the midline pulsations on the CRO is sometimes difficult because of rapid low amplitude fluctuations. The technique presented here makes possible the simultaneous presentation of electroencephalographic and echographic records, both of which are possible indicators of cerebral death.

This technique requires validation by angiography as an indicator of the presence or absence of cerebral blood flow. Furthermore, the period of absent pulsations which indicates cerebral death has not yet been determined. In the present series are two patients with clinical evidence of cerebral death, who continue to have the midline pulsating echo. Were some brains with isoelectric recordings still being irrigated? Does this suggest that neuronal death occurred as the result of ischemia but that the endothelial linings of the blood vessels remaining intact did not obstruct the flow? Perhaps four-vessel cerebral angiography via the aortic arch may provide an answer to these questions and to the question of the reliability of this new technique as a determinant of brain death.

REFERENCES

LONG-TERM THERAPY OF HEREDITARY ANGIOEDEMA (HAE). PREVENTIVE MANAGEMENT WITH FLUOXYMESTERONE AND OXYMETHOLONE IN SEVERELY AFFECTED MALES AND FEMALES

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Transmitted as an autosomal dominant trait, hereditary angioedema (HAE) is manifest as recurrent episodes of edema and abdominal pain. Typical attacks consist of nonpitting, usually nonpruritic, peripheral edema, facial swelling, or edema of the oropharynx and larynx; attacks of abdominal pain are frequently associated with nausea and vomiting (1) and may mimic an acute abdomen (2). These manifestations may occur alone or in combination during an attack. The high mortality rate of this disease is accounted for primarily by attacks of laryngeal edema and airway obstruction (3). Factors which precipitate attacks include physical trauma (such as dental work, use of hands in occupational chores) and emotional upset. In many instances there is no apparent precipitating event for an attack (3-5).

A biochemical abnormality of HAE which has served as a genetic marker is the absence from blood of affected subjects of the activity of C1 esterase inhibitor, an alpha-2-glycoprotein which blocks enzymatic activity of the first component of complement (6-8). Unopposed action of activated C1 results in consumption of C4 and C2 and culminates in localized alterations in vascular permeability and edema.

A large number of therapeutic approaches have been employed in this disease. Nonspecific measures such as antihistamines, epinephrine, phenothiazines, corticosteroids and ACTH have been without substantive benefit in most patients. Effectiveness of therapy of acute attacks of HAE has been difficult to assess because of the unpredictable and sometimes spontaneous nature of recoveries. Acute attacks are reported to have been aborted with fresh frozen plasma (containing C1 esterase inhibitor) (9,10) or with partially purified preparations of a kallikrein inhibitor (11) or C1 esterase inhibitor (12). The use of plasmin inhibitors has been shown effective in preventive management of patients with HAE (13,14). A small number of patients have been shown in treatment courses of six months to six years to respond to androgen administration with decreased frequency of attacks (3,5,6,15,16). We report here the results of long-term androgen therapy in 11 patients from six HAE kindreds, in which affected males were treated with fluoxymesterone and females received oxymetholone, an androgen of low virilizing potential.

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SUBJECTS AND METHODS

Eighteen affected patients from six kindreds are followed by the authors in the clinics at Baltimore City Hospitals and The Johns Hopkins Hospital. They range in age from 17 to 73 years. C1 esterase inhibitor deficiency (17) has been documented in all affected patients. Eleven patients have been managed preventively with androgen. All treated patients are "severely affected," defined by either (1) oropharyngeal or laryngeal edema (6 patients) or (2) complete disability (unemployability) because of frequent attacks of abdominal pain.

Patient profiles are described in Table 1. Three patients are black. Three of the 11 patients had required tracheostomies in the past for laryngeal obstruction. Patients were followed for up to 35 months (mean = 8 months) prior to initiation of androgen therapy.

During androgen therapy the patients were interviewed and examined at three or six month intervals, and routine assessments were made of liver function. Male patients received fluoxymesterone (Halotestin) 10-20 mg/day; female patients received oxymetholone (Adroyd) 2.5-5.0 mg/day.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Family History</th>
<th>Kindred</th>
<th>Age at Onset (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JW</td>
<td>F</td>
<td>40</td>
<td>+</td>
<td>I</td>
<td>16 yrs</td>
</tr>
<tr>
<td>RL</td>
<td>F</td>
<td>31</td>
<td>+</td>
<td>I</td>
<td>20 yrs</td>
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<tr>
<td>RB*</td>
<td>F</td>
<td>32</td>
<td>+</td>
<td>II</td>
<td>Childhood</td>
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<tr>
<td>EB</td>
<td>F</td>
<td>47</td>
<td>+</td>
<td>V</td>
<td>25 yrs</td>
</tr>
<tr>
<td>C.Ha.*</td>
<td>F</td>
<td>36</td>
<td>+</td>
<td>VI</td>
<td>16 yrs</td>
</tr>
<tr>
<td>JC</td>
<td>F</td>
<td>34</td>
<td>+</td>
<td>I</td>
<td>18 yrs</td>
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<tr>
<td>GS</td>
<td>M</td>
<td>44</td>
<td>+</td>
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<td>Childhood</td>
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<td>I</td>
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<td>M</td>
<td>39</td>
<td>+</td>
<td>I</td>
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<tr>
<td>C.Ho.*</td>
<td>M</td>
<td>22</td>
<td>-</td>
<td>III</td>
<td>9 yrs</td>
</tr>
<tr>
<td>JB</td>
<td>M</td>
<td>55</td>
<td>+</td>
<td>IV</td>
<td>2 yrs</td>
</tr>
</tbody>
</table>

*Patients who have required tracheostomy for laryngeal edema.

1 Kindly supplied by J. William Hendrix, M.D., The Upjohn Company, Kalamazoo, Michigan 49001
2 Kindly supplied by Robert M. Hodges, M.D., Parke Davis and Company, Ann Arbor, Michigan 48106
RESULTS

Results of therapy are shown in Tables IIa, IIb and III. Female patients have been treated for 10 to 36 months with oxymetholone (total of 116 treatment-months). While taking oxymetholone, five of six women have experienced a substantive reduction in attack rate (Tables IIb, III), regardless of attack type (peripheral or laryngeal edema, abdominal pain). Three patients who discontinued androgen therapy for brief periods noted the recurrence of pre-treatment attack rates within three to five days of stopping treatment. Patient C.Ha. has not had diminished frequency of attacks; severity of abdominal and laryngeal attacks is stated to be less severe on androgen treatment so that the patient is now regularly employed.

Five male patients have been treated for 30 to 78 months with fluoxymesterone (total of 317 treatment-months). All patients have shown a marked reduction in attack frequency while receiving androgen. Three are attack-free while employed in occupations in which local trauma is unavoidable (carpentry, pneumatic hammer operation) and one (W.S.) has undergone dental extractions uneventfully on three occasions while on androgen. Occupational trauma and dental procedures in these patients prior to androgen predictably incited attacks.

Statistical significance of the reduction in attack rates during androgen therapy has been analyzed by chi-square test (Table III).

Side-effects of androgen therapy have included moderate weight gain in three women and transient breast tenderness in two men. No change in libido has been noted and metrorrhagia has not occurred. Urinalysis, CBC, serum urea nitrogen, serum thyroid function tests, creatine phosphokinase and liver function tests have been normal except in patient J.B. (elevated serum SGOT, SGPT). No patients have resigned from the protocol.

### TABLE III

Summary of Results of Androgen Therapy of Hereditary Angioedema

<table>
<thead>
<tr>
<th>Fluoxymesterone</th>
<th>Oxymetholone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of treatment months</td>
<td>317</td>
</tr>
<tr>
<td>Pre-treatment attacks/month</td>
<td>2.2</td>
</tr>
<tr>
<td>Treatment attacks/month</td>
<td>0.1</td>
</tr>
<tr>
<td>p*</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>

*Chi-square test
While efficacy of androgen therapy in HAE has been suggested, the total number of previously reported androgen treated HAE patients is small. There has been no systematic attempt to treat affected males and females on a long-term basis. Recent reviews (7,8,9,18) of HAE have accorded no attention to this treatment modality. Our long-term experience with androgens in 11 patients treated for from 10 to 78 months has been encouraging. In contrast to previous reports of various treatment regimens of HAE, we have analyzed our data on the basis of effectiveness of therapy against specific types of attacks (peripheral edema; oropharyngeal-laryngeal edema; abdominal pain) and have shown that all three types of attacks tend to occur with decreased frequency; androgen, however, is particularly effective in the management of peripheral and oropharyngeal-laryngeal edema.

The availability of non-virilizing androgens has enabled us to carry out a long-term trial in affected females which indicates that oxymetholone alters attack frequency and severity without attendant masculinization. We have limited dosage levels to those which are thought to represent "replacement" levels in males; unpublished data (P.J. Davis) indicate that fluoxymesterone dosages up to 20 mg/day do not alter the concentration in blood of thyroxine-binding prealbumin and thyroxine-binding globulin, two proteins which are sensitive to circulating levels of androgen. In two patients low-dose androgen therapy (5-10 mg/day) has effectively reduced attack frequency. Tolerance of patients for physical trauma while they are on androgen therapy is remarkable compared to the pre-therapy period. Protection from attack risk is usually afforded within two to three days of beginning androgen therapy (protection determined by exposure to physical trauma and failure of trauma to provoke attacks). The original observation that androgen might be effective in HAE therapy (15) was determined by exposure to physical trauma and failure of trauma to provoke attacks. While efficacy of androgen therapy in HAE has been suggested, the total number of previously reported androgen treated HAE patients is small, androgen dosage schedule was adjusted downward and attack frequency increased. This patient was then changed to oxymetholone treatment from fluoxymesterone and has had no chemical evidence of liver toxicity. The development of hepatocellular carcinoma in four patients with aplastic anemia on long-term, high-dose androgen therapy has been reported by one group (19) and several isolated reports have appeared recently describing hepatoma during long-term androgen administration (20-22). Such reports however have involved androgen dosage up to fifty times that employed in our series and are almost exclusively limited to patients with bone marrow failure. The latter population may be significantly different from HAE patients in terms of tumor risk factors. While all HAE patients in the present series are α-fetoprotein-negative on androgen therapy, it should be pointed out that the emergence of liver tumor in aplastic anemia patients has not been associated with circulating α-fetoprotein.

Preventive therapy of HAE in double-blind studies involving plasmin inhibitors such as epsilon-aminocaproic acid (EACA) has been effective in reports involving a small number of treatment-months. Frank et al (13) reported a significant reduction in attack frequency in four of five patients treated with EACA for 21 treatment-months. Sheffer et al (14) used an EACA derivative, tranexamic acid, to manage 12 patients for 94 treatment-months. Results were scored excellent in seven, moderate in four and no effect in one patient. Effectiveness of plasmin inhibitors relative to specific types of attacks—peripheral or oropharyngeal edema, abdominal pain—has not been described. Weakness, muscle pain, menorrhagia, increased susceptibility to sedatives and elevated serum creatine phosphokinase were side-effects of EACA administration. However, side-effects of short-term tranexamic acid administration to HAE patients were negligible. Long-term effectiveness or risk of EACA or tranexamic acid treatment of HAE has not been established. The present report indicates that chronic androgen therapy of HAE patients is without substantive side-effects and uniformly lowers attack rates of peripheral and oropharyngeal edema in severely affected patients.

SUMMARY

Eleven patients with hereditary angioedema (HAE) have received long-term androgen therapy in a preventive management protocol. Experience of 317 patient-months in severely affected males who received fluoxymesterone and 116 patient-months in females who received oxymetholone has shown a significant reduction in attack rate or severity of attacks of oropharyngeal and peripheral edema and abdominal pain, compared with pretreatment attack rate or attack rate during lapses in therapy. No episodes of laryngeal edema have occurred in patients on androgen therapy.

ACKNOWLEDGMENTS

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REFERENCES


EARLY CONTRIBUTIONS TO THE SURGERY OF CANCER: WILLIAM S. HALSTED, HUGH H. YOUNG AND JOHN G. CLARK

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In the year 131 A.D. Galen was born at Pergamos and eventually appeared in Rome as the private surgeon and medical advisor of the young Commodus. The malignant character of cancer was well known to him and he contributed to the views of his day concerning its internal manifestations: "In the breast we often find a tumor in size and shape closely resembling the animal known as the crab, for as in the latter the limbs protrude from either side, so in the tumor the swollen veins radiate from its edges and give a perfect picture of the crab." Here stated for the first time was the reason for giving to neoplastic disease its peculiar name of cancer. Galen was concerned also with its treatment, and while he considered cancer to be the product of black bile, was not opposed to operation. However, he gave this advice: "First get rid of the black bile by appropriate remedies and then attempt a cure by milder applications, since the more severe remedies merely increase the evil." Galen thus recognized that cancer possessed a malignancy peculiarly its own, for which reason he advocated the combination of medicine and surgery.

After Galen, medicine entered a period of quiescence and in the subsequent centuries the operative treatment of cancer had its ups and downs. Even in the time of the Munros of Edinburgh, whose writings threw the operative treatment of cancer into grave repute, the failure of other remedies to fill the gap resulted in a revival of operations particularly for cancer of the breast, lip and scrotum.

Two Germans, the surgeon Thiersch and the anatomist Waldeyer, showed by their careful microscopic studies that the concept of cancer as multicentric in origin was erroneous. Their results showed that cancer had its origin in a single primary focus, which if removed completely led to permanent cure. They demonstrated that tumor appearing in areas distant from the primary focus is the result of metastasis of small groups of cells which have dislodged from the primary focus and spread through the lymphatics and blood vessels.

Following their studies surgeons attempted a more radical approach to the treatment of cancer spurred on by the methods of Lister which reduced the dangers of...