TREATMENT OF ACUTE LEUKEMIA IN CHILDREN†

Dr. Burchenal: The 2 types of compounds most useful in the treatment of acute leukemia are the antimetabolites of which amethopterin and aminopterin are examples, and the hormones such as ACTH and cortisone. Today I would like to discuss with you the indications, dosage, undesirable side effects, and results to be expected with these 2 types of therapy.

If the child with acute leukemia is in reasonably good shape, if his total leukocyte count is below 50,000, and it appears that he will probably survive at least 3 to 4 weeks even without treatment, we start him on amethopterin because we feel that the survival times of patients treated successfully by this method are superior. On the other hand, if his WBC is above 50,000, or he looks as if he would not last long enough to have an adequate course of amethopterin, then we start with ACTH or cortisone, and shift to amethopterin when the WBC has returned to more normal levels, and the general condition has improved.

It should be emphasized at this point that good clinical and hematologic remission can be achieved initially in only 30 to 50% of patients treated with amethopterin, and in only 40 to 60% with the steroid hormones. Fortunately a case that does not respond to one type may respond to the other. In addition, patients who have derived several remissions from courses of amethopterin and have finally become refractory to this type of therapy will frequently still respond to the steroids, and vice versa. In such cases, we then return to amethopterin when the inevitable relapse occurs after cortisone or ACTH. In an occasional patient there is a temporary loss of amethopterin-fastness and 1 or 2 more remissions from this drug may be obtained.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg.)</th>
<th>Preferred Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminopterin</td>
<td>0.5–1.0</td>
<td>P.O.</td>
<td>Daily</td>
</tr>
<tr>
<td>Amethopterin</td>
<td>2.5–5.0</td>
<td>P.O.</td>
<td>Daily</td>
</tr>
<tr>
<td>ACTH</td>
<td>15–25</td>
<td>I.M.</td>
<td>Every 6 hr.</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25–50</td>
<td>P.O.</td>
<td>Every 6 hr.</td>
</tr>
<tr>
<td>. Cortisone</td>
<td>100–150</td>
<td>I.M.</td>
<td>Daily*</td>
</tr>
</tbody>
</table>

* Dose may be divided if desired.

The amounts of aminopterin or amethopterin that patients need to produce remissions, or can tolerate before developing symptoms of toxicity (stomatitis, diarrhea, gastrointestinal bleeding) vary tremendously and it is to be emphasized that dosage must be suited to the individual patient. Particular care must be exercised in the administration of these drugs to severely debilitated patients, or to those with impaired renal or hepatic function. Leukemics with initial high peripheral leukocyte counts may also be extremely sensitive to antagonist therapy. The usual daily dose of these drugs in a 5 year old child would be 0.5 mg. to 1 mg. of aminopterin, or 2.5 mg. to 3 mg. of amethopterin by mouth in tablet form. Although the intramuscular administration may also be used if desired, there

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seems to be no advantage to this route. During therapy, daily determinations of hemoglobin, white blood count and differential counts should be done.

The plan of therapy used here in the treatment of some 97 children with acute leukemia calls for administration of the drug until either a complete remission occurs as evidenced by clinical signs and by the blood and marrow differentials, or until toxic manifestations of stomatitis, diarrhea or gastrointestinal bleeding appear. In the patient showing signs of toxicity, if a complete remission does not occur, therapy is resumed at a slightly lower dose in 1 or 2 weeks when the symptoms have subsided, and is continued until the signs of remission or of further toxicity appear. The first signs of remission are usually seen within from 14 to 35 days after the start of therapy, but wide variation in the time of response may occur.

Once a complete remission has been produced, maintenance therapy may be given or treatment may be temporarily stopped. We prefer the latter course. The patient is followed by means of clinic visits every 2 weeks, at which time a short interval history for symptoms of toxicity, a careful physical examination, and determination of hemoglobin, white blood count, peripheral blood and marrow differentials are done. Particular emphasis is laid on the sternal aspiration in the intermittent type of therapy as it is usually by this technic that the first evidence of relapse can be detected. Thus the treatment can be resumed and the relapse aborted, often without clinical evidence of a relapse ever appearing.

It is our experience that in some of the cases of acute leukemia which respond to therapy, a definite diagnosis of myeloblastic or lymphoblastic type can be made, but most of the cases which respond can only be designated as stem cell leukemia. The acute monocytic type does not usually respond. In those patients who have responded once, repeated remission can be expected. Eventually these responses become less and less satisfactory and finally the patient becomes resistant to therapy.

ACTH or cortisone administered in the dosage given in table 1 will bring about an initial remission in 40 to 60% of the cases. Often within 48 hours with ACTH or 5 days with cortisone there is a marked increase in appetite and feeling of well being. The first signs of an impending remission are usually an increase in the reticulocyte counts, and an increase in the percentage of erythroid elements in the marrow with a concomitant decrease in the leukemic cells. Complete remissions lasting 1 to 12 weeks may be achieved after from 10 day to 6 weeks of therapy.

When this occurs, therapy is discontinued and only restarted when there is marrow evidence of a relapse. Second remissions are fairly frequent in children, but may require higher dosage. Third remissions with these drugs, however, are rare in our experience.

The undesirable side effects of such therapy are those commonly associated with overactivity of the adrenal cortex. Sodium retention with consequent edema may be largely prevented by the use of a low salt diet. Hypokalemia may be corrected, if it does occur, by the oral administration of potassium chloride. The undue gain in weight following the increase in appetite may be largely avoided by limiting the diet to that considered adequate for a normal child of that size and age. Other side effects are not so easily controlled, and severe hypertension, with or without hypertensive encephalopathy, and the appearance of psychic disturbances, are indications for withholding therapy. Cushing's facies, acne and hirsutism are not usually of sufficient importance to contraindicate further treatment, and gradually disappear when therapy is discontinued. Severe overwhelming infections not responding promptly to vigorous use of antibiotics are occasionally seen after prolonged therapy with ACTH and cortisone. Whether these are the results of a relatively fixed output of steroids and an inability of the adrenal to respond to the stress of infection is not understood clearly at present. It may be that in such situations massive doses of cortisone by mouth will be of value.

By these technics of therapy it appears that a definite prolongation of life may be achieved in many cases. In those patients responding initially to amethopterin an average survival of over 16 months from the start of the disease, and over 14 months after the start of treatment may be expected. In those treated initially with the steroids the results are somewhat less satisfactory. By these methods it is possible to keep some children alive, and in reasonably good health, from 18 to 27 months from the onset of their disease, in the hope that they may survive long enough to benefit from new discoveries in the field of chemotherapy.

**DIAGNOSIS OF NEUROBLASTOMA**

*Dr. Dargeon: The diagnostic difficulties encountered during the early course of many tumors of childhood are familiar to all pediatricians. The multiplicity and variability of the early symptoms*
732 ROUND TABLE DISCUSSION: LEUKEMIA AND NEUROBLASTOMA

and signs of well known tumors such as those of lymphoid origin and those of the central nervous system are paralleled in the case of neuroblastoma.

A survey of 58 cases of this neoplasm in children at Memorial Hospital has been made and the data obtained pertaining to color, age, sex, previous health, racial origin, family history of cancer, initial evidence of disease, delay in diagnosis and period of survival is presented in chart 1.

CHART 1

NEUROBLASTOMA IN CHILDREN

58 Cases

<table>
<thead>
<tr>
<th>Age on Adm.</th>
<th>Color</th>
<th>Sex</th>
<th>Nationality</th>
<th>Previous</th>
<th>Family Hist.</th>
<th>1st Symp. to Therapy</th>
<th>Survivors</th>
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<tr>
<td>1 yr./6</td>
<td>White</td>
<td>M/29</td>
<td>American/23</td>
<td>Good/41</td>
<td>Positive/22</td>
<td>Mass/34 under 1 mo./10</td>
<td>10 yr./3</td>
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<tr>
<td>1-4 yr./31</td>
<td>F/29</td>
<td>Other/10</td>
<td>Poor/7</td>
<td>Negative/30</td>
<td>Pain/12</td>
<td>1-5 mo./31 over 4 yr./2</td>
<td></td>
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<tr>
<td>5-9 yr./18</td>
<td>Unknown/15</td>
<td>Unknown/10</td>
<td>Unknown/6</td>
<td>Unknown/10</td>
<td>Fever/3</td>
<td>6-10 mo./6 1-4 yr./4</td>
<td></td>
</tr>
<tr>
<td>10-14 yr./3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CNS/5 11-15 mo./4 Pallor/1 over 15 mo./2</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wt. loss/1 doubtful/3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GI/2</td>
<td></td>
</tr>
</tbody>
</table>

The diagnosis is sought by history and physical examination, roentgenographic examination, marrow studies and biopsy. Study of the tissue obtained from biopsy by tissue culture, chick embryo culture in addition to histologic examination may be helpful in identifying the nature of the tumor.

History and Physical Examination

Reference to the chart indicates that the initial findings vary so considerably that no specific symptoms should be expected and that therefore the disease should be included in the differential diagnosis of a multitude of clinical syndromes—those with tumors of the head, neck, thorax, abdomen, back or extremities, fevers of obscure origin; motor or sensory disturbances, chronic and acute abdominal symptoms, adenopathies and osseous disorders.

Roentgenography

The sites which should be examined are the thorax, the abdomen and the skeleton:
1. Thorax: In common with other thoracic neurogenic tumors the neuroblastoma arises most frequently in the posterior mediastinum.
2. Abdomen: The shadows cast by abdominal neuroblastoma are partially radio opaque and may contain calcified areas within them. Certain tumors may displace adjacent viscera or supporting structures and alter the normal configurations of the diaphragm, psoas muscles and kidneys.
3. Skeleton: Involvement of either cancellous or long bones is manifested usually by multiple small irregularly outlined osteolytic lesions. There may be periosteal reaction and the long bones show the disease in any portion of their shafts.

Marrow

The usual hematopoetic cells are diminished in number or at times completely replaced by the comparatively large neuroblasts.

Biopsy

Histology: The tumor is very cellular. The stroma is not abundant. The cells are usually arranged in rosettes but may occur in clusters. The cytoplasm is often indistinct, the nuclei stain densely. Neurofibrils may be identified by special stain. Tissue culture and chick embryo transplants will frequently produce growth of cells with neurites.

Differential Diagnosis

In considering the differential diagnosis it is known that the causes of many of the symptoms may be nonneoplastic in origin and therefore include congenital malformation, infection, metabolic defects and hyperplasias. Examples of some cases which presented differential diagnostic problems are shown: osseous tuberculosis, fibrous dysplasia, reticuloendotheliosis, reticulum cell lymphosarcoma, leukemia,
Wilms' tumor, teratoma, Hodgkin's disease, ganglioneuroma and congenital malformation of the heart.

Finally there have been frequent enough variations in the usual course of the disease in this series to suggest that we may be compelled to modify our present opinion of what constitutes the 'typical case' of neuroblastoma when satisfactory data have been studied on a sufficiently large number of cases. The following cases illustrate variations from the usual as to primary site, progression, metastasis and result.

Case 1. A boy of 3 years who has 2 types of neurogenic tumor, neuroblastoma and ganglioneuroma.

Case 2. A boy of 4 years who had a slowly growing, inoperable retroperitoneal neuroblastoma. He was followed over 2 years and the tumor did not metastasize. Death resulted from hemorrhage within the tumor.

Case 3. A male baby of 5 months with a primary tumor arising from the cervical sympathetic. This was noticed 2 days after birth.

Case 4. A male baby of 8 months with multiple cutaneous and subcutaneous lesions 0.3 to 3 cm. in diameter, axillary lymphadenopathy and no other evidence of disease. He has survived 14 years.

Case 6. A girl aged 14 months who had an extradural neuroblastoma extending from T-6 to T-9 which produced motor disturbance of the legs. Subsequent to laminectomy and irradiation evidence of disease was observed in her lungs. She has survived 2 years. There is evidence of intrathoracic extension of her disease.

Case 7. A female infant, 14 months of age, with metastasis in the cervical region from a primary intrathoracic tumor. This patient has no evidence of disease 5 years after treatment by irradiation only.

Conclusion

Neuroblastoma in common with many other tumors of the juvenile age period presents a diagnostic challenge to the clinician. The conditions should be included in the differential diagnosis of many acute and chronic syndromes in early childhood whether or not a tumor is clinically evident. The possibilities of a favorable result are not always determined solely by an early diagnosis but the prognosis in the occasional case of neuroblastoma may be favorably influenced by early recognition of the disease.
### Round Table Discussion: LEUKEMIA AND NEUROBLASTOMA

**HAROLD DARGEON, JOSEPH H. BURCHENAL, CLAYTON T. J. DODGE and ERNEST R. KIMBALL, JR.**

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