Therapeutic Results in Treatment of Hodgkin's Disease with CB 1348 and R-48

By ANTONIO ROTTINO

FOLLOWING is a report of our experience with p-di-(2-chloroethyl)-aminophenyl butyric acid (CB 1348)* and β-Naphthyl-dichlorethylamine (Cloronaftina or R-48)† administered to patients with Hodgkin's disease.

WORK WITH CB 1348

CB 1348 was synthesized in 1953 by Everetts, Roberts and Ross.1 It is a water soluble, aromatic nitrogen mustard with the following chemical formula:

\[
\begin{align*}
\text{ClCH}_2\text{CH}_2 \\
\text{ClCH}_2\text{CH}_2
\end{align*}
\]

\[
\begin{align*}
\text{N} \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}
\end{align*}
\]

The first clinical trial in malignant lymphoma appeared in 1955.2 The authors found the drug to be definitely useful in follicular lymphoma and lymphocytic leukemia, and to some extent in Hodgkin's disease. They concluded that it deserved further trial. This opinion was recently concurred in by a group of workers in this country^ who treated 24 patients.

Our work with CB 1348 involved 31 patients with Hodgkin's disease who were treated and kept under observation for a period of 31 months. Fifteen of the group were males and sixteen were females; the age range was as follows: two aged 20 years, seven 21-30 years, ten 31-40 years, nine 41-50 years, two 51-60 years and one 64 years.

Three patients of our group were persons in whom the disease had been discovered only two to three months previous to institution of CB 1348 therapy; seventeen others had had the disease one to three years; four had been diagnosed four to five years previously; seven from five to thirteen years previously.

When therapy was begun thirteen patients were in good condition, seven fair, nine poor, and two were terminal.

Two patients had had no previous therapy, one had had radical neck surgery only, 28 had previously received one or more of the following therapies: radiation, nitrogen mustard, triethylenemelamine, Butazolidin, ACTH, cortisone, Meticon.

Treatment with the chemotherapeutic agent in question was instituted for control of symptoms such as pain, pruritus, malaise, fever, chills, loss of appetite, loss of weight, presence of palpable lymph nodes, enlargement of spleen.

The following laboratory procedures were used as objective criteria for effec-

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* Supplied through the courtesy of Dr. Alexander Haddow, of the Chester Beatty Research Institute, London, England.
† Supplied through the courtesy of “Simes,” Milan, Italy.
tiveness of therapy and detection of toxicity: complete blood counts, including platelet and eosinophil counts, sedimentation rates, C-reactive protein determinations, and serum electrophoreses.

Administration and Dosage: CB 1348 was supplied to us in tablet form, 2 mg. per tablet. The precaution of storing it in the dark was observed. It was given by mouth in dosages which varied from 6 to 30 mg. (0.1 mg. to 0.9 mg. per kilo of body weight) per day, and for continuous periods of nine to 133 days. Three patients received two courses of treatment, six three courses, two four courses, one seven courses, and all others one course. A “course” means the continuous medication required to cause the disappearance of objective findings or symptoms or both, or to cause a WBC sufficiently low to make discontinuance of the drug desirable. One patient received the drug for a total of 249 days over a period of two years, four received it intermittently for one year, two others intermittently for five months. In all other cases the duration of therapy varied from nine days to three months on a continuous daily basis. Two patients who had become refractory to CB 1348 after a second and fourth course respectively were next treated with Colchicine or Thiotepa, after which CB 1348 was reinstituted to establish whether sensitivity to it had returned.

The criteria used to decide the effective dosage (which was different for each individual) were subsidence of symptoms and disappearance of nodes; if neither occurred after a minimum trial period of three weeks and there was evidence that the disease was progressing, CB 1348 was in some cases discontinued and other therapeutic modalities tried. If subjective improvement occurred, CB 1348 was continued until nodes disappeared completely or until no further shrinkage took place.

Results (table 1)

Fifteen of the 31 patients derived no benefit whatever; for five of these, patients 8, 17, 27, 29 and 30, the period of treatment may be considered as having been inadequate. This was caused by the fact that three (17, 27 and 29) were in the terminal phase of the disease when therapy was begun and died within three weeks, and two had symptoms which necessitated other and speedier forms of therapy. Three patients had remissions which lasted two to three weeks; ten had remissions of two to four months; two remissions of seven and ten months, respectively; and one had a remission which has lasted one and one-half years to date. The last-mentioned patient had only one node in the neck and no symptoms. Of the patients receiving multiple courses, the drug became ineffective after the first, second, third, fourth or fifth course. As a rule three weeks were required before any results became apparent. In general pain, pruritus, chills and fever were not subject to effective control. The usual sign of improvement was a sense of well-being. Nodes receded slowly but never completely except in one case. Once maximum improvement had taken place further therapy was ineffective—nodes and symptoms recurred despite the fact that medication was still in progress. To date we have no evidence that sensitivity to the drug is regained once it has been lost.

Toxicity: As prescribed, CB 1348 caused very few toxic symptoms. Nausea was experienced by some, but this symptom was not related to the maximum...
dosage given the group. Some patients experienced nausea when eight milligrams were given daily, others were not affected by 22 mg. daily. The deciding factor therefore appeared to be not the amount given but the recipient. Production of anemia was not common, and in general it was mild. In only one instance did the red blood count drop as much as two million; usually the drop was one-half million, and in most cases there was no change. Leukopenia, if it occurred was rarely lower than three thousand. Thrombocytopenia occurred in some instances, with a drop from initial levels of 200,000 to 70,000. In many instances there was no marked hematologic change other than that customarily seen during the course of the disease. Other complications were as follows: after 139 days of therapy, during which time 1820 mg. of the drug had been taken, one patient had severe menorrhagia. Another had massive gastrointestinal bleeding from multiple, acute ulcers of the stomach (demonstrated at autopsy). He had received 1320 mg. of drug over a period of 165 days. Two others complained of headache and dizziness.

The following case reports were selected to illustrate typical responses of patients with Hodgkin's disease to CB 1348 therapy.

CASE NO. 1

V. D., a white male born 1920. Onset of disease was with fever and node in the groin in September 1952. Diagnosis of Hodgkin's disease was established by biopsy and X-ray therapy instituted. The node receded, symptoms disappeared and the patient remained completely asymptomatic until January 1955, at which time a walnut-sized node appeared in the left axilla. There was in addition a cluster of nodes in the right axilla. X-ray examination of the mediastium showed no pathologic changes. From January 15th to February 24th he received daily 30 mg. of CB 1348 (0.36 mg. per kilo of body weight) for a total dosage of 7.14 mg. per kilo. By the end of two weeks the nodes were smaller, and in a month they were gone. To date, one year after therapy, he remains sign and symptom free. The hematologic status was normal at the beginning of therapy and remained unchanged during and after completion of therapy.

Summary. This case illustrates that a patient once effectively treated with X-ray may have a prolonged and satisfactory response of lymph node enlargement to CB 1348 administered at a later date.

CASE NO. 2

R. C., white female, born 1922. Onset with generalized pruritus in July, 1933. In November enlarged nodes were first observed, limited to the left neck. The spleen was not felt. Biopsy was done on January 21, 1954. X-ray of the chest showed widening of the superior mediastinum. CB 1348 was begun on 1-28-54, 8 mg. daily (0.1 mg. per kilo of body weight) and continued for 153 days until 7-8-54, for a total dose of 17 mg. per kilo of body weight. Improvement was very slow but progressive. The pruritus stopped, there was a 7 lb. weight gain, and a sense of well-being set in. The neck nodes disappeared. Though the chest plate by this time revealed considerable shrinkage of the mediastinal mass, it had not disappeared completely. All medication was discontinued until three months later, 10-28-54, when the patient had chills and swelling of the right neck. She was given 45 mg. of T. E. M. and symptoms subsided. On 3-3-55 she felt sick, and a node was now felt in the left neck. X-ray examination showed increase in the size of the mediastinal mass. CB 1348, 20 mg. per day, was begun and continued until 3-31-55. The neck node disappeared and the mediastinal shadow showed regression. Treatment was stopped until 10-13-55 when malaise and a node in the left neck recurred. The mediastinal mass had again enlarged. CB 1348, 10 mg. per day, was again instituted and continued until 2-1-56. Since no improvement resulted the drug was discontinued.
### Table 1 — Chart Showing Results With CB 138

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Duration</th>
<th>Daily Dose</th>
<th>Days of Treat</th>
<th>Days Between Courses</th>
<th>Total Dose (Mg.)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>22</td>
<td>2 yrs.</td>
<td>20</td>
<td>.4</td>
<td>42</td>
<td>0</td>
<td>840</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>31</td>
<td>3 mo.</td>
<td>8</td>
<td>.09</td>
<td>20</td>
<td>10</td>
<td>238</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>50</td>
<td>13 yrs.</td>
<td>6</td>
<td>.12</td>
<td>234</td>
<td>0</td>
<td>282</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>38</td>
<td>1 yr.</td>
<td>8-16</td>
<td>.15-.30</td>
<td>143</td>
<td>2 mo.</td>
<td>1840</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>40</td>
<td>5 yrs.</td>
<td>16-24</td>
<td>.3-.44</td>
<td>123</td>
<td>3 wks.</td>
<td>2220</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>34</td>
<td>3 yrs.</td>
<td>4-6</td>
<td>.1</td>
<td>50</td>
<td>0</td>
<td>284</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>48</td>
<td>2 wks.</td>
<td>20</td>
<td>.28</td>
<td>60</td>
<td>2 mo.</td>
<td>1536</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>30</td>
<td>5 yrs.</td>
<td>8</td>
<td>.13</td>
<td>14</td>
<td>0</td>
<td>112</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>42</td>
<td>2 yrs.</td>
<td>16</td>
<td>.2</td>
<td>79</td>
<td>2 mo.</td>
<td>1264</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>32</td>
<td>2 yrs.</td>
<td>16</td>
<td>.23</td>
<td>62</td>
<td>4 mo.</td>
<td>992</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>44</td>
<td>8 yrs.</td>
<td>16</td>
<td>.3</td>
<td>58</td>
<td>7</td>
<td>112</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>42</td>
<td>1 yr.</td>
<td>10</td>
<td>.2</td>
<td>35</td>
<td>0</td>
<td>350</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>38</td>
<td>8 yrs.</td>
<td>24-30</td>
<td>.2-.3</td>
<td>42</td>
<td>0</td>
<td>1176</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>35</td>
<td>3 yrs.</td>
<td>30</td>
<td>.35</td>
<td>33</td>
<td>0</td>
<td>990</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>32</td>
<td>6 yrs.</td>
<td>4-6</td>
<td>.08-.12</td>
<td>90</td>
<td>0</td>
<td>486</td>
</tr>
</tbody>
</table>

- **Pruritus and axillary node. Gen'l condition good. No result.**
- **Slow recession of neck nodes and mediastinal mass twice. 3rd course not effective. Period of therapy 2 yrs.**
- **No subjective or objective result.**
- **Subjective improvement. Node recession for 2 mo. Remission with 2nd course 10 mo. 3rd course nodes persisted.**
- **Seven courses of treatment. Nodes receded each time. Recurrence in 6-8 wks. Nodes persisted during final course. Duration of therapy 2 yrs.**
- **Subjective improvement. Recession of neck and mediastinal nodes. Recurrence in 5 wks. Negative results 2nd course.**
- **Persistent pain not affected. X-ray therapy brought relief.**
- **Partial recession of nodes for 2 mo. Second course not effective.**
- **Axillary nodes which receded with each course. Finally became refractory.**
- **Neck nodes receded but recurred in 2 wks.**
- **Nodes did not recede with drug, but did with x-ray therapy.**
- **Partial recession of nodes. Two small neck nodes receded.**
- **Neck nodes showed partial recession for a few weeks. Recurred.**
TABLE 1.—Continued

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Duration</th>
<th>Days of Dose</th>
<th>Days Between Courses</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total Dose</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

16 M 41 9 yrs. 10-12 .12 86 0 1002 Recurrent fever lasting 2-3 wks. No clearcut result.
17 M 30 3 yrs. 3 .04 9 0 27 Was in terminal phase; high fever.
18 F 50 3 yrs. 12-36 .3 -.8 42 0 1008 Pruritus, weight loss, fever. No result. Died.
19 F 30 11 yrs. 16 .3 37 0 502 Pain, fever. No result. Died.
20 M 29 2 yrs. 8-24 .1 -.3 56 30 1750 Pruritus, nodes, wt. loss, edema. Subjective improvement for 1-2 mo. Died.
21 F 18 4 yrs. 16 .32 21 60 1312 Nodes, malaise, wt. loss. Good results both times, for 2 and 3 mo. respectively. Died.
22 F 20 3 yrs. 8-16 .16-.32 42 60 1796 4 courses of treatment in 1 yr. Fever, nodes, malaise. Remissions lasting 2-3 wks. Fever, wt. loss set in. Died.
23 M 33 3 yrs. 8-16 .1 -.2 100 0 1320 Abdominal mass, pain, weakness. Good result for 2 mo. Recurrence. Died.
24 M 21 2 yrs. 8 .11 45 0 360 Rapid loss of wt. Fever, Pleural effusion. No result. Died.
25 F 44 1 yr. 6-16 .15-.30 138 0 2598 Subjective improvement with all courses for 1-2 months. Died.
26 M 64 4 mo. 20 .5 28 0 560 Malaise, wt. loss, no result. Died.
27 M 48 3 yrs. 48 .94 4 0 192 Terminal. Fever, edema. Died.
28 M 55 1 yr. 8-16 .1 -.2 35 108 1856 Remarkable recession of nodes. TEM had not been effective. Result lasting 2 mo. Died of GI bleeding.
29 F 24 4 yrs. 10-24 .1 -.4 17 0 1320 Advanced case. Died.
30 F 48 2 yrs. 4 .08 35 0 140 Therapy started for recurrence of pain.
31 F 27 2 yrs. 8-24 .32-.5 62 120 1960 Nodes, weakness, wt. loss. Partial result lasting 2-3 mo.
Summary. This case is illustrative of a good therapeutic effect on a previously untreated subject resulting from several courses of CB 1348, followed by refractoriness to the medication.

CASE NO. 3

S. M., white male born 1906. On July 9, 1954, a barber brought to the attention of the patient the fact that there were enlarged nodes in his neck. There were no subjective symptoms. Since the nodes persisted he sought medical advice on September 15, 1954. An x-ray picture at this time revealed a large mediastinum. A biopsy was done and Hodgkin's disease diagnosed. At the start of therapy there were massive nodes in the right side of the neck. CB 1348 (0.34 mg. per kilo of body weight) was begun on September 27, 1954, 2 mg. daily, and continued until November 30, 1954, for a total dose of 22.6 mg. per kilo (patient weighed 68 kilos). At the end of the period the nodes in the neck were gone and x-ray revealed disappearance of the mediastinal shadow. Two months later the nodes returned to almost the original size. The mediastinal mass also recurred. There were no subjective symptoms, general condition was good. CB 1348 was started on February 9, 1955, 30 mg daily (0.44 mg. per kilo of body weight) and continued until March 1, 1955, and then reduced to 20 mg.; the nodes had already started to recede. Medication was continued until April 25, 1955, at 20 mg. daily. At this time, seven months after institution of therapy, the nodes persisted and despite the fact that they had regressed to about 75% of their original size, it was decided to use Thiotepa.* When this proved ineffective, x-ray therapy was begun. With 2000 r. there was complete regression of neck and mediastinal nodes. After this the patient was free of nodes from June 23 until October 5, when nodes returned, pruritus developed and a 20 lb. loss of weight occurred.

Summary. This case is an example of a patient previously untreated who responded well to a first course of CB 1348, partially to a second course and completely, but for only three months, to x-ray therapy.

Work with R-48

R-48, Erysan, or Cloronaftina, with a formula

was produced by Haddow* and his associates and reported in 1948 under the name of R-48. The initial results obtained with it on Hodgkin's disease were not encouraging. Later reports published by Italian6 and Danish7 workers, however, were more optimistic.

We treated a total of 22 patients, of whom twelve had received and become refractory to CB 1348. In five instances diagnosis had been made recently and the patient had as yet received no therapy; five others had received x-ray, triethylenemelamine or thiotepa.

Administration and Dosage: The drug was administered in gelatine capsules containing 100 mg., and we gave from 100 to 400 milligrams daily for a maximum

* Triethylene thiophosphoramide, supplied to us through the courtesy of the Lederle Laboratories.
period of eight months. Medication was discontinued when symptoms of toxicity occurred or when after a reasonable period of four or five weeks either no results were observed or a rapid downhill course had set in.

Results (table 2)

Five patients responded with complete regression of nodes and symptoms, twelve with partial regression of nodes and symptoms, and the remaining five responded not at all. Among the latter was one patient who had no symptoms but who had a node upon the left pectoralis major muscle; two others were free of nodes and had no symptoms except rapid sedimentation rate; two others were in an advanced stage of the disease and were deteriorating rapidly. The patients whose response was partial enjoyed first a subsidence of symptoms followed by slow regression, but never complete disappearance, of enlarged lymph nodes. Remissions lasted from one week to three months.

In four instances there was a response to a second course of treatment but remissions have been short except in one case where at the end of six months it is still maintained.

Continuing the drug beyond the period required to produce remission appeared to serve no purpose, for in due course nodes and symptoms reappeared despite the fact that the patient was still taking the drug and had been doing so for months.

It is of interest that five patients refractory to CB 1348 showed rapid regression of nodes and symptoms after taking R-48. Following is a case illustrative of the action of R-48 preceded by CB 1348.

**L. G., Female aged 48:** Onset and diagnosis of Hodgkin's disease in 1948. Through the years she received radiation therapy, T. E. M. and colchicine. In May, 1954, because of massive enlargement of nodes in the right neck she was given CB 1348, 16 mg. daily. Her general condition was good at this time and no subjective symptoms were present. After three weeks of therapy the nodes disappeared and therapy was discontinued. In one month a node recurred, CB 1348 was again started, 16 mg. daily, and in a week the node disappeared and medication was stopped. Two months later neck nodes reappeared, together with new ones in the right axilla. After two weeks of CB 1348, 16 mg. daily, the masses again disappeared only to recur in both sites seven weeks later. Two more weeks of medication at the same dosage again resulted in subsidence. Once more the remission lasted two months only and CB 1348 was renewed and continued for two and one-half months before an effect was observed. Dizzy spells and convulsive seizures occurred and were ascribed by the patient to the drug, which was therefore discontinued. Two months after this a mass recurred in the right neck, CB 1348 was given, and dizziness and convulsive seizures ensued.* Medication was discontinued at this point. In all, the patient had five courses of treatment with CB 1348 over a period of a year and received a total of 528 milligrams. A month after discontinuance of CB 1348 R-48 was started. The nodes in the neck had persisted and grown larger though the general condition was good and there were no subjective symptoms. The dosage scheduled was 400 mg. daily. In two weeks the neck mass disappeared completely. She was maintained on 400 mg. daily for three months, after which the dosage was reduced to 100 mg. daily for the next three months. While on this reduced maintenance schedule small, shotty nodes reappeared, the dosage was increased to 200 mg. daily for one month, and the nodes disappeared. Thereafter the patient was kept on a maintenance dosage of 100 mg. daily for a period and then 100 mg. every other day for the final three months, during which

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*Note: One year after CB 1348 had been discontinued this patient had a similar convulsive seizure and we concluded, therefore, that CB 1348 had not caused these attacks.*
### Table 2.—Chart Showing Results with R-48

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Duration</th>
<th>Daily Dose</th>
<th>Days of Treat.</th>
<th>Days Between Courses</th>
<th>Total Dose in Gm.</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>33</td>
<td>2 yrs.</td>
<td>300</td>
<td>75</td>
<td>0</td>
<td>22.5</td>
<td>Subjective improvement. Nodes receded but did not disappear. Recurred last week of therapy. Transfusion given.</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>22</td>
<td>2 yrs.</td>
<td>100</td>
<td>224</td>
<td>27</td>
<td>22.4</td>
<td>Subjective improvement. Nodes subsided. Recurred in 4 wks. 2nd course given, with pos. results. Remission lasted 41 days.</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>50</td>
<td>13 yrs.</td>
<td>200</td>
<td>14</td>
<td>0</td>
<td>2.8</td>
<td>General condition deteriorated rapidly. R-48 stopped and 3025 started.</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>38</td>
<td>1 yr.</td>
<td>200</td>
<td>117</td>
<td>0</td>
<td>23.4</td>
<td>Subjective improvement. Large neck nodes subsided. New nodes appeared in latter part of period of treatment.</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>40</td>
<td>5 yrs.</td>
<td>100</td>
<td>202</td>
<td>23</td>
<td>33.7</td>
<td>Neck nodes and back pain subsided in 2 wks., recurred 3 wks. after medication stopped. Results from 2nd course positive.</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>35</td>
<td>4 yrs.</td>
<td>200</td>
<td>50</td>
<td>0</td>
<td>11.8</td>
<td>Enlarged spleen, pain, wt. loss, malaise; remission of symptoms, reduction of spleen.</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>48</td>
<td>17 mo.</td>
<td>300</td>
<td>157</td>
<td>0</td>
<td>47.1</td>
<td>Subjective symptoms controlled, nodes receded; returned during last 2 wks. of therapy.</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>32</td>
<td>7 yrs.</td>
<td>100</td>
<td>94</td>
<td>90</td>
<td>18.1</td>
<td>Backache subsided with 1st course. Negative results from 2nd course.</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>42</td>
<td>2 yrs.</td>
<td>300</td>
<td>28</td>
<td>0</td>
<td>9.4</td>
<td>Tender mass in chest wall. Tenderness subsided, size of mass unchanged.</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>34</td>
<td>4 yrs.</td>
<td>100</td>
<td>100 plus</td>
<td>42</td>
<td>16.0 plus</td>
<td>Large node in l; axilla disappeared in six days. Returned 6 wks. Persisted after 2 mo. on 200 mg. daily.</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>32</td>
<td>6 yrs.</td>
<td>300</td>
<td>14</td>
<td>0</td>
<td>4.9</td>
<td>Node receded; anemia and lobular pneumonia developed. Therapy stopped.</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>27</td>
<td>2 yrs.</td>
<td>100</td>
<td>75</td>
<td>0</td>
<td>12.9</td>
<td>Subjective improvement for 2 months.</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>30</td>
<td>1 yr.</td>
<td>100</td>
<td>34</td>
<td>0</td>
<td>3.4</td>
<td>No effect on only symptom of tiredness.</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>39</td>
<td>5 yrs.</td>
<td>100</td>
<td>178</td>
<td>90</td>
<td>30.3</td>
<td>Mediastinal mass subsided in 2 mo. Neck nodes reappeared 3 mo. after drug was stopped; disappeared 5 wks. after drug re instituted.</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>34</td>
<td>6 yrs.</td>
<td>300</td>
<td>63</td>
<td>0</td>
<td>18.9</td>
<td>Neck nodes subsided.</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>47</td>
<td>9 yrs.</td>
<td>100</td>
<td>238</td>
<td>0</td>
<td>31.0</td>
<td>Neck mass receded considerably. Residual nodes persist.</td>
</tr>
</tbody>
</table>
TABLE 2—Continued

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Duration</th>
<th>Daily Dose</th>
<th>Days of Treat</th>
<th>Days Between Courses</th>
<th>Total Dose in Gm.</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>F</td>
<td>33</td>
<td>5 mo.</td>
<td>200</td>
<td>15</td>
<td>0</td>
<td>4.6</td>
<td>Subjective improvement. Two small nodes in neck receded. Toxicity, therapy suspended.</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>47</td>
<td>1 mo.</td>
<td>200</td>
<td>82</td>
<td>0</td>
<td>22.2</td>
<td>Subjective improvement. One small node in neck receded. New nodes appeared 3 wks. later. Drug suspended.</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>26</td>
<td>3 yrs.</td>
<td>100</td>
<td>180</td>
<td>0</td>
<td>24.0</td>
<td>Marked subjective improvement. Nodes diminished in size.</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>33</td>
<td>5 mo.</td>
<td>200</td>
<td>76</td>
<td>0</td>
<td>15.2</td>
<td>Subjective improvement. Wt. gain. Lung shadows cleared.</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>30</td>
<td>6 yrs.</td>
<td>100</td>
<td>270</td>
<td>0</td>
<td>27.0</td>
<td>Subjective improvement. Wt. gain. Nodes localized to left axilla persist.</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>46</td>
<td>12 yrs.</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>11.2</td>
<td>One small node disappeared.</td>
</tr>
</tbody>
</table>

interval no nodes were present. However, the red blood count dropped from the usual level of 3.9 million to 2.7 million, the hemoglobin from 12.2 grams to 8.4 grams, the platelets from 176,000 to 40,000; the white blood cells remained at 9,000. Administration of the drug was therefore discontinued.

DISCUSSION

The difficulties encountered in attempting to evaluate a new therapeutic agent upon Hodgkin's disease are many. Not the least of these difficulties is the smallness of the group available to any one investigator and the long period of follow-up that is required. We felt that in our study two and one-half years were sufficient to allow for the effect, the duration of the effect, and the susceptibility of the patient to multiple courses of treatment. Though small, our group was composed of individuals of various ages and both sexes in different stages of the disease from incipient to terminal. Further, there were many patients who had previously received other effective forms of therapy to which they had become refractory.

Both CB 1348 and R-48 proved effective for some individuals and non-effective for others. The majority of those who did not respond were in an advanced stage of the disease, though some others also failed to respond. No evidence obtained would indicate that either drug has promise as a life-prolonging agent, but each has value as a palliative, is easy to administer and is relatively non-toxic.

The rate at which signs and symptoms were brought under control was not so rapid as we have been accustomed to see with Bis nitrogen mustard. In three instances CB 1348 caused recession of the nodes of patients who had not had relief from T. E. M. On the other hand, in some instances CB 1348 failed completely to cause recession of nodes which were subsequently completely dissolved with x-ray.

Determination of effective dosage is difficult since each patient must of necessity be his own control. Having started with one dosage schedule, evaluation of
the effect of a changed dosage for the same patient is not possible as one cannot be
sure that ensuing changes in the patient’s condition may not have been due to
delayed action from the first dosage schedule. Also an effect following upon an
increased dosage might possibly have been produced by an original, smaller
dosage had it been administered for a longer time. Comparison of the effect of a
dosage schedule on one patient cannot be compared with the effect of a different
dosage schedule upon another patient, since the original status of no two patients
is identical as to age, duration, extent and severity of disease. Thus good results
were sometimes obtained with dosages as low as 0.1 milligram per kilo of body
weight, while in other instances no benefit at all followed upon dosages of 0.3,
0.6, 0.9 mg. per kilo of body weight. Also, some patients under observation were
at one time favorably affected at a dosage level of 0.2 mg. but when, because of
exacerbation of the disease, a later course of 0.3 mg. per kilo was given, results
were negative, thus emphasizing the pertinence of stage of the disease to response
to therapy.

CB 1348 offers a considerable advantage over Bis nitrogen mustard and
triethylenemelamine in that it is easy to administer and less toxic, very rarely
causing nausea or vomiting at the dosage given. It should be useful also in those
situations where for some reason x-ray therapy is not feasible or available, and
particularly so when the disease is disseminated rather than localized. Under
controlled conditions the drug can be taken for two to three weeks at a time
without the necessity of an interval checkup.

The above comments apply to R-48. The action was in many ways similar, but
R-48 can be said to complement CB 1348 inasmuch as in five instances where the
latter was non-effective R-48 was rapidly and completely effective. As in the case
of CB 1348, however, remissions produced by R-48 were relatively short and in
due course the patients became refractory to its action.

Neither drug is useful as a prophylactic against recurrence. Despite the fact
that each was administered for months while patients were in remission, symp-
toms and enlarged nodes recurred.

SUMMARY

Forty patients with Hodgkin’s disease were treated with CB 1348 or R-48 or
both. These drugs are useful and easy to administer. They have a therapeutic
effect upon subjective symptoms and enlarged lymph nodes. The average re-
mission lasts two months, shorter in some cases and longer in other cases. Toxicity
is minimal. Hematologic depression occurs late as a rule and is reversible upon
discontinuance of the drugs. Both drugs appeared to produce the same effect at
about the same rate, and the effect lasted for about the same length of time.
R-48 proved effective in some instances where CB 1348 had not been so, and
CB 1348 sometimes induced a remission when T. E. M. had failed. In some cases
radiation therapy caused recession of nodes when both drugs had been ineffective.

SUMARIO IN INTERLINGUA

Quaranta patientes con morbo de Hodgkin esseva tractate con CB 1348 o
R-48 o ambes. Iste drogas es utile e facile a administrar. Illos exerce un effecto
therapeutic super le symptomatas subjective e super le allargate nodos lymphatic.
Le duration medie del remission es duo menses, minus in certe casos e plus in alteres. Le toxicitate es minimal. In general, depression hematologic occurre tardivemente e es reversibile per discontinuation del drogas. Ambe drogas pareva producere le mesme typo de efecto al mesme grado e durante le mesme periodo de tempore. R-48 se monstrava efficace in certe casos ubi CB 1348 habeva essite van, e CB 1348 induceva un remission in certe casos ubi TEM habeva essite van. In certe casos, therapia radiational resultava in un recession del nodos post que ambe le drogas se habeva monstrate inefficace.

REFERENCES

Therapeutic Results in Treatment of Hodgkin's Disease with CB 1348 and R-48

ANTONIO ROTTINO

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