Visual Impairment due to Optic Neuropathy in Pernicious Anemia: Report of a Case and Review of the Literature

By Henry E. Hamilton, Philip P. Ellis and Raymond F. Sheets

THOUGH the havoc wrought by blindness is not part of the classical picture of pernicious anemia, an occasional victim of this disease becomes blind from an optic nerve lesion. In America, little attention has been given to this complication. In 1897, Bastianelli reported a patient with anemia, spastic paraplegia and optic nerve atrophy, and thereafter sporadic reports of optic atrophy in patients with pernicious anemia appeared. Cohen, in 1936, first suggested that optic nerve neuropathy was a direct sequel of pernicious anemia. By 1940, Turner collected several reports and discussed the clinical problem, defining the kind of optic nerve lesion encountered. Subsequent reviews with additional case reports were made by McAlpine and Goldsmith in 1952, Benham in 1951 and Hyland and Sharpe in 1952. It is our purpose to report a case and to review the available medical writing on this topic. In the review we will stress the associated hematologic findings, neurologic lesions and response to therapy.

CLINICAL STUDY

A 47-year-old man complaining of failing vision was admitted to the service of the Department of Ophthalmology, University Hospitals, in July 1952. The initial ocular examination revealed the vision in the right eye to be 20/20 and in the left eye 20/100. Ophthalmoscopic examination of both eyes failed to reveal any abnormalities. The optic discs, the macular areas and the entire visible fundi appeared normal. The visual field in the right eye was normal; the visual field in the left eye showed a paracentral scotoma. These findings suggested a retrobulbar lesion in the left side. Accordingly, more detailed medical study was undertaken.

Medical history: Six years before admission, he was found to be “anemic” and had “low stomach acid.” He added cooked liver to his diet and took hydrochloric acid with each meal. In the preceding year he had become irritable and his judgment had deteriorated. This was in spite of the fact that the patient considered himself to be “perfectly well.” During this time, vision had failed to the extent that he was afraid to drive his car. During the preceding months he had noticed tingling and numbness of his fingers and also cramps of the legs. For a year he had complained of burning of the tongue. He had never had liver injections nor had he taken oral vitamin preparations. He was not a heavy smoker.

Past medical history: In childhood he had a severe attack of scarlet fever with no recognized residual; otherwise he had enjoyed excellent health. He worked hard as a rancher until admission to this hospital.

Family history: His father had “pernicious anemia” and had been treated for 15 years with intramuscular liver injections.

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OPTIC NEUROPATHY IN PERNICIOUS ANEMIA

Physical examination: The patient was well developed, irritable and his insight was impaired. He was suntanned on the exposed areas. The skin and sclera were not icteric. The margins of the tongue were smooth. The head and neck were normal. Except for the optic nerve involvement, the cranial nerves were intact. The chest was normal to auscultation and percussion. The blood pressure was 120/80 mm. Hg. The cardiac rate, rhythm and sounds were normal. The heart was not overaccessible or enlarged. The abdomen was normal. The spleen was not palpable and the liver was not enlarged. The rectal examination was normal and the stool was negative for occult blood. The extremities were normal. The peripheral blood vessels were normal and the lymph nodes of the neck, axillae and groin were not enlarged. The sensations of pain and temperature were intact. Pallesthesia was 10 per cent over the right shin and 30 per cent over the left. The reflexes were: biceps jerks, 1+/1±; knee jerks, 0/0 and tendon Achilles jerks, 0/0. Plantar stimulation resulted in normal flexion of the toes.

Laboratory studies: The hemoglobin was 12.4 Gm. per 100 cc. The erythrocyte count was 3.85 million per cu. mm. The packed cell volume was 40 per cent. The white blood count was 5,100. The reticulocyte count was .6 p.r cent and the platelet count, 202,000. The erythrocytes and leukocytes of the peripheral smear appeared normal. The smear made from a sternal bone marrow aspiration showed erythroid hyperplasia with rare minimal megaloblastic changes (see table 2). The chest x-ray was normal. X-ray examination of the esophagus, stomach and duodenum showed no abnormality. There was no free hydrochloric acid in the stomach after stimulation with histamine. Serum bilirubin was 0.9 mg. per cent. Plasma proteins were 4.6 Gm. of albumin and 3.0 Gm. of globulin. Serologic tests for syphilis and brucellosis were negative.

Response to vitamin B12 therapy: The patient was given intramuscular injections of 30 $\mu$G. of vitamin B$_{12}$ daily for 4 days. At the end of this time a second marrow aspiration revealed changes of erythroid hyperplasia with an increase in normoblasts (see table 2). At this time the patient returned to his home in Texas. Frequent vitamin B$_{12}$ injections were administered by his family physician, Robert M. DeLaney, M.D., Abernathy, Texas. He informed us that by December 1952, the patient's hemoglobin was 13.8 Gm. and the red blood cell count 4.5 million. These values remained in this range thereafter. Central vision improved rapidly during the first few months. We do not have precise details, but at the end of six months vision was judged by the patient to be normal. The irritability and personality changes disappeared promptly after institution of therapy. In the intervening years the patient has lived an active life.

Follow-up study: In the fall of 1957 we examined the patient again. He was free of complaints. His eyesight seemed normal to him. Physical examination was normal. He was pleasant and cooperative and had excellent insight. The tongue was no longer atrophic. Pallesthesia over the shins was normal. Reflexes were: biceps jerks, 2/2; knee jerks, 2/2 and the tendon Achilles, 1/1.

Ophthalmologic examination: The left field scotoma had disappeared completely. The discs were normal. Vision in the right eye was 20/20 and in the left, 20/30.

<table>
<thead>
<tr>
<th>Table 1.—Hematological Values</th>
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<tr>
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<tr>
<td>Hemoglobin</td>
</tr>
<tr>
<td>P.C.V. %</td>
</tr>
<tr>
<td>RBC 10$^6$/cu. mm.</td>
</tr>
<tr>
<td>WBC/cu. mm.</td>
</tr>
<tr>
<td>Platelets/cu. mm.</td>
</tr>
<tr>
<td>Reticulocytes %</td>
</tr>
<tr>
<td>Free hydrochloric acid in stomach</td>
</tr>
<tr>
<td>Shilling test (% recovery of Co$^{60}$ in urine of oral dose of Co$^{60}$-labelled vitamin B$_{12}$)</td>
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</tbody>
</table>
TABLE 2.—Bone Marrow Studies

<table>
<thead>
<tr>
<th>Nucleated Cell Types</th>
<th>Before Treatment</th>
<th>4 Days After Vitamin B12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blast forms</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Pronormoblasts</td>
<td>2.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Basophilic normoblasts</td>
<td>14</td>
<td>1.8</td>
</tr>
<tr>
<td>Polychromatophilic normoblasts</td>
<td>8.4</td>
<td>28</td>
</tr>
<tr>
<td>Orthochromatophilic normoblasts</td>
<td>8.4</td>
<td>28</td>
</tr>
<tr>
<td>Promyelocyte</td>
<td>7.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Myelocyte</td>
<td>12.4</td>
<td>13.4</td>
</tr>
<tr>
<td>Metamyelocyte</td>
<td>11.0</td>
<td>9.6</td>
</tr>
<tr>
<td>Band leukocyte</td>
<td>7.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Segmented leukocyte</td>
<td>25.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>5.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Plasma cell</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Myeloid/erythroid ratio</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>*Absolute % erythroid series.</td>
<td></td>
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</tbody>
</table>

Laboratory studies: The hemoglobin was 13.8 Gm. per 100 ml. The white blood count was 8,000. The packed cell volume was 46 per cent. The differential count revealed 70 per cent segmented polymorphonuclear leukocytes, 4 per cent eosinophils, 22 per cent lymphocytes and 4 per cent monocytes. The platelet count was 156,000 per cu. mm. The reticulocyte count was 1.3 per cent. The erythrocyte sedimentation rate was 8 mm. in one hour by the Westergren method. The urinalysis was normal. The fasting blood sugar was 75 mg. per 100 ml. and the blood uric acid was 4.4 mg. per cent.

Test for absorption of B12: The Shilling test was performed. Of the 0.5 μc. of cobalt*-labelled vitamin B12 given orally, only 0.7 per cent was recovered in the urine in 24 hours. This is consistent with an absence of intrinsic factor. Our normal range for 24-hour recovery of cobalt* in this test is approximately 7 per cent to 38 per cent. In our proved cases of pernicious anemia, the range is from 0 to 2 per cent. Radiographic studies of the stomach, duodenum and chest were normal. The stool was negative for occult blood.

Comment: The complaint of failing vision brought this man under medical care. In spite of the almost normal hematologic values, a tentative diagnosis of pernicious anemia was made in 1952. It was based upon several minor findings which were not conclusive but pointed to a disordered metabolic process resulting from vitamin B12 deficiency. There was histamine-free achlorhydria, some atrophy of the papillae of the tongue and early signs of posterior column disease. The M.C.V. was 108 μl; the M.C.H.C., 31 per cent; and the M.C.H., 32.2 Gm. x 10^12. The hyperplastic bone marrow revealed a predominance of immature erythroid cells. Four days after therapy began, a decided shift in proportion of cells to the mature forms occurred with a relative increase in the erythroid elements. These changes indicated that vitamin B12 had altered the maturation process. Therapy with vitamin B12 was followed by rapid restoration of vision and disappearance of peripheral neurologic abnormalities.

In 1957 we demonstrated the patient's inability to transport vitamin B12 across the gastrointestinal membrane by the use of tagged cobalt*-vitamin B12*. This additional evidence supported the diagnosis of Addisonian pernicious anemia. There was no evidence in the history, physical examination or clinical course to suggest a toxic, infectious or degenerative cause to account for the ophthalmologic findings.

REVIEW OF PREVIOUS CASES

We found references to 44 cases of optic neuropathy associated with pernicious anemia, not including the present reported case. Detailed studies were
OPTIC NEUROPATHY IN PERNICIOUS ANEMIA

recorded in 28 of the 44 cases. In the other 16 cases only casual reference was
made to the association of pernicious anemia and visual loss. Table 3 presents
pertinent details of 29 case reports, including the 28 referred to above and
our case. Each patient in this table is given a number and author reference.

We recorded the lowest hemoglobin or erythrocyte count and changes after
antipernicious anemia therapy. The absence of free hydrochloric acid from
the stomach contents if mentioned by the author was noted, as well as any
findings compatible with subacute combined sclerosis. A presumptive diag-
nosis of pernicious anemia was made on these data. Many case reports lacked
specific details of clinical and laboratory evidence to support a definitive
diagnosis of pernicious anemia. Bone marrow findings were rarely mentioned.
Absorption studies with cobalt\textsuperscript{60}-labelled vitamin B\textsubscript{12} have not been reported
before in cases with the combination of pernicious anemia and optic atrophy.
The 16 cases not recorded in table 3 had pernicious anemia only on the state-
ment of the author.

The onset of visual difficulty antedated other manifestations of pernicious
anemia in 9 out of the 29 cases (table 3). Anemia was the first trouble recog-
nized in 8 of the cases; and subacute combined sclerosis was first in 3. In 6
cases the presenting symptoms were both ocular and neurologic. The eye
manifestation was the only significant finding in 3 cases. Vision improved in
14 of the treated patients. No improvement was reported in 9 patients. Of the
14 patients with improvement, 7 had residual field defects. Of the 9 who
failed to improve, the possibility of coexisting cataracts, macular lesions or
ocular hemorrhages could not be excluded for no details were recorded by
the author.

**Discussion**

This review indicates that optic nerve involvement may be part of the patho-
logic findings directly attributed to Addisonian pernicious anemia. This nerve
involvement is probably similar to other neurologic lesions of pernicious
anemia. The clinical manifestations of optic nerve involvement may precede,
coincide with or follow the symptoms and signs of anemia or subacute com-
bined sclerosis. There is no early change in the optic disc. With progression
of the disease, however, optic atrophy may appear. The occurrence or the dura-
tion of pallor of the optic disc is not a valid guide for expected response to
therapy. Pallor of the disc results from a decreased number of capillaries on
the disc and does not necessarily reflect the function of the individual axis
cylinders. Gliosis after inflammation may be responsible for loss of capillaries
without significant disturbance of function of the axis cylinder. Optic pallor
actually may become more prominent after treatment and the ensuing recovery
of visual function. The field defect is a central, paracentral or central caecal
scotoma characteristic of retrobulbar neuritis. If pernicious anemia is treated
adequately early in the course of the optic nerve involvement, the prognosis
for vision is good. If treatment is started later, defects in visual acuity and
visual fields may result.

The Shilling test of gastrointestinal absorption of cobalt\textsuperscript{60}-labelled vitamin
B\textsubscript{12} may be of much value in establishing a diagnosis of pernicious anemia in
TABLE 3.—Clinical and Hematologic Data in Reported Cases of Optic Neuropathy due to Pernicious Anemia

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Author Ref.</th>
<th>Sex</th>
<th>Age</th>
<th>Anemia</th>
<th>Neuro.</th>
<th>Eye</th>
<th>Duration of Symptoms</th>
<th>Vision</th>
<th>Hematologic Values</th>
<th>Therapy</th>
<th>Year Reported</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R.T.</td>
<td>B.T. or Retics.</td>
<td>No HCL.</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A.T.</td>
<td>B.T.</td>
<td>Hemoglobin Gm./100 cc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Disc</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B.T.</td>
<td>A.T.</td>
<td>B.T.</td>
<td>A.T.</td>
</tr>
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1  1  M  33  3 Yrs.  3 Yrs.  3 Yrs.  R 20/60  L 20/60  Pale  4.2  .6*  70%*  28%*  1910
2  2  M  67  4 Yrs.  1 Yr.+  1 Yr.  Dec.  No Imp.  Pale  5.0  54%  92%  +  Liver  1936
3  3  M  63  4 Yrs.  None  2-3 Mos.  R 20/120  L 20/120  Cent.  Scot.  Conc.  30%  97%  +  Liver  1935
4  4  M  65  7 Yrs.  3 Yrs.  1 Yr.  R 20/100  L 20/100  Cent.  No Imp.  Pale  1.1  4.9  24%  97%  +  Liver  1936
5  5  M  55  3 Mos.  None  18 Mos.  R 20/200  L 20/200  Cent.  No Imp.  Pale  1.7  4.0  30%  97%  +  Liver  1936
6  6  M  46  None  None  8 Mos.  R 20/100  L 20/100  Cent.  No Imp.  Pale  4.7  ?  94%  ?  Liver  1936
7  7  M  56  None  None  9 Mos.  L 20/100  L 20/100  Cent.  No Imp.  Pale  1.8  14%  54%  Liver  1938
8  8  M  59  6 Mos.  6 Mos.  5 Mos.  R 5/200  L 5/200  Temp.  1.35  48%  5 Gm.  Liver  1938
9  9  M  50  6 Mos.  6 Mos.  6 Mos.  L 10/200  L 10/200  Temp.  0.82  22%  Blood  1938
10 10  M  64  11 Yrs.  8 Yrs.  7 Yrs.  R 20/100  L 20/100  Pale  4.05  ?  78%  ?  1938
11 11  M  47  2 Yrs.  3 Yrs.  5 Mos.  L 20/100  L 20/100  Temp.  3.0  3.7  65%  80%  +  Liver  1938
12 12  M  64  1 Mo.  2 Yrs.  2 Yrs.  No Imp.  L 20/100  L 20/100  Temp.  9.0  9.0  90%  +  Liver  1938
13 13  M  61  Cent.  Scot.  Pale  1939
14 14  M  61  Cent.  Scot.  Pale  1939
<table>
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<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Duration</th>
<th>RBC</th>
<th>SC</th>
<th>Temp</th>
<th>Palor</th>
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<tbody>
<tr>
<td>15</td>
<td>11</td>
<td>M</td>
<td>None</td>
<td>6 Mos.</td>
<td>R 20/80</td>
<td>Cent.</td>
<td>Less R</td>
<td>2.9</td>
</tr>
<tr>
<td>16</td>
<td>11</td>
<td>M</td>
<td>None</td>
<td>6 Mos.</td>
<td>L 20/120</td>
<td>Scot.</td>
<td>None L</td>
<td>5.1</td>
</tr>
<tr>
<td>17</td>
<td>11</td>
<td>M</td>
<td>None</td>
<td>8 Mos.</td>
<td>R 20/200</td>
<td>Imp.</td>
<td>Cent.</td>
<td>4.2</td>
</tr>
<tr>
<td>18</td>
<td>12</td>
<td>M</td>
<td>None</td>
<td>15 Mos.</td>
<td>R 20/80</td>
<td>Cent.</td>
<td>Imp.</td>
<td>4.3</td>
</tr>
<tr>
<td>19</td>
<td>12</td>
<td>M</td>
<td>None</td>
<td>15 Mos.</td>
<td>R 20/80</td>
<td>Cent.</td>
<td>Imp.</td>
<td>4.2</td>
</tr>
<tr>
<td>20</td>
<td>13</td>
<td>F</td>
<td>None</td>
<td>7 1/2 Yrs.</td>
<td>L 20/40</td>
<td>Scot.</td>
<td>Imp.</td>
<td>4.2</td>
</tr>
<tr>
<td>21</td>
<td>13</td>
<td>M</td>
<td>None</td>
<td>2 Yrs.</td>
<td>R 20/400</td>
<td>No Imp.</td>
<td>Imp.</td>
<td>2.8</td>
</tr>
<tr>
<td>22</td>
<td>13</td>
<td>M</td>
<td>None</td>
<td>1 Yr.</td>
<td>R 20/400</td>
<td>No Imp.</td>
<td>Imp.</td>
<td>2.8</td>
</tr>
<tr>
<td>23</td>
<td>14</td>
<td>M</td>
<td>None</td>
<td>9 Mos.</td>
<td>R 20/200</td>
<td>Cent.</td>
<td>Imp.</td>
<td>3.4</td>
</tr>
<tr>
<td>24</td>
<td>14</td>
<td>M</td>
<td>None</td>
<td>6 Mos.</td>
<td>R 20/200</td>
<td>Scot.</td>
<td>Imp.</td>
<td>3.0</td>
</tr>
<tr>
<td>25</td>
<td>14</td>
<td>F</td>
<td>None</td>
<td>6 Days</td>
<td>R 2/80</td>
<td>No Imp.</td>
<td>Imp.</td>
<td>2.7</td>
</tr>
<tr>
<td>26</td>
<td>14</td>
<td>M</td>
<td>None</td>
<td>6 Mos.</td>
<td>L 1/80</td>
<td>Scot.</td>
<td>Imp.</td>
<td>2.7</td>
</tr>
<tr>
<td>27</td>
<td>15</td>
<td>M</td>
<td>None</td>
<td>22 Mos.</td>
<td>R 20/120</td>
<td>Imp.</td>
<td>Scot.</td>
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<td>16</td>
<td>M</td>
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<td>Imp.</td>
<td>Scot.</td>
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<tr>
<td>29</td>
<td>17</td>
<td>M</td>
<td>None</td>
<td>6 Mos.</td>
<td>L 20/20</td>
<td>Imp.</td>
<td>Scot.</td>
<td>3.8</td>
</tr>
</tbody>
</table>

*Legend: Neuro. = symptoms-signs of combined sclerosis; B.T. = before therapy; A.T. = after therapy; R.B.C. = erythrocytes in millions/mm. 2; Retic. = reticulocytes %; Yr. = year; Mo. = month; R = right; L = left; *Died, pretreatment era: Dec. = decrease; Imp. = improved; Cent. = central; Scot. = scotoma; C.F. = visual acuity count fingers; Conc. = concentric; Const. = constriction; H.M. = visual acuity recognize hand movements; Temp. = temporary; Norm. = normal.*
a patient with an optic nerve lesion of obscure etiology. It is particularly helpful in patients with pernicious anemia who do not yet have anemia or those in remission from treatment with less than optional vitamin B₁₂ or folic acid containing vitamin preparation. The report of Ross²² is important for it demonstrated that treatment with folic acid therapy can be followed with progression of optic atrophy in pernicious anemia. This reaction is similar to the explosive activation of subacute combined sclerosis in patients with pernicious anemia who were treated with folic acid. It is inadvisable to treat a person with optic atrophy of unknown etiology with folic acid without first excluding pernicious anemia as a cause.

**Summary**

1. A man with optic nerve involvement and pernicious anemia regained normal vision after treatment with vitamin B₁₂.

2. In a search of the literature we found 28 cases with both pernicious anemia and optic neuropathy. The hematologic, neurologic and ophthalmologic findings were analyzed in these cases. In each case, the diagnosis of pernicious anemia was established. Optic atrophy associated with pernicious anemia may be part of the pathologic process of pernicious anemia. If the patient is treated early with vitamin B₁₂ or liver extract, optic nerve function returns.

Sixteen other cases with optic atrophy and possible pernicious anemia in the literature had inadequate information to substantiate the diagnosis.

3. The use of a cobalt⁶⁰-labelled vitamin B₁₂ absorption test may be helpful in optic nerve disorders of obscure etiology.

**Summario in Interlingua**

1. Un homine con affection del nervo optic e anemia perniciose reganiava su vision normal post tractamento con vitamina B₁₂.

2. Le scrutinio del litteratura revelava 28 casos de anemia perniciose in association con neuropathia optic. Le constatationes hematologic, neurologic, e ophthalmologic in iste casos eseva analyosate. In omne casos, le diagnose de anemia perniciose eseva establite. Atrophia optic associate con anemia perniciose es possibilemente un parte del processo pathologic de anemia perniciose. Si le patiente es tractate promptemente con vitamina B₁₂ o extracto de hepate, le function del nervo optic se restaura.

Dece-sex casos additional de atrophia optic in association con anemia perniciose possibile eseva trovate in le litteratura, sed in illos le information non eseva adequate pro verificar le diagnose.

3. Le uso del test de absorption de vitamina B₁₂ con marcage per cobalt⁶⁰ es possibilemente de valor in diagnosticar disordines de nervo optic in casos in que le etiologia es obscur.

**References**


OPTIC NEUROPATHY IN PERNICIOUS ANEMIA

18. Bastianelli, G.: Neurol. Zhl. 17:78, 1897. (quoted by Turner; see ref. 11.)
HENRY E. HAMILTON, PHILIP P. ELLIS and RAYMOND F. SHEETS

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