Central Nervous System Involvement in Burkitt’s Lymphoma


Thirty-five of 77 patients (46%) with Burkitt's lymphoma presented or developed evidence of central nervous system involvement by tumor. Neurologic abnormalities included paraplegia, cranial neuropathy, altered levels of consciousness and malignant pleocytosis. An analysis of this series disclosed the following: Paraplegia is a common presenting feature of Burkitt's lymphoma and is responsive to systemic chemotherapy. The association of cranial neuropathy and malignant pleocytosis with facial tumors points to direct tumor extension to intracranial structures (dura-arachnoid) as the pathogenesis of these lesions. Intrathecal chemotherapy temporarily reverses malignant pleocytosis but systemic chemotherapy is required to treat cranial neuropathy. A poor prognosis follows presentation or development of malignant pleocytosis. The limitations of the current forms of therapy for CNS involvement are discussed.

In patients with Burkitt's lymphoma, central nervous system (CNS) involvement is a frequent complication which is difficult to treat and is associated with a poor prognosis. Over a period of 23 years, 77 patients with Burkitt's lymphoma have been critically evaluated and studied prospectively at the Lymphoma Treatment Centre in Kampala, Uganda. Thirty-five patients or 46 per cent had neurological abnormalities appearing at some time during the course of the disease. Sequential observations were made in these patients following the presentation or development of CNS involvement by tumor, with special attention paid to the clinical manifestations, analysis of the cerebrospinal fluid (CSF) and the response to intrathecal chemotherapy. The results of these observations form the basis of this report.
CNS INVOLVEMENT IN BURKITT'S LYMPHOMA

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of Disease</th>
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<tbody>
<tr>
<td>I</td>
<td>Single facial tumor mass</td>
</tr>
<tr>
<td>II</td>
<td>Two or more separate facial tumor masses</td>
</tr>
<tr>
<td>III</td>
<td>Intrathoracic, intra-abdominal, paraspinal or osseous tumor (excluding facial bones)</td>
</tr>
<tr>
<td>IV</td>
<td>Central nervous system (malignant cells in the CSF) or generalized bone marrow involvement</td>
</tr>
</tbody>
</table>

Fig. 1.—Clinical Staging of Burkitt's Lymphoma

MATERIALS AND METHODS

Seventy-seven patients with histopathologically proven Burkitt's lymphoma were admitted to the Lymphoma Treatment Centre, Kampala, Uganda between July 1967 and February 1970. The clinical evaluation and treatment regimen have been described previously. The clinical staging criteria are shown in Fig. 1.

Initial treatment consisted of intravenous cyclophosphamide (CTX) * 40 mg/Kg. in a single dose. Patients with a complete clinical response within 2 weeks of treatment were randomized to no further therapy or to five more doses of CTX (40 mg/Kg.) at 2-3 week intervals in a clinical trial comparing minimal treatment with prolonged intensive chemotherapy. Patients with initial partial responses or patients relapsing following single doses of CTX were treated with the multiple dose regimen. Patients relapsing on CTX were treated with the following agents: vincristine (VCR) † 1.4 mg./sq. M. intravenously on day 1 and methotrexate (MTX) † 15 mg./sq. M. orally on days 1–4, followed in a 10–14 day interval by cytosine arabinoside (ARA-C) § 250 mg/sq. M. intravenously daily in a 3-day infusion; the sequence of VCR/MTX–ARA-C was administered for two cycles (cyclic chemotherapy).

A complete neurological examination and lumbar puncture were performed on all patients on admission and at follow up intervals of 4–6 weeks. Roentgenograms of the skull and vertebrae, myelography and cerebral arteriography were performed when indicated. CSF protein was measured using 3 per cent sulfosalicylic acid and cytological preparations and cell counts were performed according to the method of Skeel et al. CSF was also examined in some cases using a cytocentrifuge; | | | | cells were centrifuged at 400 rpm for 10 minutes and stained with Giemsa stain. At the time of initial lumbar puncture, the needle was left in place while the CSF cytology was examined in an adjacent laboratory; if malignant cells were present (malignant pleocytosis), intrathecal chemotherapy was instilled and the needle was withdrawn.

Several regimens of intrathecal chemotherapy were employed. Early in the study, intrathecal chemotherapy consisted of MTX, 10 mg. given weekly for 1–2 doses beyond the disappearance of malignant pleocytosis. Citrovorum factor, 5 mg. intramuscularly every 6 hours for four doses, was begun at the time of instillation. Patients relapsing following MTX were treated with weekly ARA-C, 10–50 mg. in incremental doses also administered for two doses beyond normalization of the CSF. Following the experience with these agents used singly, a sequential cyclic schedule was employed: MTX, 25 mg/sq. M. with citrovorum, alternating every 4 days with ARA-C, 50 mg./sq. M. for one complete cycle beyond normalization of CSF and a minimum of two cycles (“intrathecal cyclic chemotherapy”). More recently, MTX, 15 mg. daily (with citrovorum), has been

*Cytoxan, Mead Johnson Laboratories, Evansville, Ill.
†Oncovin, Eli Lilly and Co., Indianapolis, Ind.
‡Methotrexate, Lederle Laboratories Div., American Cyanimid Co., Pearl River, N.Y.
§NSC 63878, Ben Venue Laboratories, Bedford, Ohio.
†Calcium leucovorin, Lederle Laboratories Div., American Cyanimid Co., Pearl River, N.Y.
Table 1.—Presenting Neurological Abnormalities in 24 Patients with Burkitt’s Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>No. Patients with Malignant Pleocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>3</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>6</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
</tr>
</tbody>
</table>

given for 4 days, and repeated at 2–4 week intervals if necessary. Both MTX and ARA-C were diluted in 3 ml. of sterile isotonic saline and instilled with several exchanges of CSF in the syringe.

All chemotherapeutic regimens were established according to specific protocols which were approved by research committees at Makerere University Medical School and Mulago Hospital, Kampala, Uganda as well as at the National Cancer Institute, Bethesda, Md.

RESULTS

Patients with neurological involvement have been divided into two groups: those who presented with neurological abnormalities, and those who developed abnormalities at some time during their clinical course.

Patients Presenting With Neurologic Abnormalities

Twenty-four of the 77 patients (31%) had neurological abnormalities noted at the time they were first seen (Table 1). The first two columns in Table 1 indicate the presence or absence of malignant pleocytosis in association with these neurological findings.

Ten patients presented with paraplegia. The neurologic abnormalities in these patients ranged from mild paraparesis and deep tendon reflex abnormalities to flaccid paraplegia, urinary and fecal incontinence, and complete loss of sensation with sensory levels as high as T5. The symptoms were of relatively rapid onset and the clinical history ranged from 1–4 months in duration. The CSF in these patients revealed a high protein content (range 55–1000 mg. %) but only three patients (30%) had detectable malignant cells with cell counts of 6, 10, and 10 cells per cu. mm., respectively. CSF cytology of the remaining seven patients revealed mononuclear inflammatory cells ranging from 3–36 cells per cu. mm. There was no correlation between CSF findings and the degree of neurologic disability. Lumbar myelography performed in four patients revealed either a spinal cord block (two patients) or no abnormality (two patients).

Eight patients presented with cranial neuropathy involving extraocular muscles and six had associated malignant pleocytosis. Of the remaining six patients presenting with neurologic abnormalities, two had evidence of altered consciousness. Four were asymptomatic but were found to have malignant pleocytosis on routine lumbar puncture.

An analysis of the CSF protein, cell counts and differential cytology of the patients revealed significantly higher protein concentrations in paraplegic
Table 2.—Neurologic Abnormalities Developing in Stage I–III Patients

<table>
<thead>
<tr>
<th>Presenting Stage</th>
<th>No. Patients</th>
<th>CNS Involvement on Admission</th>
<th>Cranial Neuropathy Alone</th>
<th>Malignant Pleocytosis Alone</th>
<th>Both</th>
<th>Total (One or Both)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I–II</td>
<td>19</td>
<td>None</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>36</td>
<td>None</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>Paraplegia</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>Cranial Neuropathy</td>
<td>2</td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

patients. Protein concentrations did not correlate with the degree of malignant pleocytosis, the presence of cranial neuropathy, or altered consciousness. Patients with malignant cells in the CSF had a wide range of cell counts and differential cytology revealed more than 95 per cent of the cells to be Burkitt lymphoma cells, with rare lymphocytes or monocytes identified. No correlation was noted between CSF cell counts and the clinical neurologic findings.

Patients Developing Neurologic Abnormalities

Table 2 reviews the occurrence of cranial neuropathy and malignant pleocytosis which developed in patients with stage I–III disease on admission. Paraplegia did not develop in any patient after initial presentation. Of 19 stage I–II patients, only one patient developed malignant pleocytosis. Among 36 stage III patients, 11 developed neurological abnormalities, two with cranial neuropathy, three with malignant pleocytosis and six with both findings. In addition, four of seven surviving paraplegic patients developed cranial nerve palsies and/or malignant pleocytosis. Two patients presenting with ophthalmoplegia later developed malignant pleocytosis as shown by follow-up lumbar puncture. These findings appeared between 4 and 36 weeks (median 10 weeks) after initiation of chemotherapy. Most patients were receiving multiple doses of cyclophosphamide and had been in complete clinical remission up to the time of neurological relapse. In three patients, the involved cranial nerve was in the same anatomic region as a recurrent tumor mass. In five patients, however, there was no palpable or roentgenographic evidence of tumor along the course of the affected nerve. Most patients had multiple cranial neuropathies. The nerves most commonly involved were the third (five patients), sixth (three patients), seventh (three patients), fifth (two patients), ninth (two patients) and twelfth (one patient) cranial nerves.

No consistent temporal relationship was observed in the association of cranial neuropathy and malignant pleocytosis (eight patients). The finding of malignant cells in the CSF preceded the occurrence of cranial neuropathy in three patients, whereas the reverse situation occurred in three. The interval separating these events did not exceed 4 weeks. In the remaining two patients, the findings were observed simultaneously.

Cranial neuropathy and malignant pleocytosis on presentation or following treatment are correlated with presence of facial tumors (Table 3). There is twice the risk of these neurologic abnormalities developing in patients with facial tumors than among patients without facial tumors (chi-square test \( p < 0.05 \)).
Table 3.—Correlation of Cranial Neuropathy and/or Malignant Pleocytosis with the Presence of Facial Tumors

<table>
<thead>
<tr>
<th></th>
<th>Cranial Neuropathy and/or Malignant Pleocytosis</th>
<th>Per Cent with Neurological Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Facial tumor</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>No facial tumor</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>45</td>
</tr>
</tbody>
</table>

Response to Therapy

Three of the 10 paraplegic patients died within the first week of therapy and the remaining seven had complete regression of their gross tumor masses after cyclophosphamide. Four of the seven surviving paraplegic patients had improvement of neurologic function after therapy. These patients presented with mild paraparesis, minimal sensory deficit and reflex abnormalities. The remaining three patients with more severe neurologic dysfunction had slight or no improvement.

Of eight patients presenting with cranial neuropathy, one died before the effects of systemic chemotherapy could be assessed and five of the seven survivors had complete return of function following systemic cyclophosphamide.

Seven of eight patients developing cranial nerve palsies were resistant to further cyclophosphamide but had complete responses to systemic cyclic chemotherapy (VCR/MTX–ARA-C). Patients with involvement of the extraocular muscles showed the most rapid responses, whereas patients with facial nerve paralysis took longer to improve.

Table 4 summarizes the responses to intrathecal chemotherapy in patients with malignant cells in the CSF. Five patients treated early in the study received intrathecal MTX 10 mg. weekly for four courses and three relapsed with malignant pleocytosis 4, 15 and 27 weeks from the completion of therapy. The two remaining patients have remained in remission for 112+ and 119+ weeks with no evidence of recurrent CSF abnormality. All three patients with relapsing malignant pleocytosis were treated with intrathecal ARA-C 10–50 mg. at weekly intervals with complete responses of 3, 3 and 4 weeks’ duration.

Table 4.—Experience with Intrathecal Chemotherapy in Burkitt’s Lymphoma

<table>
<thead>
<tr>
<th>Intrathecal Treatment Regimen</th>
<th>No. Patients</th>
<th>Complete Response</th>
<th>Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg. weekly × 4</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Cytosine arabinoside</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–50 mg. weekly × 4</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cyclic chemotherapy</td>
<td>15</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg. daily × 4</td>
<td>15</td>
<td>15</td>
<td>12</td>
</tr>
</tbody>
</table>
Intrathecal cyclic chemotherapy with MTX and ARA-C was administered to 15 patients. Thirteen patients (87%) had complete disappearance of malignant cells from the CSF, usually following the third or fourth dose. The remission duration of this group of patients is shown in Fig. 2 which reveals that all patients eventually relapsed with a mean remission duration of 10 weeks from the time of completion of intrathecal therapy. Retreatment of relapsing patients with the same cyclic regimen resulted in reinduction of complete but only temporary responses. Thus, a more effective chemotherapeutic regimen was sought.

Eleven patients relapsing after one or more courses of cyclic intrathecal chemotherapy and four previously untreated patients with malignant pleocytosis were given MTX 15 mg. intrathecally daily for 4 days, with intramuscular citrovorum factor 5 mg. at 8-hour intervals for 4 days beginning with the first intrathecal dose. All 11 patients previously treated had complete responses, but relapses occurred in all patients within 6 weeks of treatment. Of the four patients without previous intrathecal treatment, one patient relapsed at 3 weeks and the remaining three have been in complete remission after one course of treatment for 4+, 10+ and 14+ weeks.

Toxicity

Intrathecal chemotherapy was generally well tolerated and few serious side effects were encountered following over 300 procedures. Nearly all patients developed an inflammatory pleocytosis and fever which subsided completely within a week of cessation of intrathecal chemotherapy. A few patients complained of headache and nausea following lumbar puncture and two patients experienced grand mal seizures. No toxic hematologic or gastrointestinal side effects could be attributed to any of the intrathecal chemotherapeutic regimens employed. In two patients receiving daily intrathecal MTX for 4 days, in whom citrovorum factor was omitted, both stomatitis and leukopenia developed in the absence of concomitant systemic chemotherapy. No patient developed meningeal infection.

Survival

Figure 3 compares the survival (life table analysis) from the time of initial therapy in three groups of patients: those presenting with malignant pleocytos-
Fig. 3.—A comparison of survival in Burkitt's lymphoma in patients presenting, developing, and without malignant cells in the cerebrospinal fluid.

esis, those developing malignant pleocytosis, and patients with normal CSF. The first group has a very poor prognosis with no survivors beyond 34 weeks. The second group has a slightly more favorable outlook with a survival of 45 per cent beyond 80 weeks. This curve includes the only two long-term survivors who are free of disease in the entire group of patients with malignant pleocytosis. Patients without malignant pleocytosis have an excellent prognosis with 72 per cent survival beyond 1 year. The latter analysis includes seven patients who died within the first week of treatment before full therapeutic benefit could be achieved. It is important to note that all but two survivors in the first two groups are living with disease, whereas all surviving patients without malignant pleocytosis are in complete remission.

The causes of death in four patients presenting with malignant pleocytosis who died within 1 week of treatment were attributable to widespread tumor involving the kidneys, gastrointestinal tract, liver and bone marrow. Patients with malignant pleocytosis who survived beyond the first few weeks following admission died with tumor which had eventually become resistant to systemic and intrathecal chemotherapy. The causes of death in six of nine patients in this group were sepsis (five patients) and hemorrhage (one patient). Three patients died at home with symptoms suggestive of increased intracranial pressure (headache, coma, convulsions).

DISCUSSION

Central nervous system involvement by Burkitt's lymphoma is a common finding as reported in retrospective clinical and pathological reviews. Frank reported 31 of 91 (34%) cases, in Kenya, of Burkitt's lymphoma with evidence of CNS involvement. The principal clinical features included altered consciousness (36%), paraplegia (29%) and facial palsy (23%). The CSF revealed tumor cells in the five patients who were evaluated. The mean survival time in this series was 2 months, and Clifford has emphasized the difficulty in successful management of these patients. Both authors postulate that involve-
mented of the CNS is the result of direct tumor growth through bone or along cranial nerves (particularly the trigeminal) from primary deposits in the facial bones.

Janota reviewed 25 autopsied cases of Burkitt's lymphoma in Nigeria and found pathologic evidence of CNS involvement in 21. He noted a high incidence of tumor invasion of the meninges, cranial nerves, spinal cord, spinal roots and the dura. Also from Nigeria, Odeku and Osuntokun reviewed 105 cases of Burkitt's lymphoma for evidence of CNS involvement and found neurologic abnormalities in 47 (45%), comparable to the incidence in our series. Twenty-three patients presented with CNS involvement and the remainder developed neurologic abnormalities during their clinical course. Lesions of the spinal cord were noted in 16 patients and 18 cases of cranial neuropathy were recorded. The remaining patients had convulsions (five), hemiplegia (two), hydrocephalus (two), or evidence of altered consciousness (three). The CSF was examined in 28 cases. Elevated protein levels were the most frequent finding. Malignant cells were identified in six, although "pleocytosis" was "the second main abnormality noted." No correlation could be made between extent of disease and CNS involvement.

The results of the present series agree substantially with the retrospective studies described above. The incidence of malignant pleocytosis is higher in our patients, however, probably because of the prospective plan of CSF surveillance in all patients and the careful attention devoted to CSF cytology.

Paraplegia is a well-recognized complication of Burkitt's lymphoma, and the clinical and diagnostic features have been adequately described. Surgical decompression of the spinal cord is not recommended, as the paraspinal tumor responds rapidly to chemotherapy. If spinal cord damage is not irreversible, substantial neurologic improvement will follow tumor regression.

The pathogenesis of paraplegia by Burkitt's lymphoma is not yet understood, although several authors have offered explanations. Cockshott and Evans suggest that epidural involvement is the result of direct spread from an osseous focus or from a paravertebral deposit through neural foramina. Wright believed that cord lesions were ischemic in origin, due to obstruction of the radicular arteries or anterior spinal artery by retroperitoneal or retropleural tumor. He was unable to identify, at postmortem, evidence of cord compression in six of nine paraplegic cases in which extradural tumor plaques were noted. It is likely that both mechanisms (cord compression and ischemia) play a role in the pathogenesis of paraplegia. Spinal cord block can be identified by myelography, and the level correlates with the neurologic findings. Some patients, however, have no abnormality on myelography, but show neuropathologic evidence of ischemia at postmortem. A clinical-neuropathological review of autopsied patients in this series is underway and may shed further light on this question.

Cranial neuropathy and malignant pleocytosis were frequently associated findings both on admission and during the clinical course. All patients presenting with these abnormalities had gross tumor involvement of bone or soft tissues in the region of the affected cranial nerve. This was not true of patients
who developed these findings during their clinical course, although they frequently had facial tumors on admission. Patients in this latter group were usually in complete clinical remission at the time the cranial neuropathy appeared. Moreover, cranial neuropathy appeared in patients while receiving multiple doses of cyclophosphamide and further courses did not affect the lesion, suggesting drug resistance. Subsequent treatment with the VCR/MTX-ARA-C cycle, however, yielded complete neurologic responses, thus indicating that the cells infiltrating the cranial nerves could be effectively attacked by other systemic cytotoxic agents.

The pathogenesis of meningeal and cranial nerve invasion by tumor is speculative. From the present series, the significant correlation between facial tumors and cranial neuropathy and/or malignant pleocytosis points to direct extension as the most likely route of invasion. Migratory extension to the dura may occur along nerve or blood vessel sheaths or directly through bone and periosteum. Once tumor cells invade the dura, penetration to the subarachnoid space is likely, as has been demonstrated in experimental leukemia in mice. Blood-borne spread to the dura, meninges, choroid plexus and brain parenchyma (Virchow-Robin spaces) is possible, but seems unlikely in view of the infrequent finding of circulating tumor cells in Burkitt’s lymphoma, and from experimental evidence of “tissue barriers” in L1210 murine leukemia.

Malignant cells in the CSF could be effectively managed with intrathecal chemotherapy in most cases, but relapse was a near-constant feature, and subsequent resistance to intrathecal agents was observed in some patients given repeated courses of MTX or ARA-C in various combinations. The association between cranial neuropathy and malignant pleocytosis may be a “feeder-reservoir” system in which a source of malignant cells outside the subarachnoid space (and accessible only to systemic chemotherapeutic agents) is seeding cells into the CSF via dura-arachnoid connections (e.g., the exit of cranial nerves from the brain). The cells in the CSF are accessible only to intrathecal chemotherapeutic agents. Thus, the logical conclusion is to administer both systemic and intrathecal agents simultaneously in order to avoid the problems presented by the pharmacologic barriers of the central nervous system. At the present time, we plan to administer intrathecal MTX or ARA-C in a randomized trial to all patients with malignant pleocytosis in a daily regimen for 10 days, with simultaneous systemic chemotherapy. In addition, a randomized schedule of “prophylactic” intrathecal chemotherapy is being administered to patients with stage I-III disease.

The observation of peripheral neuropathy and malignant pleocytosis in Burkitt’s lymphoma is very similar to the neurologic findings in “meningeal leukemia.” This complication has been noted in patients with acute lymphoblastic leukemia at any stage of the disease including complete hematological remission and is characterized by signs of increased intracranial pressure and peripheral or cranial neuropathy. Treatment with intrathecal methotrexate, and irradiation of the CNS have resulted in temporary remissions but invariable recurrence. Our experience with Burkitt’s lymphoma has been similar, although paraplegia and cranial neuropathies dominate the clinical picture, while
signs or symptoms of increased intracranial pressure are infrequent. Malignant pleocytosis occurs in approximately the same frequency as it is encountered in acute lymphatic leukemia, and responds sensitively to intrathecal chemotherapy. Moreover, patients with Burkitt's lymphoma may develop neurological relapse while otherwise in complete remission.

Recently, evidence for an active immunological anti-tumor response in patients with Burkitt's lymphoma has been reported. The finding of CNS involvement in treated patients with Burkitt's lymphoma who are otherwise in complete remission suggests that an immunological as well as a pharmacological barrier exists in the CNS. Nervous tissue is virtually devoid of lymphoid tissue and host surveillance mechanisms may be ineffective in this environment.

At some future date, when more quantitative immunological information is available, specific and nonspecific immunotherapy may play an important supplementary role in the treatment of Burkitt's lymphoma and may substantially assist in the management of patients with CNS involvement.

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REFERENCES


Central Nervous System Involvement in Burkitt's Lymphoma

JOHN L. ZIEGLER, AVRUM Z. BLUMING, RICHARD H. MORROW, JR, LEROY FASS and PAUL P. CARBONE