Review Article

Primary central nervous system lymphoma

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Primary lymphoma of the central nervous system (CNS), including reticulum cell sarcoma, microglioma, and histiocytic lymphoma, represents less than 1% of all primary brain tumors. In the last 10 years, this tumor has tripled in frequency in the nonimmunosuppressed population. By 1991, the tumor will be the most common neurological neoplasm by virtue of the increase in sporadic occurrence and in the acquired immunodeficiency syndrome (AIDS) population. Three percent of AIDS patients will develop this tumor either prior to AIDS diagnosis or during their subsequent course. In addition to acquired immunosuppression, patients with inherited disorders (such as Wiskott-Aldrich syndrome, severe combined immunodeficiency, and X-linked immunodeficiency) and other acquired disorders of the immune system are predisposed to the development of CNS lymphoma. Immunological studies have suggested a role for Epstein-Barr virus in the production of this tumor. Although subtypes exist, non-Hodgkin's lymphoma of the CNS most commonly consists of histiocytic cells or large immunoblastic cells bearing B cell surface markers in close proximity to the lateral and third ventricles. Sixty percent of these deposits are multiple, and subarachnoid invasion is seen in one-quarter of patients. Vitreous involvement of the eye occurring prior to and during the course of CNS lymphoma has been noted in up to 25% of patients. The involvement of multiple areas of the neuraxis, the eye, and multiple intracranial sites often occurs in the absence of obvious systemic lymphoma. Therapeutic trials of brain radiation therapy are associated with median survivals of less than 1 year. Uniform complete responses of intracranial deposits are recorded following chemotherapy with high-dose intravenous methotrexate, CHOP (cyclophosphamide, hydroxydaunomycin/doxorubicin, Oncovin (vincristine), and prednisone), high-dose cytosine arabinoside, and intra-arterial methotrexate with barrier modification.

Key Words • brain neoplasm • non-Hodgkin's lymphoma • lymphoma • immunosuppression

Primary central nervous system (CNS) lymphoma constitutes a rare group of neoplasms. These are non-Hodgkin's lymphomas (NHL's), mostly of B cell origin. Formerly, they represented fewer than 1% of primary brain tumors, but they have trebled in frequency in the last decade. Since 1975, over 200 publications have underscored this increasing frequency, the relationship between these tumors and immunosuppression of inherited or acquired origin, and the putative involvement of Epstein-Barr virus (EBV) in tumor development. These facts have attracted the attention of medical and radiation oncologists, primary-care physicians, epidemiologists, and infectious disease physicians, in addition to those providing care for patients with malignant neurological disease.

Historical Perspectives: Classification

The classification of tumors now recognized as primary brain lymphomas (NHL-CNS) has changed several times in this century. These changes reflect the slow acceptance by neuropathologists of progress in the nomenclature of non-CNS (systemic) lymphomas and their application to brain biopsies.

The first description of tumors classified as NHL-CNS labeled the tumors "perivascular sarcomas," reflecting their perivascular location. This term, later adopted by others, did not effectively separate such neoplasms from others composed of small cells arranged...
about blood vessels, such as medulloblastomas and other primitive neuroectodermal tumors. In Bailey's original description, 13 he recounts that one of his cases was seen by F. B. Mallory, who described it as resembling a "lymphosarcoma or malignant lymphoma."

Nine years later, Yuile 253 again noted the resemblance between these brain neoplasms and those tumors of lymph nodal origin which had been termed "reticulum cell sarcoma" (RCS). 196 Yuile consequently labeled his case as RCS, but he speculated that RCS of the brain arose from nonlymphocytic microglial cells intrinsic to the brain. The controversy generated by this belief occupied pathologists for the next 50 years. Some authors (mostly American) favored the term "reticulum cell sarcoma," while others (mostly European) preferred the term "microglioma."

Yet others considered that these were two separate but related tumor types, 1,2 and still others used both terms interchangeably or as a hyphenated group name ("RCS-microglioma group"). 17,102,208 This controversy reflected the rarity of the tumor and the lack of universal application of metallophilic (silver) stains 59 for microglia. Thus, although many of these cells attracted silver stains, pathologists were not convinced that this technique identified all brain tumor cells or established a relationship to similar tumor deposits in lymph nodes. This entire controversy became irrelevant with the growing realization that Yuile was initially correct (as was Mallory) in comparing brain RCS to neoplasms of lymph nodal origin; in other words, the realization that these tumors were, in fact, lymphomas. 94,208,236

The modern classification of non-Hodgkin's lymphomas emerged from the separation of systemic lymphomas into histological groups with differing prognoses 191 and the realization that most non-Hodgkin's lymphomas were composed of neoplastic B lymphocytes. 107 The application of increasingly sophisticated immunological and more recently molecular genetic 13,31,102,103,104,105,106,107 methods to lymphoma diagnosis and classification has given rise to a series of classification systems, 36,143,144 culminating in the International Working Formulation sponsored by the National Cancer Institute. 169

Materials and Methods

This review includes a series of patients who were seen between 1958 and 1984 at the Massachusetts General Hospital (MGH) with a neurological complaint which was found to be due to a lymphoma arising within the CNS or its coverings. The diagnosis of NHL-CNS in all of the patients in our series was confirmed by biopsy or postmortem examination. The data from this series are discussed in conjunction with data from other cases reported in the literature. We defined a case as NHL-CNS if: 1) the patient presented with a neurological complaint; 2) the complaint was proven to be due to a brain tumor that was confirmed as a lymphoma by biopsy or autopsy; and 3) at the time of the presentation workup, the patient disclosed no evidence of lymphoma except in the brain, leptomeninges, spinal cord, or eye. We specifically excluded patients with epidual lymphoma, intracranial extraocular lymphoma, or lymphoma involving the skull or vertebral column. In searching for patients, we examined all case reports or patient records carrying any of the diagnoses listed in "Historical Perspectives" (above) as well as Hodgkin's disease. In searching the MGH files, we looked for cases of systemic lymphoma in which the initial presentation was that of a CNS tumor. While we found some patients in whom a brain tumor developed after a diagnosis of systemic lymphoma, we found none who presented as NHL-CNS but were found to have systemic tumor at presentation. In order to determine how often NHL-CNS spreads outside the CNS, we included in our series patients who carried a diagnosis of NHL-CNS and developed systemic lymphoma later in their clinical course.

Ninety-six MGH case records were identified from multiple access points (surgical pathology records, autopsy records, medical records, and tumor registry). Many had been previously reported, 98,142,208,234,249 often as part of the published MGH Case Records series. 31-34,36 We reviewed the clinical, radiological, and pathological data for all potential MGH cases, and examined all pathology slides. Thirty of the originally identified potential cases failed to meet clinical or pathological criteria for inclusion as cases of NHL-CNS. Of these, seven could not be confirmed at all. Twenty-one patients were found on pathological review to have had other neurological diseases, including inflammatory disorders (one Toxoplasma encephalitis; one Aspergillus encephalitis), demyelinating diseases, and nonlymphomatous neoplasms (including primitive neuroectodermal tumors and astrocytomas). Two patients had preceding systemic lymphoma. No pathological material was available from five patients whose tumors had been previously identified on microscopic examination.

Pathological material was available from 61 cases. This was classified according to the International Working Formulation, 169 modified as suggested by Krueger, et al. 132 The review was carried out between 1981 and 1985. New cases collected through the end of 1984 and other cases selected from previous years were also studied based on frozen section and paraffin section immunohistochemical techniques for lymphocyte cell markers (see "Pathology," below) 86,87,146,216 Correlations were made between the clinical presentation and course and the significant laboratory and radiographic studies. The data from these 66 MGH cases were reviewed in light of the data from an additional 637 cases reported in the medical literature.

Epidemiology

Of the roughly 24,000 individuals in the United States who each year develop NHL, 219 between 2% and 10% will develop neurological involvement. 65,138,192 Only 0.7% to 1.5% of NHL cases involve the
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CNS. The occurrence of NHL-CNS has slowly increased since 1960, but in the 5-year interval between 1980 and 1984 the incidence has trebled in comparison to any previous 5-year interval (Fig. 1). At the MGH the finding of NHL-CNS at postmortem examination has increased from a level between 0.005% and 0.016% in the era prior to 1964 to 0.11% since that year. Similar increases have been reported at other centers.

Similarly, NHL-CNS accounts for an increasingly greater proportion of hospital admissions of patients with brain tumors. Since 1975, patients with NHL-CNS have represented 2.3% of MGH admissions for patients with primary intracranial neoplasms other than pituitary adenomas, compared to 0.6% in the preceding era. Similar increases have been seen at other institutions. Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, Dr. Nancy Eby performed a time trend analysis of NHL-CNS for the period 1973 to 1984 and found a significantly increasing incidence by a factor of threefold (unpublished data). These increases in incidence are not accounted for by changes in nosology, in referral patterns, or in use of improved diagnostic tools such as computerized tomography (CT); nor are they explained by an increased physician awareness. As will be shown, neither the acquired immunodeficiency syndrome (AIDS) nor other forms of immunosuppression fully explain the increased frequency with which this diagnosis is encountered.

In our series and in most others (reviewed by Helle, et al.), a slight male preponderance has been noted at all ages (Fig. 2). The male:female ratio among MGH patients prior to 1971 was 1.4:1; since then it has become 1.7:1. This increased frequency in males has raised the question of a relationship between NHL-CNS and AIDS. In our own series, 39 patients were men and 27 were women. The median age of occurrence for all of our patients was 55 years; the median age for men was slightly younger than for women. Three-quarters of our patient population developed NHL-CNS between 45 and 70 years of age, and similar ages at onset are reported in other large series. In our patients, the age extremes were 6 and 82 years (both in males). Although uncommon in childhood, the tumors have been reported in patients below the age of 5 years, most commonly as a consequence of inherited or acquired immunosuppression. The median age of reported NHL-CNS development is lowest for children with inherited immunosuppression (10 years), followed by transplant recipients (37 years) and AIDS patients (39 years). Despite the dramatic relationship between immunosuppression and NHL-CNS, and despite the younger ages of patients in the immunosuppressed populations, we noted that the fall in the median age of onset in our patient series from 58 years in those treated in the years 1958 to 1970 to 54.5 years in those treated between 1971 and 1984 was out of proportion to the number of immunosuppressed patients in our group. There was one patient in our series with AIDS (age 39 years), and one who had received a renal transplant (age 49 years); exclusive of these patients, the median age of the patients was 55 years in the 1971 to 1984 interval.

Predisposition and Risk Factors

Three populations are at increased risk of developing NHL-CNS: transplant recipients, patients with AIDS, and those with congenital immunodeficiencies. Our series contained one renal transplant recipient and one AIDS patient (see above). In several medical centers as many as 30% of NHL-CNS cases have been reported in patients with a renal or cardiac transplant. For kidney recipients the risk of systemic lymphoma is 2.2 cases/1000 transplant recipients/year — a figure that is 350-fold greater than for the population at large. The risk for NHL-CNS in these

![Fig. 1. New cases of primary lymphoma of the central nervous system seen at the Massachusetts General Hospital from 1960 to 1984 in 5-year groups.](image1)

![Fig. 2. Age and sex of patients with non-Hodgkin's lymphoma of the central nervous system seen at the Massachusetts General Hospital from 1958 to 1984.](image2)
patients, although smaller, is still substantial as half of all these lymphomas are NHL-CNS.\(^{177}\) The risk of NHL-CNS for heart transplant recipients may be slightly higher; Weintraub and Warnke\(^{246}\) reported three cases per 182 recipients. For both groups, the risk accrues as a result of the extent and duration of the acquired immunosuppression. A median interval of 9 months elapsed from transplantation to tumor development in the reported cases of NHL-CNS arising in transplant recipients, with a range from 5.5 to 46 months.\(^{42,53,121,217,246}\) Data do not exist on the particular risks associated with antithymocyte globulin or as a consequence of HLA dyscompatibility.

Drug- or disease-induced immunosuppression has been associated with the development of NHL-CNS accompanying many diseases. Our series includes a patient with steroid-responsive systemic lupus erythematosus who developed NHL-CNS after 12 years of therapy. There are reports of NHL-CNS accompanying sarcoidosis,\(^{52,238}\) systemic lupus erythematosus,\(^{141}\) Sjögren’s syndrome,\(^{235}\) vasculitis,\(^{111,244}\) rheumatoid arthritis,\(^{77}\) and idiopathic thrombocytopenic purpura.\(^{241}\) One of us (D.C.M.) has seen a case in a patient with Hodgkin’s disease treated with chemotherapy; in that patient the NHL-CNS became symptomatic 8 months after the biopsy diagnosis of Hodgkin’s disease, and the patient died 3 months later. At autopsy, there was no residual Hodgkin’s disease and no NHL outside the CNS. Cases of NHL-CNS have been reported in association with progressive multifocal leukoencephalopathy (PML), generally in settings of immunosuppression predisposing to both diseases. These cases include one in which the underlying immunosuppression was from a renal transplant,\(^{79}\) and one in which the patient had leukemia.\(^{71}\) Additional cases of coexisting PML and NHL-CNS have occurred in patients with AIDS.

Other acquired illnesses may be associated with NHL-CNS, even in the absence of overt immunosuppression or immunosuppressive medications. These illnesses include tuberculosis,\(^{69,207}\) multiple sclerosis,\(^{39}\) colon carcinoma,\(^{117,119}\) and glioblastoma.\(^{74}\) One case was reported in association with PML with no other proven immunosuppressive disorder.\(^{140}\) Non-Hodgkin’s lymphoma of the CNS has been reported in approximately 3% of patients with AIDS.\(^{5,9,72,104,135,139,163,176,218,224,226,244}\) This tumor, occurring in individuals otherwise considered to be at “high risk” for AIDS but as yet lacking the specific diagnosis, is considered by many to be indicative of the diagnosis.\(^{72}\)

Based on the current rate of development of NHL-CNS in AIDS patients, we would expect 600 new cases to emerge from the American population of (currently) approximately 20,000 patients with AIDS.\(^{134}\) Those already reported affect male patients who are younger (median age 39 years) than the “usual” NHL-CNS population. These patients often have other peripheral and CNS stigmata of AIDS, including cytomegalovirus or EBV infections of the brain as well as PML and toxoplasmosis, either alone or in combination. However, the CNS lymphoma may precede the appearance of AIDS-related opportunistic infections. In a report of 20 patients with AIDS and NHL-CNS, So, et al.,\(^{226}\) noted no common antecedent systemic or brain lesions.

Central nervous system lymphomas have been reported to make up 4% of the malignancies seen in patients with congenital immunodeficiency syndromes.\(^{57}\) Two disorders, namely the Wiskott-Aldrich syndrome (WAS)\(^{24,105,124,161}\) and severe combined immunodeficiency,\(^{79}\) predispose to NHL-CNS. Less common congenital immunoregulatory abnormalities have also been associated with such tumors. These include immunoglobulin (Ig) A deficiency and increased IgE.\(^{14}\) These disorders share inherited abnormalities of immunoglobulin production, deficiencies or absence of normal T cell function, and a predisposition to infection. Non-Hodgkin’s lymphoma of the CNS represents 17.9% of the 78 cases of cancer in patients with WAS reported to the Immunodeficiency Cancer Registry (ICR)\(^{60}\) and 24% of the 59 lymphomas occurring in these WAS patients. Interestingly, although another similar congenital syndrome, ataxia-telangiectasia, is clearly associated with systemic lymphoma,\(^{21,152,220}\) there are no cases of NHL-CNS reported to the ICR among the 152 tumors associated with ataxia-telangiectasia, including 67 systemic lymphomas.\(^{60}\)

Duncan’s syndrome\(^{184-187}\) or X-linked lymphoproliferative syndrome provides a link between the inability to control infection with a specific agent, the EBV, and NHL-CNS.\(^{175}\) This work complements other reports suggesting a role for EBV or papovaviruses in NHL-CNS\(^{74,73,157,164,207}\) and systemic lymphoma.\(^{70,85,148,203}\)

This relationship is not easily established from serological data. Reviewing serum samples from 20 patients with NHL-CNS, we were able to find evidence of persistent or reactivated EBV infection (EBV-nuclear antigen titers in excess of 1:40) in only six patients. However, the demonstration by Southern blot hybridization of EBV genomic material within tumor tissue from four patients with NHL-CNS (G Miller, unpublished data) suggests a causative role for this virus (Table 1). Alternatively, EBV may preferentially infect certain malignant B cells; EBV infection of selected subpopulations of B cells has been described.\(^{7}\) An additional patient (Case 5, Table 1) presented to the Children’s Hospital of Boston with brain lymphoma 5 years after receiving therapy for lymphomatoid granulomatosis of the lung (J Corey, personal communication, 1986). Three of the patients with NHL-CNS had evidence of prior immunosuppression: two with AIDS (Cases 2 and 4, Table 1) and one following a renal transplant (Case 3, Table 1).

**Patient Presentation**

The patients with NHL-CNS presented with four distinct profiles: 1) solitary or multiple discrete intracranial nodules; 2) diffuse meningeal or periventricular lesions; 3) uveal or vitreous deposits (uveitis/vitreitis);
and 4) localized intradural spinal masses. These presentations are described more fully below.

Discrete Intracranial Nodules

Solitary or multiple intracranial masses of tumor are the most common presentation of NHL-CNS. Fifty-six of our patients had supratentorial deposits and 21 had infratentorial deposits. This 3:1 ratio is identical to that reported by Helle, et al.93 for their own series, and is within the range of the previously reported cases that they reviewed (1:1.1 to 9.5:1). However, other features of the disease may be changing: half of our patients presented with multifocal intracranial tumors. This figure for multifocality is similar to the 45% recently reported by Helle, et al., but higher than the data reported previously: 0%,120 12%,137 18%,108 22%,112 28.5%,250 30%,230 33%,153 26% (literature reviewed by Helle, et al.)93, and 43%.55 It is not clear whether newer diagnostic methods such as CT scanning have artificially increased the detection of multifocal lesions, or if the higher frequency of multifocality in more recent cases reflects a genuine change in the biological behavior of these tumors. Twelve of our patients experienced a presentation that was formerly rare — that of deposits in both supratentorial and infratentorial locations.

In our series, a median interval of 2.7 months passed between the development of the first symptoms and pathological diagnosis. The reports of longer symptomatic intervals98 may reflect the use of corticosteroids or radiation therapy prior to histological confirmation of the diagnosis at biopsy or autopsy. Four of our patients had an extraordinarily long duration of symptoms prior to diagnosis and without any therapy other than steroids (45, 53, 84, and 96 months).

A febrile upper respiratory or gastrointestinal illness preceded neurological symptoms in 15% of our cases, and in six of 41 cases described by Burstein, et al.27 Within several weeks, personality changes or other symptoms were noted. The distribution of the common neurological abnormalities in our series of 66 cases is presented in Table 2.

These neurological difficulties may be indistinguishable from those associated with multiple sclerosis, encephalitis of viral, fungal, parasitic (Toxoplasma), or bacterial origin, granulomatous angiitis of the brain, or malignant gliomas (especially those involving the corpus callosum). A nonpsychotic depression may also be a presenting symptom;63 this was seen in five of our patients. Personality changes included apathy or slowness of thought (nine patients), “irresponsible” behavior or confusion,55 psychotic or schizoaffective disorders,42 and visual hallucinations. These neuropsychological changes appear to be associated with diffuse involvement of the periventricular white matter or of the corpus callosum by a tumor which infiltrates white matter tracts.

The subsequent development of motor difficulties, including hemiparesis (51% of our patients), and of speech problems (reflecting both receptive and expressive aphasia in 24%), usually precipitated neurological consultation. The late occurrence of headache (37% of our patients) reflected meningeal involvement or increased intracranial pressure. Ataxia (23%) resulted from infratentorial masses either within the cerebellum or infiltrating the brain stem and cerebellum from the fourth ventricle. Visual or cranial nerve symptoms reflecting vitreous or meningeal NHL-CNS are described below, but may also occur from visual pathway or brain-stem infiltration.

A rare form of lymphoma, “malignant angioendotheliomatosis” or “intravascular lymphomatosis” frequently presents with neurological difficulties resulting from the occlusion of small arteries of the brain with lymphoma cells.30,37,123,215,251 Sixty percent of patients with this neoplasm develop acute nonhemorrhagic cerebrovascular accidents or rapidly progressive confusion or dementia. Unlike NHL-CNS, careful evaluation usually reveals involvement of the heart, kidneys, and other organs. Only two cases with isolated CNS involvement have been reported.23,170 One of our patients, a 63-year-old woman, developed memory loss, speech hesitancy, and personality changes 8 months before a post-

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**Table 1**

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (yrs), Sex</th>
<th>Predisposition</th>
<th>Tumor Location</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1</td>
<td>48, M</td>
<td>none</td>
<td>cerebellar</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>46, M</td>
<td>AIDS</td>
<td>parietal</td>
<td>195</td>
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<td>parietal</td>
<td>58</td>
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<tr>
<td>4</td>
<td>7, F</td>
<td>AIDS</td>
<td>—</td>
<td>119</td>
</tr>
<tr>
<td>5</td>
<td>22, F</td>
<td>lymphomatoid granulomatosis</td>
<td>parietal</td>
<td>personal communication</td>
</tr>
</tbody>
</table>

* In Cases 1, 2, and 3, studies failed to reveal evidence of Epstein-Barr virus (EBV) genomic material in tissue from other organs or from nontumor brain tissue. CNS = central nervous system; AIDS = acquired immunodeficiency syndrome.

**Table 2**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of Cases with Symptom Present*</th>
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<tbody>
<tr>
<td></td>
<td>On Admission</td>
</tr>
<tr>
<td>personality change</td>
<td>24</td>
</tr>
<tr>
<td>cerebellar signs</td>
<td>21</td>
</tr>
<tr>
<td>headache</td>
<td>15</td>
</tr>
<tr>
<td>seizures</td>
<td>13</td>
</tr>
<tr>
<td>motor dysfunction</td>
<td>11</td>
</tr>
<tr>
<td>visual changes</td>
<td>8</td>
</tr>
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</table>

* Percentage of 66 patients with non-Hodgkin’s lymphoma.
mortem examination revealed extensive lymphoma within the brain vessels; there were small amounts of intravascular lymphoma in the retroperitoneum as well.

Diffuse Meningeal or Periventricular Lesions

Eight of our patients presented with diffuse meningeal neoplasms, and another eight had diffuse periventricular tumor on admission; together, these populations accounted for 24% of our 66 patients. An additional five patients had tumor within the corpus callosum or thalamus in proximity to the ependyma.

A meningeal presentation was noted in four of our patients who initially complained of headache. Three had meningitis, thought to be of viral origin. Computerized tomography scans were unrevealing other than to suggest a faint enhancement approximating the meningeal and/or ependymal surfaces. On the other hand, meningeal malignancy was diagnosed on clinical grounds in three patients in this group, after the development of an abducens paresis in one and of cervical or lumbar radiculopathy in the other two. Three further patients had ataxia of upper extremity movement or of gait as a result of proximal involvement of the cerebellum.

Meningeal or periventricular involvement can cause chemical changes in or loose cells to enter the cerebrospinal fluid (CSF). Studies of CSF revealed protein elevations in excess of 100 mg/dl in all of our patients who had lumbar punctures, and similar levels are generally recognized in the literature. Analysis of CSF also revealed lymphocytes (2 to 400/cu mm) in the MGH patients. Only two patients had more than 100 cells. As noted by Matsuda, et al., these cell populations were often initially viewed as "reactive" rather than "malignant." These "reactive" atypical cells were present in two of our 22 patients studied. An additional five patients had NHL-CNS confirmed on CSF study prior to biopsy. The finding of "malignant" NHL-CNS cells on cytological study is rare; we have found only 28 well-documented cases in the literature.

Immunocytochemical studies performed on cytocentrifuged CSF aliquots can increase the sensitivity of CSF cytology, provided that suspicious cells are present for staining. Such studies revealed monoclonal immunoglobulin surface markers in six of our patients. The demonstration of monoclonality in such a population of B lymphocytes is functional proof of their neoplastic, rather than reactive, character. Until recently, the literature contained no documentation of monoclonal B cell populations in CSF samples of patients subsequently proven to have NHL-CNS, although in 1975 Jellinger demonstrated a single heavy chain on cell populations from four patients, three of whom had a circulating monoclonal light chain marker in the CSF. More recently, cases have been reported in which the demonstration of a monoclonal B cell population in the lumbar CSF allowed a diagnosis of CNS lymphoma; in a single case, cell surface marker studies performed on a CSF specimen documented a T cell phenotype.

Patients in the MGH series with lesions in periventricular locations or within the thalamus or corpus callosum adjacent to the ventricles commonly appeared with personality changes (seven of 13 patients) including depression, memory loss, and psychosis. Abnormalities were disclosed on CT scans only after the administration of intravenous contrast agents. The most common abnormal findings were diffuse enhancement of the subependymal surfaces of the lateral or fourth ventricles which blended into the adjacent choroid plexus, corpus callosum, basal ganglia, thalamus, or cerebellum. Evaluations of CSF in these patients revealed 5 to 50 lymphocytes/cu mm in all but one patient studied; that patient had in excess of 300 cells/cu mm. The CSF protein levels in these patients ranged from 50 to 700 mg/dl.

The CSF is a common site for relapse of NHL-CNS. At the time of recurrence, lumbar CSF and ventricular seeding occurs in up to 45% of patients. In our series, 40% of the patients experienced recurrences throughout the neuraxis including the subarachnoid space; the recurrences were detected by either lumbar puncture or autopsy. The true frequency of CSF involvement may be even higher, since many lesions within the brain parenchyma abut this circulation and produce chemical abnormalities in CSF in as many as 85% of patients.

Uveal or Vitreous Deposits

Eye symptoms such as obscured, cloudy, or blurred vision or altered visual acuity accompany lymphoma involving the posterior segment of the eye, including the vitreous, choroid, and retina. This pattern of eye involvement by lymphoma often antedates the development of clinically evident deposits in the brain parenchyma or the subarachnoid space. Retro-orbital lymphoma, on the other hand, is outside the CNS and is more frequently associated with the development of tumor deposits in other systemic extranodal sites.

Patients reported to have uveal or vitreal involvement do not differ from other patients with NHL-CNS with respect to median age (57.7 years), male:female distribution (1.1:1), or the intervals between the onset of neurological symptoms and diagnosis or death. Slit-lamp examinations of the eyes disclosed bilateral anterior chamber keratic precipitates which were indistinguishable from inflammation in 82% of the patients described as having such examinations. The retina and choroid may appear normal.

In the majority of reported cases, the uveal or vitreal lymphoma is manifested before clinical signs of brain involvement appear. Four of our patients developed unilateral vitreal difficulties a median time of 9 months prior to the diagnosis of solitary or multiple masses of NHL-CNS. This interval is close to the 7-month median interval reported for 29 cases described in the litera-
The injection of single or double doses of contrast material resulted in CT delineation of lesions in 92% of our patients in whom such examination could be performed; similar sensitivity has been described at other centers.99,121,123,240,248 On admission scans, 60% of these masses are solitary, poorly defined fluffy areas of enhancement involving the corpus callosum, basal ganglia, or thalamus. A periventricular location was seen in two-thirds of our patients (Fig. 3 left).

Both CT (with contrast enhancement) and MR imaging fail to detect subarachnoid or vitreal NHL-CNS. Primary spinal NHL-CNS has usually been detected by myelography (see above), but MR imaging has the potential to provide significant improvements in diagnostic visualization of these exceptional spinal lesions. "Spin lattice" (T₁-weighted) and "spin-spin" (T₂-weighted) MR studies have demonstrated few advantages over CT in the diagnosis of brain NHL-CNS (Fig. 3 right); however, abnormalities visualized on T₂-weighted MR imaging may persist after CT masses are no longer apparent and symptoms have disappeared. This disappearance frequently follows steroid therapy or irradiation, both of which induce tumor necrosis. Clinical tumor recurrence is heralded by masses appearing on CT scans or MR images weeks to months before new symptoms appear. These lesions are often radiologically inseparable from radiation-induced necrotic masses.

Pathology

Microscopic Examination

Within the brain, NHL-CNS appears to the naked eye as one of several ill-defined nodules with irregular borders that blend into the surrounding edematous white matter. The tumor is soft, and cut surfaces are generally yellow-white; they are distinctly different from

**Fig. 3. Comparison of computerized tomography (CT) with magnetic resonance (MR) imaging. Left: Contrast-enhanced CT scan demonstrating abnormal enhancement density involving the splenium of the corpus callosum. Right: While the MR image is more sensitive than CT in depicting periventricular disease, in this instance it was less able to differentiate the tumor from the surrounding presumed edema.**
the color of normal myelinated white matter. The tumors may have a variegated appearance, with foci of hemorrhage or necrosis. They lack the cystic appearance common in glioblastoma. Whereas multicentricity is rare in glioblastoma, it is seen in the majority of NHL-CNS cases.

As expected from the radiological descriptions, these tumor masses are often periventricular, and indeed are frequently seen as subependymal sheets or plates of abnormal soft friable tissue just beneath the ventricular lining. Meningeal involvement, when florid, mimics bacterial meningitis: the leptomeninges are filled with a semifluid white tissue which lies most heavily in sulci and in the basal cisterns, and which obscures the underlying cortical surfaces. In the spinal cord the nerve roots of the cauda equina are often matted together, and the cord occupies the center of a thick sheath of tumor tissue. Lesser degrees of meningeal involvement may be manifested by thickening of cranial or spinal nerves, and/or by focal deposits of creamy white tumor tissue within the meninges. Occasionally, NHL-CNS mimics a meningioma; these tumors are attached to the inner surface of the dura, they thicken and bridge through the leptomeninges, and invade the underlying cerebral cortex by direct extension. 2,108,109,121,230,243 Several reported cases of intracranial plasmacytoma, another form of B cell neoplasia, have presented similarly. 41,128,131,227,228,243

As with many primary brain malignancies, microscopic examination generally reveals that the tumor is infiltrative far beyond the borders of the grossly observed masses. The infiltrating edges of the tumors advance along perivascular spaces, whereas in the center of the tumors this classical pattern of perivascular cuffing may be lost in a diffuse sheet of tumor cells. In contrast to malignant gliomas and many metastatic carcinomas, NHL-CNS does not produce much endothelial proliferation in the tumor or adjacent brain. As it invades along perivascular spaces, however, the tumor's cells often infiltrate into blood vessel walls, producing a histopathological appearance not very different from vasculitis.

The neoplastic cells are not seen in follicular or nodular formations; all cases of NHL-CNS fall into the "diffuse" histological categories. With this proviso, all varieties of NHL found in other extranodal sites are seen in the brain. In our series and in the literature, 132,169 subcategories of NHL-CNS include the more aggressive, "small non-cleaved" nuclei (which resemble those of Burkitt's lymphoma) and tumors composed of large cells, with either cleaved or non-cleaved nuclei: large-cell cleaved, large-cell non-cleaved, and large-cell immunoblastic tumors. Less aggressive tumors contain small cells with cleaved nuclei: the "poorly differentiated lymphocytic lymphoma" 191 or "small-cell cleaved" lymphoma. 169 Several series and case reports have described examples of primary Hodgkin's disease of the CNS. 41,27,89,94,206,254 A reevaluation of the cases in the Armed Forces Institute of Pathology series 24 using immunohistochemistry 237 demonstrated monclonal intracytoplasmic immunoglobulin in many of these supposed Hodgkin's disease tumors; this led to the suggestion that all such cases originally thought to be Hodgkin's disease were, in fact, immunoblastic B cell NHL. It is now clear that primary CNS Hodgkin's disease, if it occurs at all, must be very rare; we have seen no cases in our own series.

There are a small number of case reports of tumors with the morphological features and matching cell surface markers of T cell malignancies, 22,78,149 and there are also cases of isolated CNS involvement by lymphomatoid granulomatosis, a lymphoma (first described as affecting the lung) which contains a mixture of reactive mononuclear elements plus malignant B lymphocytes typically arranged in a vasculitis-like pattern. 12,51,129,154,210 As noted above, there are also numerous isolated reports of solitary intracranial plasmacytomas. These tumors are probably best regarded as a distinct entity separate from NHL-CNS, despite their common B cell lineage, since they are generally found as single lesions attached to dura, but rare examples have been seen as intraparenchymal brain tumors. 6,66,162,245

Many series of NHL-CNS cases have been subdivided according to varied classification schemes, often with the support of immunohistochemical typing. 6,22,27,41,49,76,89,94,103,108,112,133,137,153,171,172,190,214,225,237,250 Until recently, however, reviewers found no correlation between histological type and clinical presentation or prognosis. 49,112,120,133 In our own series of 66 cases, 61 could be wholly or partially characterized according to the International Working Formulation classification 169 (Table 3). There were no cases of nodular or follicular lymphoma. Of the five histological groups, the large-cell immunoblastic group 89,93,94,108 was most common and amounted to 39.3% of our cases (Fig. 4 left). In contrast, immunoblastic tumors constituted between 13% 239 and 7.6% 198 of all systemic lymphomas.

Patients with one histological subtype of lymphoma,

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Cases</th>
<th>% of Total</th>
<th>Median Survival† (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>small cleaved</td>
<td>11</td>
<td>18.0</td>
<td>36.5</td>
</tr>
<tr>
<td>small non-cleaved</td>
<td>5</td>
<td>8.2</td>
<td>35.0</td>
</tr>
<tr>
<td>large cleaved</td>
<td>6</td>
<td>9.8</td>
<td>15.5</td>
</tr>
<tr>
<td>large non-cleaved</td>
<td>9</td>
<td>14.9</td>
<td>13.5</td>
</tr>
<tr>
<td>large immunoblastic</td>
<td>24</td>
<td>39.3</td>
<td>11.25</td>
</tr>
<tr>
<td>large, not otherwise</td>
<td>6</td>
<td>9.8</td>
<td>—</td>
</tr>
<tr>
<td>specifiable total</td>
<td>61</td>
<td>100.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

* Classification of non-Hodgkin's lymphoma of the central nervous system (NHL-CNS) according to the International Working Formulation. 169
† Survival time is calculated from the occurrence of the first symptom to death.
Primary central nervous system lymphoma

the small-cell cleaved tumor, experienced longer survival times and slower progression of disease than those with any other type (Table 3). It is notable that even in the more favorable histological subtype there were no cures, and all patients died of their lymphoma. The survival data in our series are relatively similar to those for the same histological subtypes of lymphoma in other locations, although patients with the systemic varieties of these tumors survive longer than those with NHL-CNS. Similar correlations between the histological type of NHL-CNS and survival times have now been reported by others. Helle, et al., found that one particular type (mixed small- and large-cell) was associated with a poorer prognosis than the others. Bogdahn, et al., in a retrospective evaluation of 56 cases from the literature, reported survival data very similar to our own results (allowing for differences in the classification schemes employed). Within the histological subtypes of NHL-CNS, survival time is unaffected by the extent or presence of mitotic figures, reticulin deposition, or “starry sky” histiocytes.

Immunological Marker Studies

The demonstration of monoclonal cell surface immunoglobulins on the lymphoid cells of these brain tumors confirms the light microscopic diagnosis of NHL-CNS. Immunoperoxidase evaluations for cell surface immunoglobulins were performed on frozen or paraffin-embedded sections of tissue obtained at biopsy or autopsy from 36 of the MGH patients. Of 12 frozen sections evaluated, nine stained in a monoclonal pattern. Staining was less successful on paraffin sections: six of 24 revealed monoclonality.

Sixteen cases had positive staining in a monoclonal pattern for light chains (11 kappa, five lambda); 11 had mu heavy chains, and one had gamma heavy chains (Fig. 4 right). One tumor with IgM and kappa markers also stained with the pan-B cell monoclonal antibody B1. We have seen no proven examples of T cell NHL-CNS; however, at least four well-documented cases have been reported.

Tumor Staging

This review of staging takes into account the major sites of NHL-CNS at presentation as seen in our own patients and as reported in the literature. Involved areas included multiple brain sites in 30% to 50% of cases, CSF in 10% to 25%, and the vitreous in 10% to 20%. Recognition of these patterns mandates early evaluation by CT brain scanning enhanced with a double dose of contrast medium, CSF examination (in the absence of intracranial hypertension or after cranial irradiation), and slit-lamp eye evaluation. As NHL-CNS is a restricted neurological ailment there is little reason to perform CT scans of the chest or abdomen, bone marrow biopsy, or surgical exploration of the abdomen. We have found no patient who, at initial presentation with NHL-CNS, had evidence of systemic lymphoma.

Effects of Therapy on Period of Survival

Although therapy of NHL-CNS rests on histological diagnosis and immunohistochemical determinations,
clinicians often prescribe corticosteroids (dexamethasone, 24 mg/day in divided doses) based on a diagnosis of NHL-CNS presumed from the clinical presentation and CT scans. A partial or complete regression of the clinical and CT lesions was seen in 37% of 48 of our patients treated with this regimen for 10 days. One of our patients had clinical and CT evidence of regression of a solitary mass within 8 hours of receiving 20 mg dexamethasone intravenously. This responsiveness represents true glucocorticoid cytotoxicity for lymphoid cells. Not uncommonly, this response disappears within months but may last for years. Recurrent lesions may respond to higher doses of glucocorticoids (dexamethasone, 80 mg/day).

Untreated patients with NHL-CNS survive an average of 1.5 months. Many factors influence survival rate. These include features having a positive impact on prognosis, such as a solitary intracranial lesion, favorable histology (Table 3), and the administration of radiation therapy or chemotherapy, as well as negative features having an impact on prognosis, such as multiple or periventricular/meningeal lesions at diagnosis or recurrence, and predisposing immunosuppression. Although surgical excision may improve the duration and quality of survival for patients with solitary encapsulated NHL-CNS, only diagnostic craniotomy or stereotaxic biopsy appears indicated for other patients.

The patient's age was not a determinant of survival time in our study or in that of Bogdahn, et al., although it is our impression that patients who are under 50 years of age and without prior immunosuppression fare better than do older patients. It is estimated that between 50% and 70% of patients with NHL-CNS survive 1 year, and between 16% and 30% survive 2 years. The overall median survival time from diagnosis was 13.5 months in our 61 evaluable patients (Fig. 5), and 13.5 months for the 50 biopsied MGH patients for whom complete data were available.

Only three of our patients survived 5 years. The longest survivors (median 45 months) were the 33 patients with solitary lesions at diagnosis: one-third of these lived for 2 years. The 16 patients with multiple lesions at diagnosis survived a median of 9 months, and 19% were alive after 2 years. The eight patients with meningeal and/or periventricular presentations survived 7.5 months.

Irrespective of therapy, histopathology is a correlate of survival time; however, lack of universal acceptance of the International Working Formulation makes inter-institutional comparisons difficult. Jellinger, et al., defined lymphoblastoma (our small-cell noncleaved tumors) and immunoblastoma (our large-cell immunoblastic tumors) as tumors with a poor prognosis (1-year survival 10% and 22%, respectively) in comparison to immunocytoma (our small-cell cleaved or large-cell cleaved/non-cleaved tumors) which were associated with a 1-year survival rate of 75%. Bogdahn, et al., noted diminished survival among patients with unclassifiable high-grade (predominantly large-cell) tumors (median survival time 6.8 months) and centroblastic (large non-cleaved) tumors (median survival time 13.7 months) in comparison to those with low-grade tumors of centroblastic/centrocytic type (our large-cell noncleaved or cleaved tumors) which were associated with a median survival time of 34 months. In our study, the best prognoses were associated with the small-cell cleaved subtypes (median survival time 36.5 months in 10 cases) and small-cell non-cleaved subtypes (median survival time 35 months in five cases). The worst prognoses were noted among eight patients with the large-cell non-cleaved type (median survival time 16.6 months) and 22 with the immunoblastic variety (median survival time 11.25 months).

These observations concerning determinants of survival time may be inaccurate for patients whose NHL-CNS occurs in a setting of immunosuppression. The median life expectancy for AIDS-related NHL-CNS patients is 1.5 months. On the other hand, Starzl, et al., asserted that both polyclonal lymphoproliferative diseases and monoclonal lymphoid proliferations (that is, lymphomas) regressed if the underlying immunosuppressive state was reversed. Hanto, et al., described a patient with a lymphoma occurring after renal transplantation in whom the tumor regressed on several occasions in response to acyclovir therapy.

A variety of radiation therapy approaches have been used to treat NHL-CNS. These include cranial irradiation (2400 to 5100 rads), and neuraxis irradiation. Prolongation of survival accompanies these treatments. The rarity of the disease has precluded formal clinical trials of radiation therapy, but an ongoing study of the Radiation-Therapy Oncology Group (using whole-brain irradiation to 5400 rads) reports a 7.5-month median survival for patients over 60 years and a 32-month median survival for those aged 60 years or less. Thus, most published results reflect the use of radiation approaches tailored to each clinical situation.

FIG. 5. Total survival (in months) of 61 patients with non-Hodgkin's lymphoma of the central nervous system treated at Massachusetts General Hospital.
Primary central nervous system lymphoma

Forty-four of our patients were irradiated. Therapy to the whole brain (5000 to 6000 rads administered in 180-rad fractions) and sometimes to the spinal cord (4000 rads) depended on establishment of the extent of disease. Seventy-nine percent of the irradiated patients exhibited a partial or complete response to therapy. A concomitant improvement in survival time (median 21.5 months for the 35 evaluable patients) was noted. Our data are similar to those of others who found mean survival times of 26.2 months following irradiation of tumor volume, 14.6 months following whole-brain irradiation, and 14.5 months following craniospinal irradiation. Our own series and our review of the literature emphasize that, despite the prolongation of survival produced by irradiation compared to no treatment or surgery alone, eventually the tumors recur, so that a cure is not achieved by radiation.

Major sites of recurrence after radiation therapy in our patients and in those reported elsewhere include systemic disease in 10%, indicating that, in a minority of cases, NHL-CNS can eventually spread beyond the CNS. These recurrences involved the heart, gastrointestinal tract, spinal epidural space, and bone marrow. Neuraxis dissemination, occurring in 60% of our patients, argues strongly for a combination of craniospinal irradiation or chemotherapy plus irradiation as primary treatment for this disease.

Few studies address the role of chemotherapy. A variety of agents, including the nitrosoureas and methotrexate, have been shown to enter the brain parenchyma and CSF. This penetration may be enhanced as a result of administration by high doses via systemic or intra-arterial routes. Based on the single experience of Ervin and Canellos and on the report of Neuwelt, et al., intravenous high-dose methotrexate (3.5 gm/sq m with leukovorin rescue every 3 weeks) followed by cranial irradiation (3000 rads) has been used to treat 13 MGH patients with NHL-CNS. Twelve of the 13 patients treated prior to irradiation have shown partial (in four) or complete (in eight) responses. The longest period of response is 54+ months. Two of three treated at recurrence after irradiation showed complete responses of 30+ and 52+ weeks.

Ongoing adjuvant chemotherapy trials are in progress in five centers (Table 4). These studies make use of pre- and postirradiation administration of drugs (methotrexate, cytosine arabinoside, or 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)) used to treat other CNS tumors.

**Prospects for Future Investigations**

While a considerable number of questions raised in this review could be areas for fruitful investigation, four general paths of investigation appear to be of particular interest. The first of these is the clinical issue as to

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Irradiation</th>
<th>No. of Cases</th>
<th>PR/CR</th>
<th>Toxicity</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>preirradiation: methotrexate (3.5 gm/sq m every 3 wks, IV) with leukovorin rescue (3 courses)</td>
<td>whole brain, 5500 rads at recurrence after chemotherapy</td>
<td>15</td>
<td>13 (up to 196+ wks)</td>
<td>elevated creatine (1)</td>
<td>Massachusetts General Hospital (Hochberg)</td>
</tr>
<tr>
<td>preirradiation: methotrexate (1 gm/sq m, 2 IV doses; 12 mg, 6 IT doses) postirradiation: AraC (3 gm/sq m/day × 2 days)</td>
<td>whole brain (4000 rads) tumor boost (1440 rads)</td>
<td>12</td>
<td>11</td>
<td>renal failure, resolved (1)</td>
<td>Memorial Sloan-Kettering (DeAngelis)</td>
</tr>
<tr>
<td>preirradiation: Cytoxan (750 mg/sq m, IV); Adriamycin (10 mg/sq m, IV); vincristine (1.2 mg/sq m, IV); prednimose (100 mg/sq m) postirradiation: AraC (3 gm/sq m/12 hrs × 4, IV) alternate months for 2 cycles</td>
<td>whole brain (5040 rads) if drug failure or after 2 cycles of chemotherapy</td>
<td>7</td>
<td>6</td>
<td>transient cerebellar syndrome (1)</td>
<td>Mayo Clinic (O’Neill)</td>
</tr>
<tr>
<td>pre- or postirradiation (2 cycles): mannitol-induced BBB disruption with Cytoxan (15-30 mg/kg, IV); methotrexate 1.5 gm, IA with leukovorin rescue; procarbazine (100-150 mg/day po × 14 days; dexamethasone (24 mg/day po × 14 days) postirradiation (cycles): procarbazine 10 (60 mg/sq m, Days 8 to 21), CCNU (110 mg/sq m, Day 1), vincristine (1.4 mg/sq m, Days 1 &amp; 28)</td>
<td>variable</td>
<td>12</td>
<td>10</td>
<td>seizures</td>
<td>Oregon Health Sciences University, Portland (Neuwelt)</td>
</tr>
<tr>
<td>postirradiation (cycles): procarbazine (60 mg/sq m, Days 8 to 21), CCNU (110 mg/sq m, Day 1), vincristine (1.4 mg/ sq m, Days 1 &amp; 28)</td>
<td>whole brain (4500 rads) with hydroxyurea (300 mg/sq m every 6 hrs)</td>
<td>10</td>
<td>not available</td>
<td>severe myelosuppression (2), neuropathy (1)</td>
<td>University of California at San Francisco (Chamberlain)</td>
</tr>
</tbody>
</table>

* NHL-CNS = non-Hodgkin's lymphoma of the central nervous system; PR/CR = partial response/complete response; IV = intravenous; IT = intrathecal; IA = intra-arterial; po = by month; AraC = cytosine arabinoside; BBB = blood-brain barrier.

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whether NHL-CNS represents a single disease entity or whether, in different clinical settings (such as in patients with AIDS), it is so biologically different that it should be regarded as multiple diseases. On the one hand, the full spectrum of histological subtypes and clinical/pathological presentations described in our series and in the literature is seen in all populations with NHL-CNS. In contrast, patients with immunosuppression tend to have fewer solitary tumors and fewer of the type of tumor with intermediate-grade histology (although examples of these have been seen in such patients) and aggressive multiple tumors also occur in many or even most non-immunocompromised NHL-CNS patients.

On the other hand, the clinical course of immunosuppressed NHL-CNS patients is generally more fulminant than in otherwise normal patients,226,232 which may reflect fundamental biological differences. It also seems at least plausible that the etiological events leading to NHL-CNS may differ in immunosuppressed versus non-immunosuppressed patients. This issue may be approached by careful clinical studies of the immune status of ostensibly non-immunocompromised patients, careful analysis of the natural history and response to therapies of the tumors in the various populations, and by a better understanding of the etiologies of these tumors (see below).

This last point suggests a second avenue of investigation, which is, in the immediate sense, less speculative. As discussed previously, there is already a body of evidence associating EBV with NHL-CNS. To further investigate this possible causal relationship, we will continue to analyze NHL-CNS tumor tissue for EBV deoxyribonucleic acid (DNA); where possible, with newer methods of DNA hybridization, we will retrospectively examine tissue from earlier cases for such viral DNA. Later approaches might lead to the establishment of an animal model, very likely using transgenic mice.

Additionally, as other putative viral etiological agents are identified and probes for their nucleic acid become available, the presence or absence of these agents in tissues of NHL-CNS will also be established. Viruses now identified as requiring such investigation include various retroviruses, especially human T lymphotropic virus I,25 the AIDS virus itself (HLVI), which has been shown to activate normal B lymphocytes in vitro;213 another virus that might be examined is the newly identified human B cell lymphotropic virus, which is apparently a member of the herpes family.116,205

On a still more practical level, specific antibodies directed against NHL-CNS tumors may be utilized to carry various substances to the tumors in vivo. One early application of such antibody-conjugated delivery systems is now undergoing preliminary investigations, namely the use of monoclonal anti-B cell antibodies known to label the cells in a particular tumor biopsy, conjugated to radiolabels to provide better delineation of NHL-CNS lesions on CT, positron emission tomography, and MR imaging studies. Such investigations are already under way for a variety of animal and tumor systems with different antibodies.57,209 As the feasibility of such methods increases, antibodies might also be used to carry antineoplastic agents to the tumors in high concentrations while sparing normal tissues; such agents could include radioisotopes, radiosensitizers, and chemotherapeutic drugs such as methotrexate.

Finally, one issue that has not been substantively addressed either in this review or in the literature is that of the ultimate origin of the neoplastic cells in NHL-CNS. The CNS has neither lymphatic circulation nor endogenous accumulations of lymphoid tissue. Since lymphomas often spread aggressively within the CNS but rarely extend outside, the occurrence of these tumors as primary tumors in such an organ system, raises the question as to the source of these neoplasms. This is, in effect, a modern restatement of the issues that for so long perpetuated the controversy between “microglioma” and “reticulum cell sarcoma” as diagnostic terms for these tumors.

Two principal suggestions or schemes can be proposed to account for the origin of NHL-CNS. In the first, a non-neoplastic, reactive population of lymphocytes is attracted into the CNS by an infectious/inflammatory process, probably viral; some second event in the local site(s) then transforms a clone of the inflammatory cell population into neoplastic cells. This scheme has several advantages: it explains the primary site(s) of NHL-CNS, it is supported by the evidence that numerous viruses can infect the CNS in relatively high titers for chronic periods while evading immune surveillance, and it could explain the peculiar CNS restriction to the spread of the tumors if the neoplastic clone carries a binding molecule specific for the CNS or its endothelium. The existence of tissue- or organ-specific binding molecules on the surfaces of circulating lymphocytes has already been demonstrated for lymph nodes and Peyer’s patches in mice.229,68,231,233 These “homing molecules” apparently lead to binding by the cells with the specialized “high endothelial venules” of the specific target organ or tissue. The postcapillary venular endothelium of nonlymphoid organs can assume characteristics of the “high endothelium” in certain inflammatory states, which could then account for the homing of a selected population of lymphocytic tumor cells to the CNS and only the CNS as the neoplastic cells circulate in the blood.

In a second scheme, B lymphocytes in a lymph node or extranodal site (which already carry such a CNS-specific binding marker) are activated, caused to proliferate, and transformed to become neoplastic; these cells migrate in the bloodstream, but bind only in sites within the CNS; in the meantime, the true primary site remains obscure and undetected. As the cells bind in the CNS they multiply until they present as “primary” brain tumors. This scheme also accounts for the development of NHL-CNS, and more plausibly explains the high incidence of multifocality at the time of presentation. As with the first scheme, the presence of putative CNS-
specific binding molecules on the tumor cells would account for the low incidence of extra-CNS spread observed in patients with these neoplasms. In addition to the "homing" molecules already described, other kinds of surface molecules could account for the CNS specificity. Such specificity can be demonstrated for subclones of malignant melanomas, for example, which when injected intravenously into mice grow only in the lung, only in the brain, or even only in specific portions of the brain. 56,107,108,249

Aspects of these proposed schemes can be investigated by analyzing NHL-CNS cells for these putative marker molecules. In addition to attempting to verify the CNS binding behavior and to identify the hypothesized brain-specific homing molecule, other marker molecules shared by the nervous system and the immune system should be examined for possible roles in these processes. A variety of surface antigens are known to be shared by certain hematopoietic cells and selected neuronal populations, particularly in development. These include the class II major histocompatibility antigens (HLA-DR or Ia-like antigens) and the Leu-7/HNK-1 marker. 180 Another class of molecules that might be present on NHL-CNS cells include the neural cell adhesion molecules, 202 neural-glial cell adhesion molecules, 4 and oligodendrocyte cell adhesion molecules. 203 These molecules are known to provide specific cell-binding properties on developing CNS cells in the embryo, and to participate in such complex functions as synapse formation and axonal growth cone guidance. Chromogranin, a protein found in the cytoplasm of many neural and endocrine cells associated with dense core granules, has recently been detected immunocytochemically in a number of lymphoid tissues. 11

A search for such markers will most likely require a considerable quantity of tumor cells, especially viable cells; most biopsies are too small to provide enough material, and autopsy tissue is rarely obtained in a viable state for such studies. Thus, preliminary steps for such studies will necessarily include the development of stable cell lines in vitro or a means for perpetuating human tumors in an animal model, such as nude mice. At present, few if any stable cultures from NHL-CNS have been reported. 159,160 The development of a reproducible animal model, perhaps using transgenic techniques, would also be a valuable step in these lines of investigation.

These four areas are by no means the only ones deserving closer examination. The study of NHL-CNS remains a difficult problem: it is a disease or diseases of unknown etiology, consisting of cells of unknown sources; it is increasing in incidence for unknown reasons, and it may also be substantially changing its biological behavior. Effective treatment has remained elusive. Particular populations, namely immunosuppressed individuals, are at much higher risk for NHL-CNS and, as the number of these patients increases, NHL-CNS will continue to represent a growing problem and an enigma for modern medical practice.

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