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Neuroblastoma: an Analysis of 160 Cases

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Neuroblastoma was observed in 160 patients from 1948–1978. Ninety-seven patients were boys and 63 were girls. At diagnosis, 74 patients were less than 2 years of age, 28 between 2–3 years, and 58 over 3 years. Sixty-two (38%) patients had localized disease, while 98 (62%) had metastases. Patients were grouped by extent of disease according to the staging criteria of Evans et al.: stage I (5), stage II (31), stage III (26), stage IV (82), stage IV-S (16). Tumors occurred in the neck (3), mediastinum (16), abdomen (136), and pelvis (3). Clinical findings often included abdominal mass, weight loss, anemia, bone pain, and proptosis. Six patients had diarrhea and 3 had cerebellar ataxia and nystagmus. Lesions were often calcified (> 50%), and bone marrow aspirate frequently demonstrated tumor clumps (rosettes). Urinary VMA was elevated in 85% of cases.

Therapy varied according to stage. Stage I patients received operative excision alone and stage II patients operative resection with radiation for residual tumor and/or positive lymph nodes. Stage III patients were managed aggressively with operative resection (when possible), irradiation, and combination chemotherapy (cyclophosphamide, vincristine, DTIC, Adriamycin®, VM-26). Patients with metastases (stage IV) were initially treated with multiagent chemotherapy with late "second-look" or delayed primary laparotomy for tumor resection done in clinical responders.

Two-year disease-free survival occurred in 57 of 160 patients or 35.6%. Survival rates were best for infants under age 1 year (74%) and for patients with stage I (100%), stage II (74%) and stage IV-S (75%) tumors. There was improved survival in patients with tumors that occurred in the neck (100%), pelvis (100%), and mediastinum (75%). Survival rates were poor in patients over 2 years of age (13–17%), with abdominal tumors (28%), and with stage III (34%) and stage IV (10%) tumors. While chemotherapy and irradiation have improved tumor response, survival rate has not been improved. Immunotherapy has been disappointing. Unfortunately, at the present time, there is no specific chemotherapeutic agent that has a curative effect on this tumor.

Neuroblastoma is one of the most common tumors observed in childhood. This neoplasm is of neural crest origin and may arise anywhere along the sympathetic ganglion chain from the neck to pelvis, as well as in the adrenal medulla. Clinical manifestations of neuroblastoma may occur as a direct result of local or metastatic tumor growth or due to the elaboration of catacholamines and vasoactive peptides from the tumor. Although survival of children with other embryonal malignancies (e.g., Wilms' tumor, rhabdomyosarcoma) has been improved by using aggressive combined modalities of treatment, the use of chemotherapy and irradiation for neuroblastoma, while improving the tumor response, has failed to influence survival rate. While spontaneous disappearance of tumor and maturation from a malignant to a benign histologic type occasionally occur, especially in infants, most children with neuroblastoma continue to have a guarded prognosis [1–3]. This report evaluates the clinical course of 160 infants and children with neuroblastoma treated at a single pediatric cancer center with special emphasis directed to the current concepts in the management of this highly malignant tumor of childhood.

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Table 1. Staging of neuroblastoma according to the classification of Evans et al. [1].

I	Tumor confined to organ of origin
II	Tumor extends beyond organ of origin, but does not cross midline (regional nodes may be involved)
III	Tumor extends beyond the midline
IV	Distant metastases (skeleton, organs, soft tissues, distant lymph node groups)
IV-S	Remote disease confined only to liver, skin, or bone marrow (no evidence of bone metastases)

Patient Material

At the James Whitcomb Riley Hospital for Children on the Indiana University Medical Center campus, 160 infants and children with neuroblastoma were treated from 1948–1978. Patients were evaluated for age, stage, site of occurrence, and treatment as they relate to survival. Patients were grouped according to the extent of disease at diagnosis and the staging classification of Evans et al. [1] (Table 1). Sixty-two patients (38%) had localized disease (stages I, II, or III), while 98 patients (62%) had metastatic disease at diagnosis. Only 5 patients had stage I disease with the tumor confined to a single organ or structure of origin that allowed complete resection. Thirty-one patients had stage II disease with the tumor extending in continuity beyond the organ or structure of origin, but not crossing the midline, and 26 patients had stage III disease with large tumors that crossed the midline. Most stage II tumors were completely or almost completely resected, but patients with stage III neuroblastoma frequently had incomplete removal or simple biopsies due to the nonresectable nature of the tumor. Eighty-two patients had stage IV disease with distant metastases, especially to bone cortex. Another 16 infants under 1 year of age formed an additional and unique group classified as stage IV-S with liver metastases, subcutaneous skin nodules, and bone marrow involvement by neuroblastoma, but without cortical bone defects by radiographic examination.

The origin of the primary tumor was in the neck in 3 patients, the posterior mediastinum in 16, the abdomen in 136 (96 adrenal, 40 paraspinal) and the pelvis in 3 (Fig. 1). In 2 patients with stage IV-S disease, the site of the primary tumor could not be determined. Ninety-seven of the patients were boys and 63 were girls. Seventy-four patients were less than 2 years of age (39 under age 1 year), 28 patients were between 2–3 years of age, and 58 were over 3 years of age. Clinical manifestations were quite varied, but frequently included the presence of a large abdominal mass, weight loss, fever, bone or abdominal pain, weakness, anemia, proptosis with orbital ecchymosis, and a generalized failure to thrive. Six

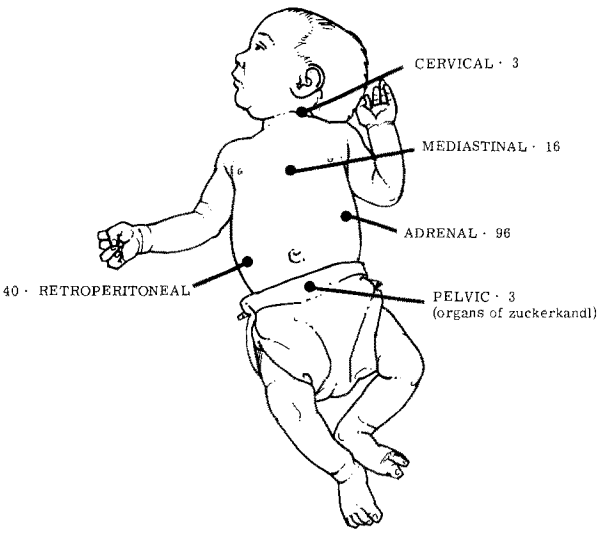

Fig. 1. Location of primary tumor in 160 patients with neuroblastoma.

patients presented with severe diarrhea and 3 patients had acute cerebellar ataxia (opsomyoclonus) with conjugate movements of the eyes (nystagmus). Patients with mediastinal neuroblastoma frequently presented with respiratory distress due to lung compression. A number of patients had paraplegia as a result of a "dumb-bell"-shaped extension of tumor through an intervertebral foramen causing extradural cord compression.

Over the past 8 years, all patients have had 24-hour urine collections for vanillylmandelic acid (VMA), homovanillic acid (HVA), metanephrines, and catecholamines. These metabolites were elevated in over 85% of patients when VMA levels were expressed as μg VMA/mg of creatinine (normal value < 20 μg/mg). All patients had erect and recumbent x-rays of the abdomen, a long bone survey, and a chest x-ray. In more than 50% of patients, punctate calcifications were seen within the tumor on the plain film. Bone scans using the isotope calcium diphosphonate ^{99m}technetium were routinely performed during the last 4 years of this study and showed a close correlation to the skeletal x-ray survey. The isotope is picked up by metastatic foci in bone as well as by the punctate calcifications in the primary tumor. Bone marrow aspiration and biopsy was routinely performed. Angiography was reserved for selected cases and, more recently, ultrasonography and computerized axial tomographic evaluation of the lesions have been done. Most patients with abdominal neoplasms had combined inferior venacavography and intravenous pyelography done with simultaneous dye injection. While not diagnostic, the inferior venacavagram proved to be a very helpful adjunct, particularly in planning the operation. As a rule, patients who had

Table 2. Survival rate according to age at time of diagnosis in 160 patients with neuroblastoma.

Age (years)	Number of patients	Survival	
		Number	%
< 1	39	29	74.3
1-2	35	15	42.8
2-3	28	5	17.8
> 3	58	8	13.7
Total	160	57	35.6

Table 3. Survival rate according to stage of disease in 160 patients with neuroblastoma.

Stage	Number of patients	Survival	
		Number	%
I	5	5	100.0
II	31	23	74.0
III	26	9	34.6
IV	82	8	10.0
IV-S	16	12	75.0
Total	160	57	35.6

complete obstruction of the inferior vena cava on this study had unresectable lesions. The intravenous pyelogram remains the mainstay in the diagnosis of this tumor. In most cases, the intravenous pyelogram demonstrated an extrinsic mass causing downward or lateral displacement of the ipsilateral kidney. Lateral displacement of the kidney and ureter were more common findings with paraspinal lesions. Most patients had evaluation of platelet count, prothrombin time, and partial thromboplastin time. In recent years, sera for carcinoembryonic antigen (CEA) has also been obtained. It was positive in approximately 25% of patients.

Therapy varied according to the extent of disease at the time of diagnosis. Prior to 1965, all patients with neuroblastoma were managed by attempted excision and radiation therapy. Since that time, patients have been treated under a number of protocols designed by the Children's Cancer Study Group (CCSG), of which James Whitcomb Riley Hospital is a member institution. At the present time, all stage I lesions (which are relatively rare) are managed by surgical therapy alone. Patients with stage II disease have operative resection and receive radiation therapy (dose range 1,200-3,400 rads according to age). Patients with stage III disease receive a more aggressive program of operative resection (when possible), radiation, and multidrug chemotherapy. Patients with metastatic disease (stage IV) are initially treated with multiagent chemotherapy including vincristine, cyclophosphamide, imidazole carboxamide (DTIC) and, more recently, the addition of sequential cyclophosphamide, Adriamycin®, and a podophyllotoxin (VM-26), with "second-look" (when a previous biopsy was obtained) or delayed primary laparotomy being done at a later date.

The 16 patients with stage IV-S disease were of special interest and will be presented in some detail. Ten of these patients were boys and 6 were girls. The mean age at diagnosis was 3 months (range: newborn-7 months), and 6 of the patients were less than 6 weeks of age (2 neonates). The site of primary tumor was the adrenal gland in 10 patients (6 right, 4 left), paraspinal in 4, and could not be determined in 2. Thirteen of these patients had liver metastases with involvement of the liver alone in 3 patients, skin metastases in addition in 5 patients, and additional bone marrow involvement in 5. Three additional infants had skin metastases only. No patients with skin involvement had tumor cells in the bone marrow aspirate or biopsy. Laparotomy was performed in 13 of the patients with resection of the primary tumor and liver biopsy in 8, and liver biopsy alone in 5. Three of the patients did not have laparotomy. Radiation therapy was given to the liver in 8 of the patients in doses ranging from 600-2,100 rads. Four patients received chemotherapy.

Results

Of interest was the relationship of survival rate to age (Table 2). A survival rate of 74% (29 of 39 patients) was achieved in infants under 1 year of age regardless of tumor stage. The survival rate dropped off to approximately 42% (15/35) between 1 and 2 years of age, was 17.8% (5/28) between 2 and 3 years of age, and was only 13.7% (8/58) in older patients. The best survival rate was observed in patients with localized disease (stage I), of which all 5 infants survived (Table 3). Twenty-three of 31 patients (74%) with stage II disease survived. However, in patients with stage III disease in whom the tumor was often so large that primary resection was impossible due to extensive involvement of the great vessels, particularly around the celiac axis and origin of the superior mesenteric artery, survival was observed in only 9 of 26 patients (34.6%). Most of these patients developed early metastases, especially if lymph nodes were positive for tumor. Patients with stage IV disease had a dismal outlook. At the present time, 14 of the 82 patients with metastases are alive, but only 8 have been free of disease for more than 2 years. In 14 of these patients, a "second-look" or delayed primary tumor excision was done. All tumor-free survivors were excluded.

Table 4. Survival rate according to location of primary tumor in 160 patients with neuroblastoma.

Site	Number of patients	Survival	
		Number	%
Neck	3	3	100.0
Mediastinum	16	12	75.0
Abdominal	138	39	28.0
Pelvic	3	3	100.0

In most patients with stage IV disease, the primary tumor was of significant size at the time of diagnosis and early excision was usually not attempted. Diagnosis was often established by the catecholamine excretion pattern and/or by the bone marrow aspirate or biopsy. Although most of the patients received multidrug therapy, there was no objective evidence that chemotherapy or irradiation improved survival.

Chemotherapy had a useful palliative role, since 70% of the patients showed a complete or partial response. Chemotherapy reduced the size of inoperable tumors so that subsequent resection was possible. Patients with metastatic disease in whom no evidence of residual tumor was demonstrated by clinical parameters following chemotherapy were considered "complete responders." Twelve of 14 patients, however, had evidence of persistent tumor at "second-look" or delayed primary laparotomy. In many, but not all, of these patients, it was possible to perform a complete resection of residual tumor. Histologic examination of resected tissues following treatment showed maturation of the tumor from a highly malignant grade IV primitive neuroblastoma obtained at the initial biopsy to a less malignant grade II ganglioneuroblastoma. The mean survival time for stage IV patients was 13 months. Prior to the year 1965, the mean survival time was only 3 months. Since then, it has been greater than 20 months. There were no survivors prior to 1965; however, 14 of 52 patients with stage IV disease treated since that time are presently alive. Nine are surviving more than 2 years, including 8 patients with no evidence of disease. All of these patients have had the primary tumor removed at a delayed primary or "second-look" procedure. Many of the patients had total lymphocyte counts done during their initial work-up, and this was found to be similar among survivors and nonsurvivors.

Twelve of 16 infants with stage IV-S disease survived. Three of the 4 deaths occurred in infants with bone marrow involvement. All 4 deaths occurred in patients under 6 weeks of age and were due to respiratory complications related to hepatomegaly and diaphragmatic elevation and sepsis, rather than to tumor spread. All infants with tumor resection, skin involvement, and those over 6 weeks of age at diagnosis survived. Survivors had a slow (6–15 months) regression of tumor, regardless of therapy employed.

The overall 2-year disease-free survival rate was 35.6%; 57 of 160 patients are presently alive. Survival was best for infants under 1 year of age (74%), and for patients with stage I (100%), stage II (74%), and stage IV-S (75%) tumors. In regard to the site of the primary tumor, all patients with neck and pelvic lesions survived and 12 of 16 patients (75%) with mediastinal tumors survived (Table 4). The worse prognosis was observed in stage IV patients, children of 2 years of age, and patients with abdominal tumors.

Discussion

Neuroblastoma is a malignant tumor with the potential to undergo spontaneous regression and mature to a benign form. This peculiar response occurs in less than 1 of 1,000 cancer patients, with 60% of the spontaneous cures being observed in 4 specific types of cancer: hypernephroma, malignant melanoma, choriocarcinoma and, most commonly, neuroblastoma. Spontaneous regression of neuroblastoma in patients who receive no therapy or unconventional therapy that is usually considered inadequate for cure, is commonly observed in stage IV-S and occasionally in stage II patients. In a recent CCSG study, 24 patients were observed to have spontaneous regression of their tumors and survived despite metastatic spread of the tumor at the time of initial diagnosis [3]. These occurrences strongly implicate an unusual tumor-host relationship, probably based on immune factors. Of considerable interest is the observation that 1% of infant autopsies in the first 3 months of life demonstrate adrenal neuroblastoma "in situ," whereas the tumor presents clinically in only 1 of 10,000 infants. This suggests that a natural immunologic surveillance mechanism may be protecting the host by preventing tumor growth. Hellstrom et al. [4] reported that the lymphocytes obtained from children with neuroblastoma and from their relatives inhibit formation of colonies of neuroblasts in culture, but do not inhibit cultured fibroblasts or cells grown from other tumor types. The sera of some patients with progressive disease prevent the lymphocyte-mediated cytotoxic response [5]. These blocking factors are antigen-antibody complexes and are composed of IgG_1, IgG_3, and IgG_4 subclasses of immunoglobulins. They often disappear after the primary tumor is removed [6]. The serum of tumor-bearing patients will inhibit the normal lymphocyte blastogenesis re-

sponse to phytohemagglutinin, and this correlates with the progressive inhibition of blastogenic responses of patients' lymphocytes to the same mitogen in groups with disseminated disease compared to localized disease and controls. In addition, skin test sensitivity and reactivity to dichlornitrobenzene (DNCB) in 67 patients with neuroblastoma correlated with survival. Of children with localized tumors, 90% had a positive response to DNCB, while of children with disseminated disease, only 27% had a positive response [7].

Clinical studies have been designed to further evaluate the immune system of these patients. Necheles et al. [8] reported an improved duration of remission in stage III and IV patients treated with chemotherapy (cyclophosphamide, vincristine, and Adriamycin®) and the methanol-extracted residue of BCG (MER) as a nonspecific immunostimulant. Unfortunately, these data have neither been duplicated by other investigators nor are they any better than results from other centers not using immunostimulants. Akeson and Seegar [9] have recently identified 3 nonspecific neural cell surface antigens on human neuroblastoma cells. To date, neuroblastoma antigens allegedly involved in immune tumor destruction have not been defined chemically or specifically [10]. A clear understanding of which antigens are immunogenic is important in developing effective immunotherapy. Studies to clarify these findings are in their early investigative stages. One must realize, however, that the tumor cell mass must be smaller than 10^6 cells (1 mg in weight) for immunotherapy to be effective. At the present time, there is no clear evidence to indicate that immunotherapy improves the survival of children with neuroblastoma.

While multiagent chemotherapy has significantly improved the survival rate in a number of other embryonal tumors (such as Wilms' tumor and rhabdomyosarcoma), no such effect can be shown for children with neuroblastoma. Evans et al. reported the data from a prospective, randomized study from the Children's Cancer Study Group (CCSG) that demonstrated chemotherapy (cyclophosphamide) had no beneficial effect in patients with localized (stage I) or regional (stage II) tumors [11]. These data and reports from other investigators indicate that there is no objective evidence to suggest that chemotherapy favorably influences survival in this tumor [12, 13]. At the present time, patients with stage I and stage II neuroblastoma do not receive chemotherapy in most centers. Many clinicians, however, employ radiation therapy in patients with stage II tumors, particularly those with microscopic or gross residual disease or lymph node involvement. This seems reasonable, since neuroblastoma is quite sensitive to radiation therapy. Although chemotherapy has not prolonged median survival time in patients with metastatic neuroblastoma in previous reports, we have observed an increase in the mean survival time from 3 months to 20 months since 1965, using chemotherapy programs according to CCSG protocols [14]. Chemotherapy can reduce tumor size, cause histologic maturation of tumor, and result in considerable palliation. Of our patients with metastatic neuroblastoma, 70% have had a response to 3-drug chemotherapy using cyclophosphamide, vincristine, and DTIC. Unfortunately, only 40% have had a complete response, while an additional 30% of patients have had no response whatsoever. Many patients with stage III neuroblastoma have unresectable tumors at the initial operation. Following courses of aggressive chemotherapy that reduce tumor size, some of these tumors are then amenable to a "second-look" resection which, when done prior to the occurrence of metastasis, may be associated with cure [15]. While complete excision of neuroblastoma in patients with localized disease results in a higher survival rate, the efficacy of resection of the primary tumor in instances of metastatic neuroblastoma has not been clearly established [13, 15]. Koop and Schnaufer [16] suggest that resection of the primary tumor in instances of stage IV disease should be done only when the operative risk is small and the patient's general condition is not severely undermined by the disseminated process. It has been our experience that in most cases of stage IV disease the tumor is usually quite large and often initially unresectable. Following drug therapy, a delayed primary operation or a "second-look" procedure may be carried out to resect the primary tumor. In a recent study from the CCSG [17], 24 of 27 patients considered to be responders to chemotherapy had residual tumor at a delayed primary or "second-look" laparotomy. It is of interest that residual tumor has been noted even in those patients considered to be complete responders without obvious clinical evidence of persistent disease [14, 15, 17]. The only survivors with metastatic neuroblastoma that we have seen have had their primary tumors resected [14]. In general, the most dismal survival data is noted in instances of stage IV neuroblastoma. Unfortunately, these patients account for more than half of all cases at the time of diagnosis.

In contrast, the favorable prognosis for stage IV-S neuroblastoma was confirmed in the present study, in which survival was achieved in 12 of 16 patients (75%). D'Angio et al. [18] and Evans et al. [11] similarly recorded survival rates of 84% (21/25) and 75% (12/16) in infants with stage IV-S disease. Deaths in these infants are rarely due to progression of malignant disease, but are more often related to complications, such as respiratory insufficiency and

sepsis. Respiratory embarrassment may occur due to diaphragmatic elevation from an enlarged liver filled with tumor. Attempts were made to decrease the size of the rapidly enlarging liver with radiation therapy in 8 patients in the present study, including 2 who died. Although a few patients experienced some decrease in liver size, the response was not uniform. Generally, tumor regression was characterized by a slow, spontaneous disappearance over a period of 6–15 months.

Schnaufer and Koop [19] reported the use of a temporary ventral hernia created by insertion of a Dacron®-reinforced Silastic® sheet to relieve intra-abdominal pressure in 2 infants with IV-S disease, 1 of whom survived. This technique was unsuccessfully employed in 1 patient in the present study who eviscerated when the Silastic® sheeting separated from the wound edge; the child subsequently died from sepsis. Much controversy surrounds the concepts of treatment for patients with IV-S disease. In some centers, no therapy is employed other than removal of the primary tumor; however, in other centers, liver irradiation and chemotherapy have been utilized. It is of interest that 3 of our 4 patients with IV-S disease who died had tumor clumps in the bone marrow. All were babies under 6 weeks of age at the time of diagnosis. The relatively poor survival rate of IV-S patients with bone marrow involvement (3/5 died) suggests that patients with this form of spread may not have the same favorable prognosis as infants with liver disease and/or skin involvement alone. D'Angio and colleagues [18] described 2 IV-S patients with positive bone marrow aspirates who died of progressive disease. These cases prompted them to suggest the use of chemotherapy for infants with positive bone marrow aspirates in IV-S disease. The theoretical dangers of simply observing clumps of tumor cells in the marrow that may progress to bone cortex metastases was raised. Employing chemotherapy, however, does not necessarily guarantee survival. Two stage IV-S patients with bone marrow involvement in this series died despite the use of chemotherapy.

Much information has accumulated concerning the behavior and treatment of neuroblastoma over the past decade. Unfortunately, none of these diagnostic and therapeutic measures have led to improved survival rates. These unusual neurogenic tumors produce secretory products that are helpful in making a diagnosis. Excessive secretion of catecholamines by the tumor produces a variety of degradation products in the urine. Urine 24-hour VMA, HVA, and metanephrine levels may be elevated, and the diurnal variation in excretion of these products as observed in normals may be lost [20]. Laug et al. [21] have placed special emphasis on the HVA:VMA ratio as an indicator of prognosis. A high ratio is associated with a poor outlook, presumably due to a greater HVA production in more primitive and immature lesions. Use of "spot tests" and "strip tests" as diagnostic screening methods is not nearly as accurate as a careful quantitative evaluation of 24-hour urine collections in patients with neuroblastoma.

Careful statistical analyses of patients with neuroblastoma suggest that the 2 critical determinants that act as independent variables that influence prognosis in this tumor are the age of the patient and the stage of disease at the time of diagnosis [12, 22]. The reasonably good prognosis for patients under 2 years of age (74%) does not pertain to older children. In addition, it is quite obvious that patients with localized tumors that can be resected (stages I and II) have a much better prognosis than patients with unresectable lesions that cross the midline (stage III) and those with metastatic disease (stage IV). Breslow and McCann [23] reported a dismal 2.5% overall survival rate in patients with stage IV disease. Although thoracic, cervical, and pelvic sites of tumor occurrence have an improved outlook in any age group, tumors at these sites are more frequently stage II lesions and occur in younger patients.

Some unusual manifestations of neuroblastoma have been of recent interest. Opsomyoclonus, which occurs in less than 2% of the cases, is a form of acute cerebellar ataxia that is accompanied by ataxic conjugate movement of the eyes. The majority of patients have thoracic lesions (posterior mediastinum) and have stage I, II, and IV-S disease. Neurologic manifestations usually improve following removal of the primary neoplasm. The most likely cause of this condition is some immune process. Altman and Baehner [24] in a review of 28 cases of neuroblastoma with opsomyoclonus reported a 2-year survival rate of 90%, suggesting that these patients may have a more favorable prognosis.

Another unusual complication of neurogenic tumors is chronic diarrhea, which has been reported in less than 10% of cases and improves following removal of the tumor. It is of interest that patients who have neural crest tumors and chronic diarrhea usually do not have elevated catecholamine levels and frequently have less malignant forms of the disease (e.g., ganglioneuroblastoma and occasionally benign ganglioneuroma). Bloom et al. [25] observed elevated levels of vasoactive intestinal polypeptide (VIP) in plasma and tumor tissue extracts in a patient with retroperitoneal ganglioneuroblastoma. VIP can produce vasodilatation of the splanchnic and systemic circulation, and is a strong stimulant of intestinal secretion and small intestinal motility. VIP is present in both the gastrointestinal tract and the central nervous system. The fact that neuroblas-

toma is of neural crest origin suggests that the tumor may have the ability to secrete VIP. Jansen-Goemans and Engelhardt [26] recently reported an additional case of a VIP-producing ganglioneuroblastoma. These authors believe that VIP is the mediator of the watery diarrhea syndrome observed in some infants and children with neurogenic tumors.

McCreadie and associates (*personal communication*) have demonstrated that neuroblastoma can be graded histologically on a scale of 1 to 4, with 1 (mature cells) being the most benign and 4 (immature cells) being the most malignant. Patients who have tumors with more than 5% of mature cells in a high-powered microscopic field appear to have a better prognosis. With this observation in mind, and the fact that in some cases the tumor undergoes spontaneous maturation from malignant to benign forms, attempts have been made to stimulate the maturation of neuroblastoma cells. These include using nerve growth factor and adrenergic agonists and/or phosphodiesterase inhibitors to raise intracellular levels of cyclic AMP. In this regard, papaverine has been used in conjunction with high-dose cyclophosphamide by Helson and associates [27] who suggested that papaverine raises cyclic AMP in the neuroblast, accelerates nucleotidase degradation, inhibits membrane transport of the neuroblastoma cell, and may stimulate maturation. Unfortunately, their data does not clearly demonstrate improved results.

Future treatment programs for neuroblastoma are presently being directed towards the operative reduction of massive tumor bulk, stimulation of tumor maturation, and delivery of more effective, sequentially administered cell-cycle-oriented chemotherapy. An example of the latter is the work of Hayes and Green [28] with Cytoxan® (a noncell-cycle-specific drug) and Adriamycin® (a cell-cycle-specific drug) administered sequentially to enhance tumor kill. Cell kinetic data suggest that the proliferating fraction of the tumor cell population in neuroblastoma is very small. A large pool of nonproliferating (resting) cells may restrict tumor destruction by chemotherapy [29]. Unfortunately, at the present time, there is no specific drug that has a curative effect on this tumor. In addition, there are many unknown factors, especially those affecting the host-tumor relationship, that probably play a significant role in the survival of patients with this unusual neoplasm.

Résumé

Entre 1948 et 1978, nous avons observé 160 malades atteints de neuroblastomes, 97 garçons et 63 filles. Au moment du diagnostic, 74 malades avaient moins de 2 ans, 28 entre 2 et 3 ans et 58 plus de 3 ans. La tumeur était localisée dans 62 cas (38%) et avec métastases dans 98 cas (62%). Les malades ont été groupés selon l'étendue de la maladie et selon les critères de Evans en: 5 stades I, 31 stades II, 26 stades III, 82 stades IV et 16 stades IV-S. La tumeur était localisée au cou dans 3 cas, au médiastin dans 16, dans l'abdomen dans 136, au petit bassin dans 3 cas. Les principaux symptomes étaient une masse abdominale, une perte de poids, une anémie, des douleurs osseuses et une exophtalmie. Six malades présentaient de la diarrhée et 3 une ataxie cérébelleuse avec nystagmus. La lésion était souvent calcifiée (> 50%) et la ponction médullaire a souvent mis en évidence des amas de cellules tumorales (rosettes). L'excrétion urinaire de VMA était élevée dans 85% des cas.

La thérapeutique a varié selon le stade de la maladie. Pour les malades au stade I, le seul traitement a été l'exérèse chirurgicale. Pour les stades II, l'exérèse a été complétée par une irradiation, soit du tissu tumoral résiduel, soit des aires ganglionnaires envahies. Le traitement des malades au stade III a été aggressif: exérèse lorsqu'elle est possible, radiothérapie et polychimiothérapie (cyclophosphamide, Vincristine, DTIC, Adriamycine, VM-26). Les malades présentant des métastases (stade IV) ont été traités au début par polychimiothérapie avec "second look" tardif ou laparotomie primitive retardée pour exérèse de la tumeur dans les cas répondant à la chimiothérapie.

La survie à deux ans sans récidive a été de 57/160 cas (35.6%). Les meilleures survies ont été obtenues chez les enfants endessous de 1 an (74%) et pour les tumeurs aux stades I (100%), II (74%) et IV-S (75%). La survie est également meilleure pour les tumeurs localisées au cou (100%), au petit bassin (100%) et dans le médiastin (75%). Les pourcentages de survie sont faibles pour les malades âgés de plus de 2 ans (13–17%), pour les tumeurs abdominales (28%), et pour les tumeurs aux stades III (34%) et IV (10%). Si la chimio- et la radiothérapie ont un effet thérapeutique sur les neuroblastomes, elles n'ont cependant pas augmenté les chances de survie. L'immunothérapie est inefficace. Il n'y a malheureusement, à l'heure actuelle, aucun agent chimiothérapique qui ait une réelle action curative sur ce type de tumeur.

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Invited Commentary

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The clinical analysis and review of neuroblastoma by Grosfeld and Baehner gives an excellent picture of the present knowledge of this malignancy. I shall attempt to supplement and reinforce a few of the many areas that they have covered.

It has been known since the report by Cushing and Wolbach in 1927 [1] that this disease can undergo spontaneous cure. In the case that they reported, the process was one of maturation to a benign ganglioneuroma. It has since been well demonstrated that most cases of spontaneous cure take place by disappearance of the lesion altogether, usually in patients younger than 6 months old. The work of Beckwith and Perrin in 1963 [2] showed that there are small neuroblastomas in the fetus ("neuroblastoma in situ"), with an incidence of 1/100 autopsies of stillborns and infants up to 3 months of age. In contrast with this, there are but 1/10,000 clinical cases among living infants and children. Therefore, most of the neuroblastomas seen in stillborns or newborn infants must regress and disappear.