NEUROBLASTOMA IN CHILDHOOD—AN EVALUATION OF SURGICAL MANAGEMENT

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An Evaluation of Surgical Management

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Ever since Cushing and Wolbach[1] reported, in 1927, the transformation of a malignant neuroblastoma (sympathicoblastoma) into a benign ganglioneuroma there has been much interest in, and speculation concerning, the unique behavior of the neuroblastoma.

Because of our observation of the survival of children in spite of management contrary to the usual principles of cancer surgery and because neuroblastoma is the most common malignant tumor we have encountered in childhood, it seemed worthwhile to record our experience with this tumor and its management. The patients under our observation also serve as a "control" for those reported series where radiation therapy was used in therapeutic doses and is logically assumed to have played a large part in the survival of patients. In the present series only 4 of 15 patients, surviving long enough to report here, received radiation in therapeutic dosage.

After the unique behavior of neuroblastoma with its tendency to change spontaneously from a malignant to a benign form was mentioned repeatedly in the literature, Farber,[2] in 1940, recorded the following: Neuroblastomas may necrose and disappear after only a biopsy, they may mature into benign ganglioneuromas and they may be successfully treated by irradiation even after local metastasis. He reported 10 of 40 patients surviving 3 to 8 years after histologic diagnosis. Wittenborg[3] later reported on 73 patients including the 40 reported by Farber; he noted that 22 of these were alive 3 or more years and emphasized the importance of irradiation therapy although indicating 2 of the survivals seemed to be "spontaneous cures." Phillips[4] after an extensive review of over 600 cases in the literature, concluded that neuroblastoma could be brought under ultimate control, if fatal termination could be prevented during the acutely malignant phase, because of the natural tendency of neuroblastoma to spontaneous remission. Snyder[5] in 1951 recorded the known surviving patients with neuroblastoma reported to that time as numbering 37. Since then 45 additional survivals have been reported and to that number we now add 15.

SUMMARY OF THE CLINICAL MATERIAL

A review of our clinical material indicates that of 45 cases, 19 are alive, but only 15 have survived 16 months or longer (Table I). Fourteen months is used as a crucial time because in our experience children with neuroblastoma who have survived 14 months without x-ray therapy have not died at a later date with 1 exception, a child whose tumor was only biopsied 11 years before his death. It is also true that a review of all of our experience with malignant tumors in childhood indicates that a 14-month period of survival is apparently equivalent to the 5-year period used to denote a "cure" in adult cancer statistics.

All of the patients in this series had histological diagnoses made at operation. Of the 41 patients reviewed 14 months after such diagnosis and/or treatment 26 are dead, a survival rate of 36.6 per cent. Table II compares this survival rate with other reported series.

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TABLE I

PATIENTS SURVIVING OPERATION FOR NEUROBLASTOMA FOURTEEN MONTHS OR LONGER

Patient	*Pathologic Diagnosis*	*Primary Site*	*Removal Incomplete*	*Metastases*	*X-ray Therapy*	*Survival*
JT	Neuroblastoma	Spinal Cord, Abdomen	+	Mediastinum, Neck nodes	No	12 yr.
BU	Neuroblastoma	Abdomen	+	Liver	No	11 yr.
LW	Neuroblastoma	Abdomen	?	No	Yes	7 yr. 11 mo.
LM	Neuroblastoma	Abdomen	+	Liver	No	6 yr. 8 mo.
MG	Neuroblastoma	Abdomen	−	No	Yes	6 yr.
SW	Neuroblastoma	Abdomen	+	Liver, Bone Marrow	No	5 yr.
CM	Neuroblastoma	Chest, Neck	+	Nodes	No	2 yr. 3 mo.
DB	Neuroblastoma	Neck	+	No	Yes	1 yr. 2 mo.
HL	Malignant Ganglioneuroma	Chest	+	No	No	4 yr. 3 mo.
CW	Malignant Ganglioneuroma	Chest	+	No	Yes	4 yr. 1 mo.
JM	Malignant Ganglioneuroma	Abdomen	+	No	No	4 yr. 1 mo.
JS	Malignant Ganglioneuroma	Abdomen, Pelvis	−	No	No	4 yr.
VA	Malignant Ganglioneuroma	Abdomen	+	Nodes	No	2 yr. 11 mo.
EB	Malignant Ganglioneuroma	Abdomen	−	No	Yes	1 yr. 4 mo.
MB	Malignant Ganglioneuroma	Abdomen	+	Kidney, Liver	Yes	1 yr. 4 mo.

The tumors in this series ranged from completely undifferentiated neuroblastomas to ganglioneuromas showing fair, but not complete, differentiation. Most of the tumors showed some differentiation, at times fairly uniform throughout the tumor, but at other times varying greatly from one area to another. Most of the surviving patients had tumors which showed at least partial differentiation but this was not invariably the case and, furthermore, many of the neuroblastomas showing appreciable differentiation proved fatal. A detailed study of the pathology is in preparation.[6]

The primary tumor was found in the retroperitoneal space in 35 patients. Four tumors were in the neck, 4 in the retropleural space, and 2 in the spinal canal. The metastatic sites in the surviving patients are indicated in Table I. Three conclusions may be drawn from these data on metastases: All patients who were free of metastases at the time of operation have survived; no patient who had metastasis to the lungs or skeleton is alive; metastases in liver, lymph nodes or bone marrow do not necessarily indicate a fatal outcome.

Bone marrow aspiration may be a valuable diagnostic and prognostic aid. Marrow aspirations were obtained from 30 patients; 9 showed neuroblastoma cells, only 1 of these survived. At the time of diagnosis the average age of those patients who have survived was 4.4 months, and for the fatal cases was 34 months.

In reviewing the operative procedures carried out in the surviving patients as compared with those who succumbed, it is obvious that the attack made upon the tumor in those patients who survived was far more radical than in the fatal cases. If one considers maximal surgical insult to be either extirpation of the tumor *in toto*, or as nearly complete removal as possible, 63 per cent of the surviving patients received such a surgical insult to the tumor, while

TABLE II

SURVIVAL IN REPORTED SERIES OF NEUROBLASTOMA

	Cases	*Survivals*
Wittenborg[3]	73	22 (30%)
Snyder[5]	24	3 (13%)
Phillips[4]	58	10 (17%)
Authors	41	15 (36%)

only 29 per cent of the fatal cases received similar therapy.

CASE REPORTS

Case I

A 17-month-old white female child was admitted February 14, 1952, because of a mass in the abdomen, discovered on routine physical examination the previous day. The child had been asymptomatic. November 15, 1951, during hospitalization for traumatic cataract, it had been noted that the spleen was enlarged.

The patient was a well-developed, well-nourished child in no acute distress. A large, hard mass extended 4 fingerbreadths below the left costal margin and the liver edge was palpable. The hemoglobin was 12.1 gm., the leukocyte count 8,500/mm.^{3} with a normal differential. Urinalysis was negative. Intravenous urograms revealed a huge tumor in the left upper quadrant. No evidence of metastases was seen on chest films or in a survey of the long bones.

Operation was performed on February 15, 1952. A large tumor mass was found in the lesser peritoneal sac surrounding the celiac axis, and extending into stomach, spleen, colon, and pancreas. Complete removal was impractical but as much of the tumor as possible was removed by blunt and sharp dissection; about half of the mass was extirpated. The liver and a mesenteric lymph node were biopsied. The report of the pathology was: malignant ganglioneuroma of the retroperitoneal region with metastasis to retroperitoneal lymph node; no histologic change in the liver tissue.

The mass was palpable after the wound healed and seemed to grow larger until it was palpable as low as the umbilicus in April, 1952. There was little change thereafter until June, 1954 when the mass was barely palpable at the left costal margin. Throughout this time the child grew and developed normally and remains well at the present time.

Case II

An 8-month-old white female was admitted to the Children's Hospital on January 18, 1942, presenting an enlarged liver. Exploratory laparotomy at another hospital had revealed an enlarged liver with nodules diagnosed on biopsy as metastatic neuroblastoma. However, the primary tumor was beneath the liver and no attempt was made to remove it. Her postoperative course was so good that she was referred for confirmation of the diagnosis.

The child was pale and well-developed with essentially no abnormal physical findings other than a hard, non-tender, nodular liver extending 4 cm. below the right costal margin. The hemoglobin was 13.0 gm., leukocyte count 13,400/mm.^{3} with 71 per cent lymphocytes. The urine was negative. Roentgenograms of the chest and long bones showed no evidence of metastases. Bone marrow was normal, without evidence of neuroblastoma cells.

Operation was performed on January 20. A 6 cm. mass, later reported as a malignant ganglioneuroma, was removed from above the right kidney and multiple metastatic nodules were noted in the liver. X-ray therapy was started on the second postoperative day and amino-an-fol,* 40 mg. by mouth daily, was started on the fifth postoperative day and continued at home through October, 1952. The child received vitamin B complex and injections of crude liver extract.

During the first postoperative year, the liver became smooth and finally just palapable at the right costal margin. The child's growth and development were within normal limits and she is well at the present time.

Case III

A 2-month-old white male was admitted to the Children's Hospital on May 24, 1948, because of anemia and a mass in the abdomen noted 2 weeks previously. He was a pale, well-nourished infant with a smooth, irregular non-tender mass in the left upper quadrant of the abdomen and an enlarged liver palpable 2 fingerbreadths below the right costal margin. The hemoglobin was 11 gm., leukocyte count 19,200/mm.^{3} with 75 per cent normal lymphocytes and 20 per cent neutrophiles. The urine was negative. Roentgenogram of the chest did not reveal any abnormality, an intravenous pyelogram showed diminished secretion but no

* A folic acid antagonist.

definite tumor. The blood NPN was 29 mg./100 ml.

Exploratory laparotomy revealed a mass involving the area of both renal hili. The liver was the site of hundreds of small, white nodules. The mass was broken into, its contents scooped and sucked out and a liver biopsy taken. Both the primary tumor and the metastases proved to be neuroblastoma. The patient was discharged June 6, 1948.

Six weeks after operation, the child developed subcutaneous nodules which were assumed to be metastases and not biopsied. Three months after operation the mass in the abdomen, which was palpable in June, 1948, was getting smaller.

The child did well at home but was admitted on June 28, 1949, because of polyuria. An intravenous pyelogram revealed moderate hydronephrosis with dilatation of the left pelvis and calyces. Neither ureter was well visualized. Retrograde pyelography demonstrated a normal right urinary tract and obstruction in the left ureter about 5 cm. above the uretero-vesicle junction. Calcification within a tumor in the abdomen in the region of L1 to L3 was noted. It was felt that further abdominal surgery was contraindicated and the boy was discharged. Repeat studies 2 years later revealed no change in the kidneys and no calcification.

The third hospital admission was on September 20, 1953, for orchiopexy and inguinal herniorrhaphy. No tumor could be felt under anesthesia and the child was asymptomatic. He remains so at the present time.

DISCUSSION

There are a number of unanswered questions concerning neuroblastomas. Do malignant tumors actually "mature" when they become ganglioneuromas? What histologic changes are evident in those tumors which remain in spite of the patients' survival? Does any therapy, whether surgical, radiation, or chemical, merely hasten a natural phenomenon, or do these materially affect the mortality?

Some of the unique characteristics of tumors in children must be recognized before answering any of these questions. Most tumors in childhood have a period of symptomatology as well as a life expectancy for the patient in fatal cases which is foreshortened, in contrast to experience with cancer in adults. Death in a fatal case is early in contrast to experience with adults and survival for 14 months after definitive diagnosis appears to approximate the conventional 5-year "cure" used in evaluating therapy of cancer in adults. The age at which the tumor first makes itself evident clinically seems to have some relationship with survival as is noted above.

The answers to the first 2 questions would seem to be impossible except by conjecture until studies are available on tumors, diagnosed as malignant by histologic examination, which have persisted in a patient who has survived in spite of apparently playing host to a neoplasm.

In answering the question concerning the effectiveness of therapy, one must confess ignorance concerning the mechanism of any type of therapy. It would seem that 2 observations can be made from our data which do not seem to be evident in the writings of other authors. First, most of the patients in the present series seem to have survived in spite of the fact that they were not treated with radiation. In the 15 surviving patients considered here, only 4 received x-ray therapy in what could be considered a therapeutic dose. Therefore, it seems obvious that we cannot assign any major role to radiation therapy in promoting survival in this series. This is in contrast to the assumption of most authors that radiation therapy is responsible for the control of neuroblastomas, if not the ultimate cure. Second, surgical attack which might be considered "radical" does seem to bear some positive relationship to survival in this series. In a tumor, known to regress spontaneously on some occasions, one does not know how to approach the tumor mass if it is not easily removable *in toto*. It has been the custom in many clinics when a child has a huge retroperitoneal tumor and gross metastases, to biopsy the primary tumor and perhaps a metastatic site but not to attempt complete excision of the tumor. There is certainly a sound basis for this type of approach in other tumors, but on the basis of our experience we can question whether this is proper

management in a patient with a neuroblastoma. Patients so treated by us have survived only rarely, 3 of 22 patients, a mortality of 87 per cent.

When we have approached a tumor of large size, even in the presence of metastases, with the intent of removing it completely or if such is impossible, with the aim of removing as much as can be done without danger to the patient, we have had survival of 12 of 19 patients or 63 per cent. In view of the survival rate in patients treated in this fashion as compared with the survival rates of those treated chiefly by x-ray therapy after histologic diagnosis, it seems valid to assume that major surgical insult might have something to do with the regression of the neuroblastoma and/or the survival of the patient.

In our experience, when a tumor can be removed *in toto* without difficulty, this course should be followed. If complete extirpation is not possible, then we remove as much of the tumor as is practicable, guided by its attachments. If the tumor is fixed to an adjacent structure, such as kidney, adrenal gland or spleen, where removal of the tumor and the attached solid viscus can be undertaken without endangering the child's future, this type of procedure is carried out without question. When a tumor mass surrounds vital areas such as both renal hili, the celiac axis or the porta of the liver, we have carried out partial extirpation of the tumor even though there may be obvious evidence of metastases. Such removal may consist of making an opening into the tumor and scooping out its central portion or separation, by blunt dissection, of the adjacent structures and the tumor. If fixation to an adjacent viscus gives way to infiltration, the tumor is cut across at that point. It is sometimes possible in a necrotic tumor to remove the bulk of the mass by vigorous suction. Such a procedure is almost always followed by rather brisk bleeding, but this has never been beyond control. Ligation of blood vessels not supporting the life of an adjacent viscus has also been carried out.

In spite of our desire to remove as much tumor as possible, we have not made it a practice to resect *en bloc* stomach, colon, or duodenum when the tumor has been tightly fixed to these structures. We feel that, because the survival rate is as good as it is by the above management and spontaneous regression is also possible, it does not seem justifiable to remove large segments of adjacent hollow viscera in an effort to remove gross evidence of invasion, when microscopic invasion probably already exists beyond that point. The reason the patients in this series did not receive x-ray therapy was that in early cases treated by us the infiltration of adjacent structures with tumor, in adition to tumor cells spilled at operation, led us to believe x-ray therapy would be of little material benefit. As this series grew, and survival seemed to be a relatively frequent occurence, we continued along the line of not administering x-ray therapy. If our thesis concerning the effect of major surgical insult is valid, radiation should be of additional value and we are currently using it in therapeutic dosage after surgery.

It is interesting that all of the patients in this series who died had metastases, but almost 50 per cent of the survivors also had metastases. No patient who was free of metastases succumbed to the primary tumor. Others have called attention to the poor prognosis associated with metastases to the skull and long bones. [3, 7, 8] Our experience certainly confirms this. No patient in this series with metastases to the lungs or skeleton survived.

SUMMARY AND CONCLUSIONS

Forty-five patients with neuroblastoma are reviewed, 41 more than 16 months postoperative. Fifteen of the forty-one are alive and well, a survival of 36.6 per cent.

There appears to be some correlation between survival of patients with neuroblastoma and a major surgical insult to the tumor. In 22 patients where biopsy alone was carried out, there was a mortality of 87 per cent. In 19 patients treated by a surgical attempt at radical removal of the tumor

without subsequent radiation therapy, 12 survived, a rate of 63 per cent.

The age of the surviving patients at the time of diagnosis was 4.4 months as contrasted with an average of 34 months for those who died.

The survival of 11 of 15 patients for periods ranging from 16 months to 12 years after diagnosis is unrelated to x-ray therapy.

No patient in this series, free of gross metastases at the time of operation, has died up to the time of this report. Forty-nine per cent of the surviving patients had gross metastases, but no patient with metastases to lung or bone survived.

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INTERLINGUA ABSTRACT

Neuroblastoma in Infantia: Un Evalutation del Tractamento Chirurgic

Depost que Cushing e Wolbach reportava in 1927 le transformation de maligne neuroblastoma (sympathicoblastoma) in benigne ganglioneuroma, le conducta extraordinari del neuroblastoma ha essite ininterrumpitemente le objecto de multe interesse e speculation.

A causa de nostre observation que juveniles con neuroblastoma superviveva in despecto de tractamento contrari al acceptate principios de cancerochirurgia e proque le neuroblastoma es le plus frequente tumor de character maligne que nos ha incontrate in juveniles, nos ha concludite que publicar nostre experientias con iste tumor e su tractamento esserea un interprisa ben valente le pena. Le patientes observate per nos servi simultaneemente de "controlo" pro ille previemente reportate series de casos in que radiation in doses therapeutic esseva usate e logicamente considerate como un factor importante in le superviventia del patientes. In le presente serie solmente 4 del 15 patientes supervivente usque al tempore del redaction del reporto ha recipite radiation in doses therapeutic.

Es revidite le casos de 45 patientes con neuroblastoma. In 41 casos del serie le operation esseva executate plus que 16 menses retro. In 15 de iste 41 casos le patientes vive e se trova ben. Isto es un superviventia de 36 pro cento. Il existe apparentemente un certe relation inter le superviventia del patientes e un major insulto chirurgic del tumor. Inter 22 patientes in qui solmente un examine bioptic esseva executate le mortalitate attingeva 87 pro cento. Inter 19 patientes in qui le essayo esseva interprendite de obliterar le tumor radicalmente per medios chirurgic e in qui nulle therapia a radiation sequeva le intervention chirurgic, le superviventia attingeva 63 pro cento. Le etate median al tempore del diagnose esseva 4,4 menses pro le gruppo del patientes supervivente; pro le patientes qui moriva le etate median al tempore del diagnose esseva 34 menses. Le facto que 11 inter 15 patientes superviveva pro periodos de inter 16 menses e 12 annos post le diagnose initial esseva sin relation al roentgenotherapia. Nulle del patientes qui esseva libere de grossier metastases al tempore del operation ha morite usque al tempore del presente reporto. Quarantanove pro cento del patientes supervivente habeva grossier metastases, sed nulle patiente ha supervivite in que le metastase habeva attingite pulmones o osso.