Neuroblastoma is one of the most common and most highly malignant tumors of infancy and childhood. Widespread metastases tend to occur early, and a rapidly downhill course is generally followed by death within a few months. In a rather extensive search, the first report we can find of a cure in a patient with neuroblastoma was that by Lehman; an abdominal neuroblastoma was removed from a baby in 1911 and the child was reported in excellent health 15 years later. Cush- ing and Wolkach describe a patient who was given Coley's toxins for a neuroblastoma; 10 years later, the malignant portions of neoplasm had disappeared but there remained a benign ganglioneuroma. During the last 25 years, documentation has appeared in the literature to indicate that occasionally this disease can be brought under control, and that cure rates, though still leaving much to be desired, are gradually improving.

**PATIENT MATERIAL**

This study and report is made by reviewing 217 cases of neuroblastoma seen at the Children's Hospital in the period between January, 1920 and January, 1957. The records have been reviewed in detail to determine what factors influence the prognosis and to evaluate the various types of therapy which have been employed. Studies from parts of this material have been published. While we have excluded all patients with neuroblastomas of intracranial origin, we have included all patients who had the neoplasm originating elsewhere in the body. In each case, there has been histologic identification of the tumor. Up to 1950, the patients of this series could be regarded as the general range of material which might enter any children's hospital or pediatric service. Since 1950, there has been a great intensification of interest in neoplastic disease in this institution, which has brought into the hospital a large number of patients with far-advanced and metastatic disease, heavily weighting the more recent material with less favorable stages of neoplasm to treat. Nevertheless, all of these recent cases have been included in the current review. In spite of this marked trend to cases with a more gloomy prognosis, the cure rates from 1950 to 1957 have risen to a figure higher than we have ever been able to attain before.
patients were under 5 years of age (Fig. 1), the youngest being 4 hours and the oldest 16 years.

From tissue of the sympathetic nervous system in any part of the body, and particularly that of the adrenal medulla, there can arise four general types of tumors: pheochromocytoma, ganglioneuroma, neuroblastoma, and sympathogonioma. The first of these has hormonal activity (giving off epinephrine-like substances); the others do not. The ganglioneuroma is a benign growth. We are concerned in this report with only the two malignant tumors, neuroblastoma and sympathogonioma.

Microscopic examination of a typical neuroblastoma shows a very cellular, rapidly growing neoplasm, with great infiltrative qualities. Blood vessel invasion is common. There is little stroma. Cells occur in broad sheets or in clusters; mitotic figures are numerous. Generally, the cell nuclei are polygonal or spherical; there is a moderate amount of chromatin which has either an even distribution or a peripheral arrangement. In some zones cells are arranged in so-called "rosettes." Occasionally, cells take on an elongated or spindle form, producing neurofibrils. The identification of rosettes and neurofibrils constitutes adequate evidence for designating a tumor as a neuroblastoma.

In a few specimens one finds a more malignant variant, in which cells are somewhat smaller and no rosettes or neurofibrils can be found. This has often been classified by others as "sympathogonioma" or "sympathicoblastoma." Because the general clinical behavior of these tumors is quite similar to that of neuroblastomas, we have made no effort to consider them as a separate group. Accordingly, in the material being reported here, all sympathogoniomas and neuroblastomas have been lumped together for statistics and study under the single category, "neuroblastoma."

Occasionally, a neuroblastoma may be found possessing some areas in which there is differentiation into a more mature type of tissue, and ganglion cells can be identified. Because this mixed type of neural tumor does contain highly malignant elements, we still classify it as a neuroblastoma, realizing that it carries a some-
what better prognosis than do those growths which show only the characteristics of neuroblastoma on multiple histologic sections.

Grossly, neuroblastomas generally have a few characteristics which permit fairly accurate recognition, even before microscopic verification is undertaken. In early stages, the neoplasm has a smoothly rounded contour, but, in more advanced lesions, it is very apt to have a finely nodular surface. Its color is reddish-gray, often with a violaceous tinge, indicative of marked vascularity. The tumor is soft and can be fragmented or broken easily. While at first it is rather well encapsulated, in more advanced lesions the limiting membrane is rather delicate and is easily ruptured during manipulation or surgical extirpation. While for a short time the neoplasm is self-contained, it soon shows a high degree of invasion of regional tissues and organs. This characteristic is seen with great frequency as the tumor pervades the pancreas, spreads along retroperitoneal spaces or pierces through the diaphragmatic crura and infiltrates the posterior mediastinum.

Neuroblastomas may arise from any site where one would normally find elements of the sympathetic nervous system, e.g., adrenal medulla, sympathetic chain on either side of the neck, thorax or abdomen. Figure 2 indicates the various sites of origin, the adrenal gland being the most common offender (40% of all cases). The tumor arose in paravertebral tissues in the thorax in 11% of cases; from the retroperitoneal sympathetic chain in 5%; from the pelvic nerves in 6%; and from the neck in 2%. In some instances, the site of the primary tumor could not be identified because the lesion was so widely disseminated through the body at the time the child was first seen or a necropsy was performed.

In two instances, microscopic examination of sacrococcygeal teratomas, excised from infants a few weeks of age, revealed, amongst many other types of mature and immature structures, some areas of neuroblastoma. Neither baby showed metastases.

Multiple neuroblastomas were encountered in four instances at necropsy. In one, both adrenals contained tumor, each thought to be primary. In another case, there was a primary tumor in the right adrenal and apparently another in the
SKULL
AND/OR BRAIN

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NEUROBLASTOMA SYMPATHETICUM

Fig. 3. Distribution of metastases.

retroperitoneal sympathetic chain. A third child (2 years old) was found to have six separate tumors arising from different parts of the retroperitoneal sympathetic chain, all presumably having arisen independently. Another patient had a large ganglio-neuroma in the chest in addition to a separate large adrenal neuroblastoma, each mass thought to be independent of the other.

Metastatic spread may be either lymphatic or blood-borne, and secondary lesions may appear in a variety of locations. Distant metastases occur rather early and widely invade bone marrow, skeleton, brain and orbit. They are not prone to appear initially in the lungs, as is the finding with some other tumors, such as embryoma of the kidney. In babies, the liver may be massively infiltrated and replaced by tumor and yet no metastases can be identified outside of the abdomen; such a distribution is seldom encountered in children beyond the first year of life. Figures 3 and 4 summarize the position of metastases and incidence of bone metastases; 70% of patients were found to have metastases at the time of initial hospitalization and study.

In general, the clinical features are similar, regardless of the site of origin of the primary tumor. Distant and widespread metastases can occur from any growth, but it is our impression that the tendency to metastasize is rather lower from primary tumors in the thorax, and particularly in the neck, than from those in the abdomen. It is possible that we find fewer metastases from neuroblastomas in the upper half of the body because the thoracic, and especially the neck, tumors come earlier to the attention of patient and physician, and are therefore being detected in earlier stages of the disease.

TREATMENT

In the period of several decades during which our observations were made, policies in handling of patients have been changing as newer techniques of therapy have developed. From an attitude of hopelessness which existed 25 years ago, it is now known that a multiple-sided attack on the problem
can effect a permanent cure in a fair number of patients, and that to others can be brought palliation and an extension of life in reasonable comfort. Therefore, no uniformity of treatment has been utilized for all of the patients, but the series is large enough, and the modes of treatment so widely varied, that it is possible to draw impressions or even definite conclusions regarding the various forms of therapeutic effort (Fig. 5). These will be commented upon briefly in the following.

**Total Surgical Excision**

Complete extirpation of the tumor (when there are no demonstrable metastases) is without doubt the treatment of choice. In 24 such cases, there was what was thought to be complete surgical excision of the mass. In most cases (all excepting three) x-ray irradiation was given over the operative site, in the belief that this might destroy any remaining bit of tumor too small to be seen by the surgeon. Whether or not this irradiation was actually improving matters, we are unable to say. Unfortunately, only 14% of all patients were seen early enough for this type of approach. Of these 24 patients with complete excision, all have been followed for 2 or more years; there have been only three deaths, a cure rate of 88%. (As we review the survivors in this group, it is important to note that there was a wide spread in ages of the patients; there was

![Fig. 4. Percentage of patients with metastases to bone when first examined.](image)

![Fig. 5. Cure rates with various treatments for 90 patients with neuroblastoma. Those patients who had metastases to bone when first seen are excluded.](image)
not a heavy weighting of material in the first 12 months of life, wherein the prognosis is known to be more favorable.)

**Partial Excision Plus X-ray Therapy**

In 22 instances the great bulk of tumor was excised, but to the operating surgeon it was quite obvious that much tumor tissue had been left in the field. These patients were then treated postoperatively with x-ray irradiation to the remaining tumor (more recently, some have also received tumor chemotherapy). Out of 22 so treated, 14 were well and free of disease for 2 or more years, a cure rate of 64%. Koop and his colleagues8,10 emphasized the value of "surgical insult" and reported cures from partial excision and no other additional therapy. Conceivably, the bodily reaction to stress of any operation could call forth the elaboration and release of adrenal corticoids, which could very well have destructive effects on the neoplasm.

It is important for the surgeon to bear in mind that he is dealing with a very radiosensitive tumor and that a patient's life should not be jeopardized on the operating table for the mere sake of obtaining as wide and complete excision as might be the aim with some other malignant lesions. Neither should a neuroblastoma be declared inoperable and its removal abandoned. The surgeon must be guided by the facts as we know them today: If a neuroblastoma can be removed in its entirety, this should be done, but if conditions are such that only a major portion of the tumor can be cut away, there is still promise of a very good cure rate, if postoperative irradiation (or irradiation and tumor chemotherapy) can be given.

X-ray therapy for all of our cases has been under the direction of Dr. E. B. D. Neuhauser, Dr. M. H. Wittenborg and Dr. G. J. D'Angio of the Department of Radiology. The various details of such treatment have been published elsewhere.7 However, a few general points seem worthy of mention. In recent years, it has been our practice to initiate x-ray therapy immediately after operation, the first treatment being given on the day of surgery, preferably before the child has recovered from anesthesia. The daily dosage is usually about 200 r, measured in air, given to alternate portals, running up to a total of 3,600-4,000 r. We have had no complications in the surgical wounds with this management.

**Biopsy and X-ray Therapy**

In view of the above results which demonstrate the radiosensitivity of neuroblastomas, the question arises as to the value of even partial excision. Can x-ray therapy alone (after suitable identification by biopsy) accomplish the same results? We have observed 24 patients who have been managed in this way; there were 9 long-term survivors, a cure rate of 38%. This compares to 64% for the previous group in which most of the tumor had been excised prior to irradiation. These comparative figures strongly indicate that surgical removal of the great bulk of a tumor (prior to irradiation) improves the probability of cure. Furthermore, they indicate that in those patients for whom it is possible only to obtain a biopsy (because of the poor condition of the patient or the great extent of a neoplasm) a fair salvage rate can still be expected by giving x-ray irradiation.

**Biopsy Only**

Prior to our adoption of x-ray therapy as a part of the treatment of neuroblastomas (about 1937), 20 patients with neuroblastoma had only biopsy and were not given any definitive therapy; all were found to be inoperable. Two infants regarded as hopeless at the time, because of widespread and nonremovable neoplasm, are now well and completely free of disease 20 and 25 years later. Presumably, the very cellular and rapidly-expanding tumor grew beyond its blood supply, then degenerated and disappeared. Possibly, there are some poorly understood antibody reactions between host and tumor, leading in some cases to dissolution of the latter. Suffice it to say that there are a few well-documented cases wherein
neuroblastoma has disappeared completely and permanently.

**Tumor Chemotherapy**

For most of a decade, there has been in this institution a professional group who have been intensively engaged in the production of and testing of chemotherapeutic agents which might be advantageously employed in treatment of various neoplasms in infancy and childhood. Not only has this group brought into play a wide variety of chemical agents which can be helpful in this regard, but in addition they have built up a program of total support of the child that has made it possible to employ more radical surgical procedures, more extensive courses of x-ray irradiation, and more prolonged courses of chemotherapy. This dynamic approach to the entire problem presented by the child and his extensive disease has without doubt brought about arrest of disease and even some cures which in previous years we would not have thought to be possible. Some of the items in this constantly-changing field of chemotherapy have been recorded elsewhere. Definite regressions of skeletal metastases from neuroblastomas have been seen in some instances, and temporary healing has been found in a few. Impressive changes clearly give a bright hope that in the future significant improvements in therapy for neuroblastoma will come from the chemotherapeutic attacks.

**FACTORS RELATED TO RESULTS**

When asking about the results of any therapy, parents and physicians always want to know about the long-term outlook. What can be said regarding the likelihood of a “cure”? How long is it necessary to wait before one can feel free of a threat to life from the neoplasm? The last question will be answered first.

**What Constitutes a “Cure”?**

The question implies that there is a span of time beyond the run of which a living patient can be classed as cured. For those physicians and surgeons who deal with neoplasms of adult life, it is customary to think in terms of 5, 7, or even 10 years before speaking of “cured” cases. When facing problems of malignancy in infancy and childhood, it is quite obvious that the processes of growth and those of neoplastic proliferation are much more accelerated. Hence, it is proper to select a much shorter period after therapy, beyond which the youngster who is still alive can be considered as cured. What is the length of this period for patients with neuroblastoma? Data relevant to this point are summarized in Figure 6, which indicates that most patients who are going to have a recurrence will show evidence of this and be dead within a few months. Furthermore, it appears that an individual who is well 2 years after treatment, and at that time shows no recurrence by physical examination or by roentgenographic study, can be regarded as permanently cured; it is extremely rare for recurrence or metastasis to appear at a later date. We have had only one patient who died of neuroblastoma beyond the 24-month waiting period. On the basis of these observations, all use of the term “cure” in this paper refers to patients who, following treatment, are alive and in good health at the end of 2 years, and who have, at that time, no evidence of neoplasm by physical examination or by roentgenologic examination of the chest and skeleton.

**Spontaneous Cures**

We have seen two patients who undoubtedly represent spontaneous cures. These were among patients seen during the early part of the series, and both were regarded as inoperable. In one, a 6-week-old infant, at surgery there was a large tumor arising out of the pelvis; biopsy showed neuroblastoma. No treatment was given. Subsequently, the abdominal mass gradually disappeared. This individual was completely asymptomatic and in robust health when examined 25 years later. The other was an 11-month-old infant with a large tumor arising from the posterior mediastinum,
90% of the deaths occurred within 12 months
99% of the deaths occurred within 2 years

Fig. 6. Survival (in months) of patients who died of neuroblastoma.

biopsy showed neuroblastoma. No treatment was given. She was asymptomatic, with a normal roentgenogram of the chest 20 years later.

In two other instances, we have encountered, at surgery, a large primary tumor of the suprarenal area with much neoplasm in the regional lymph nodes. Histologically, in each instance, both the main tumor and the smaller tumors in lymph nodes were completely benign ganglioneuromas. We suspect that these tumors were originally malignant neuroblastomas and that the primary tumor and the metastases to lymph nodes had undergone maturation into benign ganglioneuromas. Because of uncertainty, these two cases have not been included in the series in the present report.

Spontaneous cure may be expected to occur in a very small percentage of cases of neuroblastoma.

**Type of Therapy**

As shown by Figure 5, the form of therapy has an important bearing on the final outcome. There can be no doubt that total excision of a neuroblastoma (possibly combined with postoperative irradiation over the tumor site) gives the brightest outlook, and has been followed by a cure rate of 88%. It would be pleasing to be able to offer this to all patients, but unfortunately there is a selection of cases for this group, as in only 14% did we feel it was possible to get entirely around the mass and remove it completely. Nevertheless, when findings present themselves and appropriate ablative surgery is carried out, the prognosis becomes excellent.

There have been a considerable number of patients (without bony metastases) for whom exploration was performed, during which there were circumstances (because of the poor status of the patient, or more frequently because of great extent of the neoplasm) that allowed only partial resection of the neoplasm, but for whom x-ray treatment was immediately and subsequently given. While these circumstances seemed forbidding, it is surprising to find that nearly two-thirds (64%) have been cured.

Finally, for those wherein only biopsy has been possible at the time of surgery, x-ray treatment (in some combined with chemotherapy) has brought a cure rate of 38%.
Obviously, these three forms (or combinations) of therapy have not been applied to similar stages or examples of neoplastic disease; instead, there has been a selectivity of treatment based upon preoperative evaluation of patients and also largely upon what was found at operation. We have always regarded the first form of therapy (complete excision) the most desirable, but have come to learn that as we encounter earlier forms and less hopeful stages of disease, we can still obtain some worthwhile results and therefore regard secondary forms of therapeutic attack as valuable.

**Position of Primary Tumor**

The site of origin of a primary tumor apparently has some bearing on the long-term outlook (Fig. 7). We doubt if there are any important differences in the behavior of tumors from the various sites. Probably the poorer prognosis related to neuroblastomas of the adrenals and abdominal sympathetics is dependent upon the fact that these lie dormant and undetected for longer periods, and therefore are generally more advanced before coming to the attention of a physician.

**Presence of Metastases**

To those who have handled neoplasms in adults, the presence of metastases constitutes an overwhelming gloomy outlook, and forebodes complete disaster. When dealing with neuroblastomas in childhood, the same is usually true but there are notable exceptions (Fig. 8).

Distant lymph node metastases (without bone involvement) were present in 14 patients; 4 cures followed biopsy and x-ray therapy, a cure rate of 35%.

Certainly, metastases to bones (demonstrable by roentgenograms of the skeleton or identifiable by bone marrow biopsy) are indicative of a fatal outcome within a matter of months. Out of 74 patients presenting bony metastases when first seen, we have had only 1 survivor. This was a 3-month-old boy, found at surgery to have a large and inoperable neuroblastoma in the right flank; the liver was filled with metastases. Biopsies of the primary tumor and of a liver nodule both revealed typical neuroblastoma. Bony metastases were never demonstrated by roentgenologic examination, although two sternal marrow biopsies on different dates contained neuroblastoma cells. Treatment consisted of x-ray irradiation over the liver and abdominal masses, plus tumor chemotherapy. The child is now well and apparently free of disease 8 years later.

Pulmonary metastases were present in 20 patients, 19 of whom are now dead; 1 is still living, but has been followed less than 6 months. (Bone metastases were also present in 15 of the 20 patients in this group.) Neuroblastoma with metastases to the liver (even though these are massive in the liver) is curable in the majority of instances. Surgery in nine infants with neuroblastoma originating in the adrenals or in the retroperitoneal structures revealed extensive liver metastases, but roentgenograms had not shown any skeletal involvement. The lesions were positively identified by biopsy. Treatment consisted of x-ray irradiation.
One died of aplastic anemia a year later, and two died of disseminated neuroblastoma. The remaining six are living and well, with no evidence of neoplasm from 5 to 15 years later, a cure rate of 67%. It is important to note that all six of these infants were under 1 year of age at the time (the two dying of disseminated disease were 3 months and 2½ years of age). We cannot explain these unusual characteristics of liver metastases (appearing largely in the very young and carrying a far brighter outlook than metastases which appear elsewhere); neuroblastomas are unique in these respects.

Age of the Patient

The younger the child, the more favorable the outlook (Fig. 9). While a study of our entire material shows consistently that babies in the first 12 months of life have always had a far better outlook than older subjects, this difference is particularly emphasized by figures from the period 1950-1957, during which patients of all ages have experienced a cure rate of 36.7%. During this period, those patients who were under a year of age were cured in 56%, and those under 2 years in 49% of cases. In this period, patients without metastases to bone when first seen and under a year of age were cured in 70%, and those under 2 years in 65% of cases. The reasons for such striking differences are unknown. From repeated reviews of pathologic material, we cannot detect any essential differences in make-up of tumors in the younger and older subjects. Possibly, there are some immunologic differences in the two groups of hosts. Possibly, the better outlook for a baby is related to the fact that a young infant is handled more often by parents and is examined more often by physicians, thus leading to earlier detection of intra-abdominal masses.
Fig. 9. Cure rate for each year of life in 178 cases of neuroblastoma.

Fig. 10. Results of treatment of neuroblastomas, 1920-1957.
FIG. 11. Four-month-old infant with abdominal mass as outlined. At surgery this proved to be an enlarged liver filled by metastatic neuroblastoma, with a small primary in the right adrenal. Treatment consisted of x-ray irradiation (6,100 r, measured in air) over the abdomen.

Decade When Therapy Was Carried Out

As we review material from the entire series, and divide it into decades (Fig. 10), it is evident that changes have occurred in therapeutic regimens, and also in the results which have accrued therefrom. From 1920 to 1930, neuroblastoma was regarded as a hopeless disease; with no effort to treat the condition, there were no cures. About 1930, surgical attempts at excision began to come into vogue, and in a few years there were co-operative efforts by radiologists, combining to give some hope in a field which previously had been bleak. The same combinations of treatment were generally employed from 1940 to 1950, with little improvement in survival statistics. From 1950 onward (in spite of a worsening of the kind of material which has been coming to us), the addition of chemotherapy to the therapeutic armamentarium has been accompanied by a distinct and pleasing improvement in cure rates. While the treatment of any group of children with neuroblastomas will be at-

FIG. 12. Same patient as Figure 11, 14 years later. He is completely asymptomatic and free of disease.
tended by many discouraging experiences and fatalities, the fact that statistics show an upward trend in cure rates does give grounds for some optimism.

SUMMARY

The treatment of patients with neuroblastoma does not lie solely in the province of a single specialty; it requires cooperation of pediatrician, surgeon, radiologist and tumor therapist. It is essential that they all be aware of the unique characteristics of this particular tumor if optimum results are to be obtained. The many factors found to influence the prognosis for a child with neuroblastoma are discussed.

In those cases wherein there are no demonstrable metastases, the treatment of choice consists of total excision, followed by local x-ray irradiation; this has resulted in a cure rate of 88%. In those cases wherein total excision is not possible, partial surgical removal followed by x-ray irradiation and tumor chemotherapy has given a cure rate of 64%. In those cases where only biopsy has been performed, x-ray irradiation and chemotherapy has still given a salvage, with a cure rate of 38%.

When there are metastases to the liver alone, about two-thirds of babies can be cured by x-ray therapy. Whenever bony metastases have appeared in any case, the prognosis is extremely poor, and it is rare for such an individual to survive, regardless of the form of therapy.

An aggressive attack on neuroblastoma in infancy and childhood, combining surgery, x-ray irradiation and tumor chemotherapy, has shown a progressive improvement in results. During the period 1950-1957, cure rates have risen to 36.7% for all patients entering the hospital, regardless of age of the patient or extent of the neoplasm. For babies under a year of age, cures have occurred in 56%, and if there were no demonstrable metastases to bone at the time of hospitalization, the cures have been 70%.

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Robert E. Gross, Sidney Farber and Lester W. Martin

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