

THE APPARENTLY BENEFICAL EFFECTS OF CONCURRENT INFECTIONS
INFLAMMATION OR FEVER AND OF BACTERIAL
TOXIN THERAPY ON NEUROBLASTOMA



GEORGE A. FOWLER, M.D. AND HELEN C. NAUTS

MONOGRAPH #11

NEW YORK CANCER RESEARCH INSTITUTE, INC.
1225 PARK AVENUE NEW YORK, N.Y. 10028

NEW YORK 1970

INDEX

INTRODUCTION	1
CONCURRENT INFECTION, INFLAMMATION, FEVER	
SERIES A, 18 CASES	
Table 1	10
Detailed Histories	16
TOXIN TREATED CASES	
SERIES B, ¹⁰ 8 CASES	
Table 2	48
Detailed Histories	52
BIBLIOGRAPHY	79

We are indebted to C. Everett Koop, M.D. for his thoughtful review of this manuscript and for his helpful suggestions.

INTRODUCTION

THE APPARENTLY BENEFICIAL EFFECTS OF CONCURRENT INFECTIONS, INFLAMMATION OR FEVER, AND OF BACTERIAL TOXIN THERAPY ON NEUROBLASTOMA

This study of neuroblastoma comprises the known cases of this type of tumor in whom bacterial toxin therapy was administered (eight), or in whom concurrent acute infection, inflammation or fever occurred, (eighteen).

SOME CLINICAL FACTS ABOUT NEUROBLASTOMA

Neuroblastoma is found in infancy and childhood and originates from tissue from which the adrenal medulla or other portions of the sympathetic nervous system develop. Approximately 15 per cent of all cancers in children are neuroblastomas.

In the majority of patients with untreated neuroblastomas, metastases develop soon and there is a rapidly downhill course resulting in death in a few months. Because of the rapid growth of this tumor, a child well 12 to 14 months after treatment with no evidence of recurrence, probably may be considered cured. (64)

After biopsy or incomplete surgical removal, an infection, fever or without known cause, this tumor may undergo spontaneous hemorrhage and necrosis and regress completely or may undergo maturation to become a benign ganglioneuroma.

Neuroblastoma was first described by Marchand in 1891 as being derived from neural structures. (43) It was not until 1910 that they were established as a separate and distinct clinical entity by the histological observations of Wright. (77) They are neurogenic in origin and are sometimes referred to as neuroblastomas or as sympatheticoblastomas, as they arise from the undifferentiated cells of the sympathetic nervous system. Their origin is not confined to adrenal tissue. They may also arise in the sympathetic ganglions along the spine, especially in the cervical area. They are more common in males.

Stowens grouped the tumors of the sympathetic nervous system into the following: congenital neuroblastoma, neuroblastic sarcoma, ganglioneuroblastoma and ganglioneuroma. (67) The first two are indistinguishable anatomically but must be separated because of differences in biological behavior. The congenital neuroblastoma probably always occurs within the first six years of life and is fatal in 70% of the cases. The neuroblastic sarcoma occurs with random frequency throughout life and is invariably fatal. The ganglioneuroma is a benign tumor of mature tissue. It occurs mainly in the adult age group. The ganglioneuroblastoma is a tumor which combines features of both normal ganglionic tissue and neuroblastoma. It is essentially only a histological designation rather than a distinct entity. He reported that 69% are fatal. (67)

Incidence of Neuroblastomas: Koop stated that neuroblastoma was the most common tumor treated at the Children's Hospital in Philadelphia. (39) Dargen stated that it is one of the more common cancers observed on the Pediatric Service at Memorial Hospital. From 1926 to 1958 a total of 1,498 children suffering from neoplastic diseases were admitted to this service, 180 of whom had neuroblastoma. (12)

Initial Symptoms: The initial symptoms may be pain referred to the spine or legs, but in at least half the cases an enlarged palpable abdominal mass will be the most prominent observation. The clinical symptoms produced by an expanding retroperitoneal mass in infants and children include gastrointestinal disturbances, debility, anemia, blood changes, and signs suggestive of acute abdominal conditions. When an abdominal mass is felt it should

be considered malignant until proved otherwise. (54) Less often symptoms are referable initially to the chest, peripheral nodes, skin or a single bone. A tumor of the orbit or eye itself is not uncommon. In some the metastatic lesions first attract attention. Loss of weight is usually present, there may be emesis and when first seen the child is pale, undernourished and irritable. In some cases swelling about the face or skull is noted; proptosis of one or both eyes with discoloration of lids is common due to increased intracranial pressure and orbital metastases. In all such cases choked discs are present. Enlarged lymph nodes occur early or late. Bone pain from metastases may be the predominant feature at this time. The clinical course is usually a rapid decline with death in a few months.

Structure and Histology: Structurally these tumors are rather soft, hemorrhagic growths, the cut surfaces of which are white or yellowish in color, with necrotic and hemorrhagic areas, and which display a distinct lobulation. Microscopically this lobulation is found to be due to the division of the tumor growth by strands or bundles of connective tissue; the heavier strands are continuous with smaller strands of connective tissue fibers which further subdivide the lobules. Histologically these lobules vary in appearance: some may be extremely cellular, consisting of cells with small round hypochromatic nuclei and surrounded by an extremely narrow rim of cytoplasm which tends to flow out into processes. Often there are to be seen transitional stages in their development with neuroblasts, ganglion cells, nerve fibers and capsular cells. The more advanced stage of differentiation the less malignant the growth, the less cellular the area and the more abundant the intercellular network of fibrillae, some of which may be traced to their nerve cells.

The formation of rosettes by the cells is one of the characteristics, but some authors have seen rosettes in only a third of their cases. The rosettes consist of a circular arrangement of cells about bundles of fibrillae. The characteristic cell is similar to the primitive migrating cells of the sympathetic nervous system. Some authors believe that these tumors are moderately radio-sensitive, others do not. Certain pathologists believe that neuroblastoma and retinoblastoma are essentially similar neoplasms.

Cushing and Wolbach were the first to report that a malignant neuroblastoma may mature into a benign ganglioneuroma. (11) They described such a case in which this occurred following prolonged administration of Coley toxins alone (see below, Series B, Case 1). Others reporting cases of maturation of these tumors include Eyrebrook and Hewer (18), Greenfield and Shelley (29), McFarland and Sappington (42) and Wyatt and Farber (78). The latter also observed that neuroblastoma may undergo spontaneous hemorrhage and necrosis and disappear without any treatment other than biopsy.

Differential Diagnosis: Willis (74) and a few other authors have noted the similarity of neuroblastoma metastatic in bone to Ewing's sarcoma: both may have rosettes microscopically. However, Ewing's sarcoma usually occurs in later childhood and has the characteristic onion skin appearance roentgenologically. Sherman and Leeming noted that neoplasms said to be confused with neuroblastoma are Ewing's sarcoma, primary reticulum cell sarcoma of bone and rarely even certain osteogenic sarcomas. This is an added reason why the roentgenologist should be familiar with the x-ray appearance of this tumor. (60) In the present study, Series B, Cases 3 and 4 were initially regarded as Ewing's sarcoma and Cases 5 and 6 were regarded as reticulum cell sarcoma.

THERAPY

a) *Surgery*: Farber (19) and Koop (39) have stated that the first step in the treatment of any solid intra-abdominal mass in early life should be surgical removal. Bodian (2) observed that a striking feature of neuroblastoma is that by the time they are first seen the majority show x-ray evidence that the tumor has already invaded adjacent structures or metastasized. Indeed, metastases may be the first indication of the tumor and since the primary tumor may not be obvious, this feature may lead to an initial error in diagnosis. Because these tumors are highly invasive, this frequently makes any attempt at adequate surgical removal out of the question, especially in intra-abdominal growths where retroperitoneal spread frequently involves adjacent viscera and surrounds major vessels.

b) *Radiation*: As to whether irradiation should be used in these cases, opinions differ. Koop concluded in 1955 that x-ray is not as important in the survival of these cases as has hitherto been supposed. (39). In 1964 he stated that x-ray therapy is not given routinely after surgery. If it is given he recommends a total dose of approximately 1200 r rather than the higher dosage previously in vogue (40a).

Wittenborg stated: "The limiting dosage factor in the treatment of infants and small children is not the skin, but the response of the hematopoietic tissue. Vertebrae examined postmortem which were within the direct field of therapy showed evidence of bone marrow depression to the degree of complete hematopoietic stasis and fibrous displacement of marrow. This was true of calculated tumor dosage of as little as 600 r in 10 days repeated twice or a month apart. It is axiomatic that the total amount of hematopoietic tissue irradiated or the dosage to which it is subjected are the decisive factors in determining recovery of an infant or small child from the radiation effect." (75) He cited two cases that died of clinical pancytopenia and complete marrow suppression confirmed at autopsy. In the group that survived none had received x-ray to both chest and abdomen. This experience would indicate that deep x-ray therapy directed to the mediastinum and abdomen in tissue doses up to 600 r, if justifiable at all, should be undertaken with considerable reservation. Complete regression of tumor with cures has been achieved with as little as 400 r delivered in 16 days.

A number of investigators have reported on the deleterious late effects of irradiation in children treated for neuroblastoma or Wilms' tumor. King, et al reported three cases of radiation induced osteochondroma in infants irradiated at the ages of from five months to three years for neuroblastoma. (38a) Severe skeletal deformity, including scoliosis, may occur in these children as a result of radiation changes. (48b; 57a; 73a). Others have observed severe radiation nephritis which may ultimately prove fatal. Two such cases are included here as Cases 7 and 12 in Series A. (1;18).

c) *Vitamins*: Beginning in 1950, Bodian attempted to determine whether Vitamin B-12 could bring about maturation of neuroblastoma. That this idea was erroneous was evidenced in his Cases 1 and 3 where successive biopsies were obtained. (2, 3) There was progressive shrinkage of tumors in 50 per cent of the cases, compatible with destruction rather than simple differentiation of the neoplastic tissue. Encouraging results occurred in a group of patients considered unsuitable for orthodox methods of treatment, and in whom the prognosis was considered hopeless. The dosage he used was 1000 micrograms of the crystalline product (Squibb) given intramuscularly on alternate days. In some cases this was continued for two years, Bodian's Cases 1, 2, and 7 had survived 30, 13, and 14 months when he published his first

report, and the disease appeared to be arrested. (2) In Case 3, although the child finally died, there was striking regression of extensive liver metastases over a period of nine months, proven by successive liver biopsies. Sawitsky and Deposito collected the results obtained by American physicians with Vitamin B-12 alone or combined with x-ray or other agents for advanced neuroblastoma. (58) No increase in remission rate was seen in those receiving the vitamin. Possibly its effects may be more apparent if it is administered prior to other modalities and earlier in the course of the disease. If it is given after concurrent infection or fever possibly the response may be greater. (Series A, Case 14, 15)

d) *Bacterial Toxins*: Recent research had indicated that bacterial infections or their toxins may stimulate hematopoietic and reticuloendothelial function and protect these radiosensitive tissues against the lethal effects of radiation (8, 34, 63). Also bacterial toxins appear to potentiate the response of the tumor to the irradiation. (5, 49). These findings suggest that it may be advisable in treating neuroblastoma in the future to administer bacterial toxins prior to irradiation and to reduce the dosage of x-ray.

Since many observers have reported that surgical stress or trauma markedly increased the number or size of metastases in various types of tumors, it would seem advisable to administer toxins before and after all surgical procedures, including exploratory operation, to counteract this effect.

Prognosis: Many authors, especially prior to 1940 believed the prognosis in neuroblastoma was absolutely hopeless. Poore (55) and Goldring (28) quoted Redman as stating that the "clinical course in these cases is almost universally rapid, progressing to a fatal termination. The average duration of symptoms and signs is about two to five months. Irradiation produces only slight temporary response and surgical intervention is usually followed by death within several months."

Koop et al. reported in 1955 that 39 per cent of their series (10 out of 17 cases) survived even though half of them had metastases. (39) Their method of choice was surgery, even though only an incomplete removal could be effected.

Wyatt and Farber and others have concluded that a one year survival in childhood neuroblastoma is equivalent to a five year survival from the average form of adult cancer. (77) Most of the cases in the literature died within a few weeks following discovery of the disease.

FACTORS WHICH MAY CONTRIBUTE TO DECREASED RESISTANCE TO NEOPLASIA INCLUDING NEUROBLASTOMA

In reviewing the factors which appear to stimulate or inactivate resistance to neoplastic diseases it may be possible to elucidate some of the causes for the apparent increase in the incidence of neoplasms as well as leukemia in children in the past 20 years.

Decreased Stimuli to Immune Responses: Before infectious diseases were markedly curtailed, the reticuloendothelial and lymphoid tissues were repeatedly stimulated by a variety of infections and infectious diseases, from early infancy onwards. Smith (62) has presented evidence which suggests that cancer and allied diseases are still comparatively rare among the Indians of the United States, who still have a much higher incidence of infection and infectious diseases than the white population. A similar study has been done of the Canadian Indian, with similar findings. The increased responsiveness of African children with Burkitt's lymphoma to chemotherapy may be due to

the fact that most of these children had a great deal of prior infection. Of course, in these ethnic groups, genetic factors may also play a role in their relatively greater host resistance to neoplastic diseases.

Not only have children and adults been exposed to infinitely fewer bacteria in the last few decades, but when an infection did develop, an antibiotic or sulfanilamide was usually given. In addition to making it unnecessary for the natural immune responses to deal with the infection, some of these drugs may have a damaging effect upon the hematopoietic system, and possibly lead to decreased resistance to neoplastic diseases. As Meyer and Benjafield have stated: "If . . . cancer is due to a virus, may we not conclude that by damaging the tissues in some subtle manner the antibiotics may absolve the body of the need to bring the normal immunological mechanism into use — a mechanism that has been acquired and perfected through millions of years of evolution and which seldom fails — and furthermore may upset the bacteria-virus balance and so predispose the tissues to invasion by cancer cells?" (44a).

Anti-inflammatory drugs: Another group of drugs which should be used with great caution are the anti-inflammatory drugs, for there is considerable evidence to indicate that the ability of an animal or patient to elicit an acute inflammatory reaction is one of the powerful inhibitors to successful transplantation of tumors or to the formation of metastases. With cortisone it was possible for the first time to grow human neoplasms in animals successfully (67-69). There is evidence to suggest that the depressing effects of cortisone on inflammation can be completely abolished by adequate choline administration (32-33). Since the inflammatory reaction seems to be an important factor in the host's resistance to cancer, it is interesting to find that a few investigators have observed that the ability to invoke such a reaction seems to be absent in many advanced cancer patients. (65) Ungar made a statistical study of all the patients admitted to a hospital in Basle, Switzerland, in a 20 year period ending about 1947. The prior incidence of acute infections or of acute inflammatory episodes was almost nil in the cancer group. (70)

Toxin therapy, concurrent infection (48) and choline (32-33) appear to stimulate the host's ability to invoke acute inflammatory reactions. It may be worthwhile to study the possible effects of induced inflammation (vesication, fixation abscesses) on cancer patients since it is known that inflammatory exudates destroy neoplastic cells *in vitro* (41). It may be that the exudates produced by severe erysipelas infections played a salutary role in the defensive processes which resulted in regression or remission of cancer or leukemia following such infections. (48,53) One must also consider that the histamine liberated by acute inflammation appears to be a physiological activator of the RES (25,36).

In this connection it is of interest to cite the case of Dargeon (11, 49). This patient was admitted in very grave condition having been operated upon in Chicago a short time before for abdominal neuroblastoma. He deteriorated thereafter with metastases in the abdominal region in and about the laparotomy scar. He then developed herpes zoster and the visible tumefactions diminished 75 percent in size. The boy expired before any definitive treatment could be started. Postmortem studies of the regressing lesions showed some necrosis in parts of the tumors. (49)

A study was made in Germany of the incidence of neoplastic diseases among bee keepers, whose immune reactions are constantly being stimulated by exposure to bee stings. It was found that in over 18,000 German bee keepers, there was an astonishingly low incidence of neoplastic diseases: 0.36 per thousand (23).

Irradiation: This is a carcinogenic and leukemogenic agent to which the modern world is being exposed in seriously increasing amounts. A great many authors have cited the destructive action of x-ray or radium upon the hematopoietic system.

Simpson and Hemplemann (61) concluded that therapeutic radiation of infants may be an etiologic factor in thyroid cancer of children and adolescents. Its role in the production of leukemia or other tumors in children is less clear and awaits further data. They suggested that the practice of irradiating children on a large scale should be abandoned, particularly in the case of the thymus, for which there is meager evidence that the treatment has any benefits. In other cases the benefit to be derived should be carefully weighed against the possible dangers. Fluoroscopy as well as therapeutic radiation should be included in such considerations.

Pelner analyzed the effects of radiation on host-tumor antagonism. He concluded: "A review of both old and recent work on the effect of ionizing radiations of the tumor and the host suggests that our conception of proper dosage may have to be revised. Large doses of radiation may have a salutary effect on the local tumor but a detrimental effect on the resistance of the host." (51).

Further evidence which confirms this view is indicated by the investigations of Toolan (67-69) and Weder et al (73) who found that heterologous tumors, including human neoplasms will grow readily after the host has been conditioned with x-ray or cortisone. These findings corroborate the earlier work of Murphy (45) and his group who stressed the vital role played by the lymphoid tissues in natural resistance against tuberculosis and against neoplastic disease (41).

SPONTANEOUS REGRESSION AND FACTORS WHICH MAY INCREASE RESISTANCE

Recent reports on spontaneous regression of cancer indicate that the majority of such cases had some form of acute infection, fever or inflammation, often not considered by the reporting physician to have been of any consequence, because little was understood until very recently about the various host-resistance mechanisms which may be activated by such complications. (15-17; 47; 48).

It is now known that streptococcal organisms and their toxins appear to stimulate a host response to substances or tissues which do not normally elicit such a response in an animal or patient. For example, Glynn and Holborrow (27) found that four strains of Streptococci (three Group A and one Group C), and a strain of Staphylococcus aureus, when grown on agar media, gave rise to agar antibodies in antisera prepared against them. Burky found that by combining Staphylococcus with lens substance, rabbits were sensitized to lens and developed high precipitin titres for lens tissue. A diverse group of bacteria in addition to Streptococci and Staphylococci show this property, i.e. Shigella shigas, Salmonella typhi, Bacillus anthracis, Hoemophilus influenzae and Neisseria meningitidis. (4)

In order for this to occur the organisms do not need to be alive but they *must come into significant contact with the target tissue*. These findings suggest that in treating patients with toxin therapy in the future, some of the initial injections should be made in or near the tumor.

Interferon now appears to be one of the most significant medical discoveries relating to man's resistance to a great many diseases, especially those of viral origin. Interferon production is stimulated by viruses, bacteria and other microorganisms as well as by bacterial and fungal extracts and synthetic

polyanions. (55a) This remarkable substance acts in one to four hours, much faster than other immune responses.

Recent studies indicate that stimulation of interferon production in tumor-bearing rats and mice markedly increased the resistance of these animals to their tumors. There were no survivors in the untreated controls. All the treated animals were alive with no evidence of their tumors two months after cessation of treatments.

Since certain microbial infections or their toxins and probably Actinomycin D, through various mechanisms described above, appear to increase host resistance to neoplasia, it is essential that we learn how best to protect and activate any tissues responsible for this resistance and that we avoid prior use of chemotherapeutic drugs, antibiotics or heavy radiation.

END RESULTS IN THE CASES COMPRISING THIS STUDY

SERIES A. *Concurrent infection, fever or inflammatory episodes: 18 Cases.*

Eleven patients were traced well, 5 to 40 years after onset, two were traced well three and four years (Cases 1 and 3). One was alive with disease when reported four years after onset (Case 5); two died of their disease, 7 to 29 months after onset (Cases 11, 18); one of these patients received a great deal of radiation, the other had chemotherapy prior to infection for generalized disease; two died of uremia 23 and 10 years after onset (Cases 7 and 13. Case 7 had received 4050 r of x-ray therapy resulting in considerable dwarfing and chronic radiation nephritis which finally proved fatal).

SERIES B. *Toxin Treated: 9 Cases.*

Nine cases of neuroblastoma received toxin therapy (Coley toxins).

Although terminal (quadriplegic) the only case to receive Coley toxins alone recovered and is alive in 1969, 58 years after onset. This famous case, so often cited at medical meetings in which neuroblastoma is discussed, has usually been incompletely reported. It suggests the need for further clinical trial of host-stimulating microbial products such as these toxins as a primary method of treatment in neuroblastoma.

The second toxin treated case had multiple metastases over his entire body when Coley toxins were begun, nine days after radiation. The many concurrent infections he developed subsequently may have played a role in his recovery. Of special interest is the fact that exploratory laparotomy for an asymptomatic residual ganglioneuroma 20 years later was followed about a year later by reactivation of the neuroblastoma which proved fatal 25 years after onset.

The third case had multiple tiny subcutaneous metastases. He received small radium plaques to one or two of the nodules with no apparent effect. He also received a few injections of Coley toxins, recovered and was traced well over five years later.

In three of the other six cases a brief course of toxins was given concurrently with x-ray therapy before metastases had occurred (Cases 4, 5, 6). Two of these patients had recurrences. In all three there was dramatic, complete regression: no evidence of disease within four to six weeks. However, reactivation occurred promptly.

In the last three cases the disease was metastatic. In Case 7, the toxins were begun two days after x-ray and given concurrently (16 doses). Complete regression occurred in four weeks with reactivation of the disease four months later.

In Case 8 the toxins were not begun until a great deal of radiation had

been given (8038 r) and only 15 doses were administered. There was complete regression in a few weeks, but the disease reactivated following a fall and progressed rapidly.

These six cases indicate the extreme importance of more prolonged toxin therapy in order to produce a permanent result.

Case 9 was terminal with widespread disease when the toxins were begun, having received 7200 r of radiation (although only 21 months old) as well as two cytotoxic chemotherapeutic agents. There was rapid deterioration rather than improvement.

Thus it would seem that toxins are not helpful if begun after massive irradiation and chemotherapy have destroyed the immunological responsiveness of the patient.

Burchenal, in a personal communication to H.C. Nauts stated in 1968: "It certainly appears to many people working in the area of acute leukemia and Burkitt's lymphoma that stimulation of host defense is needed in addition to chemotherapy to produce long term remissions."

This page intentionally left blank.

SERIES A

TABLE 1 NEUROBLASTOMA WITH CONCURRENT INFECTION, INFLAMMATORY OR FEBRILE EPISODES: 18 CASES

Physician or Hospital References	Sex Age	Site & Extent Prior to Infection Date of Onset	Prior Therapy	Concomitant Therapy	Subsequent Therapy	Infection Inflammation Fever	Immediate & Final Results Years Traced After Onset
1. MacFarland & Sappington 42	Female 5½ yrs.	neuroblastoma apparently primary in cervical region; multiple pulmonary metastases; onset January 1931	none	February 1931 5 x-ray treatments; abscess incised, drained; tonsilectomy 1932; lemon-sized lesion excised from cervical region; neuroblastoma maturing into ganglioneuroma	x-ray (2) following surgery May 1932	February 1931 pharyngeal abscess temperature continued to rise occasionally; May 1932: slight postoperative fever for 1 wk.	complete recovery; pulmonary lesions regressed; N.E.D. alive, well late 1935, almost 4 yrs. after onset
2. Debré 13, 14	Female 7 mos.	inoperable neuroblastoma primary in rt. hypochondrium, metastases to knee, hemithorax, eyeball & supraorbital region (these regressed spontaneously in 1 mo.)	December 1930: x-ray (7)	incisional biopsy of knee lesion October 1931	none	pertussis, rubeola, December 1930 urticarial rash on legs (allergy to eggs?), further severe, extensive bullous urticaria, pruritis, supuration	by January 1935 abdominal mass had regressed 2/3; tumor on back hard, painless, very mobile; by 1938 abdominal mass still large, hard, indolent, back tumor regressing, complete recovery, all traces of primary & metastases disappeared, married, 2 children 1948, 1954; in perfect health 1969, 40 yrs. after onset
3. Rocher 56	Female newborn	inoperable congenital neuroblastoma apparently arising in the presacral sympathetic trunk, extensive mass obstructing entire hollow of pelvis from posterior sacrum almost to posterior pubis; retention of urine 8 days after birth, slight erosion S 1 vertebra	exploratory operation, condition hopeless	x-ray to pelvic region (2880 r)	none	few attacks bronchitis while hospitalized	no further retention of urine; steady complete regression in 3 mos. N.E.D. thereafter; alive & well 1937, 3 yrs. after onset

4. Fèvre 21	male infant (born pre- maturely at 8 mos.)	neuroblastoma with metastasis canthus rt. eye; onset apparent at 4 mos. (lesion on eye)	none	none	biopsy of tu- mor near rt. eye; massive doses of vitamins	diarrhea at 4 mos.	at time of diarrhea explosive development multiple tumors in soles of feet, groin, but- tocks, largest deep in rt. scro- tum, back, lt. thorax, inner canthus lt. eye; only 1 other tumor developed later on scalp; prognosis grave; com- plete regression all lesions in 2-3 mos.; alive & well Decem- ber 1957, 22 yrs. after onset
5. Roussy 57	male 22 yrs.	inoperable neuro- blastoma size of fe- tal head in rt. iliac fossa & hypochondri- um (1st noted during enteritis, June 1937)	none	none	biopsy, July 1938; x-ray; disease pro- gressed; fur- ther x-ray, Feb. 1939; tumor in- creased slow- ly; August 1939: pri- mary mass dis- sected free, 2nd mass in- volving me- socolon in- operable; further x- ray (5800 r); 1940. x-ray to bladder, lumbar, cer- vical, epi- gastric reg- ions (poorly tolerated)	June 1937: enteritis, diarrhea; after x-ray, 1939, febrile pul- monary episode (pneumonia?) Nov- ember 1939, cystitis, hematuria, lasting 6 mos.; several epis- taxis	metastatic mass appeared on lt. side after x-ray, severe con- stipation, wt. loss; disease re- activated, violent abdominal pains fall 1939; during pro- longed cystitis recurrent mass slowly but completely disap- peared; other lesions develop- ed with neurological symp- toms, severe pain: D5 verte- bra, ramus lower jaw, rib, cer- vical & epigastric regions; gen- eral condition declined; Octo- ber 1940 cephalagia, edema of eyelids, exophthalmos; cereb- ral symptoms cleared up completely each time epistaxis occurred; alive with disease when reported 1941, 4 yrs. after onset
6. VanCreveld & Van Dam 49; 71	female newborn	inoperable abdomin- al neuroblastoma, apparent from birth, May 1938; liver slightly enlarged, abdomen greatly en- larged	none	none	3 x-ray treat- ments (no effect); ex- plored, biop- sy, hemorr- hage, diffi- cult to con- trol	varicella at 1 yr; wbc. 9,600	gained weight, grew normally, tumor slowly regressed in next few yrs.; married, had normal child; alive, well 1969, 31 yrs. after onset

Physician or Hospital References	Sex Age	Site & Extent Prior to Infection Date of Onset	Prior Therapy	Concomitant Therapy	Subsequent Therapy	Infection Inflammation Fever	Immediate and Final Results Years Traced After Onset
7. Beck & Howard 1; 49	male newborn	congenital, apparently inoperable neuroblastoma lt. adrenal hepatomegaly, ascites, 1944	none	biopsy, 1945; x-ray (1,400 r tumor dose) 2 mos. later 1,250 r t. d.; 1948: 1,400 r t. d.	none	concurrent comedos, infected acne, leukocytosis (11,100 wbc); acne cleared after x-ray; 1945, influenza; 1949 another u. r. i.; 1951, otitis media	liver receded to costal margin, tumor mass regressed, no longer felt at 14 mos.; small indistinct mass palpable in upper abdomen 1948; in good health thereafter, except for dwarfing due to radiation & chronic radiation nephritis requiring hospitalization 3 times, finally caused death, February 2, 1968, 23 yrs. after onset.
8. Vigorelli 17, p. 154; 49; 72	male infant 1 mo.	congenital generalized neuroblastoma: at least 50 subcutaneous metastases over entire body except hands & feet, 1st apparent in sacral region at 1 mo., others appeared in next 5 mos.; anemic, undernourished; 1945.	none	biopsy of nodule in pectoral region July 1946	x-ray, 700 r, then 200 r to cervical region; epigastric mass excised 1952: reported as ganglioneuroma	fever at 5 mos. & again in July 1946 (to 102.2° F); leukocytosis to 20,000 wbc, decreased to 6,000 after x-ray	became afebrile, quieter, better appetite; no new nodules; those in cheeks decreased in size; irradiated nodules then decreased, others unchanged at 1st, later considerably flatter, all but 3 of the 50 lesions disappeared; in excellent health thereafter, normal development; married, fathered a child; alive, N.E.D. 1967, 22 yrs. after onset
9. Goldring 28; 49	male 4 mos.	inoperable neuroblastoma rt. upper kidney region, extending into rt. upper abdomen, numerous metastases to liver, proximal rt. humerus, skull, extensive proptosis, bilateral periorbital conjunctival hemorrhages; 1947	none	antibiotics for otitis	3 blood transfusions; x-ray rt. kidney region; explored; liver extensively involved, biopsied; 2 more blood transfusions x-ray stopped due to leukopenia (4350 wbc); anemia 4 more transfusions (total of 9)	mild otitis, pharyngitis just prior to known onset; then rhinitis; leukocytosis to 15,550 wbc; fever twice after x-ray: to 101°F.; u. r. i. April 1948, high fever, cough, bronchitis	proptosis more marked after x-ray, requiring celluloid shields for eyes; striking improvement shortly after final transfusions, continued steadily; complete recovery by Sept. 1948, proptosis, abdominal mass subsided; N.E.D. thereafter, normal mental & physical development, in excellent health, active in sports, 1969, 22 yrs. after onset

10. Greenfield & Shelley 29	female 2 yrs.	inoperable neuroblastoma with inguinal lymphadenopathy & hepatomegaly; onset at 21 mos.	none	none	inguinal biopsy; untreated	intermittent fever	complete recovery; N.E.D. when last traced 18 yrs. later.
11. Haber & Bennington 30	female newborn infant	inoperable congenital neuroblastoma l. u. q. of abdomen, numerous subcutaneous metastases (primary unresectable due to involvement of intestines, great vessels)	laparotomy x-ray, 2100 r; many lesions excised at 8½, 10 & 11 mos.; cyclophosphamide; x-ray to rt. thorax; metastases excised from lt. knee, inguinal region; laparotomy; dumbbell shaped tumor excised	none	none	post-operative course stormy: subfascial abscess (Strep. fecalis, E. coli, E. intermedium); gangrenous intestine ruptured, enterococcus fistulae	further growth of abdominal tumor noted after cyclophosphamide; death about 29 mos. after onset, in recovery room 5½ wks after excision; autopsy showed well differentiated ganglioneuroblastoma, with foci of apparent differentiation to ganglioneuroma, focal necrosis, small areas of calcification
12. Eyrebrook & Hewer 18	female infant	inoperable massive neuroblastoma rt. lumbar region, abdominal mass deforming bladder; marked foot drop, some paralysis of feet; prognosis hopeless; onset noted at 3 mos., Sept. 1949	none	explored Dec. 1949, large piece removed for biopsy	none	cystitis (coliform bacilli); pus in urine, some urinary retention; cystitis continued 10 yrs.; gross pyonephritis present at death	within 18 mos. after biopsy complete regression of abdominal neuroblastoma occurred but residual paralysis of legs remained with impaired bladder function due to compression of cauda equina; progressive deterioration of kidney function, death from uremia, almost 10 yrs. after onset, June 1959; autopsy showed peripheral portion of extensive neuroblastoma of lumbar spine had regressed remaining dumbbell shaped tumor in spinal canal had matured into a ganglioneuroma

Physician or Hospital References	Sex Age	Site & Extent Prior to Infection Date of Onset	Prior Therapy	Concomitant Therapy	Subsequent Therapy	Infection Inflammation Fever	Immediate and Final Results Years Traced After Onset
13. Ochsner Clinic 49	female newborn	congenital inoperable, generalized neuroblastoma, abdomen abnormally large at birth; widespread subcutaneous metastases appeared following Vitamin K over pubes, groins, distal abdomen, chest, back, head; hepatomegaly; prognosis hopeless	vitamin K given as her blood did not coagulate properly, biopsy, May 1950;	HN ₂ for 4 days; blood transfusion; much worse	3 remaining lesions in lt. thigh & groin excised April 1951 (neuroblastoma); HN ₂ for 4 days repeated; Nov. 1951 rt. quadrant mass excised (neuroblastoma with differentiation to ganglio neuroroma); penicillin again for 1 HN ₂ Dec., Jan.	mother developed influenza, breasts swollen, almost abscessed, but continued to nurse infant during 1st mo.; diarrhea, severe diaper rash; slight fever; u. r. i., penicillin; furunculosis; runny nose, penicillin after HN ₂ 1951, severe allergic reaction, entire body covered by red rash, eyes swollen shut; varicella at 3 yrs.; rubeola at 4 yrs.	gradually began to improve following u. r. i., penicillin; liver receded; N.E.D. by October 1951, skeletal survey normal except for mottled calcification in region of liver grew normally in every way; in excellent health 1969, 19 yrs. after onset
14. Woods 49; 67	infant female 15 mos.	extensive inoperable retroperitoneal neuroblastoma; vascular, fixed mass 17x7½ cm.; in extremis; 1954	none	explored; biopsy	x-ray, 1500 r tumor dose; persistent leukopenia, pale, apathetic, inert, refused all food; chloromycetin, no improvement; Vitamin B12 i.m. every 48 hrs. then 1 a wk. for 2 yrs. thyroid extract (0.5 gr.)	concurrent fever (104° F.); leukocytosis (19,000 wbc), no apparent cause	definite improvement within a wk. after Vitamin B-12 was begun; convalescence uneventful thereafter; wbc decreased to 8700 with lymphocytosis (76% then 43%); became subthyroid, corrected by thyroid extract; complete regression, in excellent health thereafter, no abnormalities; May 1962, developed diabetes; alive and well 1969, 16 yrs. after onset

15. Knudsen
& Amromin
38; 49

female
newborn
infant

congenital, inoperable,
very large neuroblas-
toma, involving liver,
primary site unknown;
1955

explored at
25 days liver
almost com-
pletely re-
placed by tu-
mor; x-ray,
1600 r, stop-
ped due to
leukopenia,
anemia; chl-
orambucil,
no effect

none

Vitamin B12
i.m. for 21 mos.,
biopsy lt. axilla,
May 1956: char-
acteristic neuro-
fibroma; July
1956: explora-
tory thoracoto-
my: lobulated
mass in medias-
tinum connect-
ing via apex lt.
chest with mass
in lt. neck, arm,
adherent to ribs
encircled lt.
thoracic & cer-
vical sympathe-
tic chain; por-
tions removed
for biopsy: gan-
glioneuroma;
1957: liver biop-
sy: no residual
disease

atelectasis, pneumonia,
recurred several times
in few mos. after x-
ray; fever, 101° —
104°F.

masses in lt. neck, swelling of
lt. arm apparent after x-ray;
abdominal mass regressed in 9
mos. after vitamin B-12 was be-
gun; stigmata of Recklinghaus-
en's disease, 1956; N.E.D., nor-
mal intelligence, in good health
except for scoliosis of spine with
convexity (radiation changes)
by 1969 mental development
sub-normal; fall 1969 2 spinal
fusions to relieve pain and im-
prove cosmetic appearance;
NED. 1970, 15 yrs. after onset.

Physician or Hospital References	Sex Age	Site & Extent Prior to Infection Date of Onset	Prior Therapy	Concomitant Therapy	Subsequent Therapy	Infection Inflammation Fever	Immediate and Final Results Years Traced After Onset
16. Hornstein & Mülke 35; 49	female 3 wks.	congenital, inoperable neuroblastoma rt. adrenal; multiple metastases over entire trunk, proximal lower extremities, bean to pigeon size; 1957	lesion excised for biopsy; prednisone 2 wks. 10 mg. daily	antibiotics; x-ray to 1 metastasis, no effect; 2nd biopsy; dietary restrictions; sulfonamide	1958, 3rd biopsy; inflammatory reaction present, tumor no longer malignant; 1965, 4th biopsy of inguinal mass; completely differentiated gangli-neuroma	recurrent episodes pyoderma, refractory to therapy; also nutritional disturbances; varicella at 3½ mos.	small areas necrosis, calcification in region rt. adrenal; metastases regressed notably after varicella, in 3 mos. many small lesions, especially those that had appeared last, disappeared; N.E.D., normal physically & mentally; in excellent health 1969, 12 yrs. after onset.
17. Cochran 6, Case 4; 49	male newborn infant	congenital neuroblastoma in rt. abdominal sympathetic chain, persistent bile-stained vomitus from birth; 1960	plum sized tumor biopsied at 1 wk.; 18 days later x-ray interrupted by u. r. i.	none	x-ray resumed after u.r.i. (3000 r in 60 days)	u. r. i., throat diffusely inflamed, bronchitis	complete regression; 2 yrs. later cyanotic heart disease, hepatomegaly; laparotomy revealed simple cholangioma, no trace of neuroblastoma; alive, well 1968, 8 yrs. after onset.
18. Cochran 49	male 2 yrs.	inoperable neuroblastoma rt. adrenal, widespread metastases to pelvis, lower extremities, cervical spine, cranium, scalp; head grossly swollen, anemia; onset April 1966	cyclophosphamide for 2½ mos.; blood transfusion; vitamins B-12 & A	none	vincristine for tibial metastasis (some temporary regression)	November 1966, fairly severe rubella; mild varicella 3 wks. later	disease arrested but without significant regression until cyclophosphamide stopped; more rapid regression dated from concurrent infections; grossly swollen head decreased 4 cm., scalp irregularity disappeared, cranium, tibiae recalcified, anemia ceased; N.E.D. for a mo. April 1967, sudden recurrence of tibial metastasis, 2 mos. later massive recrudescence; death few days later, June 1967, 14 mos. after onset.

SERIES A, CONCURRENT INFECTIONS. DETAILED HISTORIES

CASE 1: Neuroblastoma maturing into ganglioneuroma apparently primary in the cervical region with multiple pulmonary metasases (see below for histologic report).

Previous History: A. C., white female, aged 5½. The child's parents were both living and well. She was delivered by normal labor weighing 9½ pounds at birth. She was breast fed for one month. The first teeth erupted at three months, but all her baby teeth were poor in quality. Infancy and early childhood were uneventful. Onset, at the age of 5½ years a swelling appeared in the region of the cervical lymph nodes. This continued to enlarge and was diagnosed as tuberculous adenitis.

Radiation: A series of five x-ray treatments were given.

Clinical Course: On February 16, 1931, three weeks after the last x-ray treatment, the child was admitted to Hahnemann Hospital in Philadelphia. She appeared pale, though apparently well nourished. The breathing was slightly obstructed and the tonsils were enlarged. A large, smooth, nodular, non-tender mass was present in the right side of the neck. It did not fluctuate. Blood examination showed Hg. 70%; rbc 3,500,000; wbc 5,900. A second examination on March 4, 1931 showed Hg. 72%; rbc 4,290,000 and wbc 6,200 of which 58% were polymorphonuclears, 35% lymphocytes and 7% transitionals.

Concurrent Infection: (Abscess) The temperature varied between 97° and 99.8°F., the pulse between 76 and 118. A pharyngeal abscess developed.

Surgery: On February 23, 1931 a tonsillectomy was performed and the pharyngeal abscess was incised.

Clinical Course: The general condition then improved, though no apparent change occurred in the swelling of the neck. The temperature continued to rise occasionally. An examination of the chest on March 5, 1931 showed bronchial breathing, more tubular than usual in the mid-portion, posteriorly, with bronchophony and well transmitted tactile fremitus and rales. The heart was normal. A Mantoux test on the right forearm was reported positive. Chest films on March 10, 1931 showed distinct thickening of the roots of the lungs with extension to both bases and to the right upper lobe. There were a few calcified areas at the roots of the lungs and some mottling of both upper lobes. The disturbance in the lung roots was thought to be in the bronchial lymph nodes. On March 12, 1931 another Mantoux test and Von Pirquet test were performed and both were reported as negative. The child was discharged on April 4, 1931 at the mother's request, with a diagnosis of tuberculous adenitis.

She was readmitted on April 23, 1932 with a temperature of 100°F. Blood examination gave 7400 leukocytes of which 61% were polymorphonuclears, 38% lymphocytes and 1% basophiles. Two days later the hemoglobin was 91%, leukocytes 6,200, of which 82% were polymorphonuclears, 13% lymphocytes, 2% transitionals and 3% eosinophils. After two more days there were 65.5 polys, (55% mature, 7% immature and 3% metaleukocytes); 28% lymphocytes, 4.5% transitionals and 2% eosinophils with abundant platelets, many broken, poorly stained and degenerated white cells. Chest films on April 27, 1932 showed the condition previously reported except for pulsation in the right infraclavicular region thought to be characteristic of tuberculous infection.

Surgery: On May 4, 1932, the child was operated upon and a firm encapsulated tumor about the size of a lemon was removed from a position deep down in the neck. At the upper pole it appeared to be attached to some long structure, elsewhere it was free. The gross appearance was not character-

SERIES A: INFECTION CASES, DETAILED HISTORIES

istic of any recognized condition. There were no areas of caseation and no suggestion of tuberculosis.

MacFarland and Sappington reported the histologic findings as follows: "The tumor consists of a fibrillar background or stroma in which are scattered cells and cells in groups.

"The fibers that make up the greater part of the tumor present considerable diversity of appearance. Some are extremely fine and wavy, others coarse and collagenous. The indistinct bundles of fibers intertwine so that they are always cut both longitudinally and transversely. Some have their respective fibrils widely separated, as in edema, others are compact. There is an occasional tendency to hyalinization, and at many points a granular breaking down followed by colliquation necrosis leading to the formation of minute definite spaces.

"The nuclei of the fibrillar tissue are elongate, oval and vesicular where the fibers are coarse; elongate, slender and more uniform where they are fine and wavy. In many places distinct palisades of nuclei show indubitably that the fibers belong to nervous tissue. A few definite nerve fasciculi are seen, but may belong to antecedent nerves about which the tumor has grown. Except in them, no medullary sheaths were found.

"The cells distributed through this background of fibers seem to form an ascending series that begins with small cells not unlike lymphocytes and ends in typical ganglionic nerve cells. The various forms — neurocytes, neuroblasts, sympathoblasts and ganglion cells — occur together. Individual cells in all or any of these stages of development are scattered singly or in groups throughout the whole tumor.

"Small cell groups of spindle shape, and composed of a few large unmistakable nerve cells, with abundant cytoplasm, beautiful vesicular nuclei and large distinct nucleoli, flanked by smaller cells tapering off to very small ones at the ends of the spindle, not infrequently occur in the intervals between the fibers.

"Large collections of cells constitute a striking picture. A good many correspond with the ganglionic nerve cell groups characteristic of ganglioneuroma and adjacent to them palisade arrangement of Schwann cells. There is no doubt but that the tumor is a ganglioneuroma. But it is not without its eccentricities. Many of the cells are immature forms closely or loosely massed together in a very delicate or loose stroma, or in indefinite spaces in the stroma. These cell aggregations, so numerous, so large and so indefinite, misled some of those who first examined the tissue into the error of believing that they were looking at some form of malignant epithelial tumor.

"The cells represent all of the stages of development, but instead of each progressing regularly to the ganglion cell stage, those of all stages seem to multiply at random, then degenerate or liquify.

"Scarcely a nerve cell, primitive or advanced in development, appears to be in a state of good health. Large ganglionic cells with beautiful vesicular nuclei commonly have finely or coarsely vacuolated cytoplasm or they possess two, three or four nuclei, uniformly developed and healthy, or one or several nuclei may appear normal while others may be mitotic, pyknotic or vacuolated. Mitosis, not frequent, may be found in the cells of the same group. In adjacent groups there may be none. Judging by this criterion the growth of the tumor should have been slow and should have progressed by multiplication of cells, now here, now there.

"The retrogression and colliquation of the ganglion cells was attended by finer, then coarser vacuolation, then fraying at the edges. In some cases, there was cytopyknotic and karyopyknotic in which the nuclei became small,

SERIES A: INFECTION CASES, DETAILED HISTORIES

dark colored bodies eccentrically situated toward the surface of the cell whose cytoplasm was solid, uniform and eosinophilic. The general impression resulting from the study of sections stained by hematoxylin and eosin, iron hematoxylin, Weil's and Bielschowsky's methods may be summed up as follows. The neoplasm is a ganglioneuroma whose development began with the multiplication of embryonal neurocytes, and continued through the continued multiplication of those primitive cells and their evolving descendants up to the stage of ganglion cells. Whether perfected ganglion cells can multiply is uncertain, but many which seem to have reached perfection contain two, three and four nuclei and show an occasional mitotic figure. These ganglion cells probably give off neuraxons, which account for the nerve fibrils brought out by the Bielschowsky stain, and seem to excite the proliferation of the Schwann cell which show the palisades of nuclei. Then the ganglion cells, and many of the sympathoblasts not yet that far developed, lose their vitality, retrogress and dissolve into the jelly-like accumulations with which the collections of dying cells are surrounded. In a few instances the dead cells calcify so that occasional, small, irregularly rounded aggregations of lime salts occur in the tissue. The generations of cells that have matured, produced fibrils and disappeared, account for the neurofibromatous stroma or matrix of the tumor."

Postoperative Fever: After operation the temperature rose to about 100°F. for a week or so, then gradually returned to normal on May 20, 1932.

Further Radiation: Additional x-ray treatments were given on May 24 and 27, 1932 as a prophylactic against recurrence.

Clinical Course: The child was discharged on June 18, 1932. Two years later she was seen again and appeared to be quite well. Her mother stated, however, that she coughed during the day and was nervous during the night. She also turned her head to one side when swallowing, which was considered due to the operative scar. Careful examination revealed no evidence of recurrence of the tumor in the scar. Chest films showed no evidence of the metastatic tumors in the lungs present two years before. However, there was a curious soft swelling present, sharply limited to the left side of the tongue, thought by the mother to have developed after leaving the hospital. The case was published in November 1934, over four years after onset. Attempts to trace her since have failed.

References: 42.

CASE 2: Inoperable neuroblastoma with metastases confirmed by microscopic examination, following incisional biopsy of one of the metastatic tumors.

Previous History: C., female infant, born at full term on November 24, 1928, an only child whose development appeared normal until the age of seven months. At this time the mother first noted a tumefaction in the right hypochondrium while bathing the child. This was considered by the physician to be hypertrophy of the liver. At the eighth month, the child being with a wet nurse, there appeared and then spontaneously disappeared a metastatic lesion of the left eyeball, having the appearance of a palpebral hematoma. Shortly thereafter, there appeared a tumor the size of a nut in the supra-orbital region. This also regressed spontaneously in about a month. Nevertheless the tumor in the hypochondrium gradually increased in size. The child was first seen at the age of one year at the Hôpital des Enfants-Malades, Paris.

SERIES A: INFECTION CASES, DETAILED HISTORIES

Radiation: At this time a series of 7 x-ray treatments were given over the abdominal tumor, without evidence of diminution in size.

Clinical Course: The child's general health remained good, and her physical and psychic development was normal: first tooth at eight months, first walked at 18 months.

Concurrent Infections: At the age of two she developed whooping cough and measles, without complications.

Clinical Course: At the age of 2½ years, in April 1931, there appeared a small subcutaneous nodule on the internal aspect of the left knee.

Concurrent Urticaria: In mid-September 1931 an urticarial rash appeared on the child's legs. The mother attributed it to an allergy to eggs, which were then omitted from the diet. The child was seen in consultation by Debré at the Hôpital Beaujon on October 19, 1931. At this time there was also a metastatic mobile tumor in the posterior right hemithorax. The abdomen was enlarged, stretched, with slight collateral circulation below the umbilicus. Palpation revealed a deep-seated tumor in the right hypochondrium reaching from the umbilical region and not attached to the liver. It was hard and painless. On percussion it was dull, in contrast to the tympanism of the neighboring regions. The spleen was palpable. There was a small umbilical hernia. There remained a trace of the urticaria on the child's legs, which had developed a month previously. On the edge of the left orbit there was a slight irregularity present. The examination was otherwise negative.

Surgery: An incisional biopsy was performed on October 26, 1931 of the nodule on the left knee.

Concurrent Inflammation and Infection: The child then developed serious and extensive cutaneous lesions, with pruritis and suppuration, having the appearance of a bullous urticaria. A new metastatic nodule also developed on the anterior aspect of the right thigh. This was in November 1931. No treatment was given.

Clinical Course: The child was seen at intervals. In June 1932 no change was apparent. In April 1933 the general condition was excellent. The abdominal tumor had not increased in size, but seemed to consist of two masses, one above, limited at its lower edge by a clear-cut margin, the lower one behind it in the lumbar region. The nodule on the back also persisted. The spleen was still palpable. By January 1935 the abdominal tumor had apparently regressed one third — being the size of a fist. The little tumor on the back remained hard, painless, very mobile, and was the size of a cherry pit. Neurological examination was negative. In January 1936 the condition remained unchanged. No new nodules had appeared. (At this time the father was first examined. It was found that although he was in good health he had suffered from pytiriasis since the age of 12. Two subcutaneous nodules were present above the left elbow, one the size of a hazel nut, the other even smaller. Also there were two little naevi and a molluscum on the lateral chest wall.)

In 1938 the abdominal tumor still appeared to be very voluminous, but was indolent and hard. However, its form seemed to have changed a little. The tiny tumor on the back seemed to be in the process of regressing. The child was again examined by Debré in February 1958 and in June 1960. He found her in perfect health. The abdominal tumor present in 1938 was no longer palpable, and there was no evidence of any metastatic lesions else-

SERIES A: INFECTION CASES, DETAILED HISTORIES

where. The patient had married and had two healthy children born in 1948 and 1954. She was last traced in good health in April 1969, 40 years after onset.

Comment: In this case it is impossible to determine what factors may have produced the spontaneous regression of the lesions of the left eyeball and of the supra-orbital region at the age of eight months, while she was with her wet nurse. The absorption of these two lesions may have increased the natural resistance of this child to her neoplasm. Fortunately she received only seven x-ray treatments over the abdominal mass, so that her resistance was not depressed by heavy radiation. It is difficult to evaluate the possible influence of the pertussis and rubeola on the course of the disease. However, the development of urticaria followed by suppuration coincided with the arrest of the disease in this case.

References: 13; 21; 49; 71.

CASE 3: Inoperable neuroblastoma, apparently arising in the presacral sympathetic trunk, confirmed by microscopic examination by Professor Bonnard.

Previous History: H. C., female, aged 6 months, of Dordogne, France. The baby was born at full term, a normal delivery, of completely healthy parents. She had one sibling, aged 10. The infant developed retention of urine on the eighth day after birth, requiring catheterization. There was no fever or nausea. She was referred to Dr. H.L. Rocher of Bordeaux by Dr. Lagorce of Exideuil on January 15, 1935. At this time the child was a little constipated. Rectal examination revealed a firm, fibrous, voluminous tumor obstructing the entire hollow of the pelvis, extending from the posterior sacrum almost to the posterior pubis. The examining finger in the rectum could not be passed beyond the tumor. One got the impression that the tumefaction felt on bimanual examination below the umbilicus was the bladder, which was greatly distended. On turning the child on her stomach a tumor was seen on the right border of the sacrococcyx. It caused the skin to protrude without being adherent to the deeper structures. There was no change in the color of the tissues and no fluctuation was present. The general health appeared good. The child was not tired. X-ray examination revealed a slight erosion of the anterior aspect of the body of the first sacral vertebra. At first the condition was believed to be a tumor arising in the bone or cartilage which in developing had caused obstruction of the ureter by pressure against the pubis.

Surgery: An exploratory operation was performed. The condition was absolutely inoperable. A segment of the tumor was removed which gave the distinct impression of being a fibroma: the mass was uniform, the consistence firm, the cut surface a pinkish grey. The tumor did not bleed. The post-operative course was uneventful. The wound healed per primam. The prognosis, however, was regarded as hopeless.

Concurrent Infections: While the child was in the hospital she had a few attacks of bronchitis. She did not again have any symptoms of retention of urine after the day she was admitted and catheterization was not again required.

Radiation: X-ray therapy was given at the clinic of Professor Rechou: 16 treatments between January 16 and March 4, 1935, usually at 48 hour intervals, alternating the posterior and anterior pelvic region: 180 K.V., 10 x

10 cm. port, totalling 1800 r to the posterior and 1080 r to the anterior portal. At the end of this treatment the tumor appeared to be regressing, and there were no local or general symptoms. By March 11, 1935, when the baby was discharged, rectal examination revealed that the tumor seemed less hard and less voluminous. The operative scar was perfect and there was no recurrence at the site of the biopsy.

Clinical Course: The child was followed regularly every two months. At each examination it was found that the tumor had diminished progressively. In June 1935 there was no further pelvic tumefaction. X-ray examination early in September 1936 revealed calcium deposits or ossifications on the margins of the base of the sacrum, especially on the right side, and on the side of the hollow of the pelvis. On May 20, 1937 the child was again seen and appeared to be in perfect health, apparently cured. She had developed normally. Bimanual pelvic examination revealed absolutely no evidence of disease in the pelvis. X-ray examination revealed nothing abnormal except the calcified mass mentioned above, but on the right side only, opposite the sacroiliac notch. This was about three years after onset.

References: 56.

CASE 4: Inoperable neuroblastoma, with multiple superficial metastatic lesions, confirmed by microscopic examination of one of the nodules removed for biopsy from the external canthus of the left eye, by Professor Oberling.

Previous History: Male infant. The child was born prematurely in the eighth month in 1935. He was the grandson and nephew of physicians. The parents and two sisters, seven and six years old, were in perfect health. However, the child's mother died of multiple myeloma in the summer of 1957, 22 years later.

Concurrent Enteritis: The baby had an attack of diarrhea at four months which caused him to be a little tired and pale. Shortly thereafter the mother noticed a small subcutaneous tumor at the lateral corner of the right eye which was hard and mobile. It rapidly increased in size. During the next few days many similar small tumors developed on the plantar surface on the feet, the right groin, buttocks, scrotum, especially the right side, back, left side of the thorax, and the external canthus of the left eye. These small tumors remained the same size. However, the mother noticed that the principal tumor on the scrotum varied in size. Only one other tumor appeared after the first outbreak, on the scalp, near the anterior angle and to the right of the fontanelle. The general condition and appearance of the child was excellent after his recovery from the diarrhea; there was no loss of weight, but a normal weight increase. He was happy and gay, with a normal appetite and no fever.

Surgery: The child was first examined by Professor Mocquet and Dr. Raoul Monod. A small tumor was removed, near the external angle of the eye, a month after its appearance. The histological examination, first at Pasteur Institute, then confirmed by Professor Oberling stated, "The tumor tissue is formed of small round cells, quite regular, crowded one against the other and constituting membranes in the center of which often appears a finely fibrillar substance. Here and there are true sympatheticoblast clusters. It is a case, clearly of sympatheticoblastoma."

SERIES A: INFECTION CASES, DETAILED HISTORIES

Clinical Course: The authors, on examination of the patient, described the case as having a central tumoral region, that of the scrotum and its multiple accessory nodules. The principal tumor was deeply imbedded in the right scrotum, being an agglomeration of small round tumors, resembling hard green grapes, sharply defined, and not adherent to the scrotal sac. Less well-defined, there was nevertheless an extension of the tumor towards the median raphe of the scrotum and, apparently in the left scrotum. Further up, the tumor gradually extended towards the inguinal canal. The neoplasm was very hard, and painless. Around the principal mass, the size of a small plum placed vertically in the scrotum, there were apparently small isolated tumors. There was also a small, hard cutaneous tumor on the right scrotum. The other tumors, much smaller, were in the inguino-abdominal region of the right groin (in the zone of the subcutaneous abdominal artery), and descended towards the perineum and the buttock particularly on the right side. The tumor situated near the right eye was under the skin and was not adherent to it. It was about the size of a lentil. The tumor on the scalp was the size of a pea and in the thickness of the scalp. On the back, the small nodule was deeper, and seemed to be attached to the ribs, being somewhat mobile. The overlying tissues moved freely over this mass. There was a very small and hard nodule on the forearm, which seemed to adhere to the skin. However, the nodules on the plantar surface of the foot, particularly numerous on the right, involved the superficial tissue and protruded on the surface, being purple in color. The general health of the child remained perfect. The temperature varied from 98.6° to 99.5° F. only very occasionally reaching 100.4° F. The child was rosy and gained weight regularly. A blood test revealed nothing abnormal. The excellent general health contrasted with the tumors, which, from their quantity would make one think of a generalization of malignant tumors. The authors noted also that after the simultaneous appearance of the multiple tumors, only one new tumor appeared, that on the scalp. Also, only one had rapidly increased (the tumor by the external angle of the eye, removed for histological examination).

Given the clinical and pathological diagnosis of neuroblastoma, the authors searched very carefully, both clinically and by x-rays, for the primary tumor. There was no perceptible tumor, either lumbar or abdominal, although the left lobe of the liver, both on the x-rays and clinically, appeared to be a little increased in size. But the search for the primary tumor was negative. The tumor on the right scrotum remained preponderant in relation to the others.

The authors stated: "We were confronted with two alternatives: either the multiple tumors were benign, and we had only to wait, and perhaps remove the unattractive or annoying ones; or the multiple tumors were malignant, which was probable, in which case their multiplicity excluded the possibility of removing them, as it wouldn't have been of any use to remove the tumor on the scrotum, even if it had been the primary and principal tumor. Professor Oberling advised against x-ray therapy. With a diagnosis of neuroblastoma, we naturally gave an extremely guarded prognosis. However, we gave the parents a small gleam of hope, due to the excellent health of the child and the lack of knowledge of certain infantile tumors. We would not in any case have regretted giving them this hope, but were extremely astonished and happy to discover that the state of the child remained stationary and then improved."

Vitamin Therapy: The only treatment consisted of massive doses of vitamins. "Finally, we had the joy of seeing this child, six years later, entirely cured, and in perfect health. There is no more trace of superficial

SERIES A: INFECTION CASES, DETAILED HISTORIES

tumors. The large tumor in the scrotum has entirely disappeared. Perhaps, and it is the only clinical observation, the left lobe of the liver is slightly larger than usual. The mother told us that the tumors had disappeared progressively, in two or three months after our first examination. The explosion of the multiple tumors had only lasted about five months.

"This surprising case, this cure of malignant multiple tumors, gives matter for reflection. One must envisage the possibility of the spontaneous disappearance of neuroblastoma, the degree of its malignancy, particularly in the superficial form of multiple tumors."

The patient remained free from further evidence of the disease. He was last traced in good health in December 1957, 22 years after onset.

Comment: This case resembled that of Roussy et al (1941) in which an acute enteritis also developed early in the course of the disease. It is possible that if more cases of this type of tumor were left untreated instead of being given large amounts of x-ray therapy, which is now known to depress the natural resistance factors such as reticuloendothelial and lymphoid tissues, that many more such "spontaneous" regressions might have occurred.

This child appears to have had congenital suprarenal primary tumor which remained undetected until it apparently regressed during an attack of enteritis at four months. This was not a severe or prolonged attack, and it did not stimulate natural resistance sufficiently to prevent rapid temporary dissemination of the disease. Children appear to respond more dramatically to concurrent bacterial infections or to toxin therapy than do older patients. It has been noted in cases receiving toxin therapy that inadequate initial dosage may at first allow metastatic lesions to develop during the initial dissolution of the primary tumor. However, if further toxin treatment is given these metastases may also disappear with complete and permanent recovery.

References: 21; 49.

CASE 5: Inoperable neuroblastoma confirmed by microscopic examination at the Institut du Cancer, Paris, France, following biopsy in July 1938, of two sections of the tumor; and of the tumor mass removed at the operation in August 1939.

Previous History: Male, aged 22. The family history was difficult to ascertain with exactitude. His parents were alive and healthy. One grandfather had been operated upon at 77 for a lesion on top of his head, said to have been lupus, but two years later a mass appeared in the neck, which was still present five years later. Whether it was cancer or not was unknown. The patient had bronchopneumonia and convulsions at the age of three, and acute rheumatism at 17. He was serving in the French Marines. About January 1937 he fell about two meters landing on the abdomen. The exact date of onset is not known.

Concurrent Enteritis: In June 1937 he was seized with intestinal colic and diarrhea, with yellow liquid stools. The patient then noticed in the iliac fossa and right hypochondrium a hard fixed tumor. X-ray examination of the intestine, vesical catheterization and urinalysis were all negative.

Exploratory Operation: The surgeon in the Maritime Hospital at Brest, France decided to attempt operation in July 1938. He found a voluminous tumor in the mesentery which appeared to be inoperable. A biopsy was taken from a nodule attached to the tumor mass. The diagnosis remained uncertain but it was noted that no lymphoid tissue was found in the nodule.

SERIES A: INFECTION CASES, DETAILED HISTORIES

Radiation: X-ray therapy was given for a month (no details were reported). He was discharged from the Marines in September 1938 because of his mesenteric tumor.

Clinical Course: The patient was first seen in the Institut du Cancer six months later, in January 1939. At this time he had lost weight and suffered from severe constipation, and painful symptoms as well as pollakiuria. Examination revealed a protuberant, hard, smooth, fixed tumor in the right internal iliac fossa, reaching only slightly above the horizontal umbilical line, and apparently attached to a tumor mass that had developed a month previously immediately to the left of the median line, but less protuberant and less apparent than the primary growth. There existed a slight collateral circulation. Digital examination per rectum revealed a hard, fixed, smooth mass the size of a fetal head adherent to the anterior wall, but not to the sacrum. Rectoscopy was impossible.

Further Radiation: Having obtained the sections removed in July 1938 from the Maritime Hospital in Brest, and having diagnosed the condition as neuroblastoma, it was decided to give another course of x-ray therapy (two abdominal ports anteriorly and two posteriorly, 200 r twice daily 200 K.V.) This was given between February 5, 1939 and March 3, 1939. The tumor increased slightly and slowly in volume.

Clinical Course: In May 1939 the patient complained of pain in the thoracic region which was intermittent as to site and intensity. Chest films revealed nothing abnormal. The general health remained good until the end of July 1939. Then suddenly in early August 1939 the patient developed violent pains in the abdominal region. Examination revealed two very hard suprapubic masses and an abdominal mass a little higher up in the left side.

Surgery: On August 7, 1939, Dr. Barbier operated. He found that next to the superficial mass the tumor extended deeply backward and laterally, and was not very mobile. In the front it was encapsulated, which made it possible to split it. There existed another mass attached to the left mesocolon, which it was possible to separate from the first, and there were adhesions on its posterior portion especially to the pelvic iliac vessels. It was detached from the front and base of the bladder. The posterior-inferior pole was harder to free. The entire mass, which extended behind the rectum, was finally dissected free. A few small granulations remained on the small intestine. The second mass, involving the mesocolon could not be removed. Immediately after operation the constipation ceased entirely, and the stools were no longer flattened.

Further Radiation: Another course of x-ray therapy was then given between August 30 and September 30, 1939. (1800 r to each of two posterior abdominal ports, and 2200 r to the two anterior ports).

Concurrent Pneumonia (?): A few days after the final treatment, in October 1939, the patient had a pulmonary episode with fever, and signs in the left base with slight dullness. These symptoms improved rapidly, although the patient became thinner, lost appetite and felt tired. At first these acute symptoms were considered to be due to pulmonary metastases. Chest films revealed nothing abnormal. The patient left for the country to convalesce.

Clinical Course: Examination on November 15, 1939, showed that the abdominal incision formed a cord, hard on the deeper plane and enlarging at the umbilicus into a mass the size of an orange. There still existed the other mass in the left latero-vertebral region. The stools were again flattened, and rectal examination (digital) revealed a hard mass 4 or 5 cm. above the

SERIES A: INFECTION CASES, DETAILED HISTORIES

anus which compressed the rectum backwards. This mass was irregular and lobulated and did not appear to be adherent to the mucous membrane. It appeared to be either a recurrence of the tumor removed in August 1939 or a new growth. There were no urinary symptoms, although cystoscopy revealed that the bladder walls were very much deformed. The mucous membrane appeared normal on the upper part but the lower portion could not be seen. The general health was good. A few days later the patient again had violent pains in the abdominal and left lumbar regions which persisted and prevented his sleeping. At about this time he developed a slight intercostal neuralgia of the left side.

Concurrent Cystitis: For the next six months the patient suffered persistent cystitis at first acute with hematuria, and the paroxysms rapidly attenuated, but there was pus in the urine for a long time.

Further Radiation: On January 17, 1940 an x-ray treatment was given over the bladder region.

Concurrent Inflammation and Further Infection: There followed an epididymitis of the left side which lasted a few days. Progressively the symptoms of cystitis and hematuria improved and finally cleared up entirely by the end of April 1940 and never recurred. It is significant to note that during the period in which the patient suffered from a persistent cystitis the indurated area along the cicatrix in the mid-line became considerably softer and finally appeared to be only a fibrous scar. The subjacent mass present in November slowly regressed during this period until it was no longer present in late April 1940. However, immediately above the umbilicus a small hard mass the size of a nut had appeared in the cicatrix; also in early April there appeared to be diminution in sensation of the left half of the lower lip. The stools were still flattened and the digital examination of the rectum revealed a hard fixed mass apparently attached to the pubis.

Clinical Course: In early May the patient felt tired, the constipation became more persistent and one day intercostal pains developed, of such severity as to cause dyspnea and a sense of suffocation. At the same time generalized abdominal pains developed with nausea and emesis. The temperature remained at 101.7°F. An enema instantly stopped the pains but they returned and lasted three days. An x-ray examination revealed partial obstruction between the sigmoid and the descending colon which was situated above it. This obstruction seemed to be due to an external mass pressing on the lumen of the bowel. "Suddenly everything straightened itself out" and the patient remained well for a time. On May 29, 1940, he first experienced formication, stiffening and burning involving the lower extremities. Soon he developed difficulty in coordinating, having an inebriated, staggering walk. At examination on June 5, 1940, there was spasmodic incomplete paraplegia with hyperactive reflexes. Babinski sign was positive, bilaterally. The left cremasteric reflex was diminished. Hypoesthesia was present over the entire lower part of the trunk up to D5 accompanied by disturbance of deep sensibility and pain on pressure of the muscles of the thighs and legs. X-ray examination revealed only an erosion of the L5 vertebra.

Further Radiation: An x-ray treatment was given to the vertebral lesion. (200 r daily for 15 days, totalling 3000 r, 200 K.V.). The patient felt tired at the end of this treatment, but he was able to walk better. The tumor above the umbilicus to the left of the vertebral column did not completely disappear.

Clinical Course: The disturbance in deep sensibility disappeared and

SERIES A: INFECTION CASES, DETAILED HISTORIES

hypoesthesia was less marked. However, there was decrease in the cutaneous sensation of the upper left extremity, very marked in the inner side of the left arm, with a burning sensation in the ulnar region of the right arm. At the same time there were acute pains at the site of the ramus of the lower jaw.

Further Radiation: On July 8, 1940 x-ray therapy was resumed and given to the lumbar lesion (200 r daily, totalling 1200 r). The patient continued to suffer severe pain irradiating toward the shoulders and arms. X-ray therapy was then given to the cervical region (200 r daily alternating right and left, totalling 1400 r). The patient tolerated the therapy poorly. However, on August 1, 1940 x-ray therapy was given to the epigastric region (200 r).

Clinical Course: During July and August 1940 the patient appeared to be in good general condition although a tumor appeared at the ramus of the inferior maxilla which increased rapidly to the size of a small nut.

Further Radiation: Another course of x-ray therapy was given to this area (200 r daily, totalling 1200 r) which was concluded on September 26, 1940. This tumor did not decrease in size as a result of radiation.

Clinical Course: The patient remained just as constipated, the stools still being flattened, and he was asthenic, with no appetite and suffered violent headaches as well as pains in the chest. Chest films revealed no evidence of pathology in the lungs, ribs or vertebrae. In October 1940, the general condition declined, the appetite being irregular. At this time a tumor mass appeared on the left 8th rib at the anterior axillary line. It was hard, painless and completely adherent to the bone. In the abdominal region, to the left of the umbilicus, there still remained the epigastric mass which had been irradiated and which was still the size of a mandarin orange, hard, rounded and only slightly mobile. Thereafter this mass regressed completely. The patient continued to be constipated and to have headaches that came at no fixed hours, also he sometimes had vertigo and projectile vomiting an hour after eating. On October 22, 1940, upon awakening he found that the upper eyelid was edematous and then the lower lid of the right eye, with extremely severe headache. This edema was accompanied by exophthalmos and this syndrome appeared to represent a rapidly growing metastasis, but examination revealed that the eye was normal.

Spontaneous Regression Following Epitaxes: On October 28, 1940, without any treatment, the edema, exophthalmos and cephalgia completely disappeared. These phenomena recurred several times, sometimes lasting longer, others briefly, sometimes on the right side, sometimes on the left, and were always accompanied by epistaxis of the homologous naris.

Clinical Course: A few days later a sharp pain developed beneath the right ribs posteriorly, with thickening in this region. After a few days this pseudo-metastasis disappeared spontaneously without trace. On November 10, 1940 a thorough examination was made of the patient. His weight had increased about 3 pounds. A neurological examination revealed normal segmental muscular form; there was no disturbance of the mobility, except that he had a few muscular spasms of the legs which came on at any time of the day or night, and lasted a few seconds. Reflexes were normal. Examination of sensibility revealed the following sequellae to his old disturbances: there was painful hyperesthesia in the zone below and inside the left nipple over an area of a few centimeters, also on the anterior aspect of the left knee. There were painful phenomena at numerous points especially marked at the left hemithorax, irradiating to the upper left arm and also to the lower and outer

portion of the right scapula. At this area there was a slight degree of thickening. The right knee was painful to palpation, and the patient could not flex the leg onto the thigh without pain. This pain radiated toward the soles of the feet. These pains were very variable in intensity, with brusque crises, coming on and ceasing without apparent cause, lasting a few hours or a few days, changing site, from one arm to the other, without clinical or x-ray examination being able to determine the cause. Mostly they were of a burning type, occasionally of pinching, or of torsion. They were exaggerated by examination, and by pressure and appeared to be lessened by heat. The constipation persisted with flattened stools. Rectal examination revealed the same mass in the right pelvis. In mid-December 1940 the metastatic tumor which had developed in October and which had remained almost imperceptible for two months suddenly rapidly increased in size. About January 1, 1941, another hard, painful metastatic nodule the size of a small nut developed on the external aspect of the fifth rib.

In reporting this case on January 9, 1941 the authors noted that the primary tumor histologically had a structure quite characteristic of neuroblastoma, very slightly fibrillar. However, examination of the tumor mass 11.5 x 8.5 x 7.5 cm. in diameter removed from the abdomino-pelvic region in August 1939 revealed a completely different structure. The tumoral structures were scarce and were covered with fibrillar tissue more or less elongated. . . the neuroblasts had just about disappeared. The authors concluded that the greater part of the tissue consisted of adult ganglionic cells. They also found all the transitions between these elements and neuroblasts. In none of these types of cells was a mitotic division seen. The fibrillar zones were remarkable by their abundance. In a few isolated areas one found between the fibers little areas of calcification. Between these cellular and fibrillar tissues were vast areas formed by necrotic tissues surrounded by hemosiderotic macrophages or of very vascular connective tissue with not very dense collagenous fibers. These areas surrounded hemorrhagic suffusions and more or less clearly limited and calcified tissue. In a few areas the calcification was more diffuse and calcareous grains were isolated among the collagenous fibers. The authors searched the tumor tissue for the possible existence of lesions due to the irradiation done six months prior to operation. Absolutely no degenerative cellular alteration could be attributed to radiation. The presence of necrotic areas and calcified areas being the usual observation in this type of tumor, the authors did not attribute these to the radiation.

In summary, histological examination of the tumor removed first revealed a neuroblastoma presenting all the usual characteristics of frank malignancy. Although the second tumor removed a year later was also unquestionably neuroblastoma certain important modifications had taken place. This tumor revealed a tendency to evolve toward a more adult form (presence of ganglion cells or to a ganglioneuroma); in this case there was a transition intermediate between an embryonal neuroblastoma and an adult ganglioneuroma.

The authors cited the literature of suprarenal tumors. They noted that Frew distinguished two distinct types, with different symptoms and routes of metastases, those arising in the right side usually presenting painful phenomena localized to the abdomen and usually confined to the kidneys and liver, never to the cranium or ribs. Exophthalmos was rare. The second type, where the tumor is primary on the left side, is characterized by painful symptoms in the lower extremities, by osseous metastases, a systolic murmur in the cardiovascular area, and exophthalmos usually of the left side. The pain and systolic murmur are due partly to compression by a neoplastic mass of the lumbar plexus and partly to enlarged mediastinal vessels.

SERIES A: INFECTION CASES, DETAILED HISTORIES

The author then pointed out that in the above case at onset there was a mass on the right side which presented the classic symptoms outlined above for suprarenal tumors on that side. However, when this mass was removed at operation in August 1939, leaving only a smaller residual mass on the left side, the classic symptoms found in tumors arising on that side soon developed. (Slight evidence of some of these symptoms first developed a few months prior to this operation). They also noted that in their case the primary tumor on the right side did not rapidly spread to the liver, diaphragm or lungs, contrary to the usual course of the disease in such cases:

"By its diverse characteristics, by its slow evolution, marked by recurrences, by successive localizations which were nevertheless capable of regression, the neuroblastoma of our patient thus is distinct from the great classic types."

They then cited four cases in the literature in which the course of the disease had been remarkably slow or completely arrested.

Comment: In the light of present knowledge regarding the stimulus which bacterial toxins give to the reticuloendothelial, hematopoietic and lymphoid tissues, each of which appears to play a significant role in resistance to malignancy, one should note that this patient had a severe enteritis at the time a tumor in the right hypochondrium was first noted. This episode may have increased his natural resistance enough to delay the usual metastases which occur in such cases, and to produce the histological changes seen. The authors noted that no apparent benefit was derived from the radiation, as evidenced by the lack of regression occurring after x-ray and the lack of changes seen in the irradiated tumor which could be attributed to the treatment. This tumor did not show complete transition from neuroblastoma to ganglioneuroma. The case of neuroblastoma reported by Cushing and Wolbach, treated by the child's father in 1911, had Coley toxins alone given over two years, without radiation, and in this case the widespread involvement of the central nervous system cleared up, including the cerebellar symptoms and this patient remained well when last traced over 59 years later (see below Series B, Case 1). In publishing that case in 1927 Cushing and Wolbach stated: "A very thorough examination of the tissue removed in 1921 revealed no trace of cells similar in structure to those which in 1911 apparently constituted the entire growth. It would appear without question that the proliferative activity of the former growth subsided coincidentally with the administration of Coley's toxins. The lesion was originally an active growing sympatheticoblastoma whose cells, coincident with loss of proliferative activity, came to be differentiated in time into ganglion cells and into sheath and capsular cells. . . The case from a pathological standpoint is a unique one." (11) Unfortunately no other case of neuroblastoma was treated by toxins alone.

References: 57.

CASE 6: Inoperable neuroblastoma, confirmed by microscopic examination after exploratory operation.

Previous History: Female infant. The first child of healthy parents. The family history was negative for cancer, tuberculosis, diabetes and allergies. During pregnancy the mother had not been ill. The child was born spontaneously at full term, but she had a swollen abdomen from birth in May 1938. Growth and development were normal during the first year.

Concurrent Infection: The baby developed varicella at the end of her first year, in May 1939. This was her only illness.

Clinical Course: She was admitted to the Children's Clinic of the Municipal University of Amsterdam in October 1939. She did not appear to be ill or suffering but the abdomen was greatly swollen and did not move with respiration. There was a clear net of veins visible on the pale wall of the abdomen. On palpation the abdomen was rather taut and deep pressure seemed to cause pain. At the right lateral side below the slightly enlarged liver a round tumor the size of a tangerine could be palpated. It was of firm consistency and clearly confined especially below and at the medial side. Blood count showed 9,600 wbc, with a moderate shift to the left and no anemia. X-ray findings suggested hydronephrosis. No treatment was given. Three months later, in January 1940, the child was readmitted. Her weight had diminished somewhat, but the general condition remained fairly good and there were no special complaints although the tumor had grown somewhat. Physical examination revealed a superficial tumor palpable in the upper right abdomen, about 9 x 6 cm. in diameter. Under this tumor was a larger mass of firm consistency which reached to about 2 cm. below the umbilicus.

Radiation: Three deep x-ray treatments were given in 13 days, to the side of the abdomen, January 30, February 6 and 13, 1940 (400 r each). This did not cause any diminution in the size of the tumors. The child did not look well, had no appetite and her weight was steadily decreasing.

Surgery: At operation on February 20, 1940, Dr. Van Cappillen, the urologist, found "an inoperable vascular tumor in the right renal region, firmly grown together with the under layer."

Hemorrhage: When a small part of the tissue was removed for histological examination a hemorrhage occurred which was controlled with difficulty. The pathologic report at this time was small round cell sarcoma. The prognosis was regarded as unfavorable. No treatment was given.

Clinical Course: About 18 months later the child was seen in the outpatient department. She had gained a great deal of weight. The cicatrix was healthy and the tumor in the abdomen had regressed to the size of a tangerine. There was no anemia. A year later she was again seen and the tumor remained the same size. Four and five years after the operation the child remained in good health and there was no evidence of tumor on palpation. She had developed well. At this time (1945) the sections were re-examined and were pronounced "neuroblastoma, an extremely malignant type of tumor, due to the histologic picture." The child developed splendidly and remained in excellent health; she married in 1960 and had a normal child. Both were last traced entirely well in December 1969, 31 years after onset. (The authors cited the cases of Cushing and Wolbach, Roussy, Fèvre and Debré).

Comment: In this case the concurrent varicella infection prior to the three small doses of x-ray therapy as well as the shock of hemorrhage at exploration, may have stimulated the reticuloendothelial and hematopoietic tissues to elaborate resistance factors sufficient to cause complete regression.

References: 49; 71.

CASE 7: Apparently inoperable neuroblastoma of the left adrenal gland, confirmed by microscopic examination following biopsy by Dr. F. W. Hartman, Department of Pathology, Henry Ford Hospital, Detroit, Michigan who reported: "Sections of bits of tissue removed

SERIES A: INFECTION CASES, DETAILED HISTORIES

showed dense, pink-staining, sparsely nucleated stroma supporting large masses and columns of deeply staining oval or round cells. These had little cytoplasm, but the nucleus was hyperchromatic. There was a tendency toward whorl formation in some places, but no typical rosettes were found. The diagnosis was malignant neurocytoma of the left adrenal gland."

Previous History: W.A., male infant. The child was born normally on November 4, 1944 and seemed to be in excellent condition. He was examined at the age of three weeks for occasional vomiting and a solitary mass was felt 2 cm. below the left costal margin. X-ray examination revealed a questionable mass in the left upper quadrant of the abdomen and the liver seemed larger than usual. A complete blood count gave normal results. A fasting blood sugar level was 89 mg. per 100 cc. and after administration of 2 minims of 1:1,000 ephedrine subcutaneously it rose to 108 mg. per 100 cc. The Wasserman was negative. Cholesterol content of the blood was 222 mg. per 100 cc. The tuberculin reaction was negative to 0.01 mg. of old tuberculin.

Concurrent Infection: Comedos and acne, with small infected pimples developed over the cheeks and this was regarded as due to stimulation of sex hormones. At the age of nine weeks the mass in the left upper quadrant of the abdomen was more definite and the infant's weight was 12 pounds (5,440 gm.) The measurements were: head circumference 38 cm., chest circumference 37 cm., and abdomen 47 cm., a gross enlargement of the latter. At this time he was referred to the Henry Ford Hospital by Dr. Ruth Kraft of Detroit and was admitted. The blood count showed Hg. 11.2 gm.; rbc. 4,000,000; wbc. 11,100; 33 polymorphonuclear; 4% eosinophiles, 50% small lymphocytes and 7% mononuclear cells. The phenol sulfonphthalein-kidney function test showed 35% excretion in the first hour and 15% in the second hour. Laboratory data were blood van den Bergh test, negative; icterus index, 5 mg. per 100 cc.; blood protein nitrogen, 30 mg. per 100 cc.; fasting blood sugar, 72 mg. per 100 cc.; sugar level following administration of 2 minims of 1:1,000 ephedrine, 77 mg. per 100 cc. Urinalysis gave normal results and the stools showed a 3 plus guaiac reaction. Chest films showed normality except for moderate elevation of the left diaphragm. Flat films of the abdomen revealed only a slight increase in density in the upper abdomen, with downward displacement of the intestine. Intravenous pyelograms showed no excretion of dye into the right kidney. The left kidney was visualized and appeared normal. Examination of skull and long bones showed no abnormalities.

Surgery: A biopsy was performed and reported as above.

Radiation: X-ray therapy was begun immediately and 20 were given in 38 days, an estimated dose of 1400 r to the tumor site in the upper abdomen. Two months later he was given a second course of 16 treatments in 20 days, an estimated 1250 r tumor dose (200 K.V., 50 cm. dist. 25 ma., half value layer 1.0 mm. cu.; field size varied from 8 x 10 cm. to 15 x 15 cm.). The child's skin remained in good condition, and he improved generally. The acne did not remain on the face following radiation.

Clinical Course: By July 28, 1945, one month after radiation was completed, the liver had receded to the costal margin, but a small firm mass could still be felt in the left upper quadrant of the abdomen. At the age of 11 months he weighed 19 pounds and seemed well. At the age of 14 months the mass in the left upper quadrant could no longer be felt and the liver was of normal size.

Concurrent Infection: In November 1945 he had an attack of influenza.

Clinical Course: At 18 months complete roentgen study was made of all the long bones and the skull for possible metastases, and the only finding was "a suggestion of several calcified glands in the upper abdomen." At the age of two years the child was a happy normal boy, eating a regular diet and showing no evidence of recurrence. In August 1948 at the age of 3½ years, a small indistinct, firm mass was palpable in the upper part of the abdomen just below the xiphoid. The left lobe of the liver was palpable and smooth. He was readmitted to the hospital at this time for retrograde pyelography. This revealed the left kidney to be lower than the right, but no evidence of tumor was seen.

Further Radiation: However, with the evidence of a palpable mass and displacement of the kidney a third course of roentgen therapy was given. This consisted of 13 treatments in 16 days (1400 r tumor dose).

Further Infections: In October 1949 he had another respiratory infection. In March 1950 he had a few days of abdominal pain and vomiting. In January 1951 he had a right otitis media with tonsillitis.

Clinical Course: The child remained in good health thereafter. His development was normal. There were no palpable masses and the liver was not enlarged. The case was reported by Beck and Howard in 1951. Howard stated that the boy had not been especially subject to acute infection. He apparently had remarkably good resistance against the type of infections so common in children. Unfortunately, however, the radiation therapy caused dwarfing. There was interference with the formation of the spinal bodies and there was so-called radiation nephritis, so that his blood urea nitrogen ran approximately 40. If for some reason, such as a sore throat, the boy did not drink adequate amounts of fluids, the blood urea nitrogen rose as high as 80. With these exceptions the patient remained in good health. During adolescence he again developed a minor amount of acne. At the age of 15 years, his weight in August 1960 was 72 pounds and he was 4 feet 4 inches tall (considerable dwarfing). He obtained a part time job in a garage as a mechanic. In September 1966 and April 1967 he was hospitalized for progressive kidney failure. His blood urea nitrogen came down from 122 to about 50. Between admissions he worked as a mechanic and continued to do so part time. During his second admission he also had septicemia (*Escherichia coli*). Dr. Howard reported on August 8, 1967 that "for the extensive damage he was making an unusually good adjustment." The patient died on February 6, 1968 after prolonged hospitalization for kidney failure. The postmortem revealed bilateral radiation nephritis, with uremia and marked renal atrophy; fibrosis of the liver; sclerosis of the vertebral bone marrow (lumbar); severe pulmonary edema and congestion; anasarca; also secondary parathyroid hyperplasia and fibrinous pericarditis. Death occurred over 23 years after onset.

References: 1; 49.

CASE 8: Inoperable generalized neuroblastoma, first noted in the sacral region, with at least 50 metastases (subcutaneous) on the scalp and entire body except the face and hands, confirmed by microscopic examination following biopsies of two of the nodules, by Professor C. Cavallero, Director of the Institute of Pathological Anatomy, University of Pavia, and Professor C. Sirtori, of the Cancer Institute, Milan, Italy.

SERIES A: INFECTION CASES, DETAILED HISTORIES

Previous History: A.B., male, infant. The child was born prematurely at home in the seventh month of pregnancy, after a normal labor. At one month of age a small subcutaneous tumor in the sacral region and another on the hairy scalp were first noted by his mother. Although the infant continued to grow satisfactorily, new subcutaneous nodules kept appearing which rapidly increased from the size of a lentil grain to that of an almond or larger.

Concurrent Fever: During his fifth month fever set in.

Clinical Course: Tumors then appeared on the right cheek which interfered with sucking. On June 25, 1946, at the age of 6½ months the baby was admitted to the Pediatric Division of the District Hospital of Busto Arsizio, Italy. Physical examination revealed a pale, fragile, underdeveloped and undernourished child weighing 6400 gm. Scattered subcutaneous nodules, ranging in size from a lentil to a walnut, were present in the hairy scalp and all over the surface of the body except for the hands and feet. The nodules were rounded, somewhat soft and fleshy to palpation. Some seemed to have no attachment to the overlying skin, others were definitely fixed to the deeper strata of the skin. The nodules on the scalp and abdomen were slightly violet in color under the semitransparent skin, possibly due to vascularity. There were about 50 tumors, mostly on the back. One nodule was present on the scrotum.

Surgery: A subcutaneous nodule in the left pectoral region was biopsied on July 1946. The report at this time was "highly immature round cell sarcoma."

Further Fever: The child was hospitalized for 30 days during which time his temperature ranged from 98.6° to 102.2°F. (37° to 39° C.). He lost 100 gm. in weight. Four new nodules appeared, two on the scalp and two on the trunk. Radiation was recommended, but in view of the hopeless prognosis, the parents refused and took the child home. Three weeks later they reconsidered and had the infant readmitted. At this time there was no fever, he was quieter and had a better appetite. Blood count showed a leukocytosis (20,000 wbc.). It was noted that no new nodules had appeared and that those on the cheeks had decreased in size spontaneously.

Radiation: Five x-ray treatments were given (100 r each). The white blood count dropped to 6000 wbc.

Clinical Course: By September 22, 1946, when the baby was again seen, it was noted that the irradiated subcutaneous nodules were regressing while the others remained unchanged.

Clinical Course: Because of the contrast between the favorable general condition and the unfavorable histologic diagnosis, the child was sent to the National Institute of Tumors in Milan.

Further Surgery: A biopsy was then performed of a subcutaneous nodule in the left axilla. This was again diagnosed as sarcoma, and continuation of radiation was advised.

Further Radiation: On an outpatient basis two additional x-ray treatments were given (100 r each), this time to the nodules on the neck and the nape.

Clinical Course: When the infant was next seen, on February 16, 1947, at the age of 14 months, he looked well and the subcutaneous nodules had under-

SERIES A: INFECTION CASES, DETAILED HISTORIES

gone a general regression, those on the neck and scalp having disappeared entirely, while those on the back, although less palpable, had flattened considerably, and had acquired a fibroelastic firmness. Only the nodules on the abdomen preserved their original features. No further treatment was given. The boy was readmitted at the age of six years because one of the three remaining nodules had become more noticeable. At this time the child appeared to have developed satisfactorily, but he was somewhat anemic and undernourished.

Concurrent Infection: There were a few impetigous spots on his face. The three old subcutaneous nodules were still present: one in the epigastric region, one appended under the scrotum and one on the outer side of the right foot. Radiological examination of the skeletal system revealed nothing abnormal.

Further Surgery: An excisional biopsy of the epigastric nodule was performed on September 6, 1952. On gross examination the tissue had the appearance of white sclerotic connective tissue. This was subsequently reviewed by Professor Cavallero who reported it to be a ganglioneuroma. The sections removed earlier were also reviewed as stated above and the diagnosis of the lesions removed in 1946 was neuroblastoma.

Clinical Course: During the following years the two remaining nodules did not change in any way. The boy enjoyed excellent health thereafter. He was thoroughly reexamined at the age of 12, and in 1962, when Vigorelly reported the case. He remained strong and healthy, married and had a normal baby by August 1967. There was no further evidence of neuroblastoma. This was 22 years after onset.

References: 17, Case 29, pp. 154-159; 49; 72.

CASE 9: Inoperable neuroblastoma of the right upper kidney region extending into the upper right abdomen with numerous metastases to the liver and to the right proximal humerus and skull, including both periorbital regions, causing extensive proptosis, confirmed by microscopic examination of a biopsy from the liver taken at Mercy Hospital, Chicago, Illinois, following exploratory operation. (See below for details).

Previous History: G.S., male, aged 4 months (in March 1947). The infant was born of healthy parents, and the pregnancy had been normal. His mother had no antibiotics, antihistamines or radiation during pregnancy. At birth he weighed 6 pounds, 7 ounces, and on feedings of evaporated milk supplemented by vitamins his weight at four months was 13 pounds, his height 24½ inches.

Concurrent Infection, Mild Otitis and Pharyngitis: He was first seen by Dr. David Goldring on March 4, 1947 because of a mild upper respiratory infection and was found to have a mild otitis and pharyngitis. Physical examination was otherwise negative. His only medication was antibiotics. He was again observed a month later, at the age of five months, with a mild rhinitis but no other abnormality. His blood count on April 22, 1947 was rbc. 4,510,000; wbc 15,500 and hemoglobin 65%.

Onset: On April 28, 1947 he suddenly developed bilateral hemorrhages of the eyelids and when examined was found to be definitely anemic and to have a palpable mass in the upper right abdomen. This was firm, not too

SERIES A: INFECTION CASES, DETAILED HISTORIES

sharply outlined, but slightly movable and appeared to be beneath the liver, which was pushed somewhat upward and forward. On fluoroscopy, a radiopaque mass was seen in the right upper abdomen, and the right diaphragm was considerably higher than the left. After admission to St. Catherine's Hospital, Whiting, Indiana, the following laboratory findings were obtained: Blood — hemoglobin 7.4 gm.; erythrocytes 3,040,000; platelets 60,800; leukocytes 7,500 with a differential of 1 basophile, 2 eosinophiles, 1 juvenile, 2 stab cells, 20 segmented cells, 68 lymphocytes and 5 normoblasts per 100 leukocytes. Bleeding time was 11 minutes and clotting time $4\frac{1}{2}$ minutes. Blood chemistry — non-protein nitrogen 38 mg., chlorides 569 mg., total serum protein 6.6 gm., with albumin 5.3 gm. and globulin 1.3 gm. per 100 cc. An intravenous pyelogram showed the right kidney pelvis much lower than the left and x-rays revealed, in addition to the mass in the right upper quadrant noted on fluoroscopy, an area of localized rarefaction in the upper right humerus, and a suggestion of similar areas in the skull.

Transfusions: The child was given three whole blood transfusions of 100 cc. each.

Radiation and Concurrent Fever: He was given six deep x-ray treatments to the right kidney region in divided doses of 200 r for a total of 1200 r. This caused mild erythema. There was fever to 101°F. on two occasions following the x-ray treatment.

Surgery: The patient was then transferred to Mercy Hospital, Chicago, for surgical exploration. At this time the periorbital and conjunctival hemorrhages and proptosis were rather marked (see 28, Fig. 1 for photograph taken on admission). The infant's abdomen was explored on May 24, 1947 by Dr. John Keeley. The liver was found to be extensively involved with nodular metastases; some soft, some hard, which varied in color from light yellow to orange. Some were whitish in color. There were nodules up over the dome of the right lobe of the liver, and upon palpating the region of the right kidney the lower and middle portions were entirely normal. The upper portion of the kidney was in continuity with a retroperitoneal mass which seemed to come upward and anteriorly to involve the liver in a nodular manner. A biopsy wedge of the liver was taken. Microscopic examination of this tissue showed the liver to be involved by extensive deposits of a neuroblastoma. The tumor revealed very well-defined rosette formations over wide areas, and elsewhere it grew in more solid or cord-like closed packed masses of cells in a fibrous stroma (28, Fig. 2, 3).

Further Transfusions: The patient was given two more whole blood transfusions of 120 cc. each and was discharged.

Concurrent Infection: On May 7, 1947 the child again developed rhinitis, with a temperature of 101°F. No treatment was given.

Further Radiation: During June 1947 five more x-ray treatments were given to the right kidney region for a total of 750 r. X-ray was stopped because he developed a marked leukopenia and anemia (wbc 4,350 on June 30, 1947).

Clinical Course: The child seemed to be getting more pronounced proptosis during radiation therapy, so that protective celluloid shields had to be constructed for his eyes.

Further Transfusions: During June, the sixth and seventh transfusions were given and during July 1947 he was given his eighth and ninth trans-

SERIES A: INFECTION CASES, DETAILED HISTORIES

fusions of whole blood (120 cc. each); none caused reactions. His condition remained grave.

Clinical Course: He was again seen on August 16, 1947 and surprisingly enough showed rather striking improvement. His weight was 15 pounds eight ounces. The mass in the right side of the abdomen was smaller and the proptosis was not as marked. He showed no evidence of anemia, the wbc being 6,400, the hemoglobin 60%. A month later he was seen again. He had gained two pounds, the proptosis was very slight and the mass in the right abdomen was smaller. The child was seen periodically and continued to improve.

Further Concurrent Infection: On April 12, 1948 he developed an upper respiratory infection, with high fever, a cough and bronchitis.

Clinical Course: By September 8, 1948 he weighed 25 pounds and his height was 34 inches. At this time he showed no clinical evidence of the original tumor, his proptosis was absent, as was the mass in the right abdomen. Skeletal x-rays taken on November 24, 1948 and September 15, 1949 revealed no metastases. Blood examinations were within normal limits.

Infectious Diseases: In 1951 he had measles and varicella.

Clinical Course: The child is being seen periodically by Dr. J.M. Troy of Whiting. His last skeletal films taken in 1957 were normal. He remained well and free from further evidence of disease. On September 22, 1961 at the age of 15, his weight was 100 pounds, his height being five feet two inches. (His parents are small). By August 1961 he had grown four inches and weighed 136 pounds. His mental development was normal and he was in his normal grade in school. He remained in excellent health, quite active in sports in January 1969, almost 22 years after onset. (49)

Comment: In this case, the child developed a series of rather mild infections beginning with the otitis media, but he developed a leukocytosis of 15,500. Some of these infections occurred before radiation was given. There was fever on two occasions during the radiation, and high fever on one occasion, in the spring of 1948 following his final upper respiratory infection. During 1951 he had measles and varicella. It is of interest that in 1952 his wbc. was still 14,350. It is possible that in this case these episodes and the nine transfusions help to stimulate this child's natural resistance, so that the radiation and exploration were followed by complete regression of all the widespread disease.

References: 28; 49.

No detailed history is available for CASE 10.

CASE 11: Inoperable congenital extra-adrenal neuroblastoma, confirmed by microscopic examination following laparotomy.

Previous History: Female, newborn infant. A mass in the left upper quadrant was discovered two days after birth. An intravenous pyelogram revealed downward displacement of a normal left kidney.

Surgery: At laparotomy four days later the tumor was found to be unresectable because it involved the intestine and great vessels.

Radiation: The infant received x-ray therapy postoperatively over a four week period totalling 2100 r.

SERIES A: INFECTION CASES, DETAILED HISTORIES

Further Surgery: At the age of 8½, 10 and 11 months numerous subcutaneous metastases were excised.

Chemotherapy: At 11 months cyclophosphamide (Cytosan) was given.

Further Radiation: At this time x-ray therapy was given to the subcutaneous metastatic nodules in the right posterior thorax (2022 rads in 10 days.)

Further Surgery: Further subcutaneous metastases were excised from the left knee and inguinal region.

Further Radiation: A solitary nodule in the right lung received 840 rads (single dose).

Further Chemotherapy: Several additional courses of cytoxan were given until the child was 27 months old, when further growth of the abdominal tumor was noted.

Further Surgery and Postoperative Infection: At laparotomy a dumbbell shaped tumor was seen to have extended superiorly in the retroperitoneum; approximately 50% of it was excised before spasm of the superior mesenteric artery with resultant ischemia of the small intestine forced the surgeons to stop. Examination of the specimen revealed ganglioneuroma. The post-operative course was stormy. Two weeks later a ruptured gangrenous segment of jejunum was excised. Numerous enterocutaneous fistulae were excised on two occasions; 5½ weeks after attempted excision of the abdominal tumor, additional gangrenous segments of intestine were excised, enterococcus fistulae were closed, and dehiscence of the abdominal wound corrected. The arterial supply to the intestine was found to be occluded. The patient died in the recovery room.

Autopsy: Numerous subcutaneous metastases were noted. There was infarction from the proximal jejunum to the hepatic flexure of the colon (approximately 10 days old). Numerous defects in the wall of the small intestine were noted. *Escherichia coli*, *E. intermedium* and *Streptococcus fecalis* were cultured from a subfascial abscess which communicated with the peritoneum. The tumor completely surrounded the left and right renal and adrenal arteries and veins and the celiac artery but did not obstruct them. It surrounded the superior mesenteric artery and appeared to compress it around a 4 mm thrombus which was adherent to the intima at the site of a fine black suture in the anterior wall. The left kidney was displaced inferiorly and posteriorly by the tumor, but was not invaded by it. There were no osseous or visceral metastases. Histologically the tumor was a well differentiated ganglioneuroblastoma. Focally the tumor was necrotic and there were small areas of calcification. In conclusion the authors stated that differentiation of this extra-adrenal neuroblastoma to ganglioneuroblastoma and finally to ganglioneuroma supports the concept that the embryogenesis of sympathetic ganglia and that of the adrenal medulla are similar.

References: 30.

CASE 12: Inoperable massive neuroblastoma arising from the right lumbar region, derived from paravertebral sympathetic nerve tissue, confirmed by microscopic examination following biopsy in December 1949.

Previous History: Female, infant, born June 6, 1949. Onset, at the age of three months the child was noted to have a hard swelling in the right

lumbar muscles. Within the next month there was weakness of the left calf muscles and the lumbar swelling had grown. An abdominal swelling on the left side was readily palpable within another four weeks. The child was admitted to the Bristol Royal Hospital for Sick Children at the age of 5 months in early November 1949. At this time there was a mass below and to the left of the umbilicus and a firm ovoid mass about 4 cm. long in the right lumbar region, just to the side of the spine. The left leg was flexed at the knee and there was marked foot drop. There was no movement of the foot, but slight power of extension of the knee. In the right lower limb there was no movement of the foot, but normal control of knee and hip. X-ray examination showed a soft tissue mass in the pelvis and right abdomen with calcification in the right side of the pelvic cavity. Intravenous pyelography showed that the right kidney was high but probably normal. The left kidney was "full" with stasis in the left ureter. The bladder was deformed by an extrinsic mass lying mainly to its right side and above it.

Concurrent Infection: The urine contained pus cells and coliform bacilli.

Surgery: An incisional biopsy was performed in December 1949 through an incision parallel to the right iliac crest at the level of the third spinous process, and a hard grey lobulated mass was exposed. The tumor was adherent to the iliac crest and surrounding structures and extended anteriorly. A large piece was removed for histologic examination. The tumor showed a white cellular appearance with areas of hemorrhage. It contained the classical rosettes of neuroblastoma, but was more highly differentiated than many neuroblastoma seen at this age, in that the rosettes were numerous, and there were no ganglion cells. Since treatment was thought unlikely to benefit the child she was allowed to go home.

Further Infection: There was some urinary retention and consequent cystitis. (This continued over the next decade).

Clinical Course: She was seen a year later and appeared to be in good general health apart from deformity of the feet and the urinary retention and cystitis. The mass was no longer clearly felt, and the abdomen was much less distended. There was no evidence of metastases. The abdominal neuroblastoma disappeared completely in the 18 months following exploratory operation. During the next 8½ years the child was readmitted on 12 occasions for treatment of paralysis of the legs and the impaired bladder function caused by compression of the cauda equina. This led to progressive deterioration in kidney function and the child died of uremia at the age of 10 in June 1959 from urinary infection due to a persistent neurogenic bladder. Limited necropsy revealed no abnormality in the abdomen other than gross pyonephrosis and dilation of the bladder and ureters. The lumbar spine and sacrum were removed for detailed examination and gave histological confirmation that the peripheral portion of this extensive neuroblastoma had regressed and the remaining dumb-bell tumor in the lumbosacral canal had matured to a small ganglioneuroma. The proportion of tumor to fibrous tissue was very low.

Reference: 18.

CASE 13: Inoperable neuroblastoma, present at birth, confirmed by microscopic examinations by Dr. John Godwin and another pathologist at the Ochsner Clinic of biopsies from several different metastatic nodules removed in May 1950, April and November 1951.

SERIES A: INFECTION CASES, DETAILED HISTORIES

Previous History: M.B., female infant, of Lake Charles, Louisiana. The family history was essentially negative. The child's mother developed an itching rash or irritation of the vagina a few weeks prior to her confinement, but this was treated locally and cured in a few days. She did not receive any radiation (diagnostic or therapeutic) during her pregnancy or confinement, both of which were entirely normal. The baby was born at full term on February 2, 1950 and weighed six pounds. The mother noted that "at birth the baby's abdomen was abnormally large, and pointed this out to the physician, but he said it was nothing." The child was breast fed for two months. When she was a week old the mother contracted flu, "not especially severe." The other children also had influenza, but the infant remained asymptomatic. The mother also had some mastitis during this flu infection.

Vitamin K Therapy: The child seemed well during her first month, but at that time the local doctor gave her four injections of Vitamin K, because he said her blood did not seem to coagulate properly.

Clinical Course: At the age of two months small masses began to appear under the skin over the abdomen, groins, back and on the head. These were raised, hard and some seemed bluish in color. These continued to appear and then the local physician noted a mass in the abdomen and referred the child to the Ochsner Clinic in New Orleans. Physical examination on admission May 26, 1950, at the age of three months, showed an infant 56 cm. in height, weight 12 pounds 4 ounces. The baby looked pale, chronically ill, with a protuberant abdomen measuring 45 cm. in circumference. There were myriads of widespread subcutaneous masses 5 to 10 cm. in diameter in the groin, over the pubis, over the lower abdomen and less numerous ones scattered over the chest and back. In the abdomen a large mass, apparently the liver, was felt on the right extending from the costal margin to below the iliac crest, and medially well beyond the midline in the upper abdomen. A notch could be felt in the vicinity of the umbilicus resembling the notch between the right and left lobes of the liver. The blood count on admission showed hemoglobin 8.5 gm. Intravenous pyelograms showed both kidneys displaced downwards, and the right kidney rotated outward and pushed medially until its ureter lay in the midline of the abdomen. X-rays of the long bones and chest were negative.

Surgery: On May 29, 1950 a biopsy of two subcutaneous nodules was performed and the diagnosis was neuroblastoma.

Concurrent Infection: While the baby was hospitalized she had a case of diarrhea (not severe), but it caused severe diaper rash, also she ran a slight temperature.

Chemotherapy: Beginning June 1, 1950 she was given nitrogen mustard intravenously once daily for four days in doses of 0.56 mg. She was given a blood transfusion following this therapy.

Clinical Course: The baby was discharged June 4, 1950 with a hopeless prognosis. Her condition deteriorated.

Concurrent Infections: About two weeks later she developed a severe cold and was given penicillin by the local physician. The mother stated: "I often wondered if this did not have something to do with her cure, because she had seemed to get so much worse when we first came home from the hospital, then after her spell of cold she began to get better gradually."

SERIES A: INFECTION CASES, DETAILED HISTORIES

Clinical Course: The baby was again seen in the Ochsner Clinic on October 22, 1950, at the age of eight months, at which time she was readmitted for study. She then weighed 18 pounds. The liver was felt 5 cm. below the right costal margin, no longer reaching to the umbilicus. Only two or three subcutaneous nodules could be felt. The blood count was normal and skeletal x-rays were negative. Intravenous pyelograms showed that both kidneys had returned to a normal position. The slides of the previous biopsy were reviewed by two pathologists and the diagnosis of neuroblastoma was confirmed. The child was discharged without further treatment.

Further Concurrent Infections: When the child was about a year old she developed "a skin condition resembling boils." The only treatment recommended was the use of hexachlorophene instead of soap for bathing.

Clinical Course: The child was seen in the clinic at monthly intervals from December 1950 to April 1951. She continued to do well and gain weight. However, there were three or four nodules palpable at each visit. She was readmitted on April 9, 1951.

Further Surgery: At this time three subcutaneous nodules were removed from the left thigh and groin. The pathologists reported neuroblastoma, "with no change since previous biopsy." Because of the histologic appearance of malignancy the baby was readmitted May 15, 1951. At this time the liver was $4\frac{1}{2}$ cm. below the costal margin and it was noted that a prominent subcutaneous nodule previously repeatedly palpated in the right labium majus had disappeared. X-rays of the skull, spine and long bones were negative.

Further Chemotherapy: The baby was given nitrogen mustard intravenously once daily for four days, then a three day rest period and another four day cycle. (Her mother stated that after this therapy she developed a cold, and was again given penicillin).

Clinical Course: The child was followed in the clinic, where she was seen during July, August and September 1951. In October 1951, the liver was no longer palpable, and there were no palpable subcutaneous lesions except one on the right thigh. Complete skeletal survey at this time was negative, but x-rays of the abdomen showed mottled calcification in the region of the liver.

Further Surgery: She was therefore readmitted to the hospital on November 26, 1951 for surgical excision of this mass in the right quadriceps femoris muscle. Pathologic report on this mass was neuroblastoma with differentiation towards ganglioneuroma.

Concurrent Acute Inflammation: She was given penicillin daily for about a month and after $3\frac{1}{2}$ weeks developed a severe allergy to it; her entire body was covered with a red rash and her eyes were swollen shut. The rash disappeared when the penicillin was stopped.

Further Chemotherapy: In December 1951 and in January 1952 the baby received further courses of nitrogen mustard, each consisting of 1.5 mg. intravenously once daily for four days.

Clinical Course: The child was seen on February 15, 1952 at which time she weighed 25 pounds and exhibited no subjective or objective evidence of disease.

Further Infections or Infectious Disease: At the age of three she had chicken pox and at the age of four or five she had measles.

SERIES A: INFECTION CASES, DETAILED HISTORIES

Clinical Course: There has been no further evidence of neuroblastoma. The patient graduated from high school in June 1968. She remained in excellent health in 1970, 20 years after onset.

Comment: This case is of great interest. Note that the congenital neuroblastoma appeared to metastasize widely very shortly after administration of Vitamin K. Note that this child was nursed by her mother during an influenza infection and mastitis. The baby had diarrhea, severe diaper rash, furunculosis and finally a very severe allergic reaction to penicillin (urticaria and edema) in the period in which the tumors were regressing. Within the next two years or more she had varicella and rubeola. These concurrent infections and acute inflammatory episodes apparently stimulated this child's resistance, possibly aided by the nitrogen mustard, resulting in complete and permanent regression.

Reference: 49; 66a.

CASE 14: Extensive inoperable retroperitoneal neuroblastoma, confirmed by microscopic examination following biopsy by the Pathological Laboratory, Department of Public Health, Sydney, Australia. (See below).

Previous History: A.H., female, aged 15 months. The family history was negative for cancer or tuberculosis. Her paternal grandfather (deceased) was a diabetic. Her mother did not receive radiation, antihistamines or other anti-inflammatory drugs during her pregnancy. The child was breast fed for 12 months. The date of onset was not recorded.

Concurrent Infection: She was admitted to the Goulburn Base Hospital on July 21, 1954. She was pale, thin, very irritable and often screamed as if in severe pain. Her weight was 19 pounds 5 ounces. Her temperature was 104°F., the pulse rate 138 per minute. Examination revealed a large firm, tender, oval tumor in the lower abdomen. Its lower border was palpable by rectal examination.

Surgery: On July 24, 1954 Dr. G. H. Kennett performed an exploratory laparotomy. A large, vascular, fixed, retroperitoneal tumor was found extending across the posterior abdominal wall from flank to flank. It measured 12 by 7½ cm. in diameter, its longer diameter being transverse. Because of its extent and fixity, removal was inpracticable, and examination of the liver and adrenals was not feasible. A tentative diagnosis of retroperitoneal sarcoma was made and a section was taken for biopsy. "Sections showed the tumor to consist of a scanty hemorrhagic stroma supporting masses of rounded cells which vary somewhat in size and show frequent mitoses. Sometimes the cells are arranged in "rosette" formation. The tumor is malignant and the appearances are those of neuroblastoma."

Clinical Course: Following this exploratory operation the child was in *extremis* for a week. However, skeletal x-rays did not reveal any metastases. With careful nursing she slowly improved sufficiently to be taken to the Royal Prince Albert Hospital in Sydney (120 miles away).

Radiation Therapy: She was then given x-ray therapy calculated as 1500 r (tumor dose). Because of the persistent leukopenia this was spread over a period of 53 days.

Further Fever: On November 25, 1954 she returned home and was re-admitted to Goubern Base Hospital. She was pale, apathetic, inert, but representing interference, refusing food and drink, but apparently not in pain. Although her temperature was 105°F. and her blood count showed leukocytosis (19,000 wbc), no physical signs of intercurrent disease were apparent. Empirically, chloromycetin palmitate was given, without any improvement in her condition. The prognosis seemed hopeless.

Vitamin Therapy: On December 3, 1954 Dr. Robert G. Woods decided to try massive doses of vitamin B-12, having read Wayne's article (1954). A dose of 1000 micrograms was given intramuscularly every 48 hours for 16 days. Thereafter, this dose was given once a week. Within one week there was definite improvement in the child's condition. She began to take food willingly and she lost her listlessness. From then on her convalescence was uneventful. She gained weight — from 3 to 26 ounces a week. Serial blood counts showed that the rbc remained at about 4,000,000, the hemoglobin at 10 per ml.; the wbc diminished from 19,000 to 8,700 by January 1955. The differential was characterized by a lymphocytosis, at first 76% diminishing to 43% by January 1955. On December 19, 1954 she was discharged — a happy, smiling child who was learning to walk (she could not walk prior to admission). Wood believed that the vitamin B-12 therapy had apparently assisted the convalescence remarkably. As an out-patient the dose was reduced to 1000 micrograms weekly. The only possible ill effect of the therapy was that in about three months she became sub-thyroid; dull, apathetic, with dry crackling hair. Thyroid extract, gr. 0.5, soon corrected this. Vitamin B-12 therapy was continued weekly for two years.

Clinical Course: The extensive inoperable retroperitoneal tumor disappeared. Regular follow up examinations failed to reveal any significant abnormalities in an apparently normal, healthy child. By August 1957 she weighed 39 pounds, having doubled her weight in three years. In May 1962 she developed diabetes, requiring 65 units of Lente insulin daily. The diabetes was very labile with several hypoglycemic episodes, but otherwise the child remained very well and normal in every respect, including skeletal development. At the age of 10 years her weight was 74 pounds, her height four feet seven inches. She remained in good health in November 1969, over 15½ years after onset.

References: 49; 76.

Comment: Note that in this and the following case infection and/or fever occurred prior to the administration of Vitamin B-12. Possibly this combination is more effective than either one alone.

CASE 15: Inoperable neuroblastoma of the liver (primary site undetermined), confirmed by microscopic examination following biopsy of the liver (38, Fig. 1). The tumor consisted of small round cells with scant cytoplasm, often grouped into nests or rosettes and characteristic of neuroblastoma. The child also had Von Recklinghausen's disease (neurofibromatosis) and ganglioneuroma of the thoracic sympathetic chain, all confirmed by various biopsies.

Previous History: V.D.H., female newborn infant. The family history was non-contributory. The baby was the second-born of a 23 year old father and a 21 year old mother, the first child being a healthy boy of two years. Both parents were healthy and did not have the stigmata of neurofibromatosis. The

SERIES A: INFECTION CASES, DETAILED HISTORIES

patient was born on January 15, 1955 following a normal uncomplicated pregnancy and delivery. She weighed 9.7 pounds. Persistent vomiting began at the end of her first week and at two weeks she was discovered to have a very large abdominal mass.

Surgery: Surgical exploration on February 10, 1955 revealed a liver almost completely replaced by white nodular tumor tissue. No primary could be seen or felt.

Radiation: A course of x-ray therapy was begun post-operatively but was discontinued because of leukopenia and anemia, after 1600 r had been given.

Clinical Course: About this time a mass in the left side of the neck and swelling of the left arm were noted. The baby was then referred to the City of Hope Medical Center in Duarte, California. On admission in June 1955 she was poorly nourished and weighed 12.3 pounds. A smooth, poorly demarcated firm mass was felt in the left supraclavicular region and the entire left arm except for the hand was swollen, smooth, firm and non-pitting. The infant did not use her left arm as much as the right. The liver, which had an irregular, nodular surface, was palpated 6 cm. below the costal margin. A chest film revealed two large masses, one in the superior mediastinum. The intravenous pyelogram was negative as were the skeletal survey and a bone marrow aspiration for metastases.

Chemotherapy: A course of chlorambucil was instituted, without apparent benefit.

Concurrent Infections: In July 1955 she had a temperature of 101°F. for several days associated with a bout of aspiration pneumonia. At this time Beta hemolytic streptococcus and Staphylococcus aureus were cultured from her throat. Treatment consisted of erythromycin and terramycin. In September 1955 she had an upper respiratory infection and again in December 1955 she had a recurrent pneumonia with a temperature of 101°F. In the two years following surgery she had several other respiratory infections with fever and cough.

Vitamin Therapy: In September 1955, the child was started on Vitamin B-12 (1000 mcg. daily intramuscularly.) Gradually during the next nine months her general condition improved. The abdominal mass receded and by June 1956 it was no longer palpable (the liver metastases had entirely regressed.) During this period the other masses seemed to grow in proportion to the child's growth. A left Horner's syndrome developed.

Further Surgery: In May 1956 a biopsy of the swelling in the left axilla revealed the characteristic neural and connective tissue elements of neurofibroma. (38, Fig. 2) In July 1956 exploratory thoracotomy revealed a large lobulated mass in the superior and left mediastinum connecting via the apex of the left chest with the mass in the neck and with the swelling in the arm. It was adherent to the ribs and vertebral bodies and enveloped the left thoracic and cervical sympathetic chain. Portions of these masses were removed. Microscopically the mass in the arm was characteristic of neurofibroma, whereas the thoracic mass also had clusters of ganglion cells as observed in neuroblastoma. Recovery from this surgery was uncomplicated and the child was discharged home.

Further Vitamin Therapy: Vitamin B-12 injections were continued until June 1958, a total of 21 months.

SERIES A: INFECTION CASES, DETAILED HISTORIES

Further Infections: In October 1958 she again had pneumonia of the left lower lung, with a temperature of 104°F., which responded to penicillin. In January 1959 she was hospitalized because of pneumococcal pneumonia of the right middle lobe. Three months later she had another bout of pneumonia (left lower lobe) with a temperature of 104°F. Both were treated with penicillin.

Clinical Course: The lesions remained static. An anterior bulging deformity of the left chest developed. A previous faint pigmentation over the left shoulder area became very prominent. Large numbers of café-au-lait spots developed all over her body. A fracture of the left humerus in 1960 healed well. In 1962 enlargement of the clitoris was first noted by the child's mother. This was presumed to be due to neurofibromatosis.

Further Surgery: About June 1965 she underwent surgical reconstruction of the chest wall deformity without complication and with a good early result.

Clinical Course: The child attended school regularly and seemed to be within the normal rate of intelligence. By 1966 she weighed 62.9 pounds, her height being 53 inches. In 1967 the Horner's syndrome, swelling of the arm and intrathoracic masses persisted, and there was severe scoliosis of the dorsal spine with convexity to the right, but there was no further evidence of the neuroblastoma. Her major difficulty has been pain in various parts of her skeletal system, particularly the chest and back. By 1969 it was evident that her mental development was subnormal. Because of persistent back pain she was referred to the Orthopedic Hospital in Los Angeles where two spinal fusion operations were performed in November and December 1969 in order to relieve the pain and improve the cosmetic effect. Menarche had not occurred by January 30, 1970, 15 years after onset of the neuroblastoma.

References: 38; 49.

CASE 16: Inoperable neuroblastoma of the right suprarenal gland, with multiple cutaneous metastases, confirmed by microscopic examinations following biopsies of two metastatic lesions.

Previous History: S.K., female infant, aged 3 weeks at onset in July 1957. The pregnancy and labor were normal. The child weighed 7.3 pounds at birth. She was the second child of healthy parents and was breast fed. As a newborn she had a sore in the oral cavity, otherwise there had been no serious illness and the infant developed well. At the age of two to three weeks the mother first noted small tumors under the skin in the genital area and in both hips. At the age of three weeks the child was admitted to the Wurzburg Children's Clinic. Her weight on admission was almost 10 pounds. Examination revealed a well developed infant with numerous tumors over the entire trunk and proximal lower extremities. These were in the deep cutaneous and subcutaneous tissues and ranged in size from a bean to a pigeon egg, being of coarse consistency. They were mostly movable on the underlying tissues, somewhat adherent to the over-lying skin and painless to pressure. The over-lying skin in many places was moderately tight and red. (See 35, Fig. 1). The spleen and liver contained no palpable tumors. The superficial lymph nodes were not enlarged on palpation. The peripheral blood picture, sedimentation rate, marrow puncture, bacteriological culture of the blood, tuberculin and Wasserman reaction and side reaction, feces, urine, all skeletal and mediastinal x-rays were without pathological findings.

SERIES A: INFECTION CASES, DETAILED HISTORIES

Surgery: A single tumor was excised for biopsy. The histological findings were reported as follows:

"Epidermis and cutaneous appendages inconspicuous. In the lower corium and adjacent fatty tissue there are numerous nests and strands of undifferentiated tumor tissue of relatively small cellular lymphocytoid to monocytoid structure. They reveal clearly infiltration tendencies. The dense cellular elements are poor in cytoplasm in the majority, sometimes their nuclei are almost bare and they are only moderately differentiated from each other as far as form and size of the nucleus is concerned. Isolated mitoses amongst them, also pathological shapes, and marked pyknosis of the nuclei are conspicuous in several places. No typical formation of pseudo-rosettes. However, small spotted zones of fine filaments, weakly basophilic material, frequently surrounded by tumor cells in wreath-like arrangement. Silver impregnation according to Gomori, shows no reticulum fibrils characteristic of the tumor proper. Here and there a slight metachromasia of the stroma of the connective tissue. Histological Diagnosis: Evidently metastasis of a small cell neurogenic tumor, very probably of a neuroblastoma sympatheticum. No definite indication of reticulosis or of other systemic disease of the RES." (755/57).

Clinical Course: This clinically unexpected diagnosis, which was in strong contradiction to the satisfactory general well being of the infant, accordingly was met with considerable skepticism. More x-rays of the abdomen were done, without at first any further pathologic changes being discovered.

Concurrent Infections: At the age of about three months there was persistent pyoderma involving the head and neck which was refractory to treatment and which recurred every six or seven weeks without the general condition of the child becoming essentially deteriorated and without the development of cachexia from the tumor. The child was treated locally and systemically by antibiotics (acromycin, tetracycline, penicillin and streptomycin). She then developed nutritional disturbances which were first treated by dietary restrictions and later also with sulfonamide (Intestin-euvernil).

Hormones and Radiation: Prednisone was given daily for two weeks (10 mg. oral). At the age of $3\frac{1}{2}$ months a trial x-ray treatment was given to a metastatic lesion on the right thigh (400 r x 6 delivered in six weeks). No apparent benefit was noted. The general health remained satisfactory apart from slight anemia, although new tumors continued to develop subcutaneously.

Further Surgery: Another biopsy was performed and histologic study at the University Skin Clinic gave the same diagnosis. (35, Fig. 2, 3, 4) "Now, however, there was conspicuously a certain increase and spread of the filamentous mucoid, but no metachromatic foci which were found at the first biopsy in which some of the cell nests were embedded. Moreover, small isolated areas of necrosis and calcification were noted. Another x-ray examination revealed numerous calcifications in the area of the right adrenal so that the primary tumor could be assumed to be there." (35, Fig. 5). Review of the first x-rays revealed calcium deposits in the same area which had not been recognized with certainty due to marked meteorism.

Further Infection: At the age of $5\frac{1}{2}$ months the child developed varicella. Conspicuously from that time on the cutaneous tumors became notice-

SERIES A: INFECTION CASES, DETAILED HISTORIES

ably smaller. At 6½ months many small nodes, particularly the ones which had appeared last, had disappeared. During this entire time the child had only been under observation, her only therapy having been 6 x-ray treatments to one metastatic lesion and prednisone for two weeks, neither of which had appeared to alter the course of the disease.

Further Surgery: In January 1958 a third biopsy was performed and histologic study at the University Skin Clinic showed a completely changed picture:

"Unclearly delimited nests without signs of a tumorous proliferation, however, with extensive regression changes. There were hyaline amorphous or fine fibrillar irregularly dispersed foci recalling coagulated tissues or 'neurohyaline' moderately basophile partly free of cells or surrounded by cellular elements at the border which took dyes poorly. Also in the midst of these degenerative foci there were sparse 'verdammernde' cellular elements (Fig. 6). In the surrounding stroma of connective tissue there was a spot shaped lymphohistiocytic inflammation with single foreign body type giant cells interspersed. (Fig. 7). On the basis of this finding the histological diagnosis of an original neuroblastoma sympatheticum was no longer possible." (35)

Clinical Course: The consistency of the continuously regressing tumors became less and less homogeneous. X-rays revealed many small calcifications. When the case was published early in 1960 only very small isolated remnants of tumor were present: "at the outside of the left thigh, in the left vulva, here of very hard consistency. (35, Fig. 8). When the light falls at an oblique angle the original contours of the cutaneous tumors show some fine unevenness of the skin on the back and on the anterior side of the trunk, otherwise our little patient, now 2½ years old, appears healthy and is not retarded in any way." A fourth biopsy of these tumors was made in the summer of 1965 and reported as completely differentiated ganglioneuroma, with no evidence of malignancy. The child remained normal and happy and doing well in school, entirely healthy and symptom-free, in October 1969, 12 years after onset.

References: 35; 49.

CASE 17: Congenital neuroblastoma arising from the right abdominal sympathetic chain, confirmed by microscopic examination following biopsy.

Previous History: Male, aged one week. The infant had persistent bile-stained vomiting from birth in 1960.

Surgery: A right sided abdominal mass was explored and found to be a firm tumor the size of a plum arising from the right abdominal sympathetic chain and extending across the midline into the lesser sac. A small biopsy was taken and this showed the histological picture of classical neuroblastoma.

Radiation and Concurrent Infection: X-ray therapy was begun 18 days after operation but was interrupted by a respiratory infection. The throat was diffusely red and inflamed, there were scattered adventitious sounds in the chest and the radiological picture was that of mild bronchitic changes. A tumor dose of 3000 r was delivered in 60 days.

Clinical Course: Three weeks after radiation was completed the tumor mass was no longer palpable. Two years later the baby presented with cya-

SERIES A: INFECTION CASES, DETAILED HISTORIES

notic heart disease and a large liver with a prominent nodule in the right lobe.

Further Surgery: Laparotomy revealed the nodule to be a simple cholangioma with the contiguous liver histologically normal. No trace of the neuroblastoma was found at operation.

Clinical Course: The child remained well and free from further evidence of disease in 1968, over eight years after onset.

References: 6; 49.

CASE 18: Widely disseminated neuroblastoma primary in the left adrenal gland with widespread bony metastases to the pelvis, lower limbs, cervical spine, scalp, cranium and lungs.

Previous History: Male, aged two years. The child was seen by a succession of physicians, with nonspecific illness beginning in April 1966. The true nature of his disease did not become apparent until July 1966, when calcification in the region of the left adrenal appeared associated with nodular lesions in the scalp. The child was first seen by Mr. William Cochran, F.R.C.S. (Edin.) when the disease was generalized and there was a large abdominal tumor, also anemia "due in part to space occupation of bone marrow by tumor." Treatment was undertaken at the particular request of the parents and clinician although Cochran personally felt that the condition was too far gone, the prognosis hopeless.

Chemotherapy, Transfusion and Vitamins: Cyclophosphamide was administered supplemented by blood transfusions and Vitamin B-12. The course of the disease was halted but without significant regression until cyclophosphamide was stopped at the end of 2½ months.

Concurrent Infection: "Regression suddenly became remarkable in November 1966 following a fairly severe attack of rubella, followed within three weeks by a brief attack of what appeared to be chicken pox."

Clinical Course: Within a month the grossly swollen head decreased 4 cm., the scalp irregularity and the tumor in the left adrenal was no longer palpable. The cranium, which was largely eaten away by metastases, considerably recalcified and large translucencies in both tibiae had almost completely filled in by February 28, 1967. The hemoglobin was also at a normal level at that date. He remained free from any further evidence of disease until April 1967, when he presented with a sudden swelling of the leg, this being a recrudescence of the pre-existing tibial metastasis which had transiently disappeared within two months after his infections.

Further Chemotherapy: He was then treated with Vincristine (Lilly) with some regression until June 1967.

Clinical Course: He died in June 1967 within a few days following massive recrudescence of his neoplasm. In reporting this case to us Cochran stated this was "one instance in his experience where there may have been an inflammatory trigger to host resistance."

Reference: 35; 49.

Table 2: NEUROBLASTOMA TREATED BY COLEY TOXINS ALONE OR COMBINED WITH SURGERY AND/OR RADIATION: 9 CASES

Physician or Hospital References	Sex Age	Site & Extent Prior to Toxins Date of Onset	Prior Therapy	Concomitant Therapy	Subsequent Therapy	Infection Inflammation Fever	Type of Toxin Site, Duration Reactions	Immediate & Final Result Years Traced After Onset
1. W. B. Coley 9, 10, 11 12, 17, 49 68a, 78	male 33 mos.	inoperable paravertebral neuroblastoma at scapular level with extensive metastases involving central nervous system, nystagmus diplopia, ptosis; complete quadriplegia; prognosis regarded as 2 mos. 1911	exploratory incision of paravertebral mass (biopsy only); no other therapy	none	10 yrs. later Cushing removed remaining ganglioneuroma, spine & laminae of 5 vertebrae in attempt to improve his mobility	none	Tracy XI into tumor and i.m. with intervals of rest for 2 yrs. beginning July 1911	cerebellar symptoms ceased, no trace of nystagmus, diplopia, etc.; regained bladder control & considerable muscular power but required crutches for walking; after Cushing's operation, walking greatly improved, drove car, worked in store; N.E.D. 1970, 59 yrs. after onset
2. Memorial Hospital 24; 44; 46; 49; 54	male 4½ mos.	inoperable metastatic neuroblastoma with multiple subcutaneous lesions over entire body, especially trunk; onset May 1936	biopsy of lesion in lt. scapular region x-ray to rt. distal chest (326 r), to rt. thigh (327 r), to lt. proximal chest (326 r); no apparent effect	x-ray con'd; radium packs to lesions on back, thigh, forehead (500 mch each); no apparent effect	20 yrs. later explored at N.C.I. because of silent area calcification rt. suprarenal region; mass 12x10x8 cm incompletely removed, also subcutaneous mass in rt. flank: both ganglioneuroma; re-explored 1959, retroperitoneal mass 12x8x6 cm removed: ganglioneuroblastoma; other mass inoperable	peculiar rash on buttocks, abdominal wall, severe desquamating reaction on rt. thigh (irradiated area); broncho-pneumonia 1937; badly diseased tonsils removed 1938; poison ivy annually; 5 more bouts pneumonia, none very serious.	Parke Davis XIII toxins begun 9 days after 1st x-ray; 21 i. m. in 49 days, febrile reactions to 103.8°F.	3½ mos. after toxins were begun many smaller (unirradiated) nodules had disappeared, in excellent condition; March 1937, 2 new lesions appeared, then regressed; N.E.D. by early October 1937, in very good health; 1951 became hypertensive; 1956 consulted N.I. H. for hypertension; spontaneous pneumothorax after surgery there 1957; neuroblastoma reactivated 14 mos. later, progressed, causing death 1961, 25 yrs. after onset.

3. Memorial Hospital 66a	male infant few mos. old	inoperable neuroblastoma multiple, tiny subcutaneous metastases	1 nodule biopsied; small radium plaques applied to 1 or 2 nodules without effect.	none	none	none	Parke Davis XIII (no details as to technique)	Discharged with hopeless prognosis; nodules then began to disappear; complete regression; in perfect health 1952, over 5 yrs. after onset. (66a)
4. Memorial Hospital 44; 49	male 3 yrs.	3 times recurrent inoperable neuroblastoma; lt. thigh involving pelvis, abdominal cavity; onset, November 1944	excision December 1944; then x-ray, (600 r); recurrence removed November 1945; p.o. x-ray, (600 r); 2nd recurrence removed May 1946; further x-ray 6750 r to lt. thigh fall 1946.	December 1946 10 x-ray; 2 blood transfusions penicillin; reactions to both.	none	June 1946: very severe measles, high fever; 3rd recurrence then developed, very rapid growth, soon involved abdominal cavity, pelvis; acute strep. pharyngitis during x-ray fall 1946, fever to 105°F.	Nov. 28, 1946: Parke Davis XIII; 17 i. v. in 38 days; reactions averaged 103°-106°F.	remarkable regression evident during 1st 2 wks. of toxin therapy; N.E.D. in 4 wks., gained 2 lbs.; 2 wks. later disease reactivated, progressed very rapidly; metastases to pleurae, trachibronchial lymph nodes, lt. lung; death February 8, 1947, over 2 yrs. after onset.
5. Memorial Hospital 44	female 18 mos.	neuroblastoma of rt. thigh; onset March 1948, during u. r. i.; quiescent 4 mos; recurred during febrile episode	x-ray to rt. thigh, Aug. 1948 (600 r)	x-ray (2700 r) Aug. 1948; further x-ray during 2nd course toxins, Sept. 1949	incisional biopsy, Oct. 1948; N.E.D.; aspiration biopsy, Sept. 1949; neuroblastoma, further x-ray (4200 r); transfusions; x-ray to spine; S. K. I. 1133 (25 mg) Feb. & March 1950	July 1948, spiking fever 104°F., inflamed throat; June 1949, varicella	Aug. 21, 1948: Parke Davis XIII, 13 i. m. in 15 days, very small doses, slight or moderate reactions (average 101.2°-102°F. once 105°F.); Sept. 1949, 13 i.m. in 13 days, large doses, similar reactions plus urticaria on arms, face; Jan. 1950 large doses daily i. v.	in better health for 6 wks. after toxins than previous yr.; N.E.D., full activities; well until Sept. 1949 pain, mass recurred, improved after further toxins; then pain in lt. leg, metastases to lungs, inguinal lymph nodes, rt. distal leg, wt. loss; much better after 4th dose of final toxin course; metastasis to spine, D11; paraplegia during radiation; rapid downhill course, death April 22, 1950, 25 mos. after onset.

Physician or Hospital References	Sex Age	Site & Extent Prior to Toxins Date of Onset	Prior Therapy	Concomitant Therapy	Subsequent Therapy	Infection Inflammation Fever	Type of Toxins Site, Duration Reactions	Immediate & Final Result Years Traced After Onset
6. Memorial Hospital 44	male 14 yrs.	inoperable neuroblastoma involving lt. femur 18 cm. long; onset mid-April 1951; obese only child, psycho-neurotic mother	diathermy relieved pain briefly	May 1951: x-ray (4493 r)	October 1951 aspiration biopsy; 2 more courses x-ray totalling 8990 r	August 1951 grippe	Parke Davis XIII begun same day as 1st x-ray, May 1951: 15 i. v. in 15 days; reactions averaged 104.6°-105.4°F., chills	in excellent condition full range of motion for over 3 mos.; pain recurred following grippe; liver enlarged by Nov. 1951, though primary responded remarkably to further x-ray, good appetite; pain recurred, unbearable; death July 30, 1952, 15 mos. after onset.
7. Memorial Hospital 44	male 31 yrs.	metastatic neuroblastoma primary in rt. scapula onset September 1950	Sept. 1950, diathermy; regional procaine nerve block June 1951; aspiration, incisional biopsies of scapular mass; x-ray begun 2 days prior to toxins	x-ray to scapula 4184 r	codeine for pain due to recurrence; scapulectomy March 1952 revealed metastatic neuroblastoma; palliative x-ray to spine, 6150 r; to pelvis, 5650 r; HN ₂ ; 3 blood transfusions; further palliative x-ray to various metastases totalling 6400 r; aminofol, stilbestrol, estrogen, androgen	none	Parke Davis XIII September 1951, 16 i. v. in 16 days; reactions averaged 104.6° - 105.6° maximum 107°F., paroxysmal cough during reactions; 2nd course begun 7 days after surgery; 15 i. v. in 15 days; reactions averaged 103.4°-104.4°F.	pain relieved, 80% regression 24 days after 1st injection toxins; returned to work as dentist; complete regression in 4 wks., general condition excellent; pain recurred 4 mos. later, persisted, increased; disease widely disseminated by May 1952: ribs, sternum, spine, pelvis, femora; temporary improvement from palliative radiation; then lost 35 lbs., leukopenia, became drug addict; pathologic fracture rt. distal femur; death, April 14, 1953, 2½ yrs. after onset.

8. Memorial Hospital 44	male 2 yrs.	metastatic neuroblastoma involving entire shaft of lt. femur, probable primary paravertebral region; onset at 10 mos., Jan. 1951 pain, limp; recurrent transient attacks during teething	Jan. 1952 aspiration, incisional biopsies; x-ray, 4538 r to femur, 2500 r to chest as prophylactic	part of x-ray given during toxins	December 1952 x-ray to skull 2250 r, no apparent effect amethopterin, 6-mercaptopurine, P164, further x-ray, cortisone, testosterone, transfusions, adrenalin, also received penicillin twice for u.r.i.	January 1952, bilateral tonsillar adenopathy, abundant mucopurulent discharge, fever, 100.2°F., nasopharyngitis; cellulitis in arm; u.r.i. June 1952, measles, prompt recovery; Feb. 1953, influenza, intestinal gripe, diarrhea, fever to 102°F.; cervical adenitis	Sloan Kettering Institute XIV toxins begun 10 days after x-ray 15 i.v. in 15 days	excellent result, thigh completely normal, child very active; N.E.D. until December 1952, then metastases to skull; fell February 1953, disease then reactivated, pain, cerebral metastasis, also to mandible, vertebra L2; paraplegia; disease progressed, very widespread metastases at death, September 1953, 32 mos. after onset.
9. Johnston 37, Case 80	male 21 mos.	terminal generalized neuroblastoma, cachexia, ascites superior mediastinal syndrome, mass in lt. shoulder	biopsy, x-ray 7200 r; amethopterin, thio-TEPA	none	none	none	Johnston XV toxins: 12 i.m. in 21 days	no improvement, rapid deterioration, death 5½ mos. after onset, 3 wks. after toxins were begun

SERIES B, TOXIN TREATED, DETAILED HISTORIES

CASE 1: Inoperable neuroblastoma (paravertebral sympatheticoblastoma) of the right transverse process of the sixth thoracic vertebra, of the hourglass type, with extensive involvement of the central nervous system, based on careful study of the biopsy material from the original tumor (1911), by Drs. Harvey Cushing and S. Burt Wolbach who reported:

"At first glance the resemblance of the tumor to a fibrosarcoma (the original diagnosis in 1911) with very little intercellular substance might be conceded. However, a peculiarity is immediately noticed in that the tissue is partitioned by connective tissue bands having all the relationships of a stroma in an epithelial tumor. With the stain employed (hematoxylin and eosin), it is impossible to see cell outlines, and the impression of spindle-shaped cells is obtained wholly through the outlines of the nuclei. The nature of the tumor, however, is made apparent by the presence of an intercellular substance consisting of extremely delicate fibrils which are stained a faint bluish pink. These fibrils occur in bands of considerable width separating cell masses from the stroma, and as large bands joining widely separated groups of cells. The size and grouping of the cells, the connective tissue stroma and the presence of the delicate fibrils which resemble cytoplasmic processes of tumor cells, agree perfectly with the characteristics of the so-called 'sympathetic neuroblastoma'. . . There are no cells of a more mature type such as have been frequently described in neuroblastomas arising in the adrenal gland. (see 11 for microphotographs, Fig. 9). Presumably this slide is representative of the tumor as a whole as it existed in 1911. This tumor disappeared or diminished (cicatrized) under the influence of Coley's toxins. Symptoms of spinal pressure persisted, and years later (1912) the intraspinal lesion which remained was identified as a ganglioneuroma, the more compact extraspinal remnant of the tumor showing the same characteristics.

"A very thorough examination of the tissues removed in 1921 revealed no trace of cells similar in structure to those which in 1911 apparently constituted the entire growth. Instead we find a neoplasm composed chiefly of two elements, one representing ganglion cells and the other representing growth of capsular and sheath of Schwann cells, which is the usual combination recorded in ganglioneuromas of sympathetic origin. Therefore, one is forced to conclude that the cells of this tumor as a whole have responded to the influences of factors governing the normal differentiation of the nervous system. . . It would appear without question that the proliferative activity of the normal growth subsided coincidentally with the administration of the bacterial toxins. It is safe to presume, from the study of the original tumor and its comparison with the tumor after a ten-year interval, that the lesion was originally an actively growing sympatheticoblastoma whose cells, coincident with loss of proliferative activity, came to be differentiated in time into ganglion cells and into sheath and capsular cells. . . The case from the pathological standpoint is a unique one." (11, p. 211-212).

Previous History: W. W., Jr., male, aged 21 months (at onset), of Lacrosse, Virginia. The family history was not recorded as regards familial disease in 1911. (The child's father died of malignant melanoma in 1953). In February 1911 the father was thrown from a wagon while holding the infant in his

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

arms. Onset, it was not known at the time that the child had been injured in any way, but a month later the first suspicion was aroused by progressive weakness of the legs, associated with a paravertebral swelling opposite the middle of the scapula on the right side. The swelling increased in size and by April 1911 muscular weakness had so increased that the child could not hold up his head. The diagnosis at this time was poliomyelitis to which the paravertebral swelling was unrelated. The child was taken to a well-known surgeon, Dr. Stuart McGuire, in Richmond, Virginia. By May 1, 1911 the weakness had gradually progressed up the trunk, the arms could not be moved. Soon there was fever, nausea, vomiting, and stupor, as well as loss of sphincter control. The eyes became crossed and there was ptosis. In view of these symptoms, Dr. H. Allison Hodges, a neurologist, saw the child in the consultation with McGuire and the opinion was then expressed that the syndrome was due to some intradural extension of a disease which was possibly tuberculosis, though a lumbar puncture was negative and there was neither stiffness of the neck nor Kernig's sign. Since the paravertebral swelling was increasing in size, it was decided at the father's request, that an exploratory incision be made to determine the nature of the local lesion. Cushing and Wolbach (1927) emphasized in reporting the case that "this preliminary story is important in showing that there was widespread involvement of the central nervous system, which extended above the level of the swelling in the back." (11) The paravertebral tumor was by this time plainly palpable and semi-fluctuant. It suggested either lipoma or a tubercular abscess.

Surgery: In June 1911, McGuire, by an exploratory incision parallel to the ribs, exposed the growth and found a well-defined tumor apparently springing from the lamina or right transverse process of the sixth thoracic vertebra. The lesion was inoperable and after removing a piece of tissue for histologic examination, the wound was closed. This tissue was diagnosed as fibrosarcoma.

Clinical Course: The surgical incision healed promptly, but the tumor increased in size. McGuire regarded the prognosis as about two months but on the advice of Dr. William B. Coley it was decided to try Coley toxins.

Toxin Therapy (Tracy XI): Injections were begun late in July 1911, by the child's father, a physician. The initial dose was 1/5 minim, which caused a febrile reaction of 102°F. They were given every other day, one a week being made into the tumor, the remainder intramuscularly remote from the tumor. The maximum intratumoral dose was 2 minims, the maximum intramuscular dose was 8 minims, and on one occasion this dose caused a good deal of shock, and thereafter the intramuscular dose was kept at 2½ to 5 minims. The child's weight steadily increased during treatment, from a low of 21 pounds, until by March 1912 he weighed 29 pounds, a gain of eight pounds in seven months. By this time he had regained considerable muscular power, so that he could move both hands well, hold up his head and move his legs, although he could not walk without support. It was at this time that Coley first saw the child and that Dr. James Ewing examined the original slides. Ewing stated that the growth was "unquestionably a malignant tumor which might very well be called a sarcoma. . . I am inclined to think it is either an endothelioma secondary to the cerebral growth, or possibly a neurocytoma derived from misplaced nerve tissue in the cranium." Cushing and Wolbach noted that this statement indicated that "the view still prevailed that there had actually been an intercranial process and that the local lesion in the back was not the sole cause of the clinical picture." (11) On March 19, 1912 Dr. Foster Kennedy, of

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

New York City, made a careful neurological examination of the child and reported:

"On examination the child shows marked cerebellar attitude of the head, though the attitude referable to one lobe is not constant. Frequently there is a marked tremor of the head, precisely of the same character as that seen in advanced cases of disseminated sclerosis of the cerebellar or medullary type, or of advanced cases of Friedreich's ataxia. The pupils are brisk, the light and accommodation equal, central and regular in outline. There is no ptosis. There is marked nystagmus on lateral conjugate movement, either to the right or to the left. Query, weakness of the left sixth nerve. Jaw deviates always to the right, therefore, query, right motor fifth nerve affected. The masseter on the right side contracts less well than that on the left. Child apparently hears on both sides. There is obviously no defective vision, no change in the sensibility of the face, nor is there any facial palsy. The tongue comes out straight, and there is no tremor or wasting. Palate normal.

"Upper Extremities. There is marked motor ataxia in both arms of definitely cerebellar type. (N.B. This ataxia is not in any way dependent on any sensory defect.) Diadochokinesia right and left. The arms are very strong for all movements. There is no wasting. No paralysis in the legs. All movements can be performed, but the ataxia manifested in the arms is present in the lower limbs also. The sensory condition is everywhere normal, that is to say, the child appreciates pin-prick, touch and temperature everywhere. *There is no segment of anesthesia or hyperesthesia in any way corresponding to the situation of the tumor in the mid-dorsal region.*

"Reflexes. Arm jerks normal. Abdominal reflexes right and left, present and equal. Knee jerks increased equally. Double extensor responses. Owing to inattention of the child combined with gross nystagmoid movement of the eyeballs, it was difficult to get a clear view of the optic disks. The veins in each ocular fundus were very large. Outer edges of disks were seen in glimpses and were apparently clear, and did not present the sinuosity of outline nor the blurring usually seen after the subsidence of a neuritic process.

"We are told that the child has improved very greatly in the past six months not only as regards weight and general nutrition, but in regard to power and ability to perform movement. It is obvious, however, that there is still a gross cerebellar lesion." (11)

Cushing and Wolbach concluded: "These notes made by a highly competent observer surely indicate that the cerebellar symptoms at the time were predominant and that the spinal paraplegia had largely disappeared. Did the story end here, one might well enough assume that the symptoms had been produced, as Dr. Ewing's qualifying remark suggested, by one of the common tumors (medulloblastomas) of the fourth ventricle which had inoculated the cerebrospinal spaces and caused a spinal implantation with paraplegia, which in certain rare cases is known to disappear spontaneously.

"It may be pointed out, however, the child was then under 3 years of age (2 years, 9 months, to be exact); also that the reflex movements of the lower extremities in transverse lesions of the cord were at that time imperfectly understood, and even today when observed in infants may be difficult to distinguish from spontaneous movements. It would appear, nevertheless, that the intracranial and cerebellar symptoms were more pronounced at the time than were those referable to the spine." (11)

Although the child had improved markedly in the previous nine months, Kennedy regarded the prognosis as hopeless, and was so interested in the case that he offered to go to Virginia to do the autopsy. The child's father con-

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

tinued the toxin injections with intervals of rest, and further improvement occurred. He wrote Coley on November 23, 1912: "There is no indication of return of the growth on the back, and his general health is good, his mind seems bright. He has never regained the use of his legs, though he can move them better and they show no sign of wasting or contractions. His eye symptoms are also better and he is hearty and well developed, does not seem to suffer any and is bright and full of life." (10) During 1912 a 4 minim dose of toxins was given every third day. Cushing and Wolbach noted that during the first year in which toxin therapy was administered "the cerebellar symptoms, if such they were, seem to have fallen into the background of the picture." (11) The toxins were continued with intervals of rest for a total of over two years.

Clinical Course: For the ensuing eight years the child, though remaining paraplegic, thrived and developed in all other respects. He acquired automatic control of the bladder and rectum, and by 1912 had learned to balance himself awkwardly on crutches. The father finally came to the conclusion that an exploratory laminectomy should be undertaken. "Hence the child was admitted to Peter Bent Brigham Hospital, Boston, Massachusetts, on May 18, 1921, 10 years after the first exploratory operation. At this time he appeared well nourished, cooperative and had *no discomforts whatsoever.*" (11)

Neurological examination on May 18, 1921 "showed absolutely no signs of involvement of the brain or upper spinal cord. There was not a trace of the nystagmus, diplopia, ptosis and so on, described in the previous history. In the back was the scar of the old operation (11, Fig. 1). This was soft and movable, and palpation revealed no evidence of an underlying tumor. The x-rays of the spine, however, showed a cloudy area representing either dense fibrous tissue or ossification at the site of the original lesion. The outlines of the laminae, spines, and transverse processes were clear and without evidence of having been involved in the disease.

"The child was powerless to move the lower extremities but the slightest stimulus served to throw them into reflex movements which strongly suggested voluntary movements and even the patient was under the impression that he had some voluntary control. He could stand alone with the support of crutches and by taking advantage of a sustained adductor spasm which held the knees together, the feet being separated and turned in. When this spasm relaxed he would fall unless supported.

"Sensation was apparently completely lost up to the level of the sixth thoracic skin-field, but the sensory tests were difficult to interpret because a pin-prick or even a light touch would evoke spontaneous reflex movements which gave sensory impressions referred by the child to his legs.

"The deep reflexes both at knee and ankle showed an easily elicited and sustained clonus. There was on both sides an active dorsal toe response to almost any form of stimulation, even such as the mere exposure of the legs by removing the bed covers. The cremasteric reflexes were active. Reflex erections were easily provoked by pricking the glans or picking up the skin of the groin. Under these circumstances the legs would flex and the bladder which could retain about 200 cc., would be emptied without sensation." (11, Figs. 2 and 3).

"Whatever may have been the condition ten years previously, certainly at this time there was nothing to be seen but the evidence of a total transverse spinal lesion at about the level of the sixth thoracic segment which corresponded to the site of the original paravertebral tumor. Moreover, the x-rays disclosed a somewhat dense shadow in the region of the former tumor which, however, did not affect the normal outlines of the adjacent laminae or trans-

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

tumor tissue. This mass encircled and constricted the meninges and cord and nerve processes. It would appear from the hospital history that no preoperative diagnosis was ventured. No lumbar puncture was performed. It would almost certainly have shown a complete block with xanthochromia." (11).

"May 21, 1921. Operation (Cushing). Laminectomy with disclosure of sharply defined extradural mass of dense non-infiltrating and non-adherent apparently communicated with the relic of the original lesion through an enlarged intervertebral foramen.

"With the position of the old cicatrix as an indication of the original tumor site, the spines and laminae of the three adjacent vertebrae were at first removed. There was no apparent lesion of the bones but, on scraping off the periosteum from the laminae of the right side, a dense scar-like tissue was encountered in the spinal muscles which was taken to be the residuum of the original lesion. On the removal of the spines and laminae, instead of the usual extradural cuffs of fatty tissue, the canal was found to be filled with the same kind of dense scar-like tissue. An incision, made into this firm tissue, was carried down to a considerable depth without disclosing dura. The tissue was quite vascular.

"Realizing that the exposure was insufficient, the additional spines and laminae of the two preaxial vertebrae were then removed. This brought into view the upper margin of the lesion with normal appearing dura headward to it. Similarly the laminectomy of an additional postaxial vertebra exposed the normal dura caudal to the lesion. It therefore extended over approximately five spinal segments.

"The exposed growth was then tilted up and lifted by blunt dissection away from the dura to which it was not adherent. As the fairly rigid posterior shell of tumor was broken away from its lateral attachments, it was evident that it extended to the anterior aspect of the canal on the right side where it became much thinned out.

"A fragment of this intraspinal tissue was immediately examined (Wolbach) and was reported as probably a ganglioneuroma. With this suggestion of a possible seat of origin for the tumor in a posterior root ganglion, which might account for its hourglass shape by coincidental extension into the paravertebral muscles and spinal canal, the wound before closure, was reinvestigated. The extravertebral mass which had been taken to be cicatricial tissue was found to lie mainly between the laminae of the fifth and sixth thoracic segments just opposite the thickest portion of the residuum of the intraspinal growth. The two masses appeared to communicate by a narrow neck through the region of an enlarged intervertebral foramen. A fragment of the dense extra-vertebral tissue was then removed for comparison with that which had been removed from within the canal.

"Following the removal of the tumor the greatly compressed dura filled out its normal dimensions and resumed its pulsations. It was not opened. In the hope that the procedure would suffice to release the cord from its constriction and permit a return of function, if such a thing were possible after so many years of compression, the wound was closed as customary in successive layers.

"Postoperative Report. The child made an excellent recovery from the operation. Healing was perfect (11, Fig. 1). The preoperative symptoms remained unchanged at the time of his discharge." (11)

Cushing wrote Coley regarding this case on May 23, 1921: "He had a very extraordinary tumor which Wolbach thinks was a ganglioneuroma. . . It is extraordinary that the lesion should have been so unmistakably benefited by your toxins." (10)

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

There was slight improvement following this operation as regards walking. However, the boy's father soon wrote Cushing that he had improved greatly and had much better sphincter control. Again in 1923 some tenotomies were performed which helped him greatly. In August 1926, five years after the laminectomy, the father reported that sphincter control had continued to improve. He added that the boy could get up, dress himself, walk around the room without a crutch, though most of the time he used one crutch; that he could "hitch his pony himself and drive around anywhere he pleased." (10, p. 209). His only illness during the next few years was appendicitis, for which an appendectomy was performed (about 1931). Early in 1951 he developed hyperthyroidism, with loss of weight, and he was given iodine, with some improvement. Later he was given a thorough check-up in Richmond, Virginia, including basal metabolism test, and was put on propylthiouracil. Thereafter he improved very much. At this time he was able to drive a car and work steadily in a drug store. During 1957 he was asked to go to the National Institutes of Health in Bethesda, Maryland, for review of his case, as they were interested in following a group of cancer patients with long survivals. They found a stone in the kidney and following operation for its removal, he developed septicemia, and later osteomyelitis of the cervical spine, but recovered. In the fall of 1958 he again developed a bladder infection and returned to the N.I.H. for treatment. The thyroid condition seemed to be normal and medication was discontinued. In December 1958 he was being maintained on Mendalamine, 1 gram t.i.d. He remained well and free from any evidence of neuroblastoma in 1970, 59 years after onset.

References: 9, 10, 11, 17, 24, 49, 54, 77.

CASE 2: Metastatic generalized neuroblastoma, confirmed by microscopic examination in 1936 by Dr. James Ewing, following biopsy of the nodule in the scapular region; the sections were reviewed in 1950 by pathologists at Memorial Center, and at the National Cancer Institute, Bethesda, Maryland.

Previous History: P.W., male, aged $8\frac{1}{2}$ months, of Frankfort, Kentucky. The child's paternal great aunt died of cancer. Onset, in March 1936, when he was about $4\frac{1}{2}$ months old his mother first noticed some lumps under the left arm, apparently in the axilla. Thereafter other nodules appeared over the body, especially on the trunk. There was frequently a slight ecchymosis preceding the appearance of new nodules. The mother believed some of these had regressed or disappeared. The baby remained in good health and apparently had no pain nor discomforts.

Surgery: A biopsy was performed of the nodule in the left lateral scapular region which was reported as "probably an adrenal neurocytoma."

Clinical Course: The baby was examined by Dr. Lloyd D. Craver on September 3, 1936 at which time he appeared healthy and films of the skull, chest and abdomen showed no distinct evidence of tumor. At numerous points about the child's trunk were soft, subcutaneous tumor nodules varying from $\frac{1}{3}$ to 3 cm. in diameter, some entirely subcutaneous, others elevated about 1 cm. above the skin. Several were slightly bluish in color. There was no ulceration or attachment of the skin. Some of the larger ones were in the right infrascapular, the left suprascapular regions and below the right thigh near the perineum. At the left flank, below the costal border a flattened nodule was felt on bimanual palpation somewhat resembling a low spleen.

Radiation: Low voltage x-ray treatments were given between September

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

3 and 10, 1936 as follows: the nodule on the right lower chest posteriorly received 163 r x 2 (160 K.V. 3 mm al. filter, 30 cm. distance, 3 cm. cone; 5 milliamperes for 5 minutes). The nodule in the right upper thigh anteriorly received 327 r (same factors except for time: 10 minutes). The left upper chest posteriorly received 163 r x 2 (same factors as the lower chest). He was admitted to Memorial Hospital on September 11, 1936. He appeared to be bright, large and very active.

Toxin Therapy (Parke Davis XIII): Injections of Coley toxins were begun on September 12, 1936, nine days after the first x-ray treatment. A total of 21 were given in 49 days intramuscularly in doses of $\frac{1}{8}$, $\frac{1}{4}$, $\frac{1}{2}$, $\frac{1}{2}$, $\frac{3}{4}$, 1, $1\frac{1}{2}$, 2, $2\frac{1}{2}$, 3, $3\frac{1}{2}$, 4, 4, $4\frac{1}{2}$, 5, $5\frac{1}{2}$, 6, $6\frac{1}{2}$, 7 and $7\frac{1}{2}$ minims. These caused febrile reactions averaging 100° - 101° F. (minimum of 99.2° , maximum 103.8° F.). No chills occurred but it was noted that the baby was cross, or restless during the reactions on several occasions, and once he had a "rash on his face." By October 8, 1936 there had been "no change in the size of the tumors."

Further Radiation: On October 17, 1936 the patient was given a radium plaque treatment of 500 mch. to the tumor on his back. It was noted that day that his "general condition was excellent." A second radium plaque treatment was given (500 mch.) on October 21, 1936 to the tumor on the upper inner right thigh at 1 cm. distance. These caused a good reaction in the skin but no definite regression in size of the tumors. On October 27, 1936 a radium plaque treatment was given to the lesion on the forehead.

Clinical Course: As Dr. Norman L. Higinbotham did not feel he should receive any further toxin therapy for another two or three months the baby was discharged on November 1, 1936. Craver stated at this time: "Clinically this disease is behaving as though it was neither radio-sensitive nor highly malignant. The subcutaneous nodules that have been treated (each with 500 mch. at 1 cm.) show no regression."

Inflammation: The baby subsequently developed a peculiar rash all about the buttocks and on one or two spots on the lower abdominal walls consisting of red areas of apparently superficial denudation of skin, rather clean cut, varying in diameter from 0.5 cm. to 2 cm.; suggestion of impetigo was made by the local physician and a salve containing mercury was used. At examination on November 17, 1936 the lesions seemed somewhat softer and flatter. The large nodule in the right interscapular region seemed to have remained stationary or was perhaps a little smaller and the one on the forehead was slightly smaller. There was no evidence of new tumors and the child was in excellent condition.

Clinical Course: At examination on January 1, 1937 the child remained in excellent condition and there was no evidence of recurrence. The examining physician stated: "Apparently many of the smaller untreated nodules have disappeared." At examination on March 29, 1937 the baby remained in excellent condition. However, the mother had recently noticed two new lumps; one in left axilla and one over the left scapular region. They were at first discolored blue, but the color soon disappeared. On that date each lump was only a small movable subcutaneous soft nodule 0.5 cm. in diameter. There was no other evidence of disease. At examination on June 25, 1937 when the baby was 18 months old both Ewing and Stewart raised the question of the baby being somewhat precocious: he had 16 teeth. Craver did not agree. By October 8, 1937 all evidence of disease had regressed completely. The boy

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

had been healthy except for a tendency to large tonsils and stuffiness in cold weather.

Infection: In December 1937, the child had bronchopneumonia from which he recovered completely.

Clinical Course: In December 1938, a tonsillectomy was performed. The tonsils were said to be "badly diseased." At this time the child weighed 40 pounds.

Further Infections: During May 1939 he had mumps. That fall he had a "croupy cough."

Clinical Course: A small movable subcutaneous mass was discovered over the left scapula. The child was readmitted on October 22, 1939 for excision of this nodule for diagnostic purposes. Examination on admission revealed an unusually well developed and well nourished child who did not appear ill. The nodule was removed and showed only fat. During 1941 a pea-sized nodule appeared in the right chest or abdominal wall which disappeared spontaneously.

Infection and Further Inflammation: In January 1942 he had measles. He also had poison ivy annually.

Clinical Course: On May 25, 1942 the mother noticed small nodules in the right and left occipital regions. The child had continued to have palpable posterior cervical and inguinal nodes. When seen on August 25, 1947 he was 5 feet 2½ inches in height and weighed 127 pounds. The examining physician reported: "He has been in very good health except for poison ivy annually, evidence of which is present now. Mother noted mass in right lumbar region . . . believed to be of a few weeks duration." He was then in the sixth grade at school. He did not exercise very much; he was not a behavior problem. Examination revealed a very developed, rather obese boy of 12, with at least average intelligence. There were several lesions of poison ivy on the right hand and leg. Pubic hair was appearing. There was a nodule about 1 cm. in diameter on the right lumbar region 5 cm. lateral to the mid-vertebral line, which was not movable.

Further Infections: The boy then had "five bouts of pneumonia, none of which were very serious."

Clinical Course: Thereafter he was well until 1951 when he developed hypertension (at one time to 180). He also complained of headaches at intervals. He was considered a hypochondriac by his mother. He was not particularly interested in athletics and was only moderately "sociable." There was considerable disparity between his positive achievements and his poorer ones. His memory was very capricious. Examination on January 4, 1954 showed a fairly well developed, well nourished boy of 18 whose responses while intelligent were somewhat variable as to perceptiveness. Craver and Dargeon felt that the question of hypertension should be more thoroughly explored, especially with the consideration of a pheochromocytoma. There was hypertension in the paternal branch of the family. (Apparently nothing was done during the next two years.) The patient was admitted to the Clinical Center of the National Institute of Health in August 1956. His father had died of hypertensive cardiovascular disease a few months previously and at this time the patient became interested in his own heart problem, having been hypertensive himself for five years. His only other symptom on admission was parox-

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

ysmal headaches, associated with excitement. The hypertension had been paroxysmal in the past. These episodes were associated with palpitation, headaches at times, and characteristically a low back pain. There had been no anginal complications or symptoms. The patient had been seen in another hospital where a flat plate of the abdomen revealed an area of calcification of the right suprarenal region. The question of whether or not this could have been a pheochromocytoma was raised and led to his admission to the National Cancer Institute. Examination on admission revealed an area of post-radiation fibrosis and a telangiectasia situated in the mid-frontal region of the scalp, the right lower dorsal region of the back and the inner aspect of the thigh. In addition, there was a 3 x 4 cm. firm mass in the subcutaneous tissues of the right flank. There was one area in the mid-lower lumbar region that was tan-brown in color resembling a café-au-lait spot. His blood pressure on admission measured 160/90 in both arms. Blood and urine catechols were within normal limits.

Surgery: An excisional biopsy of the subcutaneous mass in the right flank was performed. *Histologically this proved to be a ganglioneuroma.* Intravenous pyelograms revealed the presence of a large mass partially calcified in the region of the right adrenal. This distorted the collecting system of the right kidney by rotating it laterally and inferiorly, but did not involve the kidney itself. On August 23, 1956 this area was explored, revealing a mass 12 x 10 x 8 cm. in size. The mass separated a flattened atrophic appearing adrenal from the normal appearing kidney. The mass contained about 1500 cc. of old bloody fluid. The solid tumor in the wall had the same gross appearance as the subcutaneous tumor removed from the right flank. The solid portion of this tumor grew into and could not be separated from the inferior vena cava over an area 4 cm. long. It extended around the posterior surface of the vena cava for a distance of 3 cm. Frozen section of the material removed from the adherent portion of the tumor showed it to be an adult type of ganglioneuroma. On this basis it did not seem advisable to run the added risk of resecting a portion of the vena cava which would be necessary in order to completely excise the tumor. Dr. Louis Thomas sent Dr. Frank Foote sections from the suprarenal mass. It was also noted that the subcutaneous tissue directly over the previous radiation area of the back also contained a ganglioneuroma.

Clinical Course: The wounds healed and the patient did very well. He entered a college in Maryland that autumn. He remained in good health when seen at the National Cancer Institute on July 19, 1957, "at which time he was free from evidence of neoplasm. On September 13, 1957 he was reported as having a spontaneous pneumothorax of unknown etiology. This apparently resorbed without incident and was not related to his tumor." He remained under periodic observation in the outpatient department of the National Cancer Institute. In November-December 1958 he developed abdominal pains associated with constipation. He was readmitted to the hospital in December 1958 at which time he had a 10 x 12 cm. mass palpable in the left upper quadrant of the abdomen. In addition x-ray studies revealed an area of increased density in the upper thoracic region along the right mediastinum and a fusiform mass at the level of the attachment of the left diaphragm with the aorta.

Further Surgery: He was reexplored on February 9, 1959. The abdominal mass was found to be retroperitoneal covered by the splenic flexure of the colon, adjacent to the aorta, medial to the ureter, and just below the left kidney. The mass had a very vascular capsule but did not have a definite

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

pedicle. It was not a lymph node metastasis. This mass was removed. The paravertebral fusiform mass extending under the diaphragm was outlined and believed to be inoperable. The mass along the right side of the vena cava was palpated and found to be slightly enlarged from what was left behind at the time of surgery in August 1956. Several smaller nodules were palpable along the abdominal aorta, but were not believed to be significant. Preliminary histologic studies of the 12 x 18 x 6 cm. mass removed from the left retroperitoneal area revealed it to be a ganglioneuroblastoma. There was no evidence that this was an implant or metastasis from the tumor removed from the right suprarenal area in 1956.

Clinical Course: Labile hypertension persisted. The patient was readmitted to the National Cancer Institute in 1961, at the age of 25, six years after incomplete removal of the para-adrenal tumor. Terminally there was evidence of recurrence. Death occurred during this hospitalization, over 25 years after onset of the neuroblastoma. Urine at this time contained increasing quantities of the metabolites of norepinephrine, and the tumor tissue at autopsy also contained large amounts of it. (46)

Comment: In this unpromising case the effects of small amounts of low voltage x-ray, followed immediately by toxin therapy for seven weeks and further small amounts of radiation appear to have been reinforced by the beneficial effects of the infectious diseases, infected tonsils and inflammatory episodes. As a result some of the nodules of this malignant neuroblastoma disappeared, while the lesion in the right flank and the larger mass in the region of the right adrenal did not regress, but matured into a benign ganglioneuroma and remained entirely quiescent for 20 years. Following two surgical procedures in 1956, the disease reactivated and finally caused death over 25 years after onset. (For excellent microphotos see 24).

References: 24; 44; 46; 49; 54.

The following six cases received inadequate toxin therapy combined with large amounts of radiation. The disease was not controlled.

CASE 3: Inoperable neuroblastoma with multiple tiny subcutaneous nodules confirmed by microscopic examination after biopsy of one of the nodules at Memorial Hospital by Dr. Fred Stewart. Sections were later reviewed by several other pathologists who concurred with the diagnosis.

Previous History: Male infant a few months old.

Surgery: One of the subcutaneous lesions was biopsied.

Radiation: Small radium plaques were applied to one or two of the nodules to see if they exhibited enough sensitization to warrant whole body irradiation. They did not.

Toxin Therapy (Parke Davis XIII): He also received a few injections of toxins (no details are available as to technique).

Clinical Course: After being discharged with a hopeless prognosis, the nodules began to disappear. Complete regression occurred and the child remained in perfect health in 1952, more than five years later.

Reference: 66a.

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

CASE 4: Inoperable recurrent neuroblastoma of the left thigh, confirmed by microscopic examination by Dr. F.W. Foote, Jr., pathologist at Memorial Hospital, of tissue removed at each of the three operations.

Previous History: O.W., male, age 3, of Watsontown, Pennsylvania. The child's maternal grandmother died of cancer of the pancreas, and his maternal great aunt had skin cancer which was "cured." There was no history of tuberculosis or diabetes. A maternal great aunt became a complete invalid after the birth of her last child (paraplegia). The child's mother had several allergies which were worse in spring and summer (hay fever). She was married at 20 and the patient was born 5½ years later. The pregnancy and birth were normal, although the patient's mother stated she "had nausea for seven months, and three bad falls," also a very bad cold and an annoying cough during the sixth and seventh month of her pregnancy, during which period she lost 10 pounds. The child weighed nine pounds at birth. He was breast fed for 10½ months and gained weight rapidly. He was very alert and bright, and walked and talked before he was a year old. His mother stated that "he never slept a night through; he would laugh and play all day and cry at night. It was not temper. None of several doctors could explain it." He received the usual diphtheria and scarlet fever immunization shots beginning prior to the age of one year. He was an only child (and only grandchild). His mother took care of him until he was a year old and then she went to work and he was cared for by her parents. At about 14 months he became very hoarse without any sign of a cold. He was taken to a doctor who said that if the condition did not clear up in a week, the child should come back. It cleared up then, but would return occasionally for a day or two. He never had any contagious diseases, although he played with children who were contracting at various times measles, mumps and whooping cough. He seemed and looked very healthy. Onset, in November 1944, without any known antecedent local trauma, a lump was first noticed on the left thigh. The child was then 18 months old.

Surgery: On December 12, 1944, this was removed surgically, a wide excision was made. Further operations for recurrence were performed on November 9, 1945 and May 23, 1946.

Radiation: He also received 1200 r of deep x-ray therapy, given in two courses, from January 5 to 11, 1945 and November 16 to December 14, 1945. The disease was not controlled.

Concurrent Infection: Three days after his return home from the third operation he developed measles and had a very severe case with high fever. He had large patches, not spots, his mother stated. During this attack of measles, while changing the dressing, she noticed another recurrent mass had appeared in the incision. She stated: "It seemed to grow like wildfire from that time on."

Clinical Course: In the early summer of 1946 there was involvement of the pelvis and abdominal cavity. The patient was admitted to Memorial Hospital on August 23, 1946. Examination revealed a large tumor involving the outer aspect of the left thigh and extending through the pelvis into the left lower quadrant. The provisional diagnosis included the following possibilities: Ewing's tumor, fibrosarcoma, neuroblastoma, and rhabdomyosarcoma.

Further Radiation Given Concurrently With Further Infection, Inflammation: Further deep x-ray therapy was begun on August 26, 1946 and

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

was usually given daily August 26, 27, 28, 29, 30, 31, September 3, 6, 7, 9, 10, 11, 12, 13, 16, 20, 21, 24, 24, 25 (250 r each over the left thigh, left pelvis, anterior and posterior). On August 30, 1946 the patient had a fever of 105°F. He had no complaints except that on various occasions his eyes hurt. The tonsils were large and slightly infected. The fever was 105°F. the next day and the cause was undetermined; malaria, meningitis, streptococcal infection and pyelitis were ruled out. He had no stiff neck or headache, no abnormal pain or tenderness. His chest was clear and there was no rash or adenopathy, no lethargy. The reflexes were normal. The final diagnosis was acute pharyngitis, and a culture showed non-hemolytic streptococcus. By September 2, 1946 the child was moderately ill, his throat acutely inflamed, looking like a virus infection. He was given penicillin in beeswax, but the infection did not respond to it. The next day the tonsillar nodes were slightly but definitely enlarged. By September 16 the temperature was still elevated (102.4°F.). At this time there were four erythematous areas on the buttocks from the penicillin injections which were possibly abscesses. A transfusion was given on that day. The child had had an allergic reaction to penicillin prior to admission. He had a quite generalized rash by September 17, 1946. On September 26 he was "scratching furiously" and he had four loose stools. X-ray therapy was given during most of this febrile period. When he had received a total skin dose of 2250 r x 3 to each port the skin apparently reached its tolerance and there seemed to be some regression of the process. (This totalled 6750 r. tumor dose). On November 1, 1946 the family physician, Dr. L. M. Hoffman, reported a new nodule just above the crest of the ilium, the size of a small marble. The other nodular areas had apparently disappeared. The child was readmitted on November 27, 1946.

Toxin Therapy (Sloan Kettering Institute XIV): Injections were begun by Dr. Gordon McNeer on November 28, 1946, the initial dose being 1/100 minim given intravenously. This caused nausea, emesis and a fever of 105.8°F. The child received a total of 17 intravenous injections during the next 38 days. These usually caused marked febrile reactions (103°-106°F.) and the chills occurred at least four times lasting from 5 to 45 minutes. By December 14, 1946, two weeks after the injections were begun, McNeer reported: "Remarkable regression of mass in suprapubic region and left upper quadrant. I do not believe this can in any way be attributed to the x-ray treatment as (the) lesions showed no such response previously to x-ray therapy." The patient received x-ray therapy on December 3, 5, 9, 11, 13 combined with toxin therapy. He also had blood transfusions of 250 cc. on December 11 and 12, 1946.

Further Radiation: Further x-ray therapy was given on December 16, 18, 27, 30 and 31, a total of 10 treatments given on the days toxin injections were not given. By December 26, 1946, McNeer reported: "Suprapubic mass not palpable; left upper quadrant mass not palpable; some residual induration (umbilical); right flank mass not palpable; left thigh mass not palpable; left iliac mass not palpable." A complete skeletal x-ray examination was made on December 30, and showed no evidence of disease.

Clinical Course: The patient was allowed to go home on January 6, 1947. He was to return in a few weeks for further toxin therapy, but because of a mumps epidemic in the children's ward, no bed was obtainable. His mother stated that "on his return home he was wonderful, happy, healthy appetite, but I noticed that he tired easily. However, he gained two pounds in one week. About January 17, I noticed his breathing was shallow and rapid, at

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

times becoming almost labored. Then I noticed a lump on his back." The child was admitted to St. Luke's Hospital in New York on January 1, 1947, in great discomfort, complaining severely of pain in the abdomen. He was pale, with a hot dry skin. There was marked dullness and suppression of breath sounds throughout the lower left chest. Radiographic and fluoroscopic examination of the chest showed marked widening of the mediastinal shadow. The heart was displaced to the left side which showed homogeneous density throughout, suggesting atelectasis of the lungs, probably with some overlying fluid in the pleural space. There was no evidence of respiration fluoroscopically in the left lung. The patient was treated by supportive therapy, penicillin, transfusions, thoracentesis and sedation. The disease progressed rapidly, causing death on February 8, 1947. Post mortem examination of the chest contents were permitted. This showed metastases in both pleural cavities, mediastinum, tracheobronchial lymph nodes, and left lung; hydrothorax, bilateral; partial atelectasis, both lungs. Death occurred 26 months after onset.

References: 44, 49.

CASE 5: Neuroblastoma of the right thigh, confirmed by microscopic examination at Memorial Hospital following aspiration biopsy (on clot): "on smear alone could be neuroblastoma, Ewing tumor or reticulum cell sarcoma." Previous biopsies had been reported as "inadequate material" or as showing no evidence of tumor.

Previous History: M.G., female, aged 2 years, of Queens Village, Long Island. The baby's maternal grandmother had diabetes. She had a brother of 4½ and a sister a year old, both in good health. She was born on May 31, 1946, after an uncomplicated full term pregnancy. Delivery was spontaneous after a six-hour labor. She was not breast fed. She was in good general health until onset, in March 1948 when she had an upper respiratory infection and complained of "sore legs."

Infection: In three days she was entirely asymptomatic and remained well until July 13, 1948 when she spiked a temperature of 104°F. and was given penicillin for a red throat.

Clinical Course: Two days later a lump was felt on the anterior portion of the right thigh above the knee. Five days later the swelling seemed to decrease. However, about July 28, 1948 the swelling became markedly larger and the child was taken to the Immaculate Hospital in Jamaica. X-rays of the extremities and chest were taken and the child was referred to Dr. Theodore Miller who made a diagnosis of Ewing's tumor of the right femur. The child did not complain of any pain but she was kept off her feet during the three weeks prior to admission to Memorial Hospital on August 20, 1948. Examination at this time showed a petite, friendly, white child who did not appear to be acutely ill. There was a fusiform firm slightly tender swelling of the lower third of the right thigh. Movements of the right knee joint and hip were not limited.

Radiation: X-ray therapy was begun prior to admission and by August 20, 1948 she had received 600 r. After admission radiation was continued concomitantly with Coley toxins, a total of 1400 r being given to each of two portals.

Toxin Therapy (Parke Davis XIII): Injections were begun on August 21, 1948 and were given daily intramuscularly in very small doses for 11 days,

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

then every 48 hours for the last two injections. The dosage used was $\frac{1}{8}$, $\frac{1}{4}$, $\frac{7}{8}$, $1\frac{1}{2}$, 2, $2\frac{1}{2}$ for the next six doses, 3, $3\frac{1}{2}$ minims. None of these caused any chills, although the temperature rose to 102° - 103° F. on four occasions, 103.8° F. once, the other febrile reactions being very slight (99.5° - 101.2° F.). An aspiration biopsy was performed by Miller on August 30, 1948 and was reported by Dr. Sophia Spitz as: "Inadequate material. Faint rosette pattern suggestive of neuroblastoma." The final injection in the course was given on September 4, 1948.

Concurrent Fever: On the day the child returned home, September 4, 1948, she had a fever of 105° F. This subsided with aspirin.

Clinical Course: During the next six weeks the child was at home and the mother stated she was in better health than she had been for a year. Her activity was restricted until September 23, 1948, but thereafter she was allowed full activities. Her appetite was good. She slept well, her bowels and bladder function were good.

Surgery: She was readmitted on October 14, 1948 and an incisional biopsy was performed. A soft grayish "neoplastic" tumor was found in the marrow cavity of the right femur, at the junction of the middle and lower thirds. The tissue removed for biopsy was reported as showing "no evidence of tumor." The child was discharged on October 21, 1948. The growth apparently regressed as indicated by the x-rays.

Infection: In late June 1949 she developed varicella.

Clinical Course: It was noted in August 1949 that there had been "no change in her condition." She continued to do well until September 1949 when she had recurrent pain in the right thigh. There had been no weight gain from April to September 1949. Chest films taken at this time showed pulmonary metastases in both lungs. Examination revealed several matted firm inguinal nodes. The skin showed radiation changes in the distal half of the right thigh and a firm tender swelling of the lower part of the right upper leg in the anterior portion, overlying both condyles of the femur. The child's appetite had fluctuated with febrile episodes of 100° - 101° F (rectal).

Surgery: On September 21, 1949, an aspiration biopsy was performed by Miller. This was reported as neuroblastoma on clot.

Further Radiation: X-ray therapy was given between September 23 and October 8, 1949 (250 K.V., 300 r x 7, totalling 2100 r each to the anterior and posterior right thigh). She was also given a transfusion.

2nd Course Toxin Therapy (Parke Davis XIII): Injections were begun on September 24, 1949 and were given daily for 13 days intramuscularly in doses of $\frac{1}{10}$, $\frac{1}{5}$, $\frac{1}{2}$, 1, 2, 4, 6, 12, 16 minims. A new bottle was obtained and a dose of 3 cc. given, another bottle was then used and 4 cc. was given. This dose produced pain in the leg, a mild chill lasting 30 minutes and the maximum febrile reaction (105.2° F.). The final dose on October 6, 1949 was 4.55cc., caused a moderate chill of 105° F. and hives on both arms and the face. The maximum reaction of the first 10 doses (up to 2 cc.) was 103° F., the average being 101.8° - 102.2° F. The final dose in the course was given on October 6, 1949.

Clinical Course: The child was discharged improved on October 9, 1949, but she still had pain in her leg. She was readmitted on January 16, 1950. Three weeks previously, while crawling on the floor she complained of pain in the left knee. She was examined by Miller who found spasm and suggested rest.

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

Pain in the left leg was constant day and night prior to admission and was relieved for a few hours by codeine, and barbiturates. It seemed to start at the ankle and go up the leg. Pain was also still present in the right leg but much less than prior to treatment (x-ray and toxins). The temperature had been around 100°-102°F. The child had lost some weight. Her highest weight, in August and September 1949 had been 29 pounds. By January 1 it was 27 pounds and by January 18 it was 25¾.

Further Toxin Therapy (Parke Davis XIII): Injections were resumed on January 17, 1950, and were given daily for 12 days by the intramuscular route in doses of 0.1, 0.3, 0.5, 0.75, 1, 2, 2, 2, 2.5, 3, 2.5, 4 cc. These caused only four febrile reactions of 103°-104.6°F., the others being from 100.8° to 102.2°F. Slight chills occurred briefly after three doses and lasted 45 minutes on one occasion. After only four days' treatment it was noted that the child appeared much better and was eating well. It was noted after the last four doses that she complained of severe pain in the back.

Transfusions: Transfusions were given on February 2 and 3, 1950. These were administered with difficulty due to lack of cooperation.

Further Radiation: X-ray therapy was given over the left tibia between February 3 and 17, 1950 (250 K.V., 300 r each, totalling 2100 r.) Between February 6 and 18, 1950, x-ray therapy was also given over the lumbodorsal spine as x-ray examination had revealed destruction of the body of the 11th dorsal vertebra with about 75% collapse. This area received 250 K.V., 300 r each, totalling 1800 r. During hospitalization it was felt that at times there was an emotional component to the recurrence of pain which was usually during the evening and night only. She also had occasional involuntary micturition prior to discharge, which had been attributed to peevishness until x-ray examinations had revealed metastases to the 11th dorsal vertebra. On February 5, 1950 after two or three days at home she developed paraplegia with incontinence of urine and extreme constipation. (During this period she was receiving therapy to the spine as an out-patient). By February 16, there was edema of the lower extremities, and almost constant pain especially in the back and lower extremities. The child was readmitted on February 16, appearing chronically ill and in pain (whenever either leg was moved she cried out in pain). Examination revealed definite paralysis of the right lower extremity and probable marked paralysis of the left leg. The anal sphincter was atonic, the bladder was palpable. Radiation was completed on February 18, 1950.

Chemotherapy: Sloan-Kettering 1133 was administered (a substitute nitrogen mustard) on February 18, 19, 20, 21, 24, 25, 28, 1950 in doses of 2 mg. to 2.5 mg. in H₂O (by mouth). The general condition appeared to be less good on March 7, 1950. The child complained of headaches and pain in the back of an indefinite nature. The liver was enlarged about 4 to 5 cm. below the costal margin. Four more doses of S.K. 1133 were given in doses of 2.5 mg. a day. By March 13, 1950 the child had received a total of 25 mg. of S.K. 1133, which was reported to have had no beneficial effect on the neuroblastoma. The disease progressed rapidly causing death on April 22, 1950, 25 months after onset.

Comment: Compare result in this case with Case 1 in which toxins were given alone and continued steadily for a longer period. This child had only three brief courses given during and following heavy radiation.

References: 44.

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

CASE 6: Metastatic neuroblastoma of the left femur, confirmed by microscopic examination by Dr. Fred W. Stewart following biopsy on November 8, 1951 (51-15374). The diagnosis following aspiration biopsy on May 15, 1951 had been reticulum cell sarcoma (51-7692).

Previous History: J.M., male, aged 14, of Brooklyn, N.Y. The boy's father had died of heart disease. He was an only child. He had his tonsils and adenoids removed at the age of 18 months. He had a streptococcus throat for which he was hospitalized at the age of three years. He also had asthma as a child. He fractured his left upper femur at the age of five and had it in traction five or six weeks. At the age of 7 and 11 he fractured his left forearm. Onset, about the middle of April 1951, he first developed a dull steady pain over the lateral aspect of the lower left thigh. At this time he noticed a local swelling.

Heat: The day after his local physician was consulted and he administered three diathermy treatments, with relief of symptoms. Two weeks later when pain recurred the boy received a second course of diathermy with further improvement in the pain and some diminution in the swelling.

Clinical Course: On May 10, 1951 marked pain recurred, being especially severe at night, and the patient was referred to St. Catherine's Hospital in Brooklyn, where x-rays were taken. The patient was then referred to Dr. Bradley L. Coley and was admitted to Memorial Hospital on May 15, 1951. Examination on admission revealed a well-developed, well-nourished (obese) adolescent white male, in no acute distress. (His weight was 187 pounds, and had been gradually increasing). He was alert, cooperative and intelligent. There was fullness in the distal part of the left thigh. The preliminary clinical diagnosis was osteogenic sarcoma. X-ray examination was reported as showing a lesion in the distal femur 18 cm. in length which was "regarded as a periosteal fibrosarcoma or possibly as an aneurysmal giant cell tumor." Chest films were negative.

Combined Radiation and Toxin Therapy (SKI XIV): X-ray therapy was given to the left thigh between May 18 and June 2, 1951 (1000 K.V., 316 r each, totalling 2092 r to posterior and anterior portals). This was calculated is a tumor dose of 3000 r. Injections were begun on the same day as x-ray therapy and given daily for 15 days intravenously in doses of 1/100, 1/50, 1/30, 1/15, 1/3, 2/3, 1/3, 2 1/3, 3 1/3, 4 1/2, 6, 7 2/3, 9 1/2 and 11 minims. These caused febrile reactions averaging 104.8°-105.4°F. (minimum 104.2°F., maximum 106.2°F.). There was also headache, and occasionally nausea and emesis during the reactions.

Clinical Course: The boy was discharged on June 2, 1951. The skin was in good condition, and he had full range of motion without pain. He was told that he could do mild exercise such as swimming and walking. He remained in excellent condition until September 4, 1951 when he developed pain in the treated knee. Physical examination that day revealed no objective findings. X-rays showed continued healing. The boy was advised to rest. He was again seen on September 12, 1951 and again showed no evidence of disease. The pain appeared to be muscular and came on following an attack of *grippe*. The patient was readmitted because of continuing pain in the antero-lateral aspect of the lower left thigh. Examination on readmission showed an obvious swelling and comparative measurements showed a 4 cm. difference at the suprapatellar level. This had not been present two weeks previously. An aspiration biopsy was performed on October 1, 1951.

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

Further Toxin Therapy (Sloan Kettering XIV): Injections were resumed on October 2, 1951 and 18 were given in 20 days, all but one intravenously in doses of 1/40, 1/20, 1/15, 1/7, 1/2, 1, 2, 3, 4, 5, 6, 7, 8½, 9½, 10½, 11½, 12½. The 13th injection (15 minims) was given into the tumor and caused no chill and slight febrile reaction, 100.2°F. The febrile reactions from intravenous therapy averaged 104.6°F. to 105°F. (minimum 103°F., maximum 105.6°F.) with chills lasting 20 to 120 minutes occurring after all but one of the intravenous injections.

Radiation: X-ray therapy was begun on October 23, 1951 and was given to the left anterior and posterior thigh (1000 K.V., 348 r each, totalling 2088 r to each portal). The lateral femur received one treatment on November 7, 1951, 369 r. It was noted on October 24, 1951 that the patient's mother continued to interfere with his progress and attempted to direct all procedures. (Actually she was desperately worried about the child, as her life was centered about him). The patient complained of pain only during visiting hours, and the mother's daily calls were becoming quite irritating. Measurements taken on November 2, 1951 showed a definite slight decrease in the size of the tumor in the femur. At the time of his discharge on November 8, 1951 it was noted by Coley that his appearance suggested there was probably disease elsewhere and his enlarged liver suggested that the organ might be involved.

Clinical Course: On November 26, 1951 the patient's mother called and stated he was complaining of trouble in his skull and that he had a lump on his skull. Physical examination by Coley revealed no evidence of irregularity of the contour of the calvarium. X-ray examination was also negative. At examination on December 27, 1951 Coley reported that the affected limb at the suprapatellar level measured 0.5 cm. less than the normal one, a decrease of 5 cm. in a period of three months. Coley added: "the tumor has certainly responded remarkably to the recent x-ray treatment. Patient has surprisingly little symptoms, gets about well on crutches and has a good appetite. He looks well although perhaps a trifle anemic." No further treatment was given. The patient died on July 30, 1952, "after months of unbearable pain." This was 15 months after onset.

Comment: This patient received only two courses of toxin therapy totalling 35 days given during radiation (totalling over 7500 r).

References: 44.

CASE 7: Metastatic neuroblastoma was the final diagnosis in this case, although it was first regarded as a reticulum cell sarcoma of the right scapula, based on microscopic examination by Dr. A. Purdy Stout following aspiration and incisional biopsies. Dr. Henry L. Jaffe also examined these sections and reported: "I believe. . . is suffering from a malignant tumor of the scapula which is rather difficult to pigeon-hole cytologically. I do not believe it represents a reticulum cell sarcoma. It seems to me in view of his persistent cough that there may be tumor in the lungs or somewhere else within the thoracic cavity. There is no absolute certainty that the tumor in the scapula is a primary tumor. . ." Dr. Fred W. Stewart favored plasmacytoma from examination of the aspiration and incisional biopsy tissue, but stated that a chondroblastic lesion could not be eliminated. Later Stewart reviewed the case and stated it was a metastatic neuroblastoma."

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

Previous History: M.M., Jewish male, aged 31, a dentist, of New York City. The patient's mother had diabetes, his father died of heart disease. Two uncles had cancer, one of the lung, one of the face. The family history was negative for tuberculosis. The patient had bronchopneumonia in 1942, and an appendectomy in 1944. Onset, in September 1950 he first noticed vague pains in the posterior right shoulder. These lasted several days and then subsided.

Heat: In June 1951 the patient had a severe attack of this shoulder pain which limited motion of the arm. He was treated twice weekly for 10 weeks with procaine injections (regional procaine nerve block) with moderate relief. Shortly after these injections were stopped, about August 30, 1951, he first noticed a swelling above the right scapula. X-ray examination was made about September 12, 1951 which revealed a lesion of the superior border of the right scapula. This swelling progressively enlarged. Physical examination on admission to Memorial Hospital on September 19, 1951, was negative except for a definite firmness approximately 4 x 6 cm. in diameter which appeared to be fixed to the scapula. It was not hot, tender or fluctuant. The overlying skin was not fixed or red. Motion of the right arm was limited only as regards raising it behind his back. The patient was well-developed and well-nourished. He stated he had had a marked dry cough for two weeks prior to admission. The provisional diagnosis was eosinophilic granuloma due to the long duration of symptoms, or chondrosarcoma.

Surgery: An aspiration biopsy was performed by Dr. Bradley L. Coley on September 20, 1951. The tissue was reported by Sunderland as being suggestive of plasma cell myeloma. Sternal marrow studies were made and showed no evidence of plasma cell myeloma. An incisional biopsy was performed by Coley on September 25, 1951. The tissue was examined by Stewart and Jaffee, and both regarded it as probably a reticulum cell sarcoma.

Radiation and Concurrent Toxin Therapy (S.K.I. XIV): X-ray therapy (1000 K.V.) was given between September 29 and October 20, 1951. The whole scapula was treated through two tangential ports, medial and lateral, a total tumor dose of 4184 r being delivered in this period. The patient tolerated the radiation very well. At the end of treatment there was a light erythema. Injections of Coley toxins were begun on October 1, 1951 (two days after the first x-ray treatment) and were given daily concurrently with radiation for 16 days intravenously in doses of 1/80, 1/30, 1/15, 1/10, 1/10, 1/3, 2/3, 1 1/4, 2, 3, 4, 5, 6, 7, 8, 8 minims. The febrile reactions averaged 104.6°F. to 105.6°F. (maximum 107°F. following the final dose). Chills occurred lasting 5 to 30 minutes and usually started within an hour after injection. Occasionally the patient was nauseated or vomited during the reaction. By October 3, 1951 after the third injection, the response was regarded as "satisfactory, with slight diminution in size of the scapular tumor." During the reaction to his toxins injection he developed paroxysms of coughing which required codeine for relief. By October 11, 1951 he had received 1650 r to the right shoulder. On October 13, 1951 it was noted that the pain had largely but not completely subsided. On October 16, it was noted that there had been "obvious regression of tumor," and that the general status was satisfactory. On that day he had an excessive febrile reaction to his toxin injection (107°F.) from a dose of 5 minims given intravenously. Therefore it was decided to discontinue toxin therapy and to allow the patient to have his last four x-ray treatments as an out-patient. He was discharged on October 17, 1951.

Clinical Course: At examination on October 24, 1951 it was noted that there had been 80 per cent regression of the tumor mass in the scapula and relief of pain. He had no complaints and was eating and sleeping soundly without medication. His general condition was good. He returned to work and on October 31, 1951 stated that he had a vague indefinite sort of pain, mainly discomfort in the region of the scapula and shoulder since resuming work. He was reassured by Coley. On November 7, 1951 he again stated that he could not work without pain, but "when . . . loafing he had no trouble." Examination that day showed still further diminution of the fullness beneath the scar over the right suprascapular region. The general condition was excellent. By November 21, 1951 the swelling had completely disappeared so that the affected scapula presented a normal appearance. He continued to have slight vague pains in the whole shoulder region while working. Coley felt these symptoms were not significant. X-ray examination of the right scapula on December 12, 1951 revealed considerable change: "increase in density in the area of destruction and the borders now appeared well-defined and delimited. The appearance was consistent with healing following treatment of a reticulum cell sarcoma (100-271)." He appeared asymptomatic on February 6, 1952, but when seen on February 20, by Coley he stated he had had some pain in the affected shoulder for a week. Coley noted that his range of motion was improving and stated: "I can see nothing on inspection or feel anything on palpation that suggests local activity here and the films made two weeks ago were indicative of improvement rather than otherwise." He was again seen by Coley the next day having called twice the previous evening on account of the persistent pain and low-grade fever. The pain was located right in the supraclavicular area and had recently increased in severity. Physical examination on February 22, 1952 revealed only the slightest suggestion of fullness in the treated area, particularly the upper portion. X-rays taken on February 6, 1952 by Dr. Pearson had been reported as "favorable." However, Coley asked Dr. Norman Higinbotham to see him in consultation on February 26, at which time the patient stated that the pain was now "requiring empirin and codeine practically every night" for relief. He called attention to a swelling, which was confirmed by palpation by Higinbotham, that was present in the supraspinous fossa just above the biopsy scar. This was slightly tender and the mass was fixed. From these findings Higinbotham suspected local recurrence after radiation therapy that should have been adequate for reticulum cell sarcoma. He approved of Coley's decision to perform an aspiration biopsy. Whether or not the biopsy revealed tumor, he felt that a scapulectomy should be seriously considered on the basis of symptomatology and physical findings. He added: "I have always leaned toward a diagnosis of reticulum cell sarcoma in this case. However, there was considerable equivocation amongst pathologists as to the exact nature of this tumor and for this reason I suspect it is certainly not a typical reticulum cell, and may not be a reticulum cell at all. If it were the usual type I would have anticipated complete regression for a long period of time following the adequate therapy given." Therefore instead of further radiation, he believed scapulectomy was probably the best method of treatment at that time. The patient was readmitted on March 2, 1952. Examination on admission revealed a firm hard tumor mass over the right suprascapular region which could not definitely be measured. X-ray examination showed a lytic lesion over the right supraspinous region and spinous process. The patient appeared to be well nourished and healthy.

Surgery: A right scapulectomy was performed by Coley and Higinbotham on March 3, 1952. Stewart examined the specimen and reported it was "metas-

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

tatic neuroblastoma." The gross specimen was reported as follows by Dr. C.L. Butler:

"Arising in the region of the scapula is a tumor apparently involving the scapula extending outward in both the supraspinous and infraspinous areas and also extending beneath the periosteum on the central surface of the scapula. The tumor involves the bone of both the spinous process and the body of the scapula widening it at the upper margin to a maximum width of 1.7 cm. in thickness. This upper margin of bone shows an irregular trabecular pattern with some osteoblastic and sclerotic areas and the marrow filled with a soft greyish yellow tumor tissue. . . (having) . . . the consistency of a firm lymph node. . . (and extending) outward to involve the muscle adjacent to the tumor. The glenoid fossa is lined by smooth grossly normal articular cartilage. . . The tumor is in most areas well demarcated from the muscles; in some portions in the supra- and infraspinous areas there is apparent slight infiltration. . . However, the remainder of the muscle appears grossly normal and no separate foci of tumor are noted either in the muscle or attached fat or tendinous tissue." A total of 11 sections were prepared from the specimen (52-3556).

On March 5, 1952 he first complained of slight tenderness over the right groin, which was better the next day.

Further Toxin Therapy (S.K.I. XIV): Injections of Coley toxins were begun on the seventh postoperative day and a total of 15 intravenous injections were given in 15 days, in doses of 1/60, 1/40, 1/20, 1/15, 1/10, 1/5, 1/3, 2/3, 1 1/3, 2, 2 1/2, 3, 3 1/2, 4 and 4 1/2 minims. These caused febrile reactions averaging 103.4°F. to 104.4°F. (minimum, no rise at all; maximum 105.4°F.). Chills occurred after each injection except the one on March 16, 1952 when no reaction whatever was elicited from a dose of 1/5 minim).

Clinical Course: The wound healed uneventfully and the patient was discharged on March 27, 1952 feeling extremely weak, with a guarded prognosis. He was seen in the office of Coley by April 15, 1952, and appeared to be virtually symptom-free except that he still complained of some discomfort in the abductor region of the right thigh high up near the groin. (This was first noted in the hospital chart on March 3, 1952). Coley found nothing abnormal on palpation, and stated that the symptoms were "not of long standing or very noticeable." Function of the shoulder was "about what one would expect (six weeks) following a total scapulectomy." The patient was readmitted on May 5, 1952. He stated that he had developed pains in the legs which were acute and severe and were usually associated with movement. These "occurred in small areas and would last a few days at a time." On one occasion pain developed in the left buttock of four days' duration. In mid-April 1952 the patient, while reaching high, developed "a kink in his back," and could not bend over. This disappeared in about three days. A week later he developed pain in the right ankle, which remained more or less constant, a dull aching of a chronic nature. This required hypnotics for sleep. He then developed a dull constant pain in the right thigh and calf and occasionally the right ankle. On May 1, 1952 he developed paresthesia of the lateral aspect of the right foot lasting two days. On May 3, he developed lumbago lasting 12 hours. On May 10, 1952 he developed a "kink" in the inner aspect of the left thigh in the pelvic area lasting 2 1/2 days. On May 15, 1952, on readmission, he had pain in the left thigh, tenderness in the left calf and numbness in the lateral aspect of the left foot. There was an area on the left buttock which was sensitive to touch. The right and left sacroiliac joints were also sensitive. The patient

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

stated he had limited motion of the hip joints which was considered as probably voluntary due to pain on motion.

Concurrent Fever: He also stated that he had had a spiking temperature of 101.°F. every few days for the previous few weeks, no chills, nausea or headaches. On May 14, 1952 the temperature spiked to 101.6°F. On May 15, 1952, the case was reviewed by Dr. H.J. Tagnon, who noted that the pain moved from one place to another, being at that time in the left groin, left calf, right ankle and lower back. General neurological examination, including mobility of all the limbs and face, was negative. All tendon reflexes were present and equal. The liver and spleen were not palpable. On palpation muscle masses in the left calf were tender, also on palpation the lower gluteal muscles posteriorly on both sides were tender. Elastic nodules of the consistency of tendon, were palpable in the gluteal muscles in the sacral region bilaterally and were very tender. Palpation and percussion of bone in tender areas were negative for pain. Pain seemed limited to the soft tissues. Tagnon stated that if there was no roentgenologic evidence of bone tumor, the possibility of Cocksackie virus myositis should be considered. X-rays were then taken and revealed disseminated disease in the chest, femora, pelvis — quite widespread. On May 22, 1952 Stewart reviewed the sections and stated he believed the patient had neuroblastoma.

Further Radiation: Between May 20, and June 19, 1952 super voltage x-ray therapy (1000 K.V.) was administered to the left paravertebral gutter (T8-12, anterior and posterior), 350 r each, totalling 3100 r to the anterior and 3050 r to the posterior portal. (These included both the metastases in the 4th rib and the area in the sternum). The pelvis was given 2850 r anteriorly and 2800 r posteriorly. There was some improvement evident by June 4, 1952. The patient was discharged on May 24, 1952 and continued his radiation as an outpatient.

Clinical Course: He was readmitted on June 23, 1952. He stated he had recently had tenderness in the tempero-occipital area and in the scapular vertebral border. He did not appear to be in distress and was well developed and well nourished. In the left fourth rib area, in the anterior axillary and nipple area there was a diffuse but slight enlargement of the rib. There was a tender area along the vertebral border of the scapula. There was a suggestion of a deeply situated paravertebral mass in the left abdomen, but this was quite indefinite. Firm non-tender nodes were palpable in both axillae.

Chemotherapy: The patient was given HN₂ (urethane), intravenously (the total dose was 28.4 mg.).

Clinical Course: He was discharged on June 28, 1952. During the first two weeks of July he complained of pain in the base of the neck on the left side. X-ray examination on July 10, 1952 showed that the posterior inferior portion of the body of C-6 appeared slightly radiolucent and a portion of the articular cortex could not be identified, indicating the possibility of a small, ill-defined metastasis in this region. At this time the patient looked very anemic, and his hemoglobin was found to be 9 grams. On July 16, 1952 a small mass in the soft parts of the right arm in the region of the biceps was noted. Three blood transfusions were given prior to July 23, 1952 and the patient looked a great deal better and felt better by that date.

Further Radiation: X-ray treatment was given over the left malar bone (250 K.V., 300 r x 5) between August 12 and 19, 1952. The right temporal region received 1200 r (300 r x 4); the right fifth rib received 1600 r (400 x 4)

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

and the right supraclavicular region received 1200 r (400 x 3). This radiation was completed by August 29, 1952.

Clinical Course: At examination on August 26, 1952, the chief complaint was extreme fatigability and weakness, moderate malaise and anorexia. He had gained four or five pounds since his discharge two months previously. He also complained of rather dull continuous pain in the right shoulder which had not responded to radiation therapy.

Chemotherapy: Amino-anfol therapy was begun on August 26, 1952. The initial dose was 20 mg. and thereafter 40 mg. was given daily. He had two bouts of nausea and vomiting between August 29 and September 2, 1952. He stated that pain in the right anterior rib area was better, but for three days he had noticed "pain of left shoulder radiating down occasionally to the finger tips with some restriction of motion." This was controlled by codeine and aspirin, and on September 2 appeared as more of a dull ache. The white cell count was beginning to fall. On September 14, 1952 the patient had less pain in the shoulder, but that afternoon developed an intense pain at the base of the occiput in the mid-line. If he remained perfectly still the pain was not present. The pain was less severe next day and gradually it subsided. The dose of amino-anfol was increased to 60 mg. daily. On September 23 the patient stated he felt better than he had for several weeks. He did complain of some pain in the left knee recurring at periodic intervals which disappeared when the weather was less damp. He continued on 60 mg. of amino-anfol daily until November 8, 1952 when the dose was raised to 80 mg.

Further Radiation: X-ray therapy was given to the right hip (250 K.V., 500 r x 3); to the posterior right femur totalling 700 r; to the left hip posterior, 500 r, anterior 300 r; to the right shoulder 300 r; to the left chest posterior 600 r; to the left femur, anterior and posterior 250 r each. This was completed on November 21, 1952.

Clinical Course: The patient continued to feel improved during November, but by November 25, 1952 was spending most of his time in bed. (There had been an increased amount of nausea and vomiting since the dose of antifolic had been increased). At this time the patient had double vision, complained of pain in the region of the left orbit, pain in the right shoulder, and a tender area in the lower hemithorax. The amino-anfol was discontinued in late November because of leukopenia (bone marrow showed no megaloblasts). He was readmitted on December 3, 1952. At this time he had pain in the right scapular region where there was a hard, firm, irregular non-tender mass. The chief complaint was a generalized feeling of weakness and pain in the right shoulder except when lying on his back. He had diplopia, and moderate anorexia and bouts of pain at various metastatic sites in the skeleton, lasting one or two days. He had lost 35 pounds since onset. (His normal weight in 1950 had been 170 pounds). Examination revealed a tumor in the left orbit and upper lid which indented and displaced the globe. Transfusions were given to improve the anemia.

Further Radiation: During December 1952 palliative x-ray therapy was given to this area and to the metastases in the D-VI, first dorsal vertebra and the left parietal region, also the right lateral ribs and the right knee and the right occipital region. By December 27, 1952 the patient was completely free of pain, the diplopia had subsided even on extreme lateral gaze, though there was still some blurring of vision in O.S. The patient was discharged on De-

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

cember 27, 1952. He was readmitted on March 2, 1953 for transfusion. He had lost 15 pounds in the previous two months, but stated he had very little pain.

Hormone Therapy: Stilbesterol was administered, but caused nausea and vomiting. Therefore estrogen and androgen were given intramuscularly. By March 31, 1953 the patient was thin, anemic, almost cachectic in appearance. He had become a drug addict and he had a pathologic fracture of the right lower femur. His condition rapidly deteriorated. Death occurred on April 14, 1953, 2½ years after onset.

Comment: In this case the first course of toxins consisted of only 16 intravenous injections given in a 16-day period concomitant with heavy radiation. This case is of interest because of the difficulty in establishing the diagnosis.

References: 40.

CASE 8: Neuroblastoma first found in the left femur (probable primary site, paravertebral region). The diagnosis was only arrived at following post mortem. Earlier opinions of different pathologists following biopsy of the lesion in the femur were reported as follows: Dr. Henry L. Jaffe called it a malignant tumor but could not state with certainty whether the lesion was Ewing's sarcoma or metastatic neuroblastoma. He added: "The cancer cells are somewhat compressed in some places being rather rounded in others. There is some ossification going on in connection with the presence of the tumor, but I do not think the bone formation is indigenous to the lesion." Dr. Fred W. Stewart: "Not neuroblastoma; neither do I think it typical Ewing's. Cells too spindly and bone production itself may be neoplastic. Maybe this is proof of the relation between Ewing's and osteogenic sarcoma." (#52-1787)

Previous History: G.G., Jewish male, aged 2, of Flushing, New York. The family history was negative for cancer, allergy, metabolic disease or tuberculosis. The patient's aunt had a nervous breakdown at the age of 35. The child was born after a normal pregnancy. He had one sibling, aged 4½ years who was living and well. He weighed six pounds five ounces at birth. He had no illnesses, injuries or operation prior to onset, which occurred in January 1951 at the age of ten months. At this time pain and a limp in the left leg developed which recurred at intervals of about a week and lasted several days at first. These attacks gradually recurred at longer intervals up to several months apart, and lasted only a few hours. There was no fever or other constitutional symptoms. The pain was relieved by taking the child off his feet. The consultant noted association of periodic symptoms with active teething. On January 15, 1952 the consultant first noted tenderness in the left hip. X-ray examination was reported as showing bony destruction and production involving almost the entire shaft of the left femur, measuring 14 cm. in length and associated with parallel periosteal and endocortical erosion.

Surgery: An incisional biopsy of the lesion was performed at Kew Gardens General Hospital on January 21, 1952 and reported by Jaffe and Stewart as stated above.

Clinical Course: The patient was admitted to Memorial Hospital on January 31, 1952, a year after onset of left leg limp and pain. Physical examination on admission revealed a well-developed, well-nourished 22 month child in no apparent distress.

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

Concurrent Infection: There was bilateral tonsillar adenopathy, the lymphatics being otherwise negative. There was inflammation of the nasal mucosa, with abundant mucopurulent discharge, crusting, partial nasal obstruction, post-nasal discharge; the pillars and pharynx were inflamed. The left anterior thigh was swollen in the mid-portion. The temperature ranged from 98° to 100.2°F. during the first week.

Antibiotic Therapy: Crysticillin was given daily for four days for the acute nasopharyngitis (300,000 units intramuscularly).

Radiation and Concurrent Toxin Therapy (S.K.I. XIXV): Between January 31 and February 18, 1952 x-ray therapy was given to the left femur (1000 K.V., 2234 r anterior and 2214 r posterior). He tolerated the treatment well. Prophylactic x-ray therapy was given to the chest (1250 r each, anterior and posterior) between February 19 and March 1, 1952. Injections of Coley toxins were begun on February 10, 1952, 10 days after the first x-ray treatment and were given during x-ray therapy. The initial intravenous injection of 1/70 minim caused a febrile reaction of 102.4°F., no chill and a pulse of 152. The injections were usually given daily (14 in 17 days), increasing the dose as follows: 1/60, 1/50, 1/30, 1/15, 1/2, 1, 1 1/2, 2, 2 1/2, 3, 3 1/2, 4, 4 1/2. Chills occurred only after the last four injections, lasting 15 to 40 minutes. Febrile reactions averaged 100° to 103°F., (minimum 100.4°F., maximum 105°F. which occurred when x-ray therapy was being given to the chest). Following the final injection on February 26, 1952 the patient developed cellulitis in the upper arm at the site of the intravenous injections. This area was treated with hot soaks. He also had an upper respiratory infection at this time.

Further Antibiotic Therapy: He was given penicillin for a few days. The inflammation about the arm subsided slowly.

Clinical Course: The child was discharged on March 3, 1952. He was seen by Dr. Bradley L. Coley on March 17, 1952 who reported: "Excellent result thus far. . . parents are delighted. . . boy acts normally, runs about and plays on affected leg without difficulty." By April 14, 1952 the thigh had "attained complete normal outward appearance." The child walked, ran about and played very actively with virtually no restriction. X-ray examinations that day showed there had been a definitely favorable response to recent combined x-ray and toxin therapy. Periodic physical and x-ray examinations in May and early June showed no evidence of disease. However, on June 23, 1952 the child appeared to limp a little and the parents became panicky and brought him for another check up which revealed no evidence of limp and no changes.

Concurrent Infection: Shortly thereafter he developed measles, from which he promptly recovered.

Clinical Course: At examination on July 15, 1952 the child appeared in excellent health: "Lots of motion, runs around on leg, has no limp, has good appetite and looks robust." Physical examination revealed slight signs of enlargement of the left femur, in keeping with the x-ray examinations which revealed no evidence of disease until December 11, 1952 when Coley noted that the veins in the scalp were prominent. The child was readmitted to Memorial Hospital on December 15, 1952. Physical examination on admission revealed a well-nourished, well developed 2 3/4 year old boy with prominent scalp veins and distension of these on the forehead. He was in no distress and did not appear sick. There had been no symptoms prior to admission such as headache, emesis, restlessness, personality change or tendency to

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

bruising, also no evidence of recurrence in the femur. X-ray examination revealed osteolytic metastases in the skull.

Radiation: X-ray therapy was given over the lesions in the left and right lateral skull between December 15, and 23, 1952 (250 K.V., 225 r each, or 1125 r in air to each of the two ports). This was calculated as a tumor dose of 1485 r. The child tolerated the treatment well, although the appetite was very poor. There appeared to be no change resulting from the treatment. He was discharged on December 24, 1952.

Further Infections: He remained well until the middle of February 1953 when he developed influenza with a fever of 101.5°F.-102°F., followed by intestinal grippe and diarrhea. The whole episode lasted about 2-1/2 weeks.

Clinical Course: On February 20, 1953 the child fell off a sofa landing squarely on his back on a concrete floor. For a week thereafter he complained of pain in the buttocks. X-ray examination of the pelvis, femur and knees showed no fractures. Pain continued, but by March 17, 1953 it was difficult to determine the site of pain, which was localized only to the left side. The child refused to sit on a hard chair or to lie or sit on his left side. He also cried a great deal and one could not move or touch him. He was readmitted to Memorial Hospital on March 17, 1953. He appeared to be irritable and acutely ill with symptoms of increased intracranial pressure. He was dehydrated, had a stiff neck and could not be moved without pain. As he did not void for about 24 hours, he was catheterized. Thereafter a spinal tap was made and showed xanthochromic, clear spinal fluid with initial pressure of 120 to 170. The patient was believed to have cerebral metastasis with subarachnoid hemorrhage and aseptic meningitis.

Further Radiation: Between March 17 and 27, 1953 he received 1055 r to the entire skull.

Antibiotic Therapy: He was given terramycin originally because catheterization was necessary, and during the third week of March because of fever (102°F.). On March 28, 1953 the child complained of some pain in the left lower jaw and examination revealed the left submaxillary nodes were palpable and tender. Hot compresses were applied and the lymphadenitis subsided. On April 1, 1953 it was noted that metastasis had developed in the right side of the mandible.

Further Radiation: X-ray therapy was given to this area (800 r). On April 14, 1953 the child developed paraplegia and x-ray examination revealed collapse of the second lumbar vertebra. This area received 2560 r, followed by gradual improvement and slow return of motion of the extremities.

Chemotherapy: One dose of A-methoptherin and 6-MP was given on April 15, 1953. No further doses were given for 10 days and then from April 25 through May 20, 1953 the child received 1.25 mg. of A-methoptherin daily, 25 mg. of 6-MP daily and 25 mg. of P-164 daily.

Further Radiation and Chemotherapy: During this chemotherapy, on May 7, 1953, he was noted to have a swelling on the left side of the scalp, which was treated by x-ray therapy on May 30, 1953 (300 r). On May 27, 1953 cortisone was started, and 12.5 mg. was given daily. On June 26, when seen in the clinic, the patient complained of intermittent abdominal pain of four days duration. The cortisone and A-methoptherin were discontinued temporarily. On July 2, 1953 the cortisone was resumed (12.5 mg. daily). The child was

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

readmitted to Memorial Hospital for the fourth time on July 3, 1953, complaining of epigastric pain and anorexia of two weeks' duration. The lump on the left scalp had been increasing in size and "over-night" two new masses appeared in the same area. Breath sounds were diminished in the right chest. On July 7, 1953 A-methoptherin was resumed (2.5 mg. daily) and the dose of cortisone was increased to 50 mg. daily. Further x-ray therapy was given to the left posterior parietal region from July 10 through July 21, 1953, a total dose of 2430 r. On July 23, 1953 it was noted that knee jerks were absent. On July 31, 1953 the child spiked a fever of 102°F. and was changed from terramycin to erythromycin. He developed complete paraplegia with cord bladder at approximately the waist line level. X-ray examination on August 1, 1953 revealed collapse of the second lumbar vertebra. Further x-ray therapy was given over the spine (D 11 to S 2), 1540 r tumor dose between August 5 and 17, 1953. On August 5, 1953 there was pitting edema of the extremities and the next day there was hematuria, considered to be hemorrhagic cystitis, which was treated with gantrisin. A metastatic lesion appeared on the left cheek on August 12, 1950. The next day the patient had trismus and x-ray therapy was given (750 r) to the left mandible. On August 17, 1953 he began having intermittent dyspnea. Next day a lesion was noted attached to the manubrium sternae. A chest x-ray on August 21, 1953 showed minimal pleural effusion without parenchymal disease. Urine cultured showed *B. proteus mirabilis* and hemolytic enterococcus, most sensitive to chloromycetin. This drug was started. On August 25, 1953 he was noted to have petechiae over the abdomen. During the last weeks the child received testosterone, transfusions and adrenalin. The disease progressed, causing death on September 1, 1953 after a gradual and slow course of progressively severe symptomatology due to the metastatic tumor involvement. Death occurred 18 months after onset. His weight at death was approximately 30 pounds. Autopsy revealed "neuroblastoma, first found in left femur and metastasizing to skull, manubrium, body of sternum, multiple ribs, multiple vertebrae with collapse of L 2, left mandible, right ilium, retropleural and retroperitoneal regions, left supraclavicular and esophageal lymph nodes, scalp, lungs, liver, right kidney, spleen, pancreas, dura mater, with paraplegia secondary to cord compression at levels of D 3 and 4, and L 2. Probably primary site paravertebral region." There was also acute bronchopneumonia, pulmonary congestion and edema; bilateral serosanguinous pleural effusion; fatty infiltration of the liver; focal acute congestion of the renal medulla, bilateral; focal submucosal hemorrhages and calculi in the bladder; generalized edema; x-ray necrosis of the skin over the upper lumbar vertebra; and a sacral decubitus 6 cm. in diameter.

Comment: This patient had only one course of 15 toxin injections following antibiotic and x-ray therapy. Compare with Case 1 in which toxin therapy alone was given with intervals of rest for two years. The case is of special interest due to the difficulty in establishing a correct diagnosis until postmortem. Note also the extremely widespread disease at death, which may have been due to the repeated x-ray therapy and to administration of cortisone. (67-69)

References: 44.

CASE 9: The detailed history of this case was not obtainable.

SERIES B: TOXIN TREATED CASES, DETAILED HISTORIES

SUMMARY AND CONCLUSIONS

The incidence, symptoms, histology, differential diagnosis and therapy of neuroblastoma have been reviewed.

Factors which may favorably or deleteriously affect natural resistance to neoplastic diseases, including neuroblastoma have been discussed.

The 18 known cases of this tumor with concurrent infection, leukocytosis, febrile or inflammatory episodes were presented in the form of a table followed by complete histories for those wishing to study them in detail. In some of these cases the factors which may be responsible for increased host resistance are less evident than others and may also include blood transfusions and prolonged administration of Vitamin B-12.

The only nine cases of neuroblastoma who received bacterial toxin therapy (Coley toxins) were also presented in brief and detailed form.

Although terminal, with quadriplegia, the single case who received Coley toxins alone recovered, and is alive in 1970, 59 years after onset. He received toxins with intervals of rest for two years. This famous case suggests the need for further clinical trial of microbial products such as the Coley toxins as a primary method of treatment for neuroblastoma, thus avoiding the possible late effects of radiation in children, such as dwarfing or nephritis.

The second toxin treated case might also be alive today had he not been subjected to an exploratory laparotomy and partial excision of the residual ganglioneuroma 20 years after recovery for asymptomatic calcifications seen on x-ray examination. The disease reactivated about a year later, causing death 25 years after onset.

Factors affecting prognosis in the other six cases were discussed. The most important factors appear to be the duration of toxin therapy and whether the injections were begun prior to or subsequent to radiation or chemotherapy.

BIBLIOGRAPHY

1. BECK, S. M. & HOWARD, P. J.: Neuroblastoma. Review of the literature and report of a six year cure by roentgen therapy. *A.M.A. Amer. J. Dis. Child.* 82: 325-334. 1951.
2. BODIAN, M.: Preliminary observations on the treatment of neuroblastoma with Vitamin B-12. 31st Annual Report of the British Empire Cancer Campaign. 1953. pp. 174-179.
3. BODIAN, M., WHITE, L. L. R. & JACO, N. T.: Neuroblastoma. A general review. 32nd Annual Report of the British Empire Cancer Campaign. 1954, p. 195.
4. BURKY, E. L.: The production in the rabbit of hypersensitive reactions to lens, rabbit muscle and low ragweed extracts by the action of staphylococcus toxins. *J. Allergy.* 5: 466-475. 1933-34.
5. CHANDLER, J. J., STARK, D. B., ALLEN, C. V. & FLETCHER, W. S.: Treatment of cancer with bacterial toxins. *Amer. Surg.* 31: 443-449. 1965.
6. COCHRAN, W.: Neuroblastoma (sympatheticoblastoma) in northern Ireland. A review over a ten year period. *Ulster M. J.* 82: 82-98. 1963.
7. COHEN, L.: Immunity and resistance in clinical cancer. *South African M. J.* 30: 161-167. 1956.
8. COLE, D. R., DREYER, B., ROUSSELOT, L. M. & TENDLER, M.D.: The radio-protective and anti-tumor effect of mixed bacterial toxins and anthramycin. *Amer. J. Roentg., Radium Therapy & Nuclear Medicine.* 97: 997-1002. 1966.
9. COLEY, W. B.: The treatment of malignant inoperable tumors with the mixed toxins of erysipelas and *Bacillus prodigiosus*, with a brief report of 80 cases successfully treated with toxins from 1893-1914. Brussels, M. Weissenbruch, 1914.
10. COLEY, W. B.: Office Records.
11. CUSHING, H. & WOLBACH, S. B.: The transformation of a malignant paravertebral sympatheticoblastoma into a benign ganglioneuroma. *Am. J. Path.* 3: 203-216. 1927.
12. DARGEON, H. W.: Problems in the prognosis of neuroblastoma. *Am. J. Roent. Rad. Ther. & Nucl. Med.* 83: 551-555. 1960.
13. DEBRE, R., l'HERMITTE, J., UHRY, P., PARIS, R., et OEMICHEN, Mlle.: Tumeur sympathique embryonnaire chez un enfant. *Ann. d'Anat. path. et d'Anat. norm.* 15: 1-8. 1938.
14. DOUB, H. P.: The roentgen aspect of sympathetic neuroblastoma. *J. A. M. A.* 109: 1188-1191. 1937.
15. EVERSON, T. C. & COLE, W. H.: Spontaneous regression of cancer: preliminary report. *Ann. Surg.* 144: 366-383. 1956.
16. EVERSON, T. C.: Spontaneous regression of cancer. *Conn. Med.* 22: 637-643. 1958.
17. EVERSON, T. C. & COLE, W. H.: Spontaneous regression of cancer. W. B. Saunders Company, Philadelphia and London, 1966.
18. EYRE-BROOK, A. L. & HEWER, T. F.: Spontaneous disappearance of neuroblastoma with maturation to ganglioneuroma. *J. Bone Joint Surg. (Brit.)* 44-B: 886-890. 1962.
19. FARBER, S.: Neuroblastoma. *Amer. J. Dis. Childr.* 60: 749-751. 1940.
20. FAUVET, J., CAMPAGNE, J., CHAVY, A. & PIET, G.: Guérisons, régressions et rémissions spontanées des cancers. *Revue du Prat. (Paris)* 10: 2349-2384. 1960.

21. FEVRE, M., LAMY, M., MOGGI ET BAUDOUIN, J.: Guérison spontanée d'un sympathome embryonnaire à foyers superficiels multiples chez un nourrisson. *Arch. franc. de Pédiatrie*. 1: 195-199. 1938.
22. FEVRE, M. & HUGUENIN, R.: Malformations Tumorales et Tumeurs de l'Enfant. Massons et Cie, Editeurs. Paris. 1954. p. 23.
23. FORSTER, A. K.: Statistische Untersuchungen über den hemmenden Einfluss von Bienengift auf Entstehung von Krebs bei Imkern. *Leipzig Bienen Ztg.* 57: 101. 1942.
24. FOX, F., DAVIDSON, J. & THOMAS, L. B.: Maturation of sympathicoblastoma into ganglioneuroma. Report of two patients with 20 and 46 year survivals respectively. *Cancer*. 12: 108-116. 1959.
25. GABRIELI, E. R. & HOLMGREN, H.: Effect of anti-histamine on the reticulo-endothelial system as demonstrated by the use of radioactive chromium phosphate. *Nature*. 168: 467-468. 1951.
26. GABRIELI, E. R. & AUSKAPS, A. A.: The effect of whole body irradiation on the reticulo-endothelial system as demonstrated by the use of radioactive chromium phosphate. *Yale J. Biol. & Med.* 26: 159-169. 1953-1954.
27. GLYNN, L. E. & HOLBORROW, E. J.: The production of complete antigens from polysaccharide haptens by streptococci and other organisms. *J. Path. & Bact.* 64: 775-783. 1952.
28. GOLDRING, D. L.: Neuroblastoma sympatheticum with metastases; report of a case with apparent recovery. *J. Pediatrics*. 38: 231-234. 1951.
29. GREENFIELD, L. J. & SHELLEY, W. M.: The spectrum of neurogenic tumors of the sympathetic nervous system: maturation and adrenergic function. *J. Nat. Cancer Inst.* 35: 215-226. 1965.
30. HABER, S. L. & BENNINGTON, J. L.: Maturation of congenital extra-adrenal neuroblastoma. *Arch. Path.* 76: 121-125. 1963.
31. HAGER, E. B., BAILEY, G. L., HAMPERS, M. D. & MERRILL, J. P.: Immunity against Ehrlich ascites carcinoma produced by bacterial endotoxins. *Proc. Transplantation Soc.* 1: 124-125. 1969.
32. HELLER, J. H.: Reactivation of cortisone-depressed reticulo-endothelial system. *Federation Proc.* 13: 69. 1954.
33. HELLER, J. H.: Effects of cortisone, choline and radiation upon the reticulo-endothelial system. *Federation Proc.* 14: March 1955, #726.
34. HOLLICRAFT, J. W. & SMITH, W. W.: Endotoxin treatment and x-irradiation in mice bearing transplanted tumors. *J. Nat. Cancer Inst.* 21: 311-330. 1958.
35. HORNSTEIN, O. & MULKE, G.: Kutan metastasierendes Neuroblastoma sympathicum mit "spontan" regressivem Verlauf. *Dermatologica*. 120: 35-53. 1960. (also *Z. Kinderklinik* 83: 40-83. 1959.)
36. JANSKO, M.: Histamine as a physiological activator of the reticulo-endothelial system. *Nature*. 160: 227-228. 1947.
37. JOHNSTON, B. J. & NOVALES, E.: Clinical effect of Coley's toxin II. A seven year study. *Cancer Chemoth. Repts.* 21: 43-68. 1962.
38. KNUDSON, A. G. & AMROMIN, G. D.: Neuroblastoma and ganglioneuroma in a child with multiple neurofibromatosis. Implications for the mutational origin of neuroblastoma. *Cancer* 19: 1032-1037. 1966.
- 38a. KING, R. L., STORAASLI, J. P. & BOLANDE, R. P.: Neuroblastoma, review of twenty-eight cases and presentation of two cases with metastases and long survival. *Amer. J. Roentgenol.* 85: 733-747. 1961.
39. KOOP, C. E., KIESEWETTER, W. B. & HORN, R. C.: Neuroblastoma in childhood: Survival after surgical insult to the tumor. *Surgery*. 38: 272-278. 1955.
40. KOOP, C. E.: Nephroblastoma and neuroblastoma in children. *Amer. J. Surg.* 101: 586-570. 1961.
41. LOHMANN, R.: Krebsstoffwechsel und Entzündung. *Klin. Woch.* 10: 1799-1802. 1931.

- 41a. KOOP, C. E.: Neuroblastomas in infancy and childhood. *Arch. Dis. Children*, London 39: 204-207. 1964.
42. MACFARLAND, J. & SAPPINGTON, W.: A ganglioneuroma in the neck of a child. *Am. J. Path.* 11: 429-448. 1935.
43. MARCHAND, F.: Ueber eine Geschwulst des Sympathicusanteils der Nevennieren. *Festschr. F. R. Virchow: Intern. Beitr. Z. Wissensch. Med. Berlin* 1: 578-581. 1891.
44. Memorial Hospital Records, New York, N.Y.
- 44a. MILLER, T. N. & NICHOLSON, J. T.: Enhancement of natural resistance to primary reticulum cell sarcoma of bone with bacterial toxin therapy (47 cases) or concurrent infections (5 cases). To be published, 1970.
45. MURPHY, JAMES B.: The lymphocyte in resistance to tissue grafting, malignant disease and tubercular infection. An experimental study. Monographs of the Rockefeller Institute for Medical Research #21, New York, 1926.
46. National Cancer Institute Records: Personal communications from Dr. Robert R. Smith, Chief Surgery Branch, 1957-1962.
47. NAUTS, H. C., FOWLER, G. A. & BOGATKO, F. H.: A review of the influence of bacterial products (Coley's toxins) on malignant tumors in man. A critical analysis of 30 inoperable cases selected for special study. *Acta Medica Scandinavica* Vol. 145: Supplement 276. 1953.
48. NAUTS, H. C., & FOWLER, G. A.: End results in lymphosarcoma treated by toxin therapy alone or combined with surgery and/or radiation or with concurrent bacterial infection. Monograph #6. New York Cancer Research Institute, New York, 1969.
- 48a. NAUTS, H. C.: The apparently beneficial effects of bacterial infections on host resistance to cancer: End results in 435 cases. Monograph #8. New York Cancer Research Institute, New York, 1969. 2 volumes. 832 pp. with Bibliography of 969 references.
- 48b. NEUHAUSER, E. B. D., WITTENBERG, M. H., BERMAN, C. Z. & COHEN, J. Radiation effects of roentgen therapy on the growing spine. *J. Radiology* 59: 637-650. 1952.
49. New York Cancer Research Institute Records: Personal communications from the patients or their physicians. 1953-1970.
50. NICHOLSON, J. T. End results in reticulum cell sarcoma of bone treated by toxin therapy alone or combined with surgery and/or radiation. Read before the James Ewing Society, 1962.
51. PELNER, L.: Host-tumor antagonism. V. The effect of ionizing radiations (radium and x-ray) upon tumor and host. *J. Amer. Gerat. Soc.* 5: 512-519. 1957.
52. PELNER, L. & FOWLER, G. A.: Host-tumor antagonism. XIII. Sarcoma of the soft tissue treated by bacterial toxins: Successful Series. *J. Am. Geriat. Soc.* 7: 624-647. 1959: XIV. Unsuccessful series. 698-729. 1959. (A more detailed study of these cases appeared as Monograph #3 of the New York Cancer Research Institute, Inc. 1959).
53. PELNER, L., FOWLER, G. A., & NAUTS, H. C.: The effect of concurrent infections or of bacterial toxins on leukemia. *Acta Medica Scandinavica*. 162: 1958. Supplement 338.
54. PHILLIPS, R.: Neuroblastoma, *Ann. Roy. Coll. Surg.* 12: 29-48. 1953.
55. POORE, T. N., DOCKERTY, M. B., KENNEDY, R. L. J. & WALLIN, W.: Abdominal neuroblastoma. *Surg. Clin. N. Amer. (Mayo Clinic)* 1121-1141. 1951.
- 55a. REGELSON, W.: The Antimitotic Activity of Polyanions (Antitumor, Antiviral, and Antibacterial Action of Heparin, Heparinoids, Anionic Dyes, and Synthetic Polymers. *Adv. in Chemother.* 3: 303-371. 1968.
56. ROCHER, H. L.: Un cas de volumineux sympathome embryonnaire de la région pelvique chez un bébé de six mois. Traitement radiothérapique; guérison se maintenant depuis deux ans et demi. *Paris méd.* 103: 552-554. 1937.

57. ROUSSY, HUGUENIN, PERROT ET SARACINO: Evolution d'un cas de sympathome embryonnaire. *Revue Neurol.* 73: 32-48. 1941.
- 57a. RUBIN, P., DUTHIE, R. B. & YOUNG, L. W. Significance of scoliosis in post-irradiation Wilms' tumor and neuroblastoma. *Radiology* 79: 539-558. 1962.
58. SAWITSKY, A., & DEPOSITO, F.: A survey of American experience with Vitamin B-12 therapy of neuroblastoma. *J. Pediat.* 67: 99-103. 1965.
59. SCOTT, E. & PALMER, D. M.: Intrathoracic sympatheticoblastoma. *Amer. J. Cancer* 16: 903-917. 1932.
60. SHERMAN, R. S. & LEEMING, R.: The roentgen findings in neuroblastoma. *Radiology* 60: 837-849. 1953.
61. SIMPSON, C. L. & HEMPELMANN, L. H.: The association of tumors and roentgen ray treatment of the thorax in infancy. *Cancer* 10: 42-56. 1957.
62. SMITH, R. L.: Recorded and expected mortality among the Indians of the United States with special reference to cancer. *J. Nat. Cancer Inst.* 18: 385-396. 1957.
63. SMITH, W. W., ALDERMAN, I. M. & GILLESPIE, R. E.: Hematopoietic recovery induced by bacterial endotoxin in irradiated mice. *Amer. J. Physiol.* 102: 549-566. 1968.
64. SNYDER, W. H., JR., KRUSE, C. A., GREANEY, E. M. & CHAFFLIN, L.: Retroperitoneal tumors in infants and children. Report of eighty-eight cases. *Arch. Surg.* 63: 26-38. 1951.
65. SOUTHAM, C. M., MOORE, A. E. & RHOADS, C. P.: Homotransplantation of human cell lines. *Science*, 125: 158-160. 1957.
66. STETSON, C. A., JR.: The endotoxin properties of Group A streptococci. *J. Exp. Med.* 104: 921-923. 1956.
- 66a. STEWART, F. W.: Experiences in spontaneous regression of neoplastic disease in man. *Texas Reports Biol. & Med.* 10: 239-253. 1952.
67. STOWENS, D.: Neuroblastoma and related tumors. *Arch. Path.* 63: 451-459. 1957.
68. TOOLAN, H. W.: Conditioning the host. *J. Nat. Cancer Inst.* 14: 745-761. 1953.
69. TOOLAN, H. W.: The possible role of cortisone in overcoming resistance to the growth of human tissues in heterologous hosts. *Ann. N.Y. Acad. Sc.* 59: 394-399. 1955.
70. UNGAR, F. H.: Problems of allergy and malignant tumors. *Acta Unio. Intern. Contra Cancrum.* 9: 213-326. 1953.
71. VAN CREVELD, S. & VAN DAM, R.: Prognosis in sympatheticoblastoma. *Acta Paediat.* 34: 279-288. 1947.
72. VIGORELLI, L.: Simpatoblastoma sottocutaneo multiple ad evoluzine favorevole. *Minerva Pediatrica* 14: 1219-2226. 1962.
73. WEDER, A. A., SYVERTON, J. T. & FRIEDMAN, J.: The influence of roentgen radiation and cortisone upon transplantability of mouse leukemic cell line 1. *Cancer Res.* 12: 306. 1952.
- 73a. WHITEHOUSE, W. M. & LAMPEY, I.: Osseous damage in irradiation of renal tumors in infancy and childhood. *Amer. J. Roentgenol.* 70: 721-729. 1953.
74. WILLIS, R. A.: Metastatic neuroblastoma in bone presenting Ewing syndrome with discussion of "Ewing sarcoma." *Am. J. Path.* 16: 317-322. 1940.
75. WITTENBERG, M. H.: Roentgen therapy in neuroblastoma. *Radiology.* 54: 679-688. 1950.
76. WOODS, R. G.: Survivorship in neuroblastomatosis; report of a case with commentary. *Med. J. Australia.* 125-128. 1958.
77. WRIGHT, J. H.: Neurocytoma or neuroblastoma, a kind of tumor not generally recognized. *J. Exper. Med.* 12: 556-561. 1910.
78. WYATT, G. M. & FARBER, S.: Neuroblastoma sympatheticum. Roentgenological appearances and radiation treatment. *Am. J. Roentgenol.* 46: 485-496. 1941.
79. Griffin, M.E. & Bolande, R.P.: Familial neuroblastoma with regression and maturation to ganglio-neurofibroma. *Pediatrics* 43:377-382. 1969.

ADDENDUM

THE APPARENTLY BENEFICIAL EFFECTS OF CONCURRENT INFECTIONS INFLAMMATION OR FEVER AND OF BACTERIAL TOXIN THERAPY ON NEUROBLASTOMA MONOGRAPH #11

George A. Fowler, M.D. and Helen C. Nauts
Series B, Case 10, Page 78a

The following case has recently come to our attention. It should be added to the series of nine cases in Series B known to have received Coley Toxin therapy.

DIAGNOSIS: Congenital generalized neuroblastoma, confirmed by microscopic examination at the Children's Hospital of Akron, Ohio, following biopsies of two skin nodules: the pathologist reported "sheets and nests of plump or polygonal neuroblastoma replacing dermal and subcutaneous connective tissue and infiltrating adjacent fat ... There was no evidence of neuroblast maturation into ganglion cells or of hemorrhage, necrosis and dystrophic calcification. Focal interstitial collections of lymphocytes and plasma cells were prominent. In many areas of the tumor, clumps and masses of degenerate and dying neuroblasts were found."

PREVIOUS HISTORY: L.C., female infant. With the exception of their first child, the family history was negative for tumors, neurofibromatosis, skin nodules or cafe au lait spots. (Abdominal x-rays of the entire family in 1969 revealed the presence of a small focus of adrenal calcification in the 15 year old sister.) The patient was the fifth child of these parents. Their first child had also been born with neuroblastoma and had died following extensive radiation therapy at the age of 15 months in 1949. The patient was born in November 1954, weighing 6 pounds, 9 ounces, after a full term pregnancy and uneventful delivery. At birth there were approximately 40 subcutaneous non-tender lumps all over her body, varying in size from 2 mm. to 3 mm.

SURGERY: Two of these lesion were biopsied.

CLINICAL COURSE: Because of the experience with their first child the parents refused treatment. During the next two months the skin lumps became larger and marked hepatomegaly developed. The child vomited constantly and had to be fed every hour in order to prevent dehydration. (She was not breast fed.) The parents then took her to the Cleveland Clinic in January 1955.

TOXIN THERAPY (Sloan-Kettering XIV): Injections of Coley 2toxins were administered there. (No details are available as to technique.)

CLINICAL COURSE: Gross hematuria was noted at eight months of age. By 15 months she appeared to be doing very well.

