WILMS' TUMOR

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Preface

The extraordinary improvement in the results of treatment of Wilms' tumor has made it a model for the treatment of other childhood malignancies. The steady advances in the long-term survival rate of children with this tumor have done much to dispel pessimism and have spawned a new era of cautious optimism. Wilms' tumor is a symbol of hope that improvement in the results of treatment of other childhood malignancies may also be forthcoming.

Wilms' tumor is of particular interest to the pediatrician, surgeon, and oncologist for two major reasons. First, of all the childhood malignancies this tumor has the greatest potential for cure, even when metastases are present. Second, its management exemplifies the combined roles of surgery, radiotherapy, and chemotherapy. Advances in treatment over the past decade have further improved the survival rate for patients with Wilms' tumor. This increased survival rate depends mainly on early detection of the tumor by the general practitioner or pediatrician and the subsequent coordinated efforts of the surgeon, pathologist, radiotherapist, and chemotherapist. Improved preoperative management, precise initial determination of the extent of the disease, and detailed clinical evaluation of the patient following definitive therapy are very important.

Wilms' tumor is also important in the broader biologic sense because it is known to occur both in man and in many of the lower animals. The embryonal origin of Wilms' tumor has opened up another fascinating area for investigation of the pathogenesis and genetics of this tumor.

The primary purpose of this book is to survey in depth the biologic and clinical behavior of Wilms' tumor. The many significant advances in recent years on the fundamental nature of Wilms' tumor justify the publication of such a comprehensive monograph, the first on Wilms' tumor to be published. The second purpose of this book is to provide an up-to-date compendium on the optimal management of this disease for practicing physicians.

This book was designed and edited as a close collaborative effort between Dr. Finklestein and ourselves. Dr. Finklestein helped to select the topics and authors

and approved the scientific content of each chapter. Together we edited the manuscripts to decide upon needed revisions and additions. Drs. Robert A. Price and Anthony Shaw reviewed the chapters that were relevant to their specialties, histopathology (Chapter 6) and surgery (Chapter 10).

We are very pleased to have been able to assemble an outstanding international team of oncologists to participate in the preparation of this important monograph. We are grateful also to our editors at John Wiley & Sons, Ms. Ruth Wreschner, and Mr. Alan Frankenfield, who provided a constant source of help and encouragement.

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Introduction: Historical Review of Wilms' Tumor

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CHAPTER ONE

Introduction: Historical Review of Wilms' Tumor

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With early diagnosis and treatment, Wilms' tumors can now be cured in the vast majority of cases. The history of Wilms' tumor is a therapeutic success story worth telling because of the encouragement it provides regarding treatment of childhood tumors, against which present-day therapeutic modalities are less effective. Wilms' tumor is an excellent subject for a monograph in pediatric oncology because it illustrates how successful therapy can be attained by physicians who work together as a team in treating the child with a complex disease.

Although Max Wilms published his classic monograph in 1899,[1] renal tumors of children that were presumably Wilms' tumor had been recognized much earlier in the medical literature in articles written by Rance in 1814[2] and Gairdner in 1828.[3] The first clinical description of renal cancer in a child was that of Van der Byl in *Lancet* in 1856.[4] Although his patient had an enormous tumor, one must doubt whether it was Wilms' tumor because of the long 7-year history. Nevertheless, his description of the patient is of interest as it relates the course of an untreated renal tumor in a young boy.

> The child's abdomen, soon after birth, became larger on the left side than on the right. It continued to increase in size very gradually until six months before his admission into the hospital, but it grew very rapidly afterwards. When he was admitted, the abdomen was much enlarged and crossed by large, tortuous veins. Enlargement existed especially on the left side and was produced by a tumour about eight inches in diameter. The tumour was slightly moveable, semi-elastic in some parts, and not painful on being handled. The intestines were felt over the edge of it on the right side. Four months after admission he walked a short distance, but had to be carried back to bed. He occasionally complained of great pain in the abdomen, which increased so much in size that he was soon unable to leave his bed; but he lingered on for months. His appetite was generally good, and his bowels regular; but he became gradually very thin, and died from exhaustion about 10 months after admission.

A postmortem examination performed by Van der Byl revealed a tumor originating from the left kidney. Unfortunately, the microscopic study was not complete.

By the mid-1800s it became apparent that children were dying of tumors of the kidney and that therapy was needed. On June 16, 1877, the first nephrectomy in a child was performed by Mr. Jessop at the Leeds Infirmary. The operation was described in *Lancet* 9 days later.[5] Jessop treated a child who at the age of 2 years had symptoms consisting of hematuria and irritation of the bladder. The child

> lost flesh and became more and more pallid. About two months ago a rapidly increasing tumor was discovered in the left renal region, and as the indications were those of malignant growth, Mr. Jessop determined to cut down upon it, and, if possible, to remove it. The incision was similar to that recommended for colotomy, but longer. When the diseased mass was reached, the kidney was peeled by means of the fingers, and a whipcord ligature was passed around the vessels and ureter, and firmly tied. The remainder of the growth was afterwards stripped away, and the

whipcord left to drain the wound. The operation was a formidable one owing to the large size of the diseased organ and the free venous haemorrhage which followed the separation of the growth from the surrounding structures. When removed the kidney weighed 16 ounces, and resembled encephaloid in appearance. The child was doing well on the 11th day. There was no peritonitis, the bowels acted freely, and the urine flowed abundantly, and was not stained. There was no vomiting, the temperature was but little above normal, and the child partook freely of milk.

Jessop's patient died 9 months later of metastases (reported by Czerny in 1888).[6]

The classic pathological description of what would later be called Wilms' tumor was written by Eberth in 1872,[7] who described a tumor in a 17-month-old girl who died 3 months after presentation. His description of the tumor's growth and pathology is in accord with the diagnosis of Wilms's tumor, and also represents the first well-documented histologic description. Three years later Cohnheim[8] described a congenital sarcoma of the kidney that fits into the classification of Wilms' tumor. Thus, by the late 1800s the disease had been categorized by the pathologists, and the institution of therapy had begun with the documentation of one successful nephrectomy.

In 1879 William Osler of McGill University in Montreal[9] provided the first noteworthy description by a North American. His paper recognized that the descriptions by Eberth,[7] Cohnheim,[8] Kocher and Langhans,[10] and others constituted a single, identifiable entity. Osler collected 4 cases from the literature and added 2 of his own. One patient was a 19-month-old boy who was found to have an incidental tumor on postmortem examination; the child had died from severe gastrointestinal symptomatology following a vaccination. A second patient was a 3-year-old girl who had a 6-week history of gastric and intestinal symptoms, occasional vomiting, and obstinate constipation. She had slight pain in the abdomen and, on inspection, a tumor was discovered in the left hypochondriac region just below the cartilage of the eighth rib. It was soft and apparently fluctuated. The child died suddenly, after getting up one morning and walking toward her mother's bed. Osler's pathologic description was most complete and agreed with what was eventually called Wilms' tumor. It is noteworthy that Osler collected the cases and grouped them together 20 years prior to Wilms' monograph. In 1894, Döderlein and Birch-Hirschfeld recognized that a variety of terms, namely, embryonal sarcoma, sarcoma of the kidney, adenomyosarcoma, and sarcoma musculare, were all used to designate the same tumor.[11] Wilms' tumor has also been called Birch-Hirschfeld's tumor in the older German literature.[6]

In the 1800s nephrectomies were considered major operations, with significant morbidity and mortality. The first large series of nephrectomies was reported by Israel in 1894.[12] He performed 37 operations for the following entities: malignant tumor 12; syphilis 2; tuberculosis 4; and hydronephrosis, pyelonephrosis, and kidney abscesses 19. Israel's operative mortality was 6 patients (16.2%). Two of his patients were 1 to 2 years of age; one died 5 months following surgery of liver

metastases secondary to a "sarcoma of the kidney," while the other was well 11 months after operation.

By the end of the nineteenth century, embryonal sarcoma of the kidney had been recognized by Osler, and attempts at therapy had been initiated by Jessop and followed up by Israel. In 1899, Wilms' thoroughly reviewed the literature, and added 7 cases of his own to produce the definitive volume on the subject.[1]

The next major advance in therapy of Wilms' tumor occurred in 1915, when Alfred Friedlander of Cincinnati was presented with a patient who had an abdominal growth "so large that no surgeon was willing to undertake its removal." An unnamed physician had suggested roentgen ray treatments, and Friedlander reported the first case of sarcoma of the kidney (Wilms' tumor) treated by radiotherapy.[13] "Treatments were given with the Coolidge tube. Three areas, front, back and side of the tumor, were covered at each treatment, except for the first and second, when one and two areas, respectively, were treated." Treatments were given at intervals of about a week. The dosage varied from 10 to 50 Ma. sec and consisted of 20 treatments between October, 1915, and March, 1916. By the end of the seventh treatment, the child's tumor had decreased markedly and the child had gained several pounds, looked rosy and well and played like an apparently normal child. But in March, 1916, he became listless and apathetic. The tumor had regrown, and the child died following a bout with measles. Necropsy showed a sarcoma of the left kidney with metastases to both lungs and liver.

A review of the literature from the early 1900s to the mid-1930s reveals relatively little progress in treatment of this entity. There were numerous case reports describing the symptoms and therapy, which included surgery and x-ray therapy.[14-17] In 1936, Priestley and Schulte reported on the results of nephrectomy in 39 patients with Wilms' tumor; 6 lived 5 years or more following operation, a survival rate of approximately 15%.[18] Priestley found that preliminary irradiation followed by nephrectomy and, subsequently, postoperative irradiation resulted in the best prognosis. In 1941, Ladd and White[19] described a decreasing mortality rate in Wilms' tumor, from 23% of 30 patients treated from 1914 to 1932 to 3% of patients treated between 1932 and 1941. This impressive result may have been due in part to their decision that the operative technique be performed as soon as the probable diagnosis was made. They were the first to suggest that nephrectomies could be performed in children with minimal morbidity and mortality. Ladd's survival rate was 40% of children treated between 1932 and 1941.

In 1898, William Coley attempted pharmacologic treatment of a renal tumor by administering toxins preoperatively to a 5-year-old child.[20] The child was operated upon and died within a year of surgery. Coley's attempt represents the first trial of systemic agents for this entity. It was not until the mid-1950s that the first specific chemotherapeutic agent for Wilms' tumor was described, when Farber reported that actinomycin D produced tumor regression.[21] In 1963, Sutow

et al. showed that vincristine produced significant regression of measurable disease in 8 out of 13 children with disseminated Wilms' tumor.[22] Sutow and his colleagues also showed that the increased use of chemotherapy with actinomycin D and vincristine caused further improvement in the survival rate of children with this tumor.[23] By the late 1960s patients with Wilms' tumor were usually treated with surgery, radiotherapy, and at least two active chemotherapeutic agents. Currently, a cooperative effort by clinicians throughout the country, the National Wilms' Tumor Study Group, is evaluating newer concepts in therapy. These will be described in this monograph. It seems safe to predict that by the end of this decade children with Wilms' tumor, when diagnosed and treated early, will be uniformly cured.

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