ENHANCEMENT OF NATURAL RESISTANCE TO RENAL CANCER: BENEFICAL EFFECTS OF CONCURRENT INFECTIONS AND IMMUNOTHERAPY WITH BACTERIAL VACCINES

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TABLE OF CONTENTS

INTRODUCTION

The prevailing view of cancer, among physicians and laymen alike, has been that of an inexorably progressive disease for which the only hope of treatment is eradication of every malignant cell.

Although there have been indications that this is not always true, and that cancers are frequently under some form of restraint, only in the last decade or two has sound evidence for this been forthcoming. This evidence includes the finding of immunological reactions against cancer, in man as well as animals, a fact of considerable importance for the treatment of cancer. For we now know that victims of cancer are not totally unresponsive to their disease but can make an immune response like that which accompanies infectious diseases. In fact there was a time when many infectious diseases, now eradicated or readily curable, seemed almost as relentlessly fatal in their course as cancer itself. We may now stand on the threshold of a new era in the understanding and treatment of cancer, based on immunological concepts, perhaps comparable with the era which witnessed the conquest of many infectious diseases.

Until very recently few serious attempts have been made to stimulate or enhance the natural resistance of patients with renal or other types of neoplasms because the importance of host resistance factors in the overall management of cancer has been largely ignored. The significant reports appearing in the past century relating to spontaneous regression and tumor immunity have been reviewed and analyzed by Fowler, Nauts, Pelner (1953-1970) as well as Everson and Cole (1959, 1966). The latter define spontaneous regressions as the partial or complete disappearance of a malignant tumor in the absence of all treatment, or in the presence of therapy considered inadequate to exert a significant influence on neoplastic disease.

However, it appears that most of the spontaneous regressions are not truly spontaneous but are frequently associated with certain concurrent complications such as acute infections, inflammatory or febrile episodes or they have occurred in patients receiving bacterial toxin therapy or fever therapy or some other host-stimulating agent such as BCG, zymosan or vaccinia virus (Fowler, 1969; Nauts, 1969, 1970; Old, 1961; Weiss, 1961). Still others are associated with removal of the primary tumor which in certain cases enables the patient's natural resistance to destroy the metastatic lesions, often without the benefit of an infection (See Table 2).

Cases in which the course of the disease is unusually prolonged may also be related to the immunological competence of the host. Although a number of authors (See Table 3) have reported cases of late metastases or recurrence of renal cancer, no one has attempted to study what factors other than increasing age may be responsible for reactivating these neoplasms. Of great significance are the recent reports of cases of cancer developing in patients receiving kidney transplants who have been given immunosuppressive drugs (Wilson et al, 1968; Penn et al, 1970).

Others have indicated the dangers of corticosteroids administered for various conditions such as arthritis or bursitis in accelerating the growth and dissemination of metastases in quiescent cases (Kelly, 1959, 1963).

The present study is an attempt to consider the role of host resistance factors in the etiology, incidence, diagnosis, treatment and prognosis of renal neoplasia, including Wilms' tumor.

ETIOLOGY, EPIDEMIOLOGY AND INCIDENCE

Clues to the causes of cancer of the kidney in man might be provided by a closer study of the geographic distribution of renal tumors and the influence of occupational or environmental hazards and also by the application of modern genetic techniques (Dukes, 1961).

Renal cell carcinoma is a relatively infrequent form of malignancy, representing only two percent of all neoplasms. It occurs twice as frequently in males as in females. This is true also in the frog (Lucké, 1952). Between 1940 and 1958 the incidence of all types of renal cancer increased 50 per cent. This increase was not as rapid as that for lung or bladder cancers, but in this period there has been a decreased incidence for other sites such as the stomach, esophagus, tongue and skin in this country. The death rate for renal cancer in the white population here is almost twice that for blacks, and in this country as well as England and Wales the renal cancer mortality is greater in the upper classes, while the lower socioeconomic group has a higher incidence of cancer of the stomach, mouth and skin. There is also an unexplained variation in mortality of renal cancer in different countries. The incidence is low in Japan, Venezuela and Spain and high in Denmark. Its distribution is similar to bladder cancer, but the incidence of the latter is higher except in Norway where renal cancer is more prevalent.

They rarely occur until the fifth decade, the maximum incidence being in the sixth and seventh decades. However, recently the incidence in younger adults appears to be increasing. The urinary tract is exposed to much higher concentrations of excreted metabolites than other organs. Cancer of the bladder in man is caused by aromatic amines. Kerr (1963) has reported a case of hypernephroma associated with elevated levels of bladder carcinogens in the urine.

Spontaneous renal neoplasms are very rare in both wild and domestic animals (Lombard, 1959: Sanderson, 1968). Lucké has described the geographic distribution of kidney carcinoma in the leopard frog, (Lucké, 1952). Felluga reported that an inbred strain of BALB mice has a renal tumor incidence of 60-70 %. These tumors contain virus particles which from their morphology, morphogenesis and distribution in and outside the cell, resemble virus particle types in mammary tumors and lymphomas of mice (Felluga, 1969). The polyoma virus has produced renal tumors in rats, mice, hamsters and ferrets. The bridge to man seems to have been spanned as antibodies to this virus have been found in those who work with it. Riches asks: might not a virus be responsible for the large Wilms' tumor, occasionally multiple, seen in infants? (Riches, 1964)

Animal experiments have implicated chemical agents in the production of several varieties of renal tumors. Renal cancers can be induced experimentally in male hamsters by estrogen (Kirkman and Bacon, 1950) and in rats by carcinogens. Lee reported that when aflatoxin preparations were fed to weanling rats over an 18-month period, 34% developed renal tubule adenomas, 10% hepatocellular carcinomas and 31% hyperplastic liver nodules (Lee et al, 1969). Epstein reported on renal epithelial neoplasms induced by oral aflatoxin in male Wistar rats (Epstein et al, 1969).

In particular, renal cancer can be induced in rats by long continued feeding with a diet containing large quantities of lead acetate (Dukes, 1961). This finding might concern those who work in trades which use lead (e.g. soldering used by plumbers). Is lead which is present in town air, food and water an etiological factor in human renal cancer?

Bennington and Laubscher (1968) studied the association of cigarette, pipe and cigar smoking and tobacco chewing among 100 patients with renal adenocarcinoma, as compared with that among 100 controls. They found that among men with renal cancer the proportion using all types of tobacco was significantly greater than among corresponding controls. They stated: "The estimated risk of men developing renal adenocarcinoma was increased with all forms of tobacco use". The incidence of renal cancer is 50% higher and of bladder cancer 90% higher in cigarette smokers as compared with non-smokers.

Hansen and Bichel (1952) discussed the carcinogenic effect of sulfonamides: when administered to mice and rats an increased incidence of expected tumors was produced and in addition renal adenocarcinomas occurred which were not seen in the control animals.

Renal neoplasms can be found in association with a variety of pathological conditions affecting either the kidney or other parts of the body. Some lesions such as pyelonephritis are secondary to the tumor, whereas others may be merely coincidental. It seems difficult to deny, however, that renal stones can play a role in the development of some tumors, at least squamous cell carcinoma and mucous secreting adenocarcinoma of the renal pelvis (Duvergey, 1938; Murphy, 1961; Potts, 1932; Riches, 1964; Suzuke, 1965). The coexistence of renal cancer (especially nephroblastoma) with various malformations, is especially significant (Fraumeni, 1967; R.W. Miller, 1964; Porter, 1920; Riches, 1964). Benson et al (1963) stated that malignancy involving the kidneys or adrenal glands has been noted often enough in children with congenital hemihypertrophy to justify careful regular clinical examination of these patients.

Renal carcinoma is rare in Sweden, its yearly incidence being about one per 183,000 inhabitants. Analgesic abuse was found to be a frequent feature in patients with renal pelvic carcinoma in Göteborg, Sweden, and middle aged women comprised a greater proportion of the patients than is described in the literature.

Bengtsson (1969) described a study in which 9%of patients with analgesic nephropathy developed renal pelvic carcinoma in a few years. Manifest development of the tumor usually came some years after cessation of a heavy consumption of phenacetin containing drugs. Some patients also developed carcinoma of the urinary bladder.

In another study made at the county hospital in Jökoping, most of the patients with renal pelvic carcinoma were found to be men who worked in a small arms factory and who were "heavy users of analgesics".

These findings suggest the need to study this possible cause of renal cancer in other countries.

Smith and Niles (1957) noted that renal cancers are a distinct rarity during pregnancy. They found only eight cases recorded in the literature. They noted that renal cancer seems to spare women in the child bearing age. The majority occur in the ages of 40 to 60 years.

Penn and Edelstein (1962) reported one case associated with pregnancy. After surgery and radiotherapy the pregnancy was terminated at 37 weeks and a live female was born. Post partum palliative cobalt irradiation was given and the patient was alive when reported. In this case the pregnancy did not affect the rate of tumor growth and the tumor did not adversely affect the pregnancy. These authors also reviewed the literature.

What role has radiotherapy played in the genesis of renal neoplasm? Koletsky and Gustafson (1955) appear to have been the first to produce renal cancer by whole body irradiation. Berdjis (1959) found that although spontaneously occurring kidney tumors are very rare in mice, irradiation seems to be responsible for producing kidney

tumors in 10% of irradiated mice. Spontaneously occurring renal tumors are also rare in rats. Irradiation is highly carcinogenic for rat kidney and rats are more susceptible to renal neoplasms than any other species: over a third of the rats developed kidney tumors, similar in structure to those of mice and man: multiple, bilateral, multicentric, miliary and essentially cortical. The radiation-induced kidney tumors in rats appeared to be tubular in origin as in man. This is in contrast to those in mice in which they seem to arise from the glomerular capsules, with secondary tubular involvement. Riches (1964) cites radiation, including thorotrast, as one of the causative factors of renal cancer in man. It would be of interest to know if the mothers of children with Wilms' tumor had been irradiated during pregnancy more frequently than controls as has been documented by others for leukemia and other malignancies in such children (Ford et al, 1959; MacMahon, 1962, 1964). Since renal cancer currently ranks among the most common form of malignancy in infants and children, accounting for about 25% of all neoplasms in children (Campbell, 1963), all efforts should be made to discover other possible causative factors. The embryo and the young infant should be protected against carcinogens whether they be viruses, physical agents such as radiation or carcinogenic compounds.

Wilms' tumor is one of the commonest tumors occurring in the first decade of life, rating second only to neuroblastoma. Harvey (1950) states that 75% of the cases of Wilms' tumor occur before the age of five. Klapproth analyzed 1351 cases in the world literature 1940-1958 and at the Cleveland Clinic where the incidence was one in 6000 patients.

Wilms' tumor occurs rarely in adults. Newman and Vellios (1964) reported two such cases aged 72 and 61 years and cited 77 others which had been previously reported (aged 18 to 80 years). It occurs in slightly more men than women. Symptoms and signs resemble those for hypernephroma but in general the course of the disease is more rapid, with local recurrence and distant metastases frequently occurring after surgery. These tumors are often very large. Others who have reported or reviewed such cases include Loeb (1943), Silver (1947), Esersky et al (1947), Culp and Hartman (1948), Livermore (1953), and Jagasia and Thurman (1965). Esersky et al (1947) stated that nearly 80% of the adult cases have occurred in the fourth, fifth, and sixth decades of life. "One diagnostic observation is offered: a patient with an unusually large kidney mass, along with a high elevation of temperature, without evidence of any noticeable urinary infection, should cause one to be suspicious of the possibility of Wilms' tumor."

Heredity: The possible role of heredity in renal cancer has been considered by a number of physicians. The first to do so was Walker (1897) who cites two cases in brothers and "thought this pointed to a hereditary influence".

Chapian (1948) describes a family in which the paternal grandmother had four boys and three girls. All four boys died at about the age of two of unknown causes. One of her grandsons died at the age of three, 6½ months after nephrectomy and a second sibling grandson died at three years, 5½ months after nephrectomy. Onset of the second case occurred 18 months after onset of the first.

Deuticke (1931) reported a case of two siblings with Wilms' tumor. Fitzgerald (1955) described a case of bilateral Wilms' tumor in a 14 month old girl whose father and sister had undergone nephrectomies for Wilms' tumor. Gaulin (1951) described the simultaneous onset of Wilms' tumor in identical twins, in the right kidney in one and the left in another. Both died.

Maslow (1940) reported three cases of Wilms' tumor and possibly a fourth in a family in which there had been no definite family history of cancer. It is of interest

however that the mother had three sisters and two other children who died in infancy of unknown causes. This family resembles that of Chapian cited above. Perhaps there were several other unrecognized cases of Wilms' tumor.

Strom (1957) reported a family in which five children in three generations died between the ages of one and three years with a diagnosis of renal or abdonimal tumor. In one a diagnosis was verified. In two the clinical diagnosis was renal tumor and in two abdominal tumor. (Case 5 in this family had a different mother who had previously borne a healthy child.) He stated that five previous Wilms' tumor families had been reported.

Liban (1940) reported the occurrence of unusual renal neoplasms in two male siblings, the second and fourth child of a Yemenite woman. The first case died 48 hours after birth with multiple metanephric hamartomas in his kidneys. The second case was stillborn three years later. He had multiple nodules of Wilms' tumor (bilateral). Liban considered these cases as support for the origin of Wilms' tumor from embryonic tissue.

Fitzgerald and Hardin (1955) reported bilateral Wilms' tumor in a 14 month old girl whose father and sister had undergone nephrectomies for Wilms' tumor. They reviewed previous reports of five other authors.

Klapproth (1959) stated that the occurrence of Wilms' tumor in the same family may be purely incidental. He found only eight families out of 2000 in which this had occurred.

Riches (1964, p. 354) believes that the make-up of the patient, his attitude to life and disease as well as his physical condition have a bearing on his resistance to all diseases (not merely renal cancer). Such attitudes can be similar in a family.

As to familial renal cancer occurring in adults, we found only three reports. Riches observed only one instance of two cases in a family among 130 cases (1964). Rusche (1953) reported on "silent" adenocarcinoma with solitary metastasis occurring in two brothers. Onset of the second case occurred five months after onset of the first. Both died.

Brinton (1960) reported a family in which genetic transmission of renal cancer appeared likely: the father died from "a kidney tumor", the mother from "cancer" (no autopsies). Of their five children, three developed hypernephroma, confirmed by biopsy or autopsy. Two living children of those who died were mentally retarded.

Renal Cysts

The association of renal cysts and tumors of the kidney is of such frequency as to suggest a causal relationship. Gibson (1954) stressed the importance of investigating every case of cystic disease of the kidney for associated malignancy either within the cyst where it may exist only as a minute remnant at the base, or as a well-defined growth outside and medial to the cyst.

Spence et al (1957) reported that every case of apparently benign cyst should be regarded as potentially associated with tumor, particularly if cyst contents are hemorrhagic.

PATHOLOGY AND DIAGNOSIS

Prior to 1900 nearly all malignant renal tumors were classified as sarcomas. Then they became known as hypernephromas, but pathologists are now agreed that they are carcinomas arising in the renal tubules. These comprise 80-90 % of primary malignant growths in the kidney. Cases of malignant lymphoma, hemangiopericytoma, plasma cell cytoma, leiomyosarcoma, hamartoma, mucous adenocarcinoma and mixed tumors have also been reported. Renal tumors of nervous origin are extremely rare. Exfoliative cytology is rarely useful. Exfoliation occurs late in parenchymal tumors and this test is usually negative in renal carcinomas. The histological grading of the tumor is an important prognostic factor (Riches, 1951). In adenocarcinoma, invasion of the renal vein is more probable if the growth is of a high degree of malignancy.

Renal carcinomas usually develop in the cortex and somewhat more often in the upper pole than in other areas. When first detected they are usually over 5 cm. in diameter. The size is not necessarily an indication of biologic behavior, resectability or prognosis. Almost half these tumors will have penetrated the capsule when first seen.

Metastases occur by both hematogenous and lymphatic channels. Approximately 22 % will have involved the regional lymph nodes prior to surgery. The commoner route of metastases is the venous — a unique characteristic of this tumor, probably due to the large blood flow of the kidney and its proximity to the vena cava. This significantly affects prognosis. Renal vein involvement may progress to vena caval obstruction or sudden death due to massive tumor thrombus. These tumors tend to outgrow their blood supply, resulting in necrosis and hemorrhage, with localized pain and ultimately calcification.

Diagnosis is primarily based on radiologic examinations and with the available modern techniques properly utilized, surgical exploration is seldom necessary.

Many urologists including Ochsner (1965) and Creevy (1935) have stated that malignant renal tumors should be classed with syphilis and tuberculosis as among the great mimics encountered in clinical medicine. By direct pressure, by necrosis or hemorrhage, by extension or by metastases they can produce the clinical appearance of an amazing variety of disorders. Approximately 45 % of these tumors produce no symptoms directly related to the primary tumor (Creevy, 1935). Lesions in the spine will compress the cord with subsequent paraplegia. Sciatic pain in the sacroiliac region is not uncommon. The metastatic bone lesion is osteolytic and may be interpreted as osteogenic sarcoma, giant cell tumor or tuberculosis. Bone metastases causing pain tend to be recognized earlier than those in the lung or brain.

The classical triad of flank mass, flank pain and hematuria is said to be present in only 10-15 % of the cases according to many urologists, and they are late manifestations of disease. These tumors metastasize to many different parts of the body, therefore the first presenting symptom is not uncommonly due to a metastasis, either in the lung, bone or brain.

Nausea, vomiting and constipation may occur in about 18 % of the cases, due to retroperitoneal irritation from the renal tumor. Anemia may be present in almost a third of the cases. Secondary polycythemia is seen in 3 or 4 % of these patients. Anorexia and other gastrointestinal symptoms, weakness, weight loss and anemia are usually associated with metastases or develop late in the course of the disease. Hypertension may occur, probably due to compression of the renal artery or its main tributaries.

The following observations are indicative of a fairly high grade of malignancy:

general symptoms with *fatigue* and *loss of weight*. Von Scheeb (1967) found that in his nephrectomized group, the five-year survival rate for patients with such a history was 37.8 % against 60 % for those in whom they were absent.

The five-year survival rate for the group with an ESR of less than 16 mm. was 72%, for those with 16-70 mm. it was 55 %, while for those in excess of 70 mm. it was 25%. Thus an elevated sedimentation rate at time of diagnosis is a poor prognostic sign. In 53 patients with anemia the five-year survival rate was 28 % as compared with 56 % in those without anemia. For tumors 7 to 15 cm. in diameter the five-year survival rate was 39.6% against 69.4% for those less than 7 cm. Where metastases were demonstrable the five-year survival rate was 2%, against 59 % where none were apparent (Von Scheeb, 1967).

Fever·

Fever may occur in 11 to 56 % of renal cancer patients, and is generally intermittent. Weinstein et al (1961) found fever in 11 % of 1238 cases of renal cancer at the Mayo Clinic. Nicholson (1927) reported a case of almost continuous fever with intermittent abdominal pain and general weakness in a woman aged 38, which remained undiagnosed for 11 months in spite of careful examinations. Sometimes fever is the sole presenting symptom of a hypernephroma (Rowlands, 1951). Fever may be due to hemorrhage or necrosis of the tumor with absorption, or to concurrent infection or metastases to the thalamus, or to elaboration of toxins by the tumor cells (Hempstead, 1952). Renal cancer should always be considered in the differential diagnosis of any patient who has a protracted fever of undetermined origin associated with weakness and loss of weight (McCague, 1940). If it continues after nephrectomy, metastases should be suspected (Bottiger, 1964). *Israel (1896) reported that several renal cancer patients exhibiting pyrexia had remained well for a number of years following surgery.*

Diagnostic Procedures in Renal Cancer in Adults

Walters (1933) stated: "The fact that duration of life and completeness of cure are proportionate to the degree of malignancy and the size and extent of malignant lesions of the kidney should serve as a plea for earlier diagnosis and earlier surgical management."

Since early diagnosis provides the best chance of cure, Evans et al(1961) of New York Hospital analyzed 100 cases as to diagnostic procedures. Of these 97 patients had hypernephroma, two lymphosarcoma and one a mucous adenocarcinoma. The diagnosis was established by renal biopsv, surgery and/or autopsy. Eighty-four percent of the patients were between 41 and 60, with a male to female ratio of two to one; 58% had hematuria, 15 % showed a mass and only 10-15 % showed a mass, hematuria and pain. Papanicolaou tests on urines of 55 patients were negative for tumor cells. The right and left kidneys were equally involved. In a third of the asymptomatic patients renal cancer was suspected by noting abnormal shadows during the course of other abdominal x-ray procedures. The excretory urograms and retrograde pyelograms showed some changes in over 90 % of the patients studied. Either renal arteriography or nephrotomography are felt to be more accurate diagnostic procedures. The authors used the latter. In 94 % of the cases an accurate differential diagnosis between renal cysts and cancer was accomplished by nephrotomography, as compared to a 50 % accuracy when relying only on excretory and retrograde pyelograms.

Graham (1947) reported on a survey of 195 cases of renal malignancy and noted that at the time of diagnosis 36 % of the patients showed distant metastases, 48 % in the lungs, 23 % in bone (mostly in spine, ribs, or pelvis), 9 % in the liver. Initial symptoms in 70 % were hematuria and pain, while 31 % had only hematuria. The

finding of a palpable mass in 41% indicated diagnosis had been made very late. Only 35% of the 195 cases had nephrectomy, the result of late diagnosis. Of the 77 patients having nephrectomy 42 died an average of 23 months later; 38% lived less than a year and 26% lived between one and two years. Irradiation was given to 44 inoperable cases, all of whom died within 16 months, the average duration being five months. Graham concluded: "The public must be educated to the importance of adequate investigation of hematuria when it is first noted. This one procedure would markedly improve prospects of cure in at least a third of the cases."

Melicow and Uson (1960) in their large series of 577 renal cancers reported that 185 had no symptoms directly related to the genito-urinary tract. In 95% of these cases fever, weakness, anorexia and weight loss were evident in combination or separately. Fever was present with equal frequency in the clear cell and granular cell carcinomas and occurred in 6% of their cases.

Hale & Burkland (1943) studied a series of 54 unrecognized renal tumors in 6,577 autopsies, and reported a wide variety of other manifestations than the usual triad. These included hypercalcemia, fever, hypertension, anemia, chronic fatigue, anorexia, weight loss, polycythemia and leukemoid reaction. They stated: "Physicians should think of renal disease, neoplasms in particular, in the differential diagnosis of cases of obscure abdominal distress. Urinary findings may be obscure or completely absent. The metastases may give rise to symptoms before the primary." Six of their cases had gastro-intestinal symptoms such as flatulence, nausea, gaseous eructations, epigastric pain, general abdominal distress and vomiting. In seven others central nervous system symptoms such as delirium, stupor, headache, sciatica, personality changes or parasthesias were evident.

Riches et al (1951) analyzed 2,314 cases in the British Isles, 1935-1950, and found a 75% incidence of adenocarcinoma and an 8% incidence of Wilms' tumor. This large series has confirmed the importance of accuracy of diagnosis, and brought to light the improvement in results in adenocarcinoma obtained by post-operative radiation. Of the total group, 33% survived five years.

Renal cell carcinoma is very rare in children. They found only five cases out of 1746 under the age of 20. Only about 50 cases have been reported in the literature (Palma et al, 1970). Others who have reviewed the literature include Aron and Gross (1969). They noted abdominal mass in 76% of the 30 cases they had collected, and hematuria in 45%. Borovoy and Rome (1963) collected 52 cases. They stated it is almost always unilateral, and occurs more often in boys than girls. Metastases occur by direct extension of the growth through the capsule and into the renal vein with showers of emboli into the blood stream. Carlson (1953), Grabstald (1969), Marcus and Watt (1966) give individual reports. Mogg (1957) mentions the case of Philip and Salin in 1913 which may be the first known reported case.

The most important prognostic factor is the histological grading of the tumor. In adenocarcinoma, invasion of the renal vein is more probable if the growth is of high malignancy. In the B.A.U.S. series of 1746 cases, 362 were deemed inoperable and were untreated (Riches, 1951).

Malignancy Associated Changes in Renal Cancer in Adults

Renal cancer is one of the human tumors which have acquired the capacity to elaborate a substance which profoundly modifies the host's physiology. Some of these tumors secrete an erythropoietin and cause polycythemia. This was first reported in 1929 according to Drivsholm (1960). Damon et al (1958) stated that the syndrome occurred in 4.4% of 205 cases of polycythemia, and 2.6% of 350 patients with renal cancer at Presbyterian Hospital. Of the 22 such cases, eight who underwent a nephrectomy had subsequent hematologic remission. The polycythemia can therefore

be regarded as secondary to the renal cancer. Drivsholm (1960) reviewed 41 previously reported cases and described one of his own. Others reporting such cases include Hewlett et al (1960), Rosenbach and Xefteris (1961) and Wemeau et al (1960). Murphy et al (1970) found increased erythropoietin (ESF) values in 49 plasma samples and in 14 cyst fluids of 92 patients with renal cell carcinoma or renal cyst. High levels of ESF and sometimes of erythrocytosis were observed in renal cancer patients. These subsided following nephrectomy. Those with renal cysts frequently had highly elevated ESF levels but not erythrocytosis. The ESF levels fell following cyst excision. The highest levels of ESF were seen in patients developing metastases after nephrectomy. Androgen therapy in these metastatic cases caused further substantial elevations of ESF levels. Renal neoplasms and renal cysts appear to serve as aberrant sites for production and/or storage of ESF. Also the erythrocytosis of patients with renal disorders is ESF dependent, unlike that seen in polycythemia vera which is not ESF dependent.

Others have reported that certain "renal adenocarcinomas appear to contain a parathyroid hormone-like substance" and are associated with hypercalcemia (Goldberg et al, 1954). Lytton et al (1965) noted that excision of the renal tumor results in prompt relief of symptoms and serum calcium levels return to normal. Extracts of such tumors were examined immunochemically and a parathyroid hormone-like substance was identified. Recurrence three months later was associated with recurrence of symptoms of hypercalcemia and a rise in serum calcium.

Whisenand et al (1962) studied some host factors in the development of 83 cases of renal cell carcinoma. They found an increased incidence of adrenocortical hyperplasia associated with renal cancer. Also comparatively common were adenomatous nodules of the parathyroid and pituitary glands, as compared with non-cancerous controls. A high incidence of atherosclerosis was also found associated with renal cancer.

Symptoms of Wilms' Tumor

Most children are first seen when the tumor is palpable. Often an abdominal swelling or the tumor itself is noticed by the mother when bathing the child. The lesion may be discovered by the mother after an abdominal trauma, with or without rupture of the tumor, causing enough pain to consult a physician. Fever and abdominal pain rank second in frequency. Hematuria is rather uncommon. In advanced cases the following symptoms may occur: constipation, irritability, listlessness, loss of or failure to gain weight, pallor and finally cachexia. These are caused by the increasing compression of the abdominal organs by the tumor, displacement of the kidney, traction on the renal pedicle, necrosis of renal or neoplastic tissue, hemorrhage into the pelvocalceal system and neoplastic anemia. Hypertension has been observed as a concomitant symptom by several observers, presumably caused by perirenal inflammatory reaction, renal ischemia, compression of large arteries, infiltration of renal parenchyma or thrombosis of large vessels. In several cases it was reversed by nephrectomy, in others this was only temporary (Klapproth, 1959).

Early discovery of Wilms' tumor is still the key to successful treatment. This tumor does not usually affect the child's general health until late when metastases have already appeared. Thus when a painless abdominal mass is discovered in a sick child, it is usually too late (Lattimer et al, 1959).

Danger of Diagnostic Procedures

A number of authors have cautioned against the dangers of diagnostic procedures, i.e. too numerous studies, too much palpation. The first to do so were

Burdick (1948) and Daw (1948). Burdick stressed the need of educating physicians and teachers as well as parents of the existence of Wilms' tumors in children and added abdominal tumors should "be considered as a strict emergency in children". He "advised restriction of examination and palpation to an absolute minimum". Daw observed a case of a one-year-old child who had been treated with massages after a fall on the abdomen, in whom widespread metastases developed before medical help was sought. Huguenin et al (1953) in discussing the diagnosis and treatment of Wilms' tumor warned against all procedures which may traumatize the tumor as they are dangerous and may cause rupture, hemorrhage or dissemination of metastases. They advised against pyelograms or ureteropyelography except in rare cases, believing that in most cases urography is sufficient. Spangberg (1960) describes a case of renal carcinoma with massive spread of tumor emboli to the left lung. Embolism occurred on two occasions, the first at urography, the second at operation. The probability that mechanical injury may cause detachment of tumor cell emboli is illustrated. Traumatization of malignant renal tumors at examination and at operation should be avoided so as to prevent the spread of tumor cells.

Moore et al (1960) also stated that "tumor cells may be spread by the physician and surgeon during examination, diagnostic procedures and operative manipulations".

Koop (1965) stated that at the Children's Hospital of Philadelphia Wilms' tumor is treated "like a bomb about to go off" by immediate surgery to excise the tumor, x-ray to the tumor bed and actinomycin D, on the day of surgery and for four days thereafter.

Pearson and Pointon (1964) stated that in Wilms' tumor "a minimum of investigation should be done, i.e. a blood count and urinalysis: a screening test for urinary catecholamine excretion may help in differentiating Wilms' tumor from neuroblastoma, being normal in the former and raised in the latter. Films may show calcification which is more characteristic of neuroblastoma. An intravenous pyelogram may reveal evidence varying from complete absence of function of the affected kidney to only slight distortion of the calyceal pattern".

Bilateral Renal Cancer in Children

Sheath (1953) stated that Wilms' tumor may be multiple in one kidney or involve both. Among those who have reported cases of bilateral Wilms' tumor are Feeney et al (1955) who stated that the high incidence of bilateral lesions suggests that it should be considered in all cases. They believed these tumors may have a multicentric origin. In Ritter and Scott's case the development of the second tumor occurred 10 years following the first. They reported: "In our case the x-ray therapy may have contributed to the development of sclerosis and fibrosis and thereby accelerated the progression of the disease process (renal failure) in the remnant kidney". A very large dose (6400 r) had been given. L.S. Scott (1954) collected 34 cases from the literature, half of them prior to 1914 and recorded a case of his own. He suggested that the majority of the reported cases represent metastatic spread to the opposite kidney, although a few at least do appear to represent bilateral primary growths.

Fitzgerald and Hardin (1955) reviewed previous reports by five others and described their own case of bilateral Wilms' tumor in a 14 month old girl whose father and sister had undergone nephrectomies for Wilms' tumor. Johnson and Marshall (1955) give descriptions of three bilateral cases. Abehouse (1957) collected 44 bilateral cases. Klapproth (1959) collected 17 such cases in addition to the 34 cited by Scott.

Flannery (1958) reported: "The possibility of survival after surgical removal of

bilateral Wilms' tumors accompanied by appropriate preoperative and postoperative deep x-ray therapy is illustrated by report of a case 7½ years after removal of the right kidney and five years after resection of the left. The patient continues in good health with no evidence of metastases or recurrence. In spite of removal of two-thirds of her normal kidney mass, her pattern of growth and development is unaltered."

Rickham (1957) also reported a survival in a bilateral case of Wilms' tumor. A girl was operated on for a very large tumor of the right kidney: the growth was removed with a diathermy needle after clamping the blood vessels. The left kidney and tumor (also large) was then removed. Postoperative x-ray therapy (2800 r tumor dose) was given to the whole abdomen, shielding the remains of the right kidney (only two-fifths remained). The child was thin and delicate and during the next winter she had several upper respiratory infections. She was attractive and normal, with no evidence of disease when reported 18 months later.

Gyepes and Burko (1964) reported another apparent survival of a bilateral Wilms' tumor which simulated multicystic disease in a 13 month old girl. She received Co60, x-rays and actinomycin D, which caused clinical and radiographic decrease in the size of both kidneys and a return of the ureters to normal course and position. The child was asymptomatic and the chest film was normal when the case was reported 11 months later.

Stein and Goodwin (1966) reported a patient with bilateral Wilm's tumor surviving 10 years after treatment. They stated: "This case is certainly illustrative of the fact that one cannot tell how effective radiation therapy will be until tried. Also, that one should not give up hope". They believed that the incidence of involvement of both kidneys may be as high as 5 or 10 % . "The supposedly normal kidney should be examined at the time of surgery to rule out bilateral involvement. When patients with bilateral Wilms' tumors are treated, the possibility of producing radiation nephritis must be kept in mind."

Cochran & Froggatt (1970) reported the first known cases of bilateral Wilms' tumor in siblings. They made an extensive review of the literature on bilateral cases and stated in conclusion: "Extensive partial nephrectomy leaving only 15 to 35 % of renal tissue has been shown on 15 year follow-up evaluation to be compatible with health and vigor. Given gentle handling, clamping of the pedicles can be well tolerated for at least 18 minutes, for up to 26 minutes by local cooling or cold perfusion to 23°C and perhaps for even longer by cooling to 15° to 10°C."

Knudson et al (1972) reviewed the literature on bilateral and familial cases of Wilms' tumor. They reported: "Statistical analysis of cases of Wilms' tumor supports a 2-mutation model previously reported for retinoblastoma. Comparison of data for familial, bilateral, unilateral and unselected cases reveals that familial and bilateral cases have an early average age of diagnosis with a distribution suggestive of a single-event process, while unilateral and unselected cases do not. Familial cases have an incidence of bilaterality higher than that of unselected cases and a pattern consistent with autosomal dominant inheritance. These findings suggest that Wilms' tumor may be attributed to a 2-mutational model, i.e., 2 mutations are required in all cases, but, in approximately 38 % one mutation has occurred in the germinal line of one parent and is inherited. Persons acquiring this germinal mutant develop an average of one second mutation each, which gives rise to tumor. Approximately 37 % of gene carriers do not develop tumor, and 15 % develop bilateral tumors. About 62 % of cases of Wilms' tumor are non-hereditary, both of the mutations occurring in somatic cells. The association of Wilms' tumor with aniridia, hemihypertrophy and genitourinary anomalies is fitted to the model. The familial pattern is noted to be similar to that of a delayed mutation; new germinal mutations may be attributable to a vertically transmitted tumor virus resembling the virus causing renal sarcoma in chickens."

Bilateral Cases in Adults

Among those reporting bilateral renal cancer in adults were Campbell (1948) who believed their occurrence appears confirmatory of the congenital nature of the lesion and Bastable (1950) who collected 20 cases in the literature, all fatal except one who was alive 18 months after the second operation which was performed 15 years after the first. One of his own cases survived 10 years, the other 14 years. Thompson et al (1958) reported a case of bilateral squamous cell carcinoma of the kidney in a 52 year old man who died 29 days after admission.

Klotz (1960) reported a case in a 59 year old woman who 20 years previously had had her other kidney removed for hypernephroma. "The specimen showed evidence of lymphatic invasion." She remained well except for mild diabetes mellitus and a benign duodenal polyp removed in 1950. A mass the size of an orange was resected from her remaining kidney in 1958 and she remained in good health with no evidence of disease a year later.

The predisposition of patients afflicted with retinal angiomatosis to have in addition intracranial lesions such as cerebellar cysts, cerebellar and medullary angioblastic tumors, pancreatic cysts, renal cysts and hypernephroid tumors was initially described by Lindau in 1921. This occurs in 20% of patients with retinal angiomas (Kaplan et al, 1961). These authors describe two cases at Mayo Clinic with bilateral renal cancers. In each the renal lesions presented a greater threat to life than the intracranial lesion.

Others reporting on bilateral renal cancer include Brocks et al (1963) and Carroll (1965) who reviewed 11 cases in the American literature as well as a personal case.

Second Primary in Patients with Renal Cancer

Rarely dissimilar tumors may develop simultaneously in the same kidney and ureter of the same upper urinary tract. Ravich et al (1964) reported a case of two primary clear cell carcinomas developing in the same kidney. Richardson and Woodburn (1963) describe a case of hypernephroma of the right kidney and transitional cell papillary carcinoma of the right ureter, Grade 1. This patient was alive and well a year after operation. Rupel and Sutton (1950) described a case of carcinoma of the renal parenchyma associated with papillary carcinoma of the same kidney and metastases to the skin.

A number of authors have reported cases of renal cancer who developed a different type of malignancy. Kline (1955) reported a case of adenocarcinoma of the kidney with simultaneous papillary carcinoma of the bladder. Lent et al (1960) reported a case of transitional cell carcinoma of the renal pelvis who developed a tumor of the bladder three years later. Marshall (1961) described a case with squamous cell carcinoma of the renal pelvis in the surgically removed right kidney who died 18 months later of pulmonary metastasis which showed the picture of a muco-epidermoid carcinoma with goblet cells. Wilson (1961) described a case of two simultaneous malignancies in the kidney and colon, which is rare indeed. Only 17 cases had been reported in the literature, chiefly in autopsy material.

Whisenand et al (1962) collected 14 cases of multiple primaries occurring in patients with renal cancer. The second primary occurred in the lung, stomach, colon and prostate, in descending order of frequency.

Hajdu and Thomas (1967) analyzed 100 autopsied cases of renal cell carcinoma. Of these 30 had a second primary malignant neoplasm, almost all of whom were men, six years older on the average than patients with renal cancer alone. They also found that the most common sites were the lungs, stomach, and colon. This high incidence in elderly men suggests the need to rule out the presence of a second primary before the non-urogenital symptoms are attributed to a renal cell carcinoma.

Only two references were found to reports of a second primary in patients with Wilms' tumor. Ritter and Scott (1949) described a case in which an embryoma of the contralateral kidney developed 10 years after nephrectomy for Wilms' tumor in a 5½ month old child.

They stated that the pre-operative x-ray therapy (6400 r) given in this case may have accelerated the progression of the disease process (renal failure) in the remaining kidney. This patient died over 10 years after onset of the Wilms' tumor.

Regelson (1965) describes a case of Wilms' tumor treated by radiation who developed a chondrosarcoma of a rib 15 years after irradiation (in the area irradiated for lung metastases).

Carcinomas of the kidney usually metastasize via the inferior vena cava to involve the lungs (Arkless, 1965). One of the main routes in reaching the bones is the paravertebral venous plexus of Batson. This helps explain a) the frequency of axial metastases, b) the frequency of involvement of those lumbar vertebrae nearest the primary and c) the tendency for involvement of the ipsilateral bones. Spread via the lymphatics is also felt to play a role in the metastases reaching the mediastinal and supraclavicular areas. A better understanding of the modes of spread may help determine the proper diagnostic procedures and assist in guiding the rationale of surgery and immunotherapy.

The dangers of pre-operative mismanagement, too numerous diagnostic studies, etc., have already been discussed.

As to the sites of metastases in renal cancer, pulmonary metastases occur most frequently. Fried (1946) noted that of 203 patients dying of renal cancer 54 % had pulmonary, pleural or mediastinal metastases and 45 % had skeletal metastases. Nalle (1947) reported that in his series 46 % metastasized to the lungs or pleura. These may be asymptomatic or may give rise to hemoptysis, chest pain or dyspnea and chest films will show round areas of increased density. Some cases may stimulate a primary bronchogenic carcinoma (Maytum and Vinson, 1936; Nofsinger and Vinson, 1942).

Gerle and Felson (1963) state that patients with metastatic endobronchial metastases often develop hemoptysis and other pulmonary symptoms as well as x-ray and pathological evidence of the endobronchial lesion before the primary renal tumor becomes evident. Thus a diagnosis of bronchogenic carcinoma is often made initially. Histologic examinations of the expectorated masses will establish the correct diagnosis.

Silverberg et al (1969) discussed the clinical and pathological features of initial metastatic presentations of renal cell carcinoma, and gave two examples. The first was a case involving an expectorated endobronchial tumor and the other a solitary costal lesion. They cautioned: "The absence of clinical or laboratory findings suggestive of a primary renal tumor does not rule out this diagnosis and a high level of suspicion must be maintained."

Other sites in which renal cancer may metastasize include the inguinal, mediastinal and supraclavicular lymph nodes (15 % in Nalle's series); the urinary tract and adrenals, the liver, brain, mesentery, colon and spleen. Others have reported the following incidence of metastases: lung 55 %, liver 30 %, regional lymph nodes 35%. Bone involvement is so common that any obscure instance of bone tumor in patients over 40 should suggest renal neoplasm. The absence of clinical or laboratory findings suggestive of renal tumor does not rule out the diagnosis of a solitary renal cancer metastasis (Silverberg et al, 1969).

Renal cancer may also metastasize to the thyroid gland. Caylor (1936) reported such a case occurring 13 years after nephrectomy (Table 3, Case 4). Linton et al (1946) reported another case and stated it was the 16th proven case in the literature and the first ever seen at Massachusetts General Hospital (Table 3, Case 5). In Denton and McClintock's case (1949) the thyroid metastasis occurred eight years after nephrectomy (Table 3, case 7).

Jenssen (1952) reported a case of renal carcinoma that metastasized to the pancreas 14 years after nephrectomy (Table 3, Case 9).

Abeshouse (1961) found 12 cases of penile metastases from renal carcinoma, priapism being the initial symptom in these patients.

Middleton (1967) reviewed 503 cases of renal cancer at New York Hospital between 1932 and 1965. When first seen, 28 % of these patients had distant metastases. Nevertheless 23 % were subjected to nephrectomy, but none is known to have survived two years. In this series none of the distant metastases regressed, with or without nephrectomy. In contrast, Middleton noted that nephrectomy and excision of a solitary metastasis from renal cancer is worthwhile. The survival rate in the reported cases is essentially the same as that following nephrectomy in the apparent absence of metastases. This will be discussed in greater detail below (See Table 5).

Garrow and Kienan (1912) reported a case of latent hypernephroma with a solitary metastasis to the spine. McClanahan and Bonann (1953) reported on three cases in which osseous metastases were the first evidence of the presence of a renal carcinoma.

Tavernier (1941-42) reported a case of hypernephroma with metastasis to the humerus. The metastatic lesion was resected 20 days after nephrectomy. X-ray therapy was then given to the supraclavicular lymphadenopathy which subsided. The patient gained over 25 pounds and remained well when the case was reported some weeks later.

Rusche (1953) reported silent adenocarcinoma of the kidney with solitary metastasis occurring in two brothers. In the first, a physician, aged 33, the metastasis was to a rib. He refused all surgery and died eight months after onset of bizarre symptoms. Onset in his 33 year old brother's case occurred 15 months later: severe headaches due to a metastasis in the right occipital region: biopsy only, death a year later.

Edelman (1941) reported a case of hypernephroma with solitary metastasis to the cerebellum. Onset occurred following an upper respiratory infection of one week's duration, with severe headaches, dizziness and unsteadiness in a 51 year old female. The brain lesion was removed with marked improvement mentally and physically followed about five weeks later by nephrectomy and deep x-ray. The patient was well two years later.

Stortebecker (1951) reported on 19 cases of brain metastases from hypernephroma, of whom 17 were operated. One patient lived 14 years after brain surgery (Table 5, case 4). The most favorable prognosis was in those in whom nephrectomy was done prior to development of cerebral symptoms.

Starr and Miller (1952) reported on a case in which a solitary jejeunal metastasis developed 20 years after nephrectomy for renal cell carcinoma (Table 3, Case 8).

Klimpel (1957) describes an unusual case: a male aged 65 had a right nephrectomy for a tumor the size of two fists adherent to the peritoneum. He was given postoperative x-ray therapy. About 22 months after surgery a piece of tumor the size of a plum and several smaller pieces were excreted during defecation, followed by periods of intestinal hemmorhage. These were partially necrotic, markedly hemorrhagic but still recognizable hypernephroma which after metastasizing and perforation into the intestine were spontaneously discharged. Three weeks later another plum-sized piece which proved to be metastatic hypernephroma was discharged at stool, again a brief period of intestinal bleeding occurred; 12 days later a piece the size of a chestnut and several blood clots were excreted at stool. Barium enema then revealed an uneven jagged outline in the area of the cecum apparently the site of the metastasis. He remained well thereafter until May 1956, when gastroenterostomy was performed for benign pyloric stenosis due to an ulcer scar. There was no evidence of renal cancer present in the para-aortic lymph nodes, intestine, mesentery or liver. (See Table 2, Case 6)

Cutaneous metastases from renal cancer were discussed by Connor et al (1963). They found 52 such lesions in 40 patients in a series of 588 surgically removed renal carcinomas. They noted the frequency of involvement of the skin of the face and scalp. In eight of 15 examples in which the pathologist had no reason to suspect the presence of a renal cancer, the lesions were interpreted as primary cutaneous tumors most often of sweat gland origin.

Ferris and Beare (1947) reported on an unusual metastatic lesion occurring in the urinary bladder at the ureteral orifice in a child six months after right nephrectomy for Wilms' tumor.

Falkinburg et al (1954) reported an unusual case of Wilms' tumor of the left kidney in a seven year old child that remained asymptomatic eight years after removal of a tumor 20x15x10 cm. which had invaded the renal vein. Following surgery postoperative radiation was given (1800 r). As a result of a diffuse phlegmon, a fecal fistula appeared in the left loin (fever, pain, bowel obstruction). She was explored and a hard metastatic mass in the left colon was resected. She developed severe left shoulder pain and ascites. Death occurred about 10 years after onset, and two months after resection of the metastasis (Table 3, Case 10).

Altug et al (1964) reviewed the literature on Wilms' tumor in adults and reported a personal case. In this patient the initially successful removal of multiple bilateral pulmonary metastases occurred seven years after surgical control of the primary and was followed by two operations for removal of cerebral metastases. Death occurred 8½ years after onset.

Culp and Hartman (1948) collected 97 cases from the literature and added eight of their own. Altug et al (1964) stated that 37 more cases have been reported since 1948 including their own case. In adults the peak incidence appears to be in the fifth decade.

Wilms' tumor varies considerably in size. It may grow enormously and destroy the kidney and surrounding structures and fill the abdomen. The largest tumor, reported by Van Gulik weighed 22 pounds.

Dean and Pack (1932) noted that cutaneous metastases occur rather infrequently in patients with Wilms' tumor.

Goulding (1947) noted the rarity of orbital metastases from Wilms' tumor. He described a case in which the child was struck in the eye when he fell out of bed. Three weeks later metastasis had developed at the site of the injury. Post-mortem showed a Wilms' tumor of the kidney with ocular metastasis as well as lesions in the flat bones of the skull.

Renal cancers may very rarely metastasize to the testis. Bandler and Roen (1946) record such a case in which the metastasis antedated the clinical detection of hypernephroma by two years. The patient remained well 3½ years after orchiectomy and a year after nephrectomy. In this case there was a concurrent abscess in the testicular metastasis. This may well have exerted a retarding effect on the primary which lasted two years.

Gore and Barr (1958) reported two rare cases of cancer metastasizing to cancer. In each case a widespread carcinoma originating in the prostate and breast respectively formed secondary deposits in a localized hypernephroma. This sequence was true, they stated, in more than two-thirds of the reported cases. It was suggested that the success or failure of a secondary tumor to implant and grow depended upon competition with the host tumor for nutrients. The rarity of metastases to cancer would indicate that most often the supply of these substances is inadequate for the simultaneous support of two malignant growths. Localized hypernephroid tumors are considered dormant growths, which have not yet attained the degree of anaerobic metabolism which characterize fully malignant neoplasms. The smaller nutritive requirements of this form of tumor might well explain its relative frequency as the recipient neoplasm.

Sometimes pulmonary metastases are present when the diagnosis of renal cancer is made. In other cases they may develop many years after nephrectomy (see Table 3).

Urologists and thoracic surgeons should be more optimistic about attempting resection, lobectomy or pneumonectomy for cases with one or two lesions, especially when only one lung is involved, whether these are present prior to nephrectomy or develop later.

Barney and Churchill (1939, 1944) appear to have been the first to successfully resect pulmonary metastases in a case of renal carcinoma. In this case host resistance had apparently been stimulated by pulmonary tuberculosis in the other lung. The patient made a complete recovery and lived 25 years, dying of coronary artery disease. Table 5 gives 29 examples of such cases. Many more have undoubtedly been obtained but have not been published.

Lent et al (1960) stated: "Surgical treatment of pulmonary metastases from malignancies of various types has proved to be a valuable addition to the treatment of cancer. The presence of one or two metastatic nodules in the lung no longer means that all hope for cure or palliation is gone. Rather the presence of these nodules should evoke an all-out effort to further and possible complete eradication of the malignancy."

Groves and Effler (1956) reported on 30 cases of lung metastases treated surgically at the Cleveland Clinic. Two of their cases are cited in Table 3. These authors believe that the *minimal resection* that allows total removal of a metastatic lesion with a margin of normal tissue on all sides generally is indicated.

Halliday (1959) reported on the results in 27 cases of renal cancer in which resections of pulmonary metastases were performed. In the six cases in which the metastasis was discovered simultaneously with or prior to the primary lesion, 50% survived. He concluded: "Because of the excellent preliminary results that have been obtained in many of these patients an aggressive surgical attitude appears fully justified even though the variability of behavior of this tumor requires a longer period of observation for final evaluation of results."

Cliffton and Pool (1967) reported on the good results which may be obtained with surgery for lung metastases in children with Wilms' tumor. Four of their cases are cited in Table 5.

Spontaneous Regression

A number of authors have observed cases of renal cancer in which there was evidence of spontaneous regressive changes in the primary tumor. Fabricius (1911) and Kraft (1920) reported cases of hypernephroma in which extensive areas were fibrotic, calcified or cystic. Goldstein and Abeshouse (1938) reviewed the literature on cases of calcification and ossification and stated they felt that in their experience "calcification of a renal neoplasm may be considered a favorable sign". However, in the same year Cahill and Melicow reported that they believed calcification was a bad sign. Only one of their cases with calcification survived a two-year period without metastases.

Goodwin et al (1967) discussed the circumstances under which regression of hypernephroma occurs. They reported: "It seems reasonable to accept the evidence that primary renal tumors not infrequently show evidence of death and some regression (but not 'cure'). Perhaps this is most commonly found in conjunction with calcification. We may also accept that there are a number of reported cases in which a proved or supposed metastasis (usually pulmonary) has disappeared after removal of the primary tumor." He added: "The factors associated with or governing this regression are as yet ill defined and obscure. We intend to continue our policy of recommending surgical removal of seemingly incurable hypernephromas in most cases, even when they occur with known local invasion or distant metastases."

Hultquist (1944) and Bartley and Hultquist (1950) reported on spontaneous regression of hypernephromas. They thought that regressive changes such as fibrous transformation, in conjunction with hyalinization, calcification and ossification often occurs in hypernephroma. They mention the possibility that tuberculosis or endocrine substances are important factors in such regressions. By 1950 they had found healed scars at autopsy in 26 patients who died of other diseases. In 10, the scars contained hypernephromatous tissue, and in seven, cells resembling hypernephroma cells. They were considered healed hypernephromas and were unlike scars following renal infarction, tuberculosis or pyelonephritis.

Bartley and Helander (1962) reported on three cases of hypernephroma in which there were clear regressive changes, demonstrated angiographically. In two the neoplastic tissue had virtually disappeared, and the growths had undergone cystic transformation. In the third the lesion could not be differentiated at operation from an ordinary cyst, and only the demonstration of very spare hypernephroma cells with marked regressive changes in the cyst wall seemed to establish the diagnosis.

Martin and Beckwith (1968) have reported that *a positive correlation between length of survival and tumor lymphocyte infiltration has been well documented* in neuroblastoma. In a few renal cancers with long survival lymphoctyic infiltration was reported.

Dickey and Chandler (1949) regarded calcification in Wilms' tumor as a good prognostic sign. All three of his cases in which this was present were living and well following nephrectomy.

Everson and Cole (1959, 1964, 1966) collected 31 cases of possible spontaneous regression of hypernephroma, of which 28 involved regression of pulmonary metastases. Their comprehensive textbook on spontaneous regression (1966) is illustrated with chest films. We have assembled 40 cases of spontaneous regression of pulmonary metastases following nephrectomy for renal cancer (See Table 2).

As to some of the reasons why renal cancers may reactivate, the following points may be considered. When metastases or recurrences develop quite late this may often

be due to the fact that with advancing age immune responses weaken. This has been true of mice immunized against Ehrlich ascites tumor (Bailif, 1965).

Also as patients get older they may develop other conditions such as arthritis or bursitis for which corticosteroids or butazolidin are administered, or they may be subjected to annual diagnostic x-ray examinations. Each of these may be an additional insult to aging immunologic mechanisms. Many physicians are beginning to recognize the dangers of corticosteroids and other anti-inflammatory agents as well as certain antibiotics or other immunosuppressive agents, especially when used on patients who have had cancer or who have a family history of cancer (Kelly, 1959, 1963; Fowler, 1969-70; Nauts, 1969-70; Miller and Nicholson, 1971).

Spontaneous regression, disappearance of metastases after surgical excision of the primary, relapse after many years of apparent cure and evidence that large numbers of tumor cells are often present in the peripheral blood without development of metastases all suggest the existence of a significant tumor-host antagonism, which may be of an immunologic nature.

There is growing evidence that viruses may be implicated in the etiology of many human cancers. In most of the population such viruses may remain latent or disappear. However, a recent study by Riley (1971) indicates that if immunosuppressants are administered LDH viruses are readily demonstrable within 24 hours. The immunosuppressants he tested were total body irradiation (350 r), cortisone acetate (100 mg/kg), asparaginase (5000 IU/kg) and antilymphocyte serum. After the eclipsed LDH-virus is activated by this process, it is readily infectious for normal unconditioned animals. This model is being used for studying the *de novo* appearance of oncogenic viruses in irradiated animals and for examining the lysogenous-like behavior of mammalian viruses *in vivo* and *in vitro*.

The immune responses of most cancer patients are not equal to the task of destroying both the primary and the metastatic lesions. However, if the primary is removed, and no immunosuppressives are administered, the natural host resistance mechanisms are sufficient in many cases to cause regression of the pulmonary (or other) metastases. The evidence indicates that this occurs more often in patients with fever, concurrent infection, lymphocytic infiltration, or when regressive changes are also apparent in the primary at the time of the nephrectomy (Table 6).

In recent years the homotransplantation of organs to immunosuppressed patients has been accompanied in some instances by the development of neoplasms in the recipients (Kaye et al, 1970). This may occur by spread of cancer cells inadvertently transplanted in the donor organ as recorded by McIntosh et al (1965), McKhan (1969), Williams et al (1969) and Wilson et al (1968). In other cases immunosuppression may reactivate an excised primary cancer in the recipient, as reported by Hume (1969) and Starzl (1969). Still others have reported the *de novo* development of lymphomas or leukemias in transplant recipients, usually many months after transplantation (Deodar et al, 1969; McIntosh, 1965; McKhan, 1969; Merrill, 1969; Penn et al, 1969). The *de novo* development of tumors of nonimmunogenic tissues have also been reported (McKhan, 1969); Siegel et al, 1969; Starzl. (1969)

Jochimsen et al (1969) reported successful renal allotransplantation for bilateral multiple hamartomas and clear cell tumors in patients with tuberous sclerosis. They believed that clear cell tumors in these patients do not offer a contradistinction to transplantation. Merrill (1969) in an editorial on this subject stated: "It is clear that kidneys should not be transplanted from donors who have malignancies (with the possible exception of glioblastomas)."

Since antibiotics may also exert an immunosuppressive effect, routine use of antibiotics should be avoided in surgery for renal cancer or its metastases. Further

reasons for abandoning antibiotics as a routine are given by Johnstone (1963) who reviewed the experiences of about 20 surgeons in using antibiotics prophylactically to prevent infection. All these surgeons reported a considerably higher incidence of infections in patients given such treatment as compared with the controls. In some cases the most susceptible organisms were obliterated, leaving the most resistant organisms a clear field in which to multiply. This is also discussed by Fowler, 1969, Monograph # 10.

Another point to be considered in this connection is the danger of using immunosuppressive cancer chemotherapy. It is pertinent to remember that immunosuppression seems to be an essential part of experimental carcinogenesis. Clinically it has been observed that some patients receiving these agents to which their tumors were relatively resistant, exhibited sudden rapid growth of their primary tumors and appearance of widespread metastases. Others rapidly generalized after radiation therapy. These cases are undoubtedly due to suppression of host resistance by these agents.

These reports emphasize the vital importance of preserving and stimulating immunogenic tissues in patients with renal and other types of cancer, not only before and after surgery, but all the rest of their lives.

In studying the evidence of host resistance factors in renal cancer we have searched the medical literature and consulted a large number of urologists. The cases thus found are grouped as follows:

Table 1: Spontaneous regression of primary renal cancer: 7 cases
Table 2: Spontaneous regression of metastases, mostly pulmonary: 41 cases
Table 3: Late metastases or recurrence: 20 cases
Table 4: Unusually slow progression of the disease: 16 cases
Table 5: Metastases successfully treated by surgery: 34 cases
Table 6: Concurrent infection: 29 cases
Table 7: Immunotherapy: Coley toxins: 11 cases, Miscellaneous: 3 cases

* Of the 41 cases in Table 2, nine had concurrent infection, fever, inflammation or leukocytosis and are also listed in Table 6. Thus the total number of cases in this study is 152.

In attempting to analyze how regression is triggered, either spontaneously or as a result of infection and bacterial toxin therapy, the following studies are pertinent:

Böttiger (1962) reported that it has been possible to produce, from plant and kidney tissue, polysaccharides with an endotoxic effect, which are supposed to have a tumor-destroying effect as well. He added: "It seems extremely attractive to explain the disappearance of renal tumors by this kind of self-destruction through the production of a polysaccharide with endotoxic effect. However, there is as yet no proof of the existence of such a factor. The reason for the regression of renal cancer and also the disappearance of lung metastases must remain for the present an open question but the explanation lies presumably in the immunological and endocrinological field."

Braun (1962) has reviewed the biodynamic effects of a group of substances that has a striking stimulatory effect on rates of deoxyribonucleic acid (DNA) synthesis and which elicits stimulatory effects on a multitude of biological agents. These include host-parasite interactions and immune responses. Such effects are produced by oligodeoxyribonucleotides, present in enzymatic digests of DNA from many different sources, and also by certain oligomers of ribonucleotides. Stimulators of a similar or possibly even identical nature are also formed and released under natural conditions. Braun and Kessel (1964) have collected data indicating that the stimulatory effects of bacterial endotoxin on antibody synthesis and host resistance may be associated with the release of cell breakdown products from macrophages and other cells. They believe that the stimulation of host resistance by endotoxin may involve the

stimulation of pre-existing specific antibody forming cells by oligonucleotides in cell breakdown products that are released as the result of antigen-antibody reactions on cell surfaces. "Such rapid triggering of immune defenses . . . can occur only in cases where more than one exposure has been experienced . . ."

DNA fragments have proved capable of restoring immune responses in immunologically suppressed animals (Feldman et al, 1963; Taliaferro and Janoslow, 1960).

Braun concluded that the stimulation of antibody forming cells may require two factors: 1) the actual stimulation and 2) a factor permitting the entrance of this stimulator into the target cells. It is well known that bacterial endotoxins, one of the potent stimulators of antibody formation, can produce their effects in the absence of specific antigen (Michael et al, 1961). This appears to be due to the ability of endotoxins to alter membrane permeability, thereby providing both of the required factors, i.e., release of endogenous stimulator and altered permeability of the cells to be stimulated (Braun & Firshen, 1967).

Perhaps the reason why the largest number of so called spontaneous regressions of cancer which occurred following bacterial infections were those with streptococcal infections, since the hyaluronidase, streptodornase and streptokinase produced by streptococci are most potent in increasing tissue and membrane permeability (Nauts, 1969; Nauts and Fowler, 1969). Tillett et al (1950) found that with streptococcal enzymatic debridement there is an outpouring of leukocytes. The effective clearing of the site of infection through enzymatic action renders the area permeable to humoral and cellular forces of both natural and specifically acquired immunity or to circulating antibiotics that are capable of eliminating the infecting organisms. The rapid rate of regeneration of soft tissues and epithelium following debridement has also been observed in many instances.

Miller and Ketcham (1962) reported that tumor incidence in mice was significantly reduced by streptococcal (56%) or Escherichia coli (68%) infections over controls (96%). *Intimate association between bacteria and tumor cells appeared necessary for suppression of tumor growth.* Infection at a distant site had no effect in these experiments. Nauts (1969) found that concurrent infections in cancer patients also seemed to be more dramatic in their effects if they occurred in the region of the tumor or its metastases. However, many cases were benefited in which the infection did not develop locally.

Certain bacteria or their toxins are able to stimulate a host response to substances or tissues which do not normally elicit such a response in an animal or patient. Glynn and Holborrow (1952) 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 sera prepared against them. Burky (1933-34) found that by combining staphylococcus with lens substance, rabbits were sensitized to lens and developed high preciptin titres for lens tissue. In addition to streptococci they reported that the following bacteria also show this property: Shigelli shigae, Salmonella typhi, Bacillus arthracis, Hoemophillus influenzae and Neisseria meningitidis. Recently Stewart and Tolnai (1969) found that intradermal injections of extracts of hemolytic streptococci (Varidase) caused regression of a skin lesion regarded as mycosis fungoides or plasmacytoma. They stated that the resemblance of this delayed hypersensitivity reaction to a small area of erysipelas was very marked.

Older surgeons here and in Europe were aware that if their patients developed post-operative wound infections or pelvic abscesses they were more apt to remain free from recurrence or metastases. (Fowler, 1969, Monograph #10).

Zwaveling (1962) concluded from his animal experiments that tumor cells have

less chance to grow in a milieu in which there is suppuration resulting from bacterial infection. Jordan et al (1958) reported that induced streptococcal infections caused complete regression of a transplantable leukemia in mice.

Christensen's studies at the State Serum Institute in Copenhagen have shown that when rabbits with Brown Pearce carcinoma were subjected to massive infection with hemolytic streptococci, none of the infected animals developed metastases as compared with 50% of the controls who did so (Christensen, 1959).

Since there is increasing evidence that acute concurrent infections, fever and inflammation may cause complete or partial regressions of cancer and lessen the incidence of recurrence or metastases, one must question the wisdom of administering antibiotics as a routine procedure before and after cancer surgery.

Physicians also have not usually considered the possibly deleterious effects on tissue permeability, antigenic stimuli, hypersensitivity reactions, phagocytosis, etc. which may be produced by certain drugs other than the immunosuppressive agents cited above. For example, salicylates depress tissue permeability and also inhibit antibody formation. Tranquilizers decrease vascular permeability, cortisone, cortisol and chloroquine make membranes tougher, while stilbestrol and progesterone make them more permeable.

Concurrent bacterial infections do not seem to have been reported nearly as often in patients with genito-urinary tract cancers as in other malignancies (Fowler 1953-1970; Nauts 1946-1970). However, the cases we have been able to collect which occurred in both operable, metastatic or operable cases are given in Table 6. Some of the cases with an extremely slow course had concurrent malaria (Sabadini, 1946-47) or tuberculosis (Walter and Gillespie, 1960) which may have been responsible. Walter and Gillespie's patient died at 81, 50 years after onset.

Another case which may be cited here was reported by Ocherblad and Carlson (1943): A child with Wilms' tumor whose mother had had a very stormy pregnancy, with pyelitis, pernicious vomiting and threatened abortion. The child was born prematurely, regurgitated food and gained poorly. A mass in the left abdomen was palpable at one month. At nephrectomy a large tumor of the left kidney was removed followed by x-ray (266 r to abdomen, 411 r to chest). This child was in excellent health 8½ years later. This was the 13th known cure up to about 1951. Did this mother's pyelitis and stormy pregnancy increase her child's resistance to this congenital neoplasm?

In reviewing the factors which may affect host resistance in renal cancer patients one must consider not only concurrent infections, but the use of microbial products. This is discussed below in the section on treatment with immunoadjuvants. The results obtained in the small series of cases who received Coley toxins * indicate that such therapy has proved effective in both inoperable and terminal cases. The only two operable cases who received adequate Coley toxin therapy as an adjuvant to nephrectomy survived 20 and 59 years. One was a huge hypernephroma, the other a Wilms' tumor in an 18 month old child (see Table 7).

Lagèze (1960) treated a patient with an extract of Trypanosoma cruzi as an immunoadjuvant. This patient's extensive bilateral pulmonary metastases then regressed (see Table 7, case 12).

These few cases suggest that various immunoadjuvants should now be administered before and after surgery for both operable and inoperable renal neoplasms. Such therapy would be of special value in patients with bilateral renal cancer.

* The mixed toxins of Streptococcus pyogenes and Serratia marcescens.

TREATMENT AND SURVIVAL

Surgery

Neoplasm of the kidney has always been a mandatory indication for nephrectomy when the function of the contralateral kidney has been proven adequate to preserve life. But it is an entirely different matter in cases of renal tumor when the contralateral kidney is absent or its function so impaired that its ability to preserve life may be questioned. Ljunggren (1960) believes that here we are justified in an attempted removal of the tumor, that is, to perform a partial nephrectomy if this is at all possible. Since a number of patients are being seen at the present time who have lost one kidney due to other causes, and since the incidence of renal cancers has increased approximately 50% in the last 25 years, one may be confronted with an increasing number of patients with renal carcinoma of a solitary kidney. This is a challenge which must be met by immunotherapy combined with conservative resection of the tumor in order to spare as much of the solitary kidney as possible.

In some cases where exploration of a tumor in a solitary kidney is made, it may be impossible to carry out resection of the tumor for technical reasons (Ljunggren, 1959-60). Renal transplantation is not indicated in such cases since the administration of immunosuppressive drugs to a cancer patient will increase the likelihood of rapid generalization of his neoplasm (or of the development of another primary; Penn, 1969, 1970; Schneck, 1970; Siegal, 1969; Wilson, 1968.)

In cases of bilateral renal tumors there is often a primary growth in one kidney and the tumor which develops in the other kidney is a metastasis. Under such circumstances, there is a great risk that other metastases are present.

A long observation time is necessary to judge the result of partial nephrectomy for renal cancer. Exploration of the kidney is justified in all cases of renal tumors in a solitary kidney. In some of these patients lives may be saved by partial nephrectomy (Ljunggren, 1960). Among those who have reported on their experiences with partial nephrectomy are Hanley (1950), Dufour (1951), Semb (1954, 1956), Svab (1956), Cibert (1958), Culp (1959), Kerr (1959) and Kaufman et al (1968). The latter were able to collect 21 cases from the literature of renal cell carcinoma occurring in the solitary kidney to which they added six personally observed. One of their patients was doing well and was apparently free from disease after removal of a tumor in the solitary kidney followed by lobectomy for a solitary pulmonary nodule. They concluded that some long survivals reported in such cases, and the propensity for renal tumors to regress or become latent for long intervals, justify aggressive approaches. Arteriography has aided in establishing the diagnosis, in defining areas of tumor involvement, and in demonstrating the arterial distribution in the kidney. Knowledge of the vascular architecture of the kidney, prior to surgery, improved surgical skills and judicious use of immunoadjuvants and (in Wilms' tumor especially) radiotherapy, and dactinomycin, will also help to salvage some patients with this infrequent but challenging problem.

Jessop (1877) appears to have been the first to perform a nephrectomy for Wilms' tumor in a child, while Israel (1894) reported the first *surgical cure* of Wilms' tumor in a two-year old boy who was operated on March 3, 1887 and remained well in 1893. Abbe (1894, 1912) reported two cases of Wilms' tumor successfully treated by nephrectomy in 1892. One of these children had a huge tumor weighing 7½ pounds after nephrectomy. She developed a fever of 105°F. next day but recovered and remained well 20 years later (See Table 6, Case 1).

Walker (1897) is the first to have critically reviewed the end results in Wilms' tumor in children (then designated as sarcomas). He reviewed a series of 145 cases, only four of whom were living and well after nephrectomy (5.47%).

Martin and Kloecker (1961) discussed the surgical treatment of Wilms' tumor. They advocated taking advantage of a wide transperitoneal exposure to palpate, inspect and if necessary treat the other kidney. For bilateral cases, they recommend bilateral partial nephrectomy or, in more advanced disease excision of the kidney (with perirenal fascia and regional lymph nodes) together with contralateral partial nephrectomy and the preservation of one adrenal gland.

Geschicter and Widenhorn (1934) reported that only four of 200 cases of renal cancer treated at Johns Hopkins Hospital prior to 1934 had lived over five years and two more survived three years. One of the five year survivals was a Wilms' tumor.

Cahill and Melicow (1938) thought that the prognosis of tumors with calcification was less encouraging than those without calcification.

McNeil and Chilko (1938) believed that only 10 percent of Wilms' tumor cases survived.

Nesbit and Adams (1946) reported that 50% of their series of 16 children were apparent cures. (A few of these also had postoperative radiation).

Ladd and White (1941) believed that their unusually high five-year survival rate (47.3%) in Wilms' tumor was due to their employment of early ligation of the pedicle while carrying out transperitoneal nephrectomy without irradiation. Their results remained unduplicated for at least 20 years.

Lattimer et al (1959) and others have observed that the prognosis in Wilms' tumor is more favorable in infants under a year of age. Of the children operated before the age of two, 73.3% were alive three years later. Of those operated before the age of one year 90% were alive, while only 18.5% of those over two at surgery were alive three or more years later. Of the 22 cases treated prior to 1933 only 9% survived.

It has now become possible to perform successful nephrectomies on infants only three days old. The operative mortality is less than 2%. The operative approach depends on the size of the tumor and the skill of the surgeon, the main objective being to ligate the renal artery and vein with as little manipulation of the kidney and the tumor as possible. Abeshouse (1957) stated that the transperitoneal approach was preferred by the majority of surgeons.

A survival period of two years without recurrence or metastasis indicates a very high probability of permanent cure (Pollock et al, 1960; Garcia et al, 1963).

Painstaking study of all available published cases do not reveal satisfactory reasons for the wide range of results of treatment of Wilms' tumor encountered in various medical centers in a given period.

As to the end results in renal carcinoma in adults

Thockmorton (1955) reported a five year survival rate of 36.3% in their series of 42 cases treated prior to 1950. He concluded: "We have the impression from the literature and from our cases that the greatest danger in hypernephroma is distant metastasis. The largest problem to be solved before individual prognosis can be accurate, is why tumor cells in the blood stream cause metastases in some but not in others." He reported one case that had a "hurricane course": nephrectomy four months after onset, death three months later from local recurrence and metastases.

Murphy and Fishbein (1961) reviewed a series of 90 cases of hypernephroma and found that the clear cell type had a better prognosis than the granular. Their five year survival rate for the entire series was 17%. In a later report further evidence was given as to the better survival rates for clear cell carcinoma (Murphy and Mostofi, 1965).

Gloor and Bandi (1966) reported a five year survival rate of 25-46% in 1400 cases of renal cancer.

Bottiger (1970) analyzed the factors affecting prognosis in 100 patients

collected as a prospective study. Malignancy grading was valuable in determining prognosis in an individual case, but staging gave an even better correlation with survival. The two most important factors were the presence of metastases and an elevated ESR. The grade, size of tumor and invasion of the renal vein also correlated well with prognosis but were of less importance than the first two factors.

Rolson et al (1969) suggested a modification of previous systems of staging and demonstrated that staging has a very definite prognostic value.

Walters and Brasch (1935) reported a five-year survival rate of 42% in a series of 256 renal cancers in adults following nephrectomy at the Mayo Clinic between 1901 and 1927. X-ray therapy was also given in 33 of the survivors. *They noted, however, that "radiation sometimes seemed to hasten the end".*

Humphreys and Foot (1960) reported that only 18-23 % of their series of 235 cases of renal cell and transitional cell tumors of the kidney survived 10 years after nephrectomy. Almost half their cases died within two years of recurrence.

Rolson (1963) reported on the results of radical nephrectomy by the thoraco-abdominal route: 45 of 51 cases survived three years and 66.3 % survived five years. He feels that improvement in prognosis following this procedure results from a) removal of nodes (involved in 22.5% of his patients); b) ligation of the pedicle before extensive manipulation; c) removal of fat and fascia with the kidney.

Grabstald (1964), in discussing the treatment of renal cell cancer, stated that judicious and adequate therapy for these tumors requires thoughtful consideration of different sets of circumstances. Age and physical condition of the patient are important, especially the cardiovascular and renal status and pulmonary function. "After one decides that the degree of operative risk does not negate surgery in a particular patient, there are four vital factors to consider: (1) prognosis in the treated as contrasted with the untreated patient with renal-cell cancer without demonstrable metastases (the risk with the elderly patient might indicate that the operable primary tumor should be left alone); (2) prognosis in the treated as contrasted with the untreated patient with metastases; (3) the risk of the proposed surgery, especially when it is to include a vigorous attempt to remove all primary and metastatic tumor; and (4) availability of therapeutic alternatives to surgery, such as radiation and chemotherapy."

Radical nephrectomy as soon as diagnosis is made is the treatment of choice for renal cell adenocarcinoma without metastases. An incision appropriate to remove the kidney, the perirenal fat and fascia and the adjacent lymph node is preferable, with early ligation of the renal artery and vein, before any manipulation of tumor mass is undertaken. Grabstald prefers a thoraco-abdominal incision, with removal of the tenth rib, particularly for removal of large or previously explored tumors.

The incidence of direct extension into the perirenal fascia is higher than previously supposed. Therefore, radical nephrectomy should include removal of the surrounding perirenal fat and fascia. Five-year survival rates in Memorial Hospital were 71%, 68.7% and 33.3 % in patients with stages A, B and C tumors.

When metastases are present, nephrectomy may be considered on three bases: a) as a part of a planned approach in which both the primary and the metastatic disease are to be removed (see Table 5 for 34 successful cases); b) with the faint hope that metastases may regress spontaneously after nephrectomy (see Table 2 for 41 such cases); and c) for palliation of local or systemic symptoms.

One may be more inclined toward removal of a metastases if the primary lesion is of the clear cell rather than the granular cell type of carcinoma, if at nephrectomy the primary has not invaded the renal vein, capsule, surrounding tissues or adjacent lymph nodes, or if the tumor is of low rather than high grade malignancy.

The extent of surgery required to remove the metastasis must also be considered.

One will be more inclined to remove a single rib metastasis, a chest wall resection, or pulmonary lobectomy, rather than amputation of an extremity or pneumonectomy. However, excellent results have been obtained in some patients with bone metastases from renal cancer in whom definitive surgery was performed for both the primary and the metastases.

The first successful removal of a solitary lung metastasis was performed by Barney and Churchill. This patient also had concurrent pulmonary tuberculosis in the other lung (See Table 6, case 5). She remained free from further evidence of disease until her death from coronary disease over 25 years after onset (Barney and Churchill, 1939, 1944 and personal communications).

Strieder (1950) reported two male renal cancer patients with pulmonary metastases who remained well 8 and 4½ years after resection of their lung lesions (Table 5, Cases 7 and 8).

Others who have reported successful results in such cases in 1956 include Tinney and McDonald(Table 5, Case 3), and Groves and Effler (Table 5, Case 9). One of their patients had a brain metastasis as well as a lung metastasis. Both were removed and the patient was alive and well 5½ years later. They believed that the minimal resection which allows total removal of a metastatic lesion with a margin of normal tissue on all sides is generally indicated. Gale and Brooks (1957) reported on 14 cases in which pulmonary resections have been performed for renal cancer metastases. The only Wilms' tumor in the series was alive 22 months after right upper lobectomy. They concluded that in at least a few such cases marked benefit can be obtained (Table 5, Case 10).

Samellas (1963) cautioned that evaluation of pulmonary function is necessary in these patients where chronic infection or emphysema is present, which diminishes respiratory reserve. Since pulmonary metastatic lesions occupy a small area of the lung much less tissue is sacrificed than is required in a primary lung cancer. He added that the presence of a solitary pulmonary metastasis does not constitute a prognostic sign and it should be removed if the requirements for surgery are present (Table 5, Case 15).

Other not clinically apparent foci may undergo spontaneous regression. If pulmonary or other metastases are left untreated, most of these patients will die, although 41 cases have been reported in which such lesions regressed spontaneously, usually after a palliative nephrectomy had been performed (Table 2).

Potampa (1961) reported a five-year cure following removal of bilateral pulmonary metastases in a 62-year old male (Table 5, Case 12). He felt that the answer to the cause, prevention and correct treatment of cancer is to be found in a biological change in the individual and not in extensive surgery, irradiation or biochemicals — *i.e. to host resistance factors not yet fully understood.*

Cliffton and Pool (1967) reported on a series of 27 children in whom lung metastases were treated by combined therapy, surgery, chemotherapy and radiation. Four of their successful cases were Wilms' tumors, three of whom had multiple bilateral pulmonary lesions. These children remained well when last traced up to eight years later (Table 5, Cases 23, 25, 26, 27).

Middleton (1967) stated that the survival rate in patients with solitary metastases following nephrectomy and excision of the metastatic lesion is essentially the same as that following nephrectomy in the apparent absence of metastases.

Fernbach (1966) and in a personal communication (1971) concluded that metastatic lesions should be removed surgically whenever they are accessible. Radiotherapy should be limited to the local treatment of lesions that cannot be removed surgically.

Only a few surgeons have reported on the successful surgical removal of brain, hepatic or jejeunal metastases from renal cancer. Stortebaker (1951) reported a

series of 17 cases with brain metastases who were operated, with a surgical mortality of 30%. One of these patients lived 14 years after neurosurgery. The most favorable prognosis is found in those where nephrectomy was performed prior to the development of cerebral symptoms.

Starr and Miller (1952) described a case in whom a solitary jejeunal metastasis developed 20 years after nephrectomy in a 72-year old woman. She recovered following resection and anastamosis. It is of interest that this woman had developed an adenoma of the thyroid, an adenocarcinoma of the colon and an extensive ovarian fibroma in the interval between nephrectomy and development of metastases (Table 3, Case 8).

Straus and Scanlon (1956) reported a case of hypernephroma with metastases to the left lobe of the liver who was well and free from disease five years after resection of the hepatic lesion and 10 years after nephrectomy The tumor weighed 1500 gm. (Table 5, Case 6).

From the experiences outlined above it would seem that wherever possible such cases should be given the benefit of surgical resection of their metastatic lesions. Whether the surgeon is dealing with a primary or a metastatic renal cancer, *it is extremely important that the tumor be manipulated as little as possible prior to removal, in order to avoid the dissemination of tumor cells through the blood stream.* Of interest in this connection is the report of Daw (1948) who observed a child with Wilms' tumor who had been treated by massage after a fall on the abdomen, in whom widespread metastases developed before medical help was sought.

Radiation

When considering the pros and cons of using radiation one must consider its deleterious effects on the normal tissues.

Doub et al (1927) reported that the kidney is the most susceptible organ for anatomical changes and loss of function following radiation. Direct radiation of the kidney produces nephritis with hypertension in clinical cases as well as in the experimental animals. They cautioned that such direct radiation should be avoided especially in young individuals.

Hartmann et al (1926) produced radiation nephritis experimentally in dogs using moderate doses of x-rays. Koletsky and Gustafson (1955) produced renal cancer experimentally following whole body radiation.

Zuelzer et al (1950) reported an unusual glomerulonephritis in young children who had received radiation of 5850 to 6850 r over the kidney region. All died 4½ to 7 months after beginning radiation therapy.

Luxton (1953) described 27 cases of radiation nephritis, five of which were fatal. He also described two cases of malignant hypertension occurring 18 to 24 months after radiation. Both children died within seven weeks of onset of symptoms. Levitt and Oran (1956) also described a case of irradiation induced malignant hypertension which was cured by nephrectomy. Others reporting such cases include Hazard et al (1949) and DeVries (1954).

Levitt (1957) showed that doses as low as 1000 to 2000 rads may give rise to acute or chronic radiation nephritis, possibly with a fatal outcome. In view of these risks the use of radiation therapy as a supplement to nephrectomy should be restricted to highly malignant tumors. The onset of the acute condition occurs after a latent period of weeks or months after the irradiation. Clinically symptoms include headache, dyspnea, lassitude, nausea and vomiting. Edema is frequent and variable as to degree. Anemia may be severe. The urine has a low specific gravity and albuminuria is persistent. Chronic nephritis may follow the acute type, or may develop insidiously. Repeated follow-up studies of every patient who has been given radiation to the upper abdomen should be made, in order to detect the development

of radiation nephritis so that timely treatment may be instituted. He added: "It has to be faced that the radiation dose which is necessary for the treatment of most types of malignant disease is also the dose which is likely to produce renal damage . . . However, with the greater efficiency of cobalt and supervoltage methods of irradiation therapy it will be easier in future to treat unilateral lesions with minimal irradiation of the opposite kidney and so the proportion of bilateral renal damage will probably be reduced."

Mitus et al (1969) reported on the late effects of radiation on renal functions of 108 children treated at the Children's Cancer Research Foundation in Boston. They concluded: "Normal renal function can be preserved in pediatric patients after unilateral nephrectomy, irradiation and the administration of antitumor drugs, provided that the x-ray exposure of the remaining kidney is kept below 1200 r. Urinary tract infections, though frequent, do not present a serious problem if treated properly." Four of their patients who died in renal failure, showed characteristics of radiation nephritis at autopsy.

Another serious sequela of irradiation of children with Wilms' tumor is vertebral damage and unilateral underdevelopment of the ilium. Nesbit and Adams (1946) were the first to report such a case. This child received fairly intensive radiation totalling 1850 r in 13 days resulting in severe vertebral damage and scoliosis.

Whitehouse and Lampey (1953) reported four such cases and concluded that in order to avoid osseous damage one should use as small a field as possible, relatively small daily doses with adequate protection and avoid excessive total doses. Arkin and Simon (1950) reported that a single dose of 1000 r is sufficient to produce structural scoliosis in the spine of young rabbits by irradiating the vertebrae asymmetrically. The resulting uneven bone growth yields wedging of the vertebral bodies.

Others reporting on the deleterious radiation effects on the growing spine in these cases include Neuhauser et al (1952) and Rubin et al (1962). Neuhauser noted that radiation dosages above 2000 r to bone produce retardation of bone growth irrespective of the child's age. (Younger patients are more susceptible.) When the spine is in the field, the most constant effect is scoliosis, due to interference with the growth of the vertebrae. Ordinarily, the abdominal fields cross the midline and include the whole width of the vertebrae, and yet unilateral wedge changes of the vertebral bodies can be produced.

Owings and Radakovich (1959) noted that among their surviving cases of Wilms' tumor, there was a high incidence of late skeletal changes resulting from irradiation: gibbus deformities of the spine and hypoplasia of the ilium. They concluded: "As long as surgery is included, the survival rate for Wilms' tumor in patients under 18 months is high regardless of therapy. In this age group there may be some justification for individualizing irradiation in an effort to eliminate late bony deformities."

Rubin (1962) noted that scoliosis is apparent 12 months after treatment and is related to the age of the child and the dose, but not to whether the fields were unilateral or included the whole spine. Once established it is permanent. They commented, "The question has been raised whether the degree of scoliosis is too debilitating to warrant routine use of irradiation in conjunction with surgery."

Pearson and Pointon (1964) reported that all surviving patients in their series of 96 cases of Wilms' tumor had some shortening of the spine (long legs for their body height). Fortunately in their experience the growth disturbance was symmetrical, so that no scoliosis occurred. They noted that in girls who had survived puberty, one had complete amenorrhea and lack of sex development for which hormone treatment had been necessary. Two had shown normal breast development and the female appearance of hair distribution but no menses to date. Their technique consisted of

giving x-ray therapy in parallel opposed fields (250-300 KV) the field subtends the whole abdomen from nipple line to lower edge of symphysis pubis but with shielding of the femoral epiphyses. The opposite kidney is shielded for part of the treatment. Adjustment is made to the daily dose if the total w.b.c. falls below 2000. The overall survival rate was 30 %, but in early cases treated by nephrectomy and postoperative radiation 48% survived.

Berdjis (1959) studied the effect of irradiation on 1000 mice and concluded that although spontaneously occurring kidney tumors are rare and occur principally in old mice, irradiation produced renal tumors in 10 % of the mice. In 1963 he reported that irradiation is highly carcinogenic for rat kidney: over a third of the irradiated rats developed kidney tumors similar in structure to those of mice and man.

Berdon et al (1965) reviewed the literature on various benign and malignant sequelae to childhood radiation therapy. An unusual case of unilateral hyperlucent lung in a child cured of metastatic Wilms' tumor was cited.

Kerr and Flynn (1956) describe a case of a child with Wilms' tumor who died as a result of irradiation for pulmonary metastases.

Ritter and Scott (1949) reported a case in whom x-ray therapy for Wilms' tumor may have contributed to the development of sclerosis and fibrosis in the contralateral kidney in which an embryoma subsequently developed 10 years later.

Regelson (1965) describes a case of a child with Wilms' tumor whose lung metastases had been treated by radiation who developed a chondrosarcoma of the rib 15 years later in the irradiated area. Lent et al (1960) reported an apparent cure of a case of Wilms' tumor following lobectomy for recurrent pulmonary metastases which had not responded to radiation (3400 rads). This child subsequently developed chrondrosarcoma of a rib in the irradiated chest area, which proved fatal 9 years after onset of the radiation-induced bone tumor.

Kunkler et al (1952) believed that the adult renal tolerance for x-ray therapy is 1700 r in five weeks, and that doses of 2800 r in this period causes radiation nephritis in a high proportion of cases.

As noted above Walters (1935) observed that "radiation sometimes hastens the end " — i.e. decreases resistance of the patient to his tumor.

Having reviewed the deleterious or dangerous effects of radiation we may now consider the possible indications for radiation in renal cancer.

(A.) Wilms Tumor or Renal Cell Carcinoma in Children

Ockerblad and Carlson (1943) reported the 13th known cure following nephrectomy and radiation. The child was operated upon at 11 weeks for a large Wilms' tumor. Six days after nephrectomy x-ray was given (266 r to the abdomen, 411 r to the chest in 25 days). The child remained in excellent health 8½ years later.

McNeill and Chilka (1938) and Nesbit and Adams (1946) also reported successful results with radiation following nephrectomy in these tumors. (They believed it was indicated in all patients). Flannery (1958) and Koop (1961) advocated pre-operative and post-operative radiation for Wilms' tumor.

Scott (1956) noted that radiotherapy alone leaves viable cancer cells in the tumor and metastases are not uncommon four or five years after apparent cures by radiation. He felt that small infants are best treated by nephrectomy without irradiation. He added: "Irradiation is an essential part of the post-operative therapy and is best begun while the child is still under the anesthetic." As regards pre-operative radiation he stated: "It is a mistake to delay nephrectomy because of

dramatic improvement after radiotherapy. Delay only increases the chance of dissemination of the inevitable tumor cells remaining."

Klapproth (1959) stated that Heimann was the first to introduce post-operative radiation in the treatment of Wilms' tumor 20 years after Roentgen's discovery. Friedlander (1916) reported one of the first cases of Wilms' tumor in whom x-ray was used as a primary treatment. The child had concurrent measles and bronchopneumonia and died but there was widespread necrosis of the tumor.

Dean and Pack (1932) advocated radiation prior to nephrectomy. McNeill and Chilko (1938) stated that they knew of only one other case of Wilms' tumor besides their own treated by radiation alone who survived at least three years. This was reported by Pohle and Ritchie (1935). This ten-month old male child had a tumor which filled half the abdomen. In March 1931 he received small doses (50 r) daily for six days totalling 750 r following exploratory operation. He was in extremely poor condition. Further x-ray was given four months later resulting in almost complete regression by September 1931. A severe respiratory infection at this time prevented operation. He was explored again in June 1932. The tumor had entirely regressed from the kidney but a remnant 4 cm. in diameter extended along the vessels (Table 6, Case 4).

Kerr (1939) reported two radiation cures in a series of 14 cases of renal tumors in children. The first was a four year old male, in which operation had been refused. Two years after onset x-ray was given in two courses totalling 5500 r and the child was traced well 4½ years later. In a four year old female, in which lung metastases had developed four months after onset, x-ray was given in two courses to the lungs (8500 r) and the child remained well 52 months later. In this case the pulmonary lesions disappeared twice under x-ray therapy. Kerr advocated radiation prior to nephrectomy.

Mertz et al (1941) reported that in their experience "postoperative radiation in the child or the adult who has had a renal tumor removed, has given no definite evidence of benefit".

Sugarbaker (1944) believed that preoperative x-ray therapy for Wilms' tumor does considerable harm by delaying surgery. He added: "Local post-operative irradiation should probably be given but not empirically and a more careful attempt should be made at evaluating its results." He described a case in a 12-year-old boy in which a 1760 gm. tumor was successfully removed in a two-stage operation six days apart. Post-operative x-ray (2000 r x 2) was then given and the boy remained well two years later. It is of interest that in this case onset was apparent after appendectomy.

Dean (1941, 1945) reported one five-year survival in a child treated by radiotherapy. He noted that this case was "by far the most neglected of the series". He also had concurrent pyelitis (Table 6, Case 6). Dean stated that local recurrences as well as metastases to the lungs or skin have been successfully treated by radiation in a number of cases.

Sauer (1948) gave over 6200 r in three courses to a two-year-old child with Wilms' tumor. Ascites were present when the second course was given but cleared in two months. A calcified mass remained, but the child was in good health in 1948, 10 years after onset. He believed that 90 % of Wilms' tumor patients died of their disease. Kinzel et al (1960) also discussed the use of radiation in Wilms' tumor.

Vaeth and Levitt (1963) reported the five-year survivals in Wilms' tumor at the University of California Hospital from 1926-1956. (An earlier report from this hospital is that of Ng and Low-Beer, 1956.) The only child treated by radiotherapy alone died. Three of the five with nephrectomy, and five of 11 of those given post-operative radiation (3000 r in four weeks) survived, while eight of 10 of those in whom radiation was given before and after nephrectomy survived. They concluded

that although the number of patients was too small for any definitive conclusions, it would appear that pre-operative is better than post-operative radiotherapy. In view of the extremely aggressive and radiosensitive behavior of these tumors such a conclusion would be logical. Vaeth et al. (1962) noted, however, that in all 12 of the irradiated survivors there were late tissue changes, skin pigmentation, and atrophy, and the higher the dose, the more skeletal changes were observed. The majority had 2500 r in three to four weeks, followed by transperitoneal nephrectomy and a similar course two weeks after surgery.

Scott (1956) reported on 61 cases of Wilms' tumor treated at the Royal Hospital for Sick Children in Glasgow, Scotland, and reviewed and analyzed 1141 cases abstracted from the literature. He noted that in some clinics pre-operative radiotherapy is used routinely to shrink the tumor to operable size, much as iodine is used in preparation for thyroid surgery. Radiotherapy alone leaves viable cancer cells in the tumor and metastases are not uncommon four or more years after apparent cures by radiation. Small infants are best treated by early nephrectomy without irradiation. Of 16 cases so treated nine developed highly radio-resistant recurrences under the scars within nine months after nephrectomy. Hematuria was present in about 25 % of his 61 cases and he stated that this symptom is of grave prognostic significance. Few such patients survive over a year. He added that it is a mistake to delay nephrectomy because of dramatic improvement after radiotherapy. Delay only increases the chance of dissemination of viable tumor cells.

Palma et al (1970) noted that renal cell carcinoma is a very rare tumor in children. Only 50 cases have been reported in the literature and they found four at Roswell Park Memorial Institute in the preceding 30 years. Two were well 8 and 11 years after nephrectomy, two were alive less than a year after radiation and chemotherapy.

(B.) Radiation Therapy for Renal Cancer in Adults

Grabstald (1969) stated that W.B. Coley was probably the first to report a renal tumor treated by radiation. Dean and Pack (1932) reported the results of the first series of renal cancers so treated. Barringer (1938) was one of the earliest advocates of radiation for renal tumors but he based his opinion on sporadic cases.

Kunkler et al (1952) studied the renal tolerance to radiation in adults and concluded that 2800 r in five weeks results in radiation nephritis in a high percentage of cases.

The use of radiation therapy in renal cancer is not reported frequently. This may be because it apparently is not effective enough to warrant serious attention.

Grabstald (1969) outlined the possible use of radiotherapy in these cases.

Radiation As Sole Form of Therapy

1. In elderly or poor risk patients who might not tolerate nephrectomy.

2. In the patient with massive hematuria or severe pain resulting from tumor which, for one reason or another, including refusal by the patient, cannot be removed. While radiation may control bleeding or pain, its effect on length of survival is unknown.

3. In patients with locally extensive and inoperable metastatic disease when surgery is not considered feasible. However, he added that the role of radiation therapy in terms of prolonging life under these circumstances has not been demonstrated. A short palliative course may temporarily restrain tumor growth and relieve pressure symptoms. Royce and Tormey (1955) found x-ray therapy to be of

no significant benefit whether given pre- or post-operative or as the only mode of therapy when the tumor was biopsied but not removed.

Radiation Pre-operatively

In certain rare circumstances this might possibly be considered.

1. In anticipation of technical difficulty at time of operation because of tumor size or previous exploration and closure for a tumor considered inoperable. Bixler et al (1944) reported a case in which pre-operative irradiation permitted a successful nephrectomy not possible before radiation. Grabstald knew of no other such cases.

2. In the hope that pre-operative irradiation may alter cellular activity to the extent that should metastases or local spillage occur, it may lessen the tumor's growth potential. Waters et al (1934, 1935) were some of the first to advocate pre-operative radiation for renal cancer. Some radiologists suggest a dose of 3000 r in three or four weeks. Others, such as Flocks and Kadesky (1958) use 7000 r through several ports in three weeks and nephrectomy is performed six weeks later. They noted shrinkage of dilated veins and no increased difficulty in dissection at surgery. They believed that the results from this combined treatment were superior to surgery alone. However, the numbers of cases treated were too small to prove this.

Miller (1949) reported the successful treatment of a case given 7500 r pre-operatively after a transfusion. This man had leukocytosis (11,500). Hematuria subsided, the patient gained 16 pounds and was well for six months. Symptoms then recurred, and there was further leukocytosis (15,000) with occasional pus cells in the urine. After another transfusion nephrectomy was performed 11 months after onset and radiation, "a tumor the size of a grapefruit" was removed. The patient gained weight and was entirely well six years later.

Hudgins and Collins (1966) cautioned that if surgery is to follow radiation it should be delayed from four to six weeks so that the early phase of hyperemia and edema incident to therapy will not complicate the surgery.

Grabstald (1969) stated that based on his experience at Memorial Hospital with the high morbidity associated with high doses of radiation (over 6000 r), in patients later subjected to cystectomy, he would hesitate to suggest any protocol in which high doses of radiation are followed by surgery for almost any tumor.

Riches, speaking before the International Society of Urology, urged that a pre-operative course of 3000 r be given to the kidney in two opposing fields. A two week course will not "cure" the cancer, but it will cause the perinephric veins to shrink and reduce the operative bleeding. Some tumors will become appreciably smaller, adhesions will often be less dense, and the operation will be easier. Hematuria may be checked and the renal pedicle can be secured at an earlier stage, before manipulation of the kidney can cause spread of tumor cells into the renal vein. He stressed the importance of waiting three weeks after radiotherapy before operating. At an earlier stage the tissues are edematous, adhesions are more vascular, and the operation more difficult. He concluded that if the radiotherapists agree to limit the dosage to 3000 r, and the surgeons to wait three weeks before operating, we might get much better results in these cases.

Radiation Post-operatively

One of the most controversial aspects of renal cancer treatment is whether or not postoperative radiation is routinely indicated after nephrectomy.

Charteris (1951) reported 26% five-year survival with nephrectomy alone and 36% with nephrectomy and postoperative irradiation.

Riches (1958) believed its value was uncertain, but recommended its use in 1) high grade tumors, 2) when the renal vein is invaded, or 3) when there is local extension.

The disadvantage of waiting until after nephrectomy before giving irradiation is that nothing has been done to prevent the dissemination of tumor cells from the inevitable manipulation during surgery.

The decision as to when to begin postoperative irradiation lies with the radiologist. Three to ten days is usually advised, provided normal healing has occurred. The importance of dosage is also generally recognized. Radiation nephritis is the most dangerous sequela. Persistent hypertension of the remaining kidney may also occur. Others, especially in children, have already been discussed.

Ochsner (1965) reported on the five year survival of 70 cases of renal cancer. Of those treated by nephrectomy alone 9 % survived, while 39 % of those given postoperative radiation after nephrectomy survived.

Peeling et al (1969) reported a survival rate of 33-48 % in 240 renal cancer patients seen at the London Hospital between 1940 and 1965. Of the 96 who had only nephrectomy 52 % survived; of the 68 who had nephrectomy and postoperative radiation only 25 % survived. "Further analysis of these results with regard to tumor stage and grade showed that irradiation to the renal bed had not improved the prognosis over nephrectomy alone."

Hudgins and Collins (1966) stated that the prognosis of renal adenocarcinoma can be favorably influenced by radiotherapy if advantage is taken of the characteristic features of the disease and if the patient's condition is evaluated in terms of the likely benefits to be derived from such treatment. Patient factors to be considered are the individual's tolerance for surgery or radiotherapy, which includes an assessment of the hematologic, nutritional status, the age and the function of the uninvolved kidney.

In judging the success of any form of treatment, they cautioned, in some instances apparent cure, the absence of evident metastases may be due to the fact that metastatic deposits have not had sufficient time to reach the proportions which would allow their detection. "Thus it becomes apparent that in such instances even no treatment at all is to be preferred over a vigorous assault on the tumor which will incidentally devastate a relatively compatible host." These authors noted that the cure of renal adenocarcinoma with radiation alone is rare but when these tumors are carefully managed and full advantage taken of the natural course of the disease, satisfactory control for long periods may be achieved. Treatment is designed to include the known extent of the disease and is given to the predicted tolerance of the patient. The opposite kidney must be spared from all but very minimal irradiation to avoid radiation nephritis. The spinal cord is rarely of concern at the level of the kidney since only a small terminal portion is ever included in the intense radiation zone in treating renal cancer in adults. The small bowel is a very real limiting factor and its inclusion in the heavily irradiated tumor zone can hardly be avoided. It is the structure which prevents administration of radiation doses intended to eradicate local disease.

Recurrences after surgery are also worth treating by irradiation. They stated that postoperative radiotherapy is offered only if there is known residual disease in the tumor bed or in regional lymph nodes, since the hazards of small bowel injury hardly justify its routine prophylactic use.

Radiation Therapy of Metastases

Treatment of metastatic disease may be given with the expectation of preventing pathologic fracture, to promote healing of such fractures, to relieve pain, cough, hemoptysis or to allay a life-threatening complication. Tumor doses of 5000 r to bone metastases are recommended by Grabstald (1964). These lesions will often respond to therapy with amelioration of symptoms, but the degree of regression after irradiation is variable.

Bratherton (1964) reporting at a symposium on renal cancer held at the Annual Congress of the British Institute of Radiology stated: "The place of radiotherapy in the treatment of hypernephromas has yet to be established on a firm basis. Procedure varies very considerably in different radiotherapy centers in the British Isles". The radiosensitivity of hypernephroma would appear to be the same as that of adenocarcinoma elsewhere. Bratherton therefore believes that it is desirable to give a dose of the order of 4000 rads in four weeks if tumor regression is to be obtained.

Evidence is increasing that oxygenation has an important part to play in the radiosensitivity of tumors and that anoxic cells have a considerable degree of protection from radiation effects. There is clear evidence of anoxia in these renal tumors. Thus it would seem helpful to administer bacterial endotoxins a few hours before each x-ray treatment in order to cause vasodilation and thus reduce the anoxia.

When using radiation postoperatively Bratherton believes it is important that the entire tumor bed from which the tumor was removed should be irradiated along with the scar in which metastases may frequently be found. The sensitivity of the organs to be irradiated must be considered. The spinal cord will be irradiated if the field is taken across the midline. Tolerance for a length of spinal cord 15 cm. long is of the order of 3500 r in four weeks at 250 kv, or 4000 r at 4 mv. It is thus just within the range of tolerance for hypernephroma. Normal kidney has been shown to be more sensitive than the spinal cord and it is now considered unsafe to go much above 2000 r if the whole of the remaining kidney has to be irradiated. The bowel is usually the limiting factor in irradiation as diarrhea supervenes at doses much above 3000 r.

Bratherton (1964) suggests that several different techniques are acceptable, the simplest being the use of two opposing fields. This avoids the opposite kidney and gives effective treatment to the scar. Attempts to cross the midline do, however, cause full irradiation to the spinal cord which may well receive a dose higher than that of the tumor bed. Two wedged fields at an angle are a considerable improvement on this technique as they will avoid the spinal cord and tend to build up the dose in the tumor area. A further improvement is the use of three wedged fields (Bratherton, 1964, Figure 8): the posterior field is directed as near the spinal cord as it is felt to be safe; the anterior field avoids the opposite kidney narrowly, and the lateral field is designed to bring the dose to the tumor bed while giving a minimum to the spine. Thus it is possible to attain a tumor dose of about 4000 r in four weeks.

Bratherton described two cases in which such treatment given after incomplete removal resulted in apparent cure (traced seven years). Other inoperable cases in his experience led him to the conclusion that there is a range of radiosensitivity in renal carcinomas and that disappearance with x-ray treatment can be obtained in some cases.

In conclusion he stated that there was an increase in 10-year survival from 26 to 33 % due to radiation therapy — not statistically significant.

CHEMOTHERAPY ALONE OR COMBINED WITH SURGERY AND—OR RADIATION

Before considering the possible benefits which may result from the use of various forms of chemotherapy in renal cancers, one must recognize that there is experimental evidence that many of these toxic compounds may indirectly accelerate tumor growth by inhibiting the normal defense mechanisms as suggested by Moore et al (1960), who warned that the successful application of the proper anticancer agent will depend on balancing its cytotoxic activity on malignant tissue against coincident injury to host factors. It is now apparent that most of the drugs used for cancer chemotherapy are immunosuppressive and many patients receiving kidney transplants and immunosuppressive therapy have developed cancer (Martin et al, 1965; R.E. Wilson et al, 1968; Penn et al 1969, 1970).

For Wilms' Tumor

Farber (1960, 1966) was among the first to use *actinomycin D* (dactinomycin) and found it a valuable adjunct to the treatment of this tumor in infants and children. He stated (1960): "It is a toxic material, but serious toxicity may be prevented by careful calculation of the dose for a given patient. The toxicity is a serious drawback to the exploitation of the full carcinolytic properties of actinomycin D. The potentiation of x-ray treatment effects by actinomycin D opens an era of great importance in the treatment of cancer . . . Of particular importance is the possibility of destroying pulmonary metastases by treatment so combined that x-ray therapy will be effective at a level lower than the minimum required to produce radiation pneumonitis . . . Actinomycin D is carcinolytic when used alone in the treatment of children with widespread metastases from Wilms' tumor. It is much more effective when used in combination with x-ray therapy. This combination is the best method yet discovered for the treatment of metastases from Wilms' tumor. A long range program designed to prevent metastases from Wilms' tumor involves the administration of actinomycin D at the time of surgical removal of the primary tumor and local radiotherapy for all patients . . . including those in whom no evidence of metastasis can be demonstrated . . . The addition of this form of chemotherapy to the techniques of surgery and radiotherapy . . . is directed toward the 50 or 60 % of such children who have not been cured by former methods of treatment . . . " Six years later Farber reported that when dactinomycin was administered routinely at the time of nephrectomy, followed by local irradiation, in Wilms' tumor, metastases were prevented in almost all patients and the two year survival (equivalent, with rare exceptions, to cure) was raised from the 40 % average level when surgery and irradiation were used alone, to more than double that figure (89 %). When metastases to the lungs were present at the time of discovery of the tumor, or in the course of the disease, a condition generally regarded as incurable except under rare and special circumstances, the combination of dactinomycin and radiotherapy, in amounts not harmful to the lungs, destroyed completely all evidence of tumor in the lungs and permitted long term survival, good health and apparent cure in 58 % (Farber et al, 1966). Some of the failures they attributed to presence of metastases in the liver, skeleton or brain, which require special and different therapeutic regimens.

Others who have reported on the use of dactinomycin in these cases include Altman (1961), Schweisguth and Bamberger (1965), and Fernbach and Martin (1966). The latter reported a 92 % four year survival in cases receiving surgery, radiation and dactinomycin versus 47 % with surgery and radiation. They attributed the beneficial effect of the drug to its action on small or poorly established metastases. Burgert and Glidewell (1967) noted that timing is critical: *children started on dactinomycin on the day of surgery had a clearly improved survival.* This drug

improved survival even when metastases were evident at operation. Survival did not differ between sexes and was better in younger than in older children. It is of interest that in the experience of Maier and Harshaw (1967) at Walter Reed Hospital, the addition of dactinomycin had not influenced the two-year cure rate of 44 % in a seven year period.

D.G. Johnson et al (1967) reported on their experience at the Children's Hospital in Philadelphia in the combined use of dactinomycin with nephrectomy and irradiation. The standard course they used was 15 micrograms/kg. daily for five days after surgery, with the drug therapy being initiated during the operative procedure. Radiotherapy using orthovoltage techniques was begun a few hours after surgery. In the group over one year of age 100 % of the infants survived with dactinomycin while only 33 % did so without the drug.

Lattimer and Conway (1968) reported that in their experience at Presbyterian Hospital, New York City, when dactinomycin is used with surgery and radiation the two year survival rate was 89 % as compared with 40 % for surgery and radiation alone, thus duplicating the results of Farber.

Rubin (1968) stated: "Death of children with Wilms' tumor is invariably due to lung metastases. . .Dactinomycin is the end of a long odyssey in search of a means to prevent metastases and to achieve a better survival." Not only is there laboratory evidence for a direct tumoricidal effect, but it appears to be a radiosensitizer and auguments the radiation effect on Wilms' tumor. He added that dactinomycin is more effective in the eradication of metastases in their occult stage when they are small or in elimination of circulating cancer cells than in its action on established secondaries. "The direction for chemotherapeutic advancement clearly lies in preventing metastases rather than seeking dramatic regression of widespread disease. *It is the most favorable patients rather than the terminal cases that need more study and exploration for chemotherapy combined with conventional therapy.*"

Sutow et al (1963) reported on the marked antitumor effects of *vincristine* in the treatment of *metastatic* Wilms' tumor, stating that the disease was temporarily controlled in nine of 13 children. The response to the drug was prompt, becoming apparent in three weeks in 75 per cent of the patients. The duration of the response was comparatively short, being less than two months in half the cases. No cross resistance in antitumor effect with previously administered chemotherapy was seen. Vincristine was used by Sutow in "primary" doses for five days, and thereafter in weekly maintenance doses. Although some of the patients had two or more toxic manifestations i.e., alopecia, nausea, vomiting, increased irritability, pain in the abdomen and the jaws, disturbances of gait and hematuria, only two required a temporary alteration of the dosage regimen. Two years later Sutow and Sullivan reported on the use of vincristine in the *primary* treatment of Wilms' tumor. They found that this drug, in conjunction with surgery and radiation, successfully prevented metastases or recurrence in six out of seven cases of Wilms' tumor, traced 11 to 35 months after surgery, although five of these children were considered poor risks prognostically (Sutow and Sullivan, 1965).

Vietti et al (1970) reported that complete regression of metastatic disease occurred in 16 of 22 (73%) of their Wilms' tumor cases treated by a combination of vincristine sulfate and radiation to the metastases. Ten (22%) were living and well more than two years after treatment of their metastases. These authors thought that the survival figure might have been improved by more intensive irradiation, since three of the children failed to receive radiation to all known metastatic sites. They stated that the response rate and quality and duration of response to vincristine plus radiation appear similar if not superior to that reported for dactinomycin plus radiation in these tumors.

Uson et al (1970) reported that the current treatment of Wilms' tumor consists of surgery, chemotherapy and radiotherapy, according to the specific needs of each case. Despite today's improved therapeutic means, the best chance of survival still depends greatly upon early diagnosis. They added: "However in the past decade chemotherapy with dactinomycin and vincristine sulfate had contributed significantly to the increased number of survivals, especially in the dangerous age group (over 2) of children with inoperable Wilms' tumors or with obvious metastases. As expected, maintenance or prophylactic courses of dactinomycin given at critical time intervals are needed and have yielded better results than the single course schedule. Postoperative radiotherapy is now less indicated in the management of Wilms' tumors since the newer and easier to handle carcinolytic agents have proven effective. However radiotherapy should be given in those cases with local tumor extension and in some instances of so-called isolated metastases."

Sullivan (1965) stated that vincristine may produce extremely rapid and virtually complete regressions of metastases from Wilms' tumor in all sites outside the central nervous system. He believed that the short duration of the antitumor response precluded long term maintenance therapy, but recommended its use as an adjuvant to surgery or radiation. In conclusion he stated: "It may be possible to significantly improve the cure rates in these diseases by the skillful manipulation of the various components of trimodal therapy, radiation, surgery and chemotherapy."

Fernbach in a personal communication (1971) stated that all Wilms' tumor patients should receive combination therapy with dactinomycin and vincristine since these two agents are extremely effective against this tumor. He reported one case in their series where massive pulmonary metastases disappeared following treatment with vincristine alone. Two years later there is still no evidence of recurrence. Similar experiences have been seen by other members of the Southwest Cancer Chemotherapy Study Group, who have reported that the combination of radiotherapy plus chemotherapy to the lungs seems to be more effective than chemotherapy alone (308).

CHEMOTHERAPY ALONE OR COMBINED WITH OTHER MODALITIES FOR RENAL CANCER IN ADULTS

Bennington and Kradjian (1967) state: "Systemic chemotherapy is of very little value in the management of renal carcinoma. In all reports its therapeutic effect has been indisguishable from the variations usual to the course of the disease."

Grabstald (1964) noted that there have been scattered single case reports of favorable responses to such agents as ThioTEPA, chlorambucil, methotrexate, cyclophosphamide, 6-aminonicotinamide, vinblastine sulfate and probably to others. However, he pointed out, there are also well documented cases of long term survival of many patients with known recurrent and or metastatic disease *without treatment of any kind.* For this reason it is difficult adequately to evaluate any agent. He concluded: "At the present time we must conclude that there are no known chemotherapeutic agents which consistently alter the course of a patient with renal cell cancer, whether it be metastatic, inoperable or recurrent."

Analysis of results in Wilms' tumor or renal carcinoma with surgery, radiation and chemotherapy, indicates that they may be quite unpredictable. Some patients with early, operable lesions may rapidly succumb to their disease (Throckmorton, 1955), while other much less promising, far advanced cases may survive (Abbe, 1894, 1912; Dean, 1941). We believe that these differences are due to varying host resistance in individual patients.

The considerable number of cases assembled in the course of the present study clearly indicate that some renal cancer patients have or develop sufficient immunological competence to cause spontaneous regression of their primary tumor (Table 1, 7 cases); or of their metastases (Table 2, 41 cases); or to prevent recurrence or spread until late in the course of the disease (Table 3, 20 cases); or to effect unusually slow progression of the disease (Table 4, 16 cases); or to enable the patient to survive, usually without further evidence of disease after surgical removal of pulmonary, hepatic or brain metastases (Table 5, 34 cases).

Analysis of possible causes of increased immunological competence in renal cancer patients suggests that lymphocytic infiltration of the tumor area, leukocytosis, inflammation, concurrent infection and possibly fever increase host resistance. (Table 6, 29 cases) In other patients, if the actively growing primary is removed surgically, the immunological defenses are sometimes sufficiently effective to cause complete regression of the metastatic lesions (Table 2, 41 cases).

W.B. Coley was the first to employ immunotherapy in neoplastic diseases. He treated only inoperable cases at first, using injections of the mixed toxins of Streptococcus pyogenes and Serratia marcescens (then known as Bacillus prodigiosus). This was done after preliminary attempts at inducing erysipelas in ten cancer patients proved difficult or dangerous. (W.B. Coley, 1909-1936; Fowler, 1968-1970; Miller and Nicholson, 1971; Nauts 1946-1970; Pelner, 1959-1960)

Only eight cases of renal carcinoma and three of Wilms tumor received Coley toxin therapy (Table 7). Three other renal cancer patients received other immunoadjuvants: Trypanosoma cruzi, Borrel's serum and goat serum (See Table 7, Cases 12-14).

Of the three cases of Wilms' tumor who received toxin therapy, the first in 1898 was a child of five with a very large tumor in whom Coley toxins were given for a short time prior to nephrectomy without apparent benefit. Metastasis developed and death occurred within a year. (At that time Coley had not yet conceived of the idea of giving toxins following surgery in order to help prevent recurrence or metastases.) The second case was a boy of 18 months who received injections of Coley toxins at intervals for 2½ years following nephrectomy in 1904 for a large tumor. He remained in good health with no further evidence of disease, became governor of his state and died of heart failure and acute pancreatitis 59 years after onset. In reporting this case in 1935 Coley stated he had not appreciated its importance until he had reviewed the literature on the results obtained after nephrectomy alone and found only two cases in the United States reported well over five years. (Abbe, 1894, 1912; Geschickter and Widenhorn, 1934.) It is of interest that Abbe's case, a 14 month old girl, had a huge tumor weighing 7½ pounds and the child weighed only 15 pounds following nephrectomy, requiring "liberal" use of hot water bottles and enemas of hot coffee to survive the shock of the operation. Next day her temperature rose to 105°F. These factors may have stimulated her host defenses in a similar fashion to the febrile reactions elicited by toxin therapy.

The third case was a child in whom nephrectomy was performed in Nebraska

and toxins were begun postoperatively by Coley and continued for a short period by the family physician. The weaker commercial preparation was used and was not administered aggressively. The child died within a year.

Only one operable hypernephroma received Coley toxins. This 44 year old patient had an immense adenocarcinoma of the right kidney with a 55 pound weight loss. Nephrectomy was performed by Barringer in December 1928. The tumor weighed 1022 gm. The postoperative course was stormy due to shock. Two x-ray treatments and 27 toxin injections were given in the next three months. He recovered completely and died of a coronary thrombosis 20 years after onset.

Of the six inoperable or terminal patients with hypernephroma who received Coley toxins (at least 10 injections), three were successful and were traced. One, treated by Harmer, regressed and the patient gained 50 pounds, but he was not traced subsequently. The permanent results in three of the other six cases are remarkable and detailed histories are given below.

Of the three inoperable failures, the first was treated by Coley in 1908 for an extensive inoperable recurrent renal cell carcinoma with metastases just above the crest of the ilium. Twenty-six intramuscular injections were given in seven weeks (only four marked febrile reactions) with no apparent improvement. The second treated by R.M. Green in 1911, received only 10 subcutaneous injections in 10 days with slight febrile reactions following an exploratory operation for a large sloughing tumor which filled the whole flank. There was no apparent benefit. Death occurred two months later. The third treated in 1962 by Johnston, had bilateral pulmonary and pelvic metastases. He received 55 intravenous injections in six months without apparent improvement. Death occurred 11 months after onset.

The other three cases in Table 7 suggest that toxins or serums other than Coley toxins may have a beneficial immunoadjuvant effect in such cases.

It would appear from these cases that in order to produce permanent results in a high percentage of inoperable and operable renal tumors, a potent preparation of bacterial toxins should be used, the injections should be begun prior to surgery and resumed immediately after surgery and continued for approximately four months. Cases such as Johnston's with extensive metastases may not respond. However, the results obtained by Coley, Leach and Connell in hopelessly inoperable cases should now encourage urologists to utilize some form of immunotherapy such as Coley toxins in similar cases.

DETAILED HISTORIES OF INOPERABLE RENAL CANCER TREATED BY COLEY TOXINS

Case 6: Twice-recurrent inoperable hypernephroma of the right kidney, confirmed by microscopic examination with metastatic growths involving much of the intestines.

Previous History: H.H., male, aged 33. The family history was negative for malignancy or specific disease. There was no history of trauma. The patient had been ill six months, suffering from cough, but examination of the lungs revealed nothing but "bronchial trouble" — he was being treated for *pulmonary tuberculosis.* The patient's normal weight was 180 pounds, and he had lost 40 pounds in the previous six months. Examination of the abdomen revealed an enormous, solid, non-fluctuating growth which filled the whole abdominal cavity. Urinalysis was negative, and the patient did not recollect having ever passed blood or pus. There was dullness on percussion over the entire tumor, and tympanites over the upper left quadrant of the abdomen. The tumor moved with respiration and apparently sprang from the back or the right side.

Surgery: An exploratory operation was performed on May 30, 1908 through an incision from the epigastrium to the pubis. No fluid was found in the abdominal cavity. Examination through the wound revealed a solid tumor of the right kidney with large blood vessels shining through the periosteum. As it was evident that the growth could not be removed without bisecting it, a couter opening was made in the loin. A pedicle was clamped through the incision in the loin, thus controlling the blood vessels. The tumor was then removed by an incision through its center. The vessels were tied, and the ureter examined and found not diseased. The tumor weighed 13½ pounds and was practically solid except for a few cysts the size of a pigeon's egg. The patient made a smooth recovery and was discharged from the hospital on June 26, 1908. The patient returned to the hospital on April 17, 1910 with a swelling in the groin the size of an orange. This was found to be an omental hernia with malignant degeneration. The whole omentum was removed up to the stomach. No other growth was apparent in the abdominal cavity. On June 27, 1910 the patient was readmitted to the hospital with irregular recurrent growths on the right side of the abdomen. Exploratory incision proved the growths to be inoperable as they involved so much of the intestines.

Toxin Therapy (Tracy XI): After recovery from this exploratory operation, Dr. Henry M. Leach of Saginaw, Michigan administered Coley toxins causing marked reactions on several occasions. A total of 41 injections were given and in two months the recurrent tumors entirely disappeared. The patient regained the 40 pounds he had lost and his former strength.

Clinical Course: He was reported perfectly well in January 1916 over six years after onset. He was not traced subsequently. (85)

Case 7: Recurrent inoperable hypernephroma, confirmed by microscopic examination by Professor Beattie.

Previous History: M.W., female, age 57. The patient was married and had two children. In 1908 she first noticed a lump on the right side. There was indefinite pain in the right loin and semilunar line below the costal margin, a feeling of constriction of the waist, and occasional fainting. In October 1910 hematuria occurred the day after taking a long walk. This reappeared in August 1911. On both these occasions it

quickly cleared up. The patient was admitted to the Royal Infirmary in Sheffield, England on January 31, 1912, complaining of severe pain in the right loin and a great desire to micturate. Early that morning she had had intense pain, which cleared up on passing three or four long blood clots. For a few days previous to admission she had been passing very dark blood.

Surgery: On February 1, 1912, the right kidney was explored from behind. The surface was found to be irregular and gave the impression of polycystic disease. It was deemed imprudent to perform a nephrectomy, but a small piece was removed for microscopic examination. The capsule was carefully closed with catgut sutures. The wound healed and two weeks later she was discharged to a convalescent home. On March 18, 1912 she was readmitted and a transperitoneal nephrectomy was performed. Three months later the patient returned, looking very ill, with a huge recurrent tumor in the right kidney pouch.

Toxin Therapy (Parke Davis XIII): She was readmitted at once, and injections were begun the following day, June 13, 1912, by Professor Arthur Connell of the University of Sheffield. They were continued for 4½ months, with the result that the tumor disappeared entirely and the patient regained her former health. Connell stated that when she was discharged from the hospital on October 26, 1912, no trace of tumor could be felt and her general condition was excellent.

Clinical Course: He examined the patient thoroughly the following autumn and reported that he found her free from any lesion. He added that she looked the picture of health, had gained weight, and never felt better. She was last traced in good health and free from recurrence in 1926, 14 years after toxin therapy. (83, 84, 85)

Case 9: Extensive inoperable hypernephroma of the kidney, involving the retroperitoneal lymph nodes, confirmed by microscopical examination by Dr. W.A. Lindsay, Pathologist at the Victoria General Hospital, Halifax and graduate of Edinburgh University.

Previous History: M.P., female, aged 27, of Waterville, Nova Scotia. The family history was apparently negative as regards malignancy in 1912, but in 1945 the patient's mother had a radical mastectomy and the patient's eldest sister had a "cyst" in her uterus requiring a hysterectomy. The youngest sister had tuberculosis. In the winter of 1895, at the age of 10, the patient was injured in the back over the right kidney region while skating. Following this she developed jaundice and in the summer "blood-poisoning" in her right hand. Two or three years later she had scarlet fever and the attending physician told her that the "glands of the neck and kidneys were injured". In 1902 she had pertussis. Menses began at 12 and were very irregular for three years, with severe headache, constipation, nausea, some pain and excess flow. Thereafter until menopause, menstruation was normal. Onset, early in 1912 her health rapidly began to deteriorate. In the latter part of August, nine months after onset, the family physician found a large mass in the ileolumbar region. The patient was taken to Halifax and consulted Drs. H.K. McDonald and John Stewart (a pupil of Lord Lister).

Surgery: An exploratory operation was made, through a loin incision, and the kidney was exposed. The upper and middle third were found apparently normal; the lower pole was occupied by a large tumor which was adherent to a much larger growth anteriorly. A section was removed for microscopic examination. The patient was then turned upon her back and a laparotomy made, disclosing a large retroperitoneal mass which could not be removed.

Clinical Course: She made a very poor operative recovery and a sinus developed at the site of the loin incision. She was hospitalized about four weeks. The condition was regarded as absolutely hopeless, and she was removed on a stretcher and special car to her home. No one believed she would live through the journey.

Toxin Therapy (Tracy XI): Injections were begun by Dr. McDonald September 21, 1912, three weeks after operation, and were given intramuscularly in the buttocks for seven weeks. McDonald stated that her condition at this time was so bad the toxins were used as a last resort and he thought that "if they were of no benefit, they would perhaps have the other effect and put the patient out of her misery." However, after the first injection she began to improve. When a dose of four minims had been reached, the sinuses in the lumbar region closed. Marked febrile reactions occurred after each injection, the temperature rose to 105° F, dropping to normal by late afternoon. The tumor began to show marked decrease in size, and after 18 injections had been given, Dr. Arthur S. Burns, the home physician, stated that the mass in the loin had practically disappeared and that the patient was rapidly gaining weight and in every way showing marked improvement. The final injection was given on November 9, 1912.

Clinical Course: By January 23, 1913, the patient had gained 20 pounds in weight. She ate and slept well, was up and around the house, and was making steady improvement. Careful examination by two physicians failed to reveal any evidence of a tumor or mass of any kind. Coley advised that the injections be continued until the end of January. However, the recovery was so rapid that the family physician did not consider this necessary. Improvement continued and by June 14, 1913 she had gained 32 pounds. She was seen two or three times a year by McDonald, who reported that in 1927, 15 years after treatment, at the age of 42, the patient developed "a severe uterine condition" — multiple fibroids. McDonald performed a supravaginal hysterectomy, and at the same time made a very complete and thorough examination of the abdomen, particularly at the site of the former tumor, and found no evidence of disease. She made a good operative recovery and McDonald stated that she enjoyed excellent health thereafter. During her 70's she had several attacks of influenza for which she was hospitalized. Also in January 1963 a stroke and heart attack. She remained in fair health in March 1965. Death occurred in November 1966 due to cerebrovascular disease, 54½ years after onset of her hypernephroma. (83, 84, 85, 300, 301)

DISCUSSION AND CONCLUSIONS

In general the prospects for adult patients with renal carcinoma are considered to be poor. This is due not only to the aggressiveness of the tumor, but largely to the occult growth and metastatic spread of the tumor before onset of symptoms, and to the patient's delay in consulting a physician once symptoms occur. This patient delay is estimated as being of almost two years' duration.

The average diameter of renal carcinomas when discovered has been reported as 5 to 7.5 cm. and 40 % have already grown through the pseudo-capsule or through the true renal capsule when first seen. In spite of the extensive growth within the kidney and local invasion, the presenting symptoms of many patients are referable to distant metastases rather than to the primary tumor.

Carcinoma in any other organ would be considered far advanced and inoperable at this stage yet nephrectomy is almost routinely performed under these circumstances. Even though a substantial number of such patients are found to have occult distant metastases at nephrectomy, the 10 year survival rate is 18 to 23 per cent. In comparison with neoplasms of other organs these survival rates are remarkably high. Possibly this may be due to the fact that the blood supply to the kidney is greater than to most organs or tissues so that the humoral and cellular immune substances can reach these tumors more effectively.

Although the prognosis and end results in Wilms' tumors have improved very markedly in the past dozen years since dactinomycin has been added to the regimen of surgery and radiation, end results could be improved by the use of immunoadjuvants which are non-toxic and produce no deleterious side effects or late sequelae such as have occurred in so many children who survived radiation for Wilms' tumor.

The results in the cases assembled for this study suggest that host resistance factors play a significant role in the prognosis of renal cancers in children and adults. Concurrent infections, inflammatory episodes, fever or surgical removal of the primary may help reinforce these defensive mechanisms, but one may do so more effectively by administering some form of immunotherapy, such as Coley toxins or other bacterial toxins containing streptococci and staphylococci, BCG or yeast extracts or synthetic products. Such therapy should be utilized prior to as well as following surgery and irradiation, to lessen the chance of causing metastases due to manipulations incident to diagnostic, surgical or radiological procedures and to cause regression of early metastases not yet clinically apparent, as well as in the treatment of inoperable cases.

Bacterial toxins stimulate wound healing and protect the normal tissues against the deleterious effects of radiation (Ainsworth, 1961), while potentiating the response of the tumor to the radiation (Miller and Nicholson, 1971). This important factor will enable radiologists to utilize smaller doses of radiation, thus avoiding the dangers of injuring the intestines or the gonads, skeletal deformities to children with Wilms' tumor, or radiation nephritis in the remaining kidney in children or adults. Such adjuvant therapy may be of special significance in treating cases of bilateral Wilms' tumor or renal carcinoma, in order to preserve as much of the remaining kidney as possible.

Recent studies by Martin et al (1961) have shown that the response to chemotherapy is inversely proportionate to the size of the tumor mass. In their experiments, reduction of tumor size by simple surgery restored the curative efficacy of chemotherapy. Their data show that "cure" can never or rarely be effected on large, well established transplantable tumors by chemotherapy alone, immunotherapy (zymosan) alone or surgery alone. However, by combining the three therapeutic

modalities, they produced striking cure rates in the range of 70-80 per cent which could, in turn, be nullified by cortisone (an immunosuppressant). In a later report Martin et al (1964) stated their data furnished additional evidence that immune phenomena may be strengthened to afford more effective treatment of cancer patients. They note a critical relationship between the dose of zymosan and the time of its administration.

Microbial products exert their beneficial effects on cancer patients through stimulation of the reticuloendothelial and lymphoid tissues, and of interferon. They seem to increase the antigenicity of tumor cells and the immunocompetence of the patient.

Many great cancer centers in a number of countries are becoming increasingly aware of the vital importance of immune factors in cancer, and are beginning to treat leukemia or various forms of cancer with immunoadjuvants. It is hoped therefore that urologists, surgeons and radiologists who are concerned with the treatment of renal cancer in children and adults will begin to utilize these agents in a coordinated program in order to increase the survival rates significantly.

TABLE 1: RENAL CANCER WITH SPONTANEOUS REGRESSION OF THE PRIMARY TUMOR: 7 CASES

Author Date Published (References)	Sex Age, Date of Onset	Histological Diagnosis Extent of Disease	Treatment	End Result Years Traced After Onset
1. Hall 1908-09 (119, 173)	F 45	hypernephroma 6 x 4 cm., completely separated from kidney substance, "tumor tissue was dead at time of nephrectomy."	?	12 years prior to nephrectomy pain in left kidney intermittent hematuria several mos., next 12 years some pain in left kidney
2. Hall 1908-09 (119,173)	M 50	hypernephroma, cachexia, very thin; tumor entirely necrotic within capsule of kidney at autopsy	Untreated	patient died before any treatment was given (one year after onset)
3. Rae 1935 (119, 338)	F 61	large calcified hypernephroma 13 cm. in diameter; tumor stony hard, required a saw to cut it: calcified except for a piece the size of a marble; many cystic spaces containing soft grayish yellow jelly-like material	left nephrectomy	?
4. Griffith & Thackray 1949 (165)	adult	parenchymal carcinoma of kidney, low grade	biopsy, nephrectomy abandoned as unfeasible	alive 7 years later
5. Griffith & Thackray 1949 (165)	adult	parenchymal carcinoma of kidney, with calcification	nephrectomy	alive 6 years later
6. Griffith & Thackray 1949 (165)	adult	parenchymal carcinoma of kidney with calcification	nephrectomy	alive 11 years later
7. Ljunggren 1960 (247)	F 58	hypernephroma about 4 cm. in diameter with cystic degeneration, incontinence	exploratory surgery, a cyst with clear contents was biopsied: wall of cyst composed of sclerotic connective tissue, with a small zone of hypernephroid tissue; nephrectomy: in remaining wall of cyst, there was a little further hypernephroid tissue	?

TABLE 2: METASTASES OF RENAL CANCER, MOSTLY PULMONARY, WHICH REGRESSED SPONTANEOUSLY: 41 CASES

Author Date Published (References)	Sex Age	Histological Diagnosis Extent of Disease	Treatment of Primary	Treatment of Metastases	End Result Years Traced After Onset
1. Bumpus 1928 (61, 119)	M 59	hypernephroma, multiple pulmonary metastases (also had 3 attacks hemiplegia with foot drop)	nephrectomy	untreated	complete recovery, all metastases disappeared; well NED* until death 1938, at 73, 14 years
2. Hyman 1933 (192)	? adult	hypernephroma, pulmonary metastases	excision of primary 1929	untreated	metastases disappeared; well, NED 1933, over 4 years
3. Beer 1937 (30)	M adult	hypernephroma, bilateral pulmonary metastases with cough occurred after nephrectomy	nephrectomy	untreated	multiple large and small metastatic nodules in lungs disappeared 5 mos. later. Not traced
4. Mann 1948 Schapiro 1967 (119, 266, 370)	M 62	hypernephroma, bilateral pulmonary metastases, increased in size and number for 7 weeks after nephrectomy	nephrectomy 1943	untreated	after leaving hospital he appeared to deteriorate summer 1945, frank hemoptysis occurred; thereafter improved, gained weight, strength, complete regression all metastases 22 mos. after nephrectomy; only abnormality some linear fibrosis in right lung asymptomatic except for a left inguinal hernia. Led normal life until March 1963; death cerebrovascular accident, at 82, 20 years after onset
5. Bacher 1952 (20)	F 60	hospitalized 1949 metastases in both lungs, no primary appeared until June 1950, blood clots in urine: hypernephroma (patient inclined to allergic symptoms)	nephrectomy July 1950 tumor yellow, partly encapsulated	testoviron (200 mg.) implanted December 2, 1949 and after nephectomy	pulmonary lesions regressed completely by January 31, 1949; condition improved considerably, gained weight; complete recovery NED 1952, over 3 years after onset
6. Klimpel 1957 (119, 220; 308)	M 65	extensive hypernephroma, size of 2 fists adherent to peritoneum, hematuria, reduced kidney function; patient markedly hirsute over chest, lower abdomen, back	rt. nephrectomy, then x-ray	none	22 mos. after nephrectomy piece of tumor size of plum and several small pieces excreted in feces, following 2 brief intestinal hemorrhages ("markedly hemorrhagic, partially necrotic hypernephroma metastases which after perforation into cecum had been spontaneously discharged in feces."); again brief intestinal bleeding; again histologically confirmed metastatic hypernephroma; 12 days later a chestnut-sized piece excreted with several blood clots; barium enema revealed jagged outline in area of cecum; hirsutism then markedly decreased; in good health until pyloric stenosis due to ulcer scars, gastroenterostomy, NED, over 5 years after onset

* NED = No evidence disease

Author Date Published (References)	Sex Age	Histological Diagnosis Extent of Disease	Treatment of Primary	Treatment of Metastases	End Result Years Traced After Onset
7. Arcomano 1958 (13, 119)	M 37	extensive hypernephroma 66 x 10 x 6 cm.; multiple bilateral pulmonary metastases	nephrectomy January 1955, discharging fistula in scar	pulmonary metastases untreated; craniotomy, surgical removal 6 wks later; asymptomatic almost 2 years	pulmonary metastases disappeared in 8 mos.; well 20 mos., then brain metastases; died further cerebral involvement October 1958, nearly 5 years after onset
8. Lageze 1958 Cibert 1958 (78, 119 247a)	F 56	extensive very adherent hypernephroma with extensive bilateral pulmonary metastases; cachexia; onset January 1956	right nephrectomy April 1956; vena cava torn; lung lesions increased, also dyspnea, weight loss in next 8 mos.	July 1956: Cortanyl given for 3 mos. (90 mg. in all)	condition deteriorated: terrible bilateral lumbar pain, severe dyspnea, lost 6 more lbs., metastases to lung increased markedly after cortisone, painful edema left leg; then recovered, metastases disappeared; gained 44 lbs. by 1958; alive and well 1970, at 69, over 14 years after onset.
9. Hallahan 1959 (119, 174)	M 75	large adenocarcinoma left kidney, 5 or more pulmonary metastases	February 1956 nephrectomy, metastatic nodule found in perirenal fat	transfusion 1 pint blood postoperatively, oral iron for 6 weeks, tracheo-bronchitis, penicillin	lung metastases disappeared in 12 mos. after tracheobronchitis; well until death, October 1958 of congestive heart failure due to arteriosclerotic and hypertensive cardiovascular disease, over 3 years after onset
10. Kessel Leizor 1959 (19, 237)	M 65	adenocarcinoma left kidney, bilateral pulmonary metastases	nephrectomy	untreated	lung lesions increased in size and number for 3 mos. after nephrectomy, condition remained poor, then began to improve; complete regression all metastases, NED until sudden death, coronary occlusion, August 1967, over 8 years after onset
11. Jenkins 1959; 1965 (119, 199, 200)	M 57	recurrent hypernephroma with invasion of blood vessels, bilateral pulmonary metastases; chronic nephritis	nephrectomy 1950	metastases untreated; recurrence in scar excised 1959; 2nd recurrence biopsied, given x-ray	metastases increased in size and number for a year; marked regression then occurred; still apparent 1954 when admitted for perforated gastric ulcer, stenosing duodenal ulcer; all lung lesions regressed except one small nodule, in excellent health; 1960: recurrence in scar, another massive inoperable recurrence; 1963, disease generalized after biposy, x-ray; also had arteriosclerotic heart disease, terminal staph. pneumonia; death June 1963, 13 years after onset
12. Cliffton 1959 (80, 119)	M 56	hypernephroma, bilateral pulmonary metastases involving pleura, in lower chest and diaphragm, largest 6 x 8 cm.	primary in right kidney remained asymptomatic and was untreated	exploratory thoracotomy, biopsy of largest pleural mass, and one of lung nodules by wedge resection; antibiotics for 12 days; concurrent left pleural effusion, fever for 3 days after thoracotomy	general condition improved, marked regression lung metastases, gained 12 lbs. in 2 mos.; well until sudden death, coronary occlusion 3 years after onset; chest clear at last film a month earlier

TABLE 2: METASTASES OF RENAL CANCER, MOSTLY PULMONARY, WHICH REGRESSED SPONTANEOUSLY: 41 CASES

Author Date Published (References)	Sex Age	Histological Diagnosis Extent of Disease	Treatment of Primary	Treatment of Metastases	End Result Years Traced After Onset
13. Ljunggren 1959 (119, 246, 308)	M 34	hypernephroma, multiple bilateral pulmonary metastases first seen September 1956, increased in size and number for 3 mos. (no urinary symptoms)	right nephrectomy May 1957, after pulmonary metastases had regressed	exploratory thoracotomy, biopsies from 3 areas; x-ray to frontal lobe metastasis, fall 1957 (2700 r x 3); also to lesion in right hilar region, January 1958	lung metastases regressed spontaneously by March 1957, except for a nodule in right hilar region; cerebral metastases (frontal) September 1957, death December 1958 about 2½ years after onset. Autopsy: one lesion remained in right hilar region, 2 in left kidney; frontal lobe metastasis entirely necrotic, another present in cerebellum
14. Ljunggren 1959 (119, 246, 247a, 308)	M 50	hypernephroma, bilateral pulmonary metastases (10)	left nephrectomy September 1958	untreated	marked regression pulmonary metastases 2½ mos. after nephrectomy; 4 mos. later only 1 small nodule remained in lower lobe; complete recovery, well 1972, over 11 years after onset
15. De Veer 1960 (102)	M 81	renal carcinoma, very extensive pulmonary metastases concurrent fever	?	untreated	very extensive pulmonary metastases regressed spontaneously 1958; death May 1959
16. Buehler 1960 (59, 119)	M 59	clear cell carcinoma 15 x 30 cm. extending into caval and aortic areas, involving renal vein, bilateral lung metastases	left nephrectomy November 1958 about 2 years after onset; staph. infection post-operatively cleared very slowly	untreated	10 mos. after nephrectomy almost complete disappearance lung metastases, 20 lb. wt. gain; chest clear 4 mos. later; further metastases to perirenal region, brain, lung, spring 1961; death May 1961 about 5 years after onset
17. Buehler 1960 (59, 119)	F 59	carcinoma left kidney bilateral pulmonary metastases, apparent 1 month after nephrectomy	nephrectomy, several transfusions April 1958	untreated	marked regression of lung metastases by September 1958; complete disappearance by January 1960; well 22 mos. then disease metastasized to jejunum, causing death February 1961, over 3 years after onset
18. Nicholls & Siddons 1960 (310)	M 55	hypernephroma, metastases to suprarenal and to right lower lung	left nephrectomy November 1955	right exploratory thoracotomy 2½ mos. after nephrectomy revealed multiple pulmonary metastases, no attmept at removal	lung metastases disappeared; symptom-free 2 years, then metastases to sacrum; death despite radiation 2½ years after nephrectomy; NED in lungs at autopsy

19. Lageze 1960 (232)	M 58	hypernephroma, bilateral pulmonary metastases (onset of primary May 1958; 12 lb. wt. loss)	left nephrectomy August 1958; hematoma in wound suppurated, 2 fistulae discharged pus; antibiotics given, febrile 4 weeks (to 101°F); 1 fistula suppurated for 6 mos.	in period that metastases grew he received hydrocortanyl; 20 mg. at first then 10 mg. daily; beginning January 1959 Trypanosoma cruzi injections daily for 3 mos., every 48 hours for 2 mos.	lung metastases increased in next 7 mos., but were asymptomatic; patient in excellent condition, gained weight (24 lbs.); metastases began to regress by June 1959, completely disappeared by September 1959, well 1960
20. Kolar 1961 Jakoubková 1965 (198, 222)	M 55	advanced hypernephroma, multiple bilateral pulmonary metastases (onset November 1958)	right nephrectomy April 30, 1959, condition then deteriorated.	iron, Vitamin B complex	4 mos. after nephrectomy definite improvement, 10 lb. wt. gain; all but largest lung lesion disappeared in next 2 mos., this also disappeared several mos. later; by April 1961 patient had gained over 34 lbs.; NED 1971, over 12 years after onset
21. Samellas & Marks 1961, 1963 (366,367)	M 43	adenocarcinoma left kidney, multiple pulmonary metastases (renal vein filled) onset 1957	left nephrectomy December 1958	none	returned to work, lungs cleared completely; returned 2 years later with mild heart failure, again returned to work; well over 6 years after onset
22. Hultborn 1961 (119)	M 48	hypernephroma, 3 metastases in right lung	right nephrectomy March 1961	untreated	metastases increased in size and appeared in left lung within 4½ mos.; all disappeared in next 3½ mos.; NED November 1962, over 18 mos. after onset
23. Hultbron 1961 (119)	F 70	hypernephroma, large number metastases in both lungs (onset summer 1960)	right nephrectomy July 1961	untreated	2 mos. after nephrectomy almost complete regression of lung metastases (only 1 nodule still apparent in each lung); May 1962 lungs clear; NED October 1962, over 2 years after onset
24. Prentiss 1962 (119,335)	F 63	extensive hypernephroma grade IV; multiple bilateral pulmonary metastases.	right nephrectomy 1947 (growth extended into pedicle and renal vein)	untreated	concurrent pyuria; sulfathiozole given; metastases still present 3 mos. after nephrectomy, but 10 mos. later chest entirely clear; NED in good health 1971, 24 years after onset, at age 87

TABLE 2: METASTASES OF RENAL CANCER, MOSTLY PULMONARY, WHICH REGRESSED SPONTANEOUSLY: 41 CASES

Author Date Published (References)	Sex Age	Histological Diagnosis Extent of Disease	Treatment of Primary	Treatment of Metastases	End Result Years Traced After Onset
25. H. C. Miller 1962 (285)	M 57	extensive hypernephroma, bilateral pulmonary metastases (some 6 cm. in diameter)	right nephrectomy May 1959: *"marked necrosis, aggregations of lymphocytes"* in tumor area.	untreated	cough, sore throat, fever, generalized malaise; antibiotics given 7 weeks prior to nephrectomy; extensive metastases in both lungs disappeared in 6 mos.; alive, well 1970 over 10½ years after onset
26. Miyagawa & Kodama 1963 (288)	M 64	hypernephroma, multiple bilateral pulmonary metastases.	nephrectomy	untreated	metastases gradually decreased in size and number, completely disappeared in 18 mos., healthy, asymptomatic
27. Sakula 1963 (119, 365)	M 61 (obese)	spindle cell carcinoma left kidney (at autopsy); bilateral multiple pulmonary metastases; 28 lb. wt. loss; onset August 29, 1958, multiple non-specific symptoms; no renal disease apparent.	untreated	untreated	chest films December 1958, 5 weeks after 1st, showed marked clearing of lesions in lungs, except for 1 in right upper zone; patient felt so well he wished to work; disease reactivated, then pain, hematuria first apparent, death February 1959, 6 mos. after onset
28. Gonick & Jackiw 1964 (154, 268)	M 58	large fungating clear cell adenocarcinoma, metastases in lower lobe and lingular of left lung, possible lesions in right lung	right nephrectomy September 1950	left thoracotomy October 1950: a lingular and 3 metastatic nodules from left base were resected; wbc 10,600, fever 99°-100°F for 2 weeks after thoracotomy; further fever, chills, night sweats productive cough 1957 (consolidation at upper lobe, hilar mass, right side), antibiotics; 4 mos. later hemoptysis; 15 lb. wt. loss; wbc 11,300, 2 biopsies of the right upper lobe bronchus negative (inflammatory)	suspected nodules in right lung became more definite immediately after thoracotomy, but then regressed until they had disappeared by August 1951; in 1956 a nodular lesion reappeared in a different area of right lung; death 9 years after onset, 8 years after nephrectomy: lobulated area in entire upper half of right lung and 4 x 8 cm. oval density projected from right lateral chest wall

29. Grabstald 1964 (119)	M 41	renal cell carcinoma, pulmonary metastases	left nephrectomy	thalidomide for 3 mos. beginning Dec. 27, 1962.	chest clear by March 26, 1962; NED June 1963, over 18 mos. after onset; then died of widespread metastases
30. Grabstald 1964 (159; 170)	adult	renal cell carcinoma, widespread pleuropulmonary metastases	untreated	exploratory thoracotomy, metastases biopsied.	spontaneous regression of all metastases; disease reactivated, causing death 6 mos. later
31. Ljunggren & Claes 1964 (119; 246; 247; 247a; 308)	F 56	hypernephroma, bilateral lung metastases, fever	left nephrectomy April 1964 (renal vein involved)	none	almost complete regression of metastases "except for infinitesimal remnant" in 5 mos.; NED thereafter; alive and well 1972, 8 yrs. after onset
32. Andrews 1965 (12)	F 49	massive hypernephroma, multiple pulmonary metastases; onset July 1960	right nephrectomy 9 mos. after onset.	untreated	2 mos. after nephrectomy chest clear; good health nearly 8 years, then metastases to spine, rapid down-hill course after x-ray, death June 1969, 9 years after onset; extensive lesions in spine, liver, adrenals, skull, myocardium, paravertebral gutters, psoas muscles; NED in right renal bed and lungs
33. Adolffson 1966 (6)	M 32	hypernephroma size of child's head, abundant metastases on peritoneum, bilateral pulmonary metastases evident January 1962	nephrectomy; postoperative x-ray September 1961.	untreated	metastases disappeared by November 1962, chest films clear October 1963; died in nursing home a month later, no autopsy
34. Adolffson 1966 (6)	M 56	hypernephroma, tumor thrombus in bilateral external iliac vein February 1961; pulmonary metastases April 1961	nephrectomy deferred due to extent of disease x-ray to right kidney, gradual recovery January: "highly regressive transformed hypernephroma".	original lung lesions untreated; lesion in left lung given x-ray 1963; that in right lung given x-ray Sept. 1964; cytotoxic drugs.	lung metastases disappeared by October 1961; chest films May 1963 showed lesion in left lung; May 1964 one in right lung; several more November 1964; condition deteriorated; death agranulocytosis, 3 years after nephrectomy; autopsy: metastases to lungs, pancreas

TABLE 2: METASTASES OF RENAL CANCER, MOSTLY PULMONARY, WHICH REGRESSED SPONTANEOUSLY: 41 CASES

Author Date Published (References)	Sex Age	Histological Diagnosis Extent of Disease	Treatment of Primary	Treatment of Metastases	End Result Years Traced After Onset
35. Mims et al 1966 (155; 287)	M 51	clear cell carcinoma rt kidney; asymptomatic osteolytic metastases to inferior ramus rt. public bone & proximal rt. humerus; pathologic fracture February 1964 before renal cancer was suspected	rt. nephrectomy April 1964; pathologist reported: "inflammatory tissue reaction with many lymphocytes surrounding the tumor . . . histological appearance of an early host rejection reaction."	biopsy of rt. humerus; cells suggestive of metastatic renal carcinoma: "considerable amount of lymphocytic infiltrate around stroma"	osteolytic lesions showed marked calcification and regression; complete recovery, gained 5 lbs., returned to work; after bone metastases had healed radiotherapist advised x-ray to scapula and rib cage; during this period several metastases appeared in lungs; death occurred of multiple pulmonary and other metastases January 1966, over 2 years after onset
36. Markewitz 1967 (268)	M 53	large hypernephroma diffuse pulmonary metastases; onset June 1964	nephrectomy; "tumor centrally necrotic, numerous intermingled leukocytes around and within tumor cells"	recurrence in flank biopsied; metastases untreated	within 4 weeks after nephrectomy lung metastases began to regress; dramatic improvement, gained 20 lbs., cough ceased; very rapid deterioration after biopsy of recurrence; died a week later, 18 mos. after onset: widespread metastases present but only 2 in lungs; "focal infiltration with lymphocytes, plasma cells, portions wholly necrotic, suggesting immunologic phenomenon"
37. Goodwin 1967 (155)	F 53	adenocarcinoma involving renal vein, bilateral lung metastases; weakness, wt. loss for 2 years (80 lbs.) onset 1946	5 blood transfusions in 2 years; left nephrectomy November 1948	untreated	less than 4 mos. after nephrectomy, metastases had disappeared; alive, well, NED 5 years after onset, 3 years after nephrectomy
38. Goodwin 1967 (155)	M 47	adenocarcinoma, invasion of renal vein; onset October 1954, phlebitis right leg, right flank mass; September 1957, solitary metastasis left lung, several more developed in next 5 mos.; January 1963 metastasis in left femur caused pathologic fracture	right nephrectomy December 1954	September 1954 inadequate x-ray to each lung (100 r); lesion in upper lobe increased; May 1963, amputation for femoral metastases	1959-60, remarkable regression metastases in lungs; condition then deteriorated, nausea, emesis, dyspnea, diabetes mellitus; August 1961, semi-stuporous; lung metastasis then disappeared; January 1963 pathologic fracture left femur; fall 1963, condition again deteriorated; death November 22, 1963, generalized arteriosclerosis, myocardial infarction, abdominal abscesses, diffuse metastases, 9 years after onset; autopsy: calcified hematoma, tumor abscess formation, bilateral pulmonary metastases, bronchopneumonia with abscess, metastases to brain, left adrenal, subcutaineous tissue of thorax
39. Robinson 1969 (352)	M 70	renal cell carcinoma rt. kidney 10 cm. in diameter with abdominal lymph node metastases, 30 lb. wt. loss, anemia, by January 1967 bilateral lung metastases, liver and brain metastases; also had chronic pyelonephritis; onset January 1964	refused surgery for 3 yrs., given ferrous sulfate for anemia (300 mg. daily); 1967 gross hematuria, persistent renal sepsis; nephrectomy over 3 yrs. after onset; tumor weighed 394 g.; evidence of marked diffuse chronic inflammation in renal parenchyma	untreated	cerebrovascular accident April 1965 with residual hemiparesis, generalized muscle weakness; in next 13 mos. gained 40 lbs., lung lesions disappeared, remarkably well; then condition declined, lost 30 lbs.; disease progressed after nephrectomy, further lung, liver metastases; death July 14, 1967, 3½ yrs. after onset; autopsy: metastases to lungs, mediastinum, liver, brain

40. **Ljunggren** 1970 (247a; 308)	M 54	hypernephroma with pulmonary metastases; local recurrence developed a year after surgery, also metastases to distal lt. femur	nephrectomy 1959	lung metastases untreated, 3 recurrent nodules size of walnut, hazelnut & bean excised 1960; femoral lesion untreated	1 yr. after excision of local recurrences, x-rays showed femoral lesion was sclerotic; NED thereafter; alive and well 1972, over 12 yrs. after onset
41. **Ridings** 1971 (350)	M 36	inoperable adenocarcinoma involving upper half of rt. kidney, multiple bilateral pulmonary metastases; 45 lb. wt. loss; concurrent peptic ulcer of 9 years duration, leukocytosis (15,300); onset July 1967	October 1967; cobalt 60,500 rads; well tolerated; wbc remained somewhat elevated (11,200); lesion regressed 50% in 2½ mos.; right nephrectomy April 15, 1968 at same time as gastric resection; tumor largely filled with reddish-brown semi-liquid, necrotic material; postoperative course stormy, pneumonitis	untreated	some lung lesions increased following radiation of primary, but all then disappeared in 2½ mos., primary 50% smaller, but large duodenal ulcer required subtotal gastric resection, tube duodenostomy; complete recovery, did well 7 mos., then fistula in rt. hepatic flexure, fever 102°F at colectomy; gained 45 lbs., works regularly. NED over 3 yrs after onset

TABLE 3: RENAL CANCER WITH LATE RECURRENCE OR METASTASES: 20 CASES

Author Date Published (References)	Sex Age	Histological Diagnosis	Treatment of Primary	Recurrence or Metastases, Site, Interval	Treatment of Recurrence or Metastases	End Results; Years Traced After Onset
1. Abbe 1897 (2, 84)	child	Wilms' tumor	nephrectomy	metastases in other kidney 4¾ years after nephrectomy	?	alive 5 years after onset
2. Broster 1923 (56)	F 61	hypernephroma	nephrectomy 1914	9 years after nephrectomy, metastasis to femur, pathologic fracture	disarticulation, good recovery	well August 1923, 10 years after onset
3. Graves 1935 (163)	M 53	adenocarcinoma; onset, fall 1910.	nephrectomy January 1913	recurrent mass in scar 20 years after nephrectomy	biopsy only	died January 1934, 24 years after onset
4. Caylor 1936 (73)	M 59	hypernephroma	nephrectomy	inoperable metastasis to thyroid 13 years after nephrectomy	x-ray (6000 r) severe gastric or esophageal hemorrhages 48 hours later	end result unknown
5. Linton 1946 (244)	M 55	hypernephroma left kidney	left nephrectomy 1934; in good health except for chronic sinusitis	November 1943, after several u.r.i. insidious onset fatigue, frontal headache, anorexia, 18 lb. weight loss; metastases to thyroid evident December 1943, 9 years after onset, increased slowly, then rapidly metastases to right kidney	April 1944, thyroidectomy; right renal tumor biopsied; x-ray (3600 r)	myxedema after thyroidectomy, corrected by thyroid extract; well 6 mos. except for headaches and cervical pains; September 1944, inoperable right renal metastasis; well 7 mos. after biopsy, x-ray; wanted to return to work; end result unknown
6. Bastable 1950 (28)		renal carcinoma	nephrectomy	metastases to other kidney 15 years later	resection of 2nd lesion	alive and well 18 mos. after 2nd operation
7. Denton & McClintoch 1949 (99)	M 49	hypernephroma	nephrectomy; well 8 years	metastasis to thyroid 8 years later	thyroidectomy	died 13 mos. after thyroidectomy, 9 years after nephrectomy
8. Starr & Miller 1952 (392)	F 52	clear cell renal carcinoma, 1931	nephrectomy, 1931 (*necrosis, hemorrhage, fibrosis, inflammation present in kidney not involved by tumor*); well 20 years	solitary polypoid jejeunal metastasis 1951, 20 years later	explored early 1951, metastases resected, anastamosis	thyroidectomy 1937 for adenoma, resection for adenocarcinoma colon 1942; 4500 gm cystic edematous ovarian fibroma also removed; alive 1951, 21 years after onset

9. Jenssen 1952 (201)	M adult	hypernephroma	nephrectomy December 1936; well 14 years	1950; pallor, dyspnea, fist-size metastasis in head of pancreas	metastasis removed	well a year later, 15 years after nephrectomy
10. Falkinburg 1954 (121)	F 7 at onset	Wilms' tumor invading renal vein (20 x 15 x 12 cm)	left nephrectomy 10 mos. after onset; x-ray (1800 r) well 8 years	then diffuse phlegmon, fever, hard metastases lt. colon, fecal fistula, bowel obstruction, distention, rectal bleeding, further recurrence	explored, resection of affected colon; February 1951; x-ray to recurrent mass in abdomen December 1951 (6600 r)	ascites, severe left shoulder pain, death 1952, over 10 years after onset
11. Feeney 1955 (125)	F 4½	Wilms' tumor	nephrectomy 1947; well 7 years	local recurrences	excision of recurrences February 1952 and January 1954	alive and well 1971, 24 years after onset
12. Groves & Eppler 1956 (168)	? adult	renal carcinoma	nephrectomy, well 7 years	metastases to brain and lung	both lesions resected	alive, well 5½ years later, 12½ years after onset
13. Groves & Eppler 1956 (168)	adult	renal carcinoma	nephrectomy; well 5 years	metastases invading and obstructing major bronchus	lobectomy	well over 2 years later, 7 years after onset.
14. Caplan 1959 (69)	M 49	renal carcinoma	nephrectomy; well 8 years	endobronchial metastasis, hemoptysis; also had polycythemia	bronchoscopy, firm whitish mass ressembling slough removed from lower stem bronchus: necrotic tumor	well, NED 1959, 18 mos. later, over 9½ years after onset
15. Rosof 1960 (356)	F 63	hypernephroma	right nephrectomy; well 20 years	metastases to lung, femur and scapula	apparently untreated	died several mos. after being sent to nursing home
16. Tandon 1963 (409)	F 40 at onset	renal carcinoma	nephrectomy; well 20 years	recurrence in scar	refused surgery for 18 mos., until ulceration, extension to vertebrae (15 x 8 x 10 cm.); excision 1961	alive March 1963, NED except for metastasis still present in vertebrae
17. Riches 1964 (347)	M 49	low grade renal carcinoma	left nephrectomy; well about 10 years	metastases to lungs, thyroid, right kidney	?	died over 14 years after onset, extensive t.b. and metastases, (developed tuberculosis 8 years after nephrectomy)

TABLE 3: RENAL CANCER WITH LATE RECURRENCE OR METASTASES: 20 CASES

Author Date Published (References)	Sex Age	Histological Diagnosis	Treatment of Primary	Recurrence or Metastases, Site, Interval	Treatment of Recurrence or Metastases	End Results; Years Traced After Onset
18. Kradjian (227; 308)	F 65	renal carcinoma	nephrectomy; well 31 years	recurrence deep in area of incision	explored; recurrence excised	NED 5 yrs. later, over 36 years after onset
19. Goodwin 1967 (155)	M 54	renal carcinoma	right radical nephrectomy, including portion of involved peritoneum 1950; well 15 years	asymptomatic until 1965, then small subcutaneous nodule, right lateral chest wall	metastatic nodule excised	remained well 1967 17 years after onset
20. Goodwin 1967 (155)	M 56	renal carcinoma	left nephrectomy, May 1954; x-ray (5562 r)	well 9 years, then metastases to bone	?	died carcinomatosis August 1964 over 10½ years years after onset

TABLE 4: RENAL CANCER WITH UNUSUALLY SLOW PROGRESSION OF THE DISEASE: 16 CASES

Author Date Published (References)	Sex Age	Histologic Diagnosis Extent of Disease	Treatment of Primary	Recurrence or Metastases	Treatment of Recurrence or Metastases	Possible Causes of Slow Course	End Result
1. McCague 1938 (254)	M 50	bilateral renal carcinoma; onset 1927 backache, painful frequent urination, also squamous cell carcinoma of bladder	untreated	not evident until autopsy; comparatively small in number and extent, considering size of primary tumors; pea sized nodules with smaller lesions in pleural surface of upper lobe of right lung; several small pedunculated polyp-like submucosal nodules in small intestine and jejunum; *hemorrhage present in many areas of the primary and metastatic growths*	untreated	concurrent chronic urinary tract infection, purulent urine: (bilateral renal infection, chronic cystitis last 7 years)	condition declined, intense nausea, vomiting, thrombophlebitis of both legs; extreme emaciation; death 1937, 10 years after onset
2. Carlson & Ockerblad 1941 (70)	M adult	hypernephroma; pyelography revealed filling defect typical of neoplasm; 10-year history of hematuria	refused surgery; returned 9 years later; nephrectomy then done	subsequent metastases temporal region.	untreated	?	alive over 10 years after onset
3. Sabadini 1946-47 (364)	M 10 (at onset)	1925 tumor left hypochondrium so large he had to sleep on right side; 1st pain, hematuria 1941; 2nd episode 1944; 3rd, 1945: enormous renal carcinoma.	explored 1945: cystic mass size of adult head, covered with varicosities, very adherent, considerable black thick fluid evacuated, *large areas of calcification;* large portion of massive growth removed for biopsy; 5 days later nephrectomy; 2 courses x-ray then given			rather severe malaria while growth remained quiescent; fever until 6 days after nephrectomy	in excellent health 1947, 22 years after onset, 2 years after nephrectomy

4. Estragant 1948 (116)	F 51 at onset	renal cell carcinoma; episodes pain, hematuria for 19 years	nephrectomy at 70, 19 years after onset				died 17 days after surgery, 19 years after onset
5. Brown & Peterson 1954 (575)	F 27	Wilms' tumor; onset severe nausea, emesis for 3 days; diarrhea, pain in back, progressive abdominal distension for 2 years	at laparotomy, 2 years after onset large amount serosanguineous fluid removed from what was considered a perinephritic cyst; biopsy: Wilms' tumor; nephrectomy, *mass necrotic, numerous hemorrhagic areas "inflammatory changes due to long continued drainage"*			leukocytosis; 15,050 wbc (89% polys)	2½ years later spontaneous abortion at 12 weeks; another 6 years after nephrectomy, at 9 weeks; 2 years later again threatened to abort at 12 weeks; with bed rest conservative treatment had full-term child; alive well 11 years after onset; 9 yrs. after nephrectomy
6. Bruce & McLeod 1955 (58)	M adult	renal carcinoma, episodes pain, hematuria 1930-1934, large mass in lt. kidney	refused surgery 9 yrs., then had nephrectomy; specimen showed areas *marked hemorrhage and necrosis*	relatively well 6 yrs. then metastases to lt. flank and rt. lung	large fixed mass involving descending colon and abdominal wall removed	?	did well 2 yrs. after removal of metastasis; died 24 yrs. after onset
7. Walter & Gillespie 1960 (430)	F 31 at onset	hypernephroma, onset 1907 (no hematuria)	untreated 10 yrs. then nephrectomy because of size of tumor; well 30 yrs.	1947: pulmonary metastases apparent (40 yrs. after onset)	untreated	concurrent t.b. 1947, frequent attacks pneumonia, severe dyspnea next 3 yrs. given antibiotics	died 1957 at 81, 50 yrs. after onset, metastases to lungs, liver (autopsy)
8. Gordon & Bateson 1962 (156)	M 53	inoperable renal adenocarcinoma; onset prior to 1952 of low grade of malignancy; lung metastasis	laparotomy 4 yrs. after onset; x-ray to left renal area	slow growing partly calcified lung metastasis present 8 yrs. before death	untreated	?	died 1960, 4 yrs. after laparotomy, over 8 yrs. after onset
9. Bratherton 1964 (51)	M 79	hypernephroma 1947	nephrectomy (renal vein involved)	asymptomatic solitary metastasis in lt. lung 7 yrs. later at 85	untreated	?	metastasis progressed very slowly for 7 yrs., no clinical symptoms; died at 94, 14 yrs. after nephrectomy
10. Bratherton 1964 (51)	M 58	hypernephroma	nephrectomy	retroperitoneal recurrence 15 yrs. later	?	?	?

TABLE 4: RENAL CANCER WITH UNUSUALLY SLOW PROGRESSION OF THE DISEASE: 16 CASES

Author Date Published (References)	Sex Age	Histologic Diagnosis Extent of Disease	Treatment of Primary	Recurrence or Metastases	Treatment of Recurrence or Metastases	Possible Causes of Slow Course	End Result
11. Altug 1964 (10a)	M 33	Wilms' tumor 15 x 5 x 7 cm. involving ⅔ of kidney	December 1953 lt. nephrectomy, x-ray post-operatively (3000 r)	bilateral lung metastasis evident January 1957; x-ray; disappearance	nodule in rt. lung reappeared September 1957, asymptomatic 2 years; disease then reactivated; several resections, lobectomy, lingulectomy, also x-ray to lungs; brain metastasis resected	?	death 9 years after onset
12. Takats & Osapo 1966 (407)	adult	inoperable renal carcinoma (no mitotic activity)	laparotomy, incisional biopsy; well nearly 37 years	metastases then developed	untreated	?	died nearly 37 yrs. after onset
13. Haas & Jackson 1967 (170)	M 4½	Wilms' tumor lt. kidney	September 1946 laparotomy; considered inoperable; x-ray (1300 r); considerable regression; January 1947 nephrectomy; then x-ray to whole upper abdomen (2120 r); gained 18 lbs., well	asymptomatic nodule rt. upper lobe early 1949, not recognzied till 1951	lobectomy, well 3 yrs., gained 11 lbs.; April 1955, recurrence below lt. costal margin; x-ray (3200 r); no longer palpable; laparotomy 1955: 15 cm. inoperable recurrence in posterior abdominal wall adherent to viscera; x-ray (2500 r); well until October 1956; again recurred, again disappeared after x-ray (3900 r) March 1957	?	downhill course, after final x-ray, further abdominal and liver metastases, death August 1957, over 11 yrs. after onset

14. Ljunggren 1970 (247a)	M 47	extensive hypernephroma size of 2 fists, metastasis size of tangerine on rt lung; onset hematuria 1960	rt. nephrectomy	metastases present at time of nephrectomy	lesion in psoas muscle removed	?	lung metastases grew very slowly; 2 yrs. later lesions appeared in lt. lung; death 8 yrs. after nephrectomy
15. Ljunggren 1970 (247a)	F 67	extensive carcinoma lt. kidney, onset hematuria 1959	April 1962 lt. nephrectomy	metastases to rt. kidney and adrenal	rt. kidney explored, multiple small metastases present, 4 cm. lesion in adrenal; no attempt at removal	?	patient made a good recovery; death occurred 7 yrs. later 10 yrs. after onset
16. Young & Deming 1955 (447a)	M 44 at onset	carcinoma rt. kidney (7 cm.) with shell-like calcifications of periphery, many areas of necrosis and hemorrhage, few mitoses; (asymptomatic mass present 1941-1949; onset hematuria, dysuria, 1949)	1942, concurrent chronic hypertrophic gastritis, ulcer, repair of rt. inguinal hernia, 1942 (kidney region not explored); in good health until Jan. 1949; nephrectomy, partial ureterectomy Feb. 1949; uneventful recovery			?	alive and well, N.E.D. 1956, 15 yrs. after onset

TABLE 5: METASTASES FROM RENAL CANCER (MOSTLY PULMONARY), SUCCESSFULLY TREATED BY SURGERY: 34 CASES

Author Date Published (References)	Sex Age	Histological Diagnosis	Treatment of Primary	Treatment of Metastases	End Results Years Traced
1. Barney & Churchill 1939; 1944 (23; 24)	F 55	adenocarcinoma kidney; onset early 1931; metastases appeared in left lung November 1931 (also had concurrent t.b. of *right* lung, wbc 11,500)	left nephrectomy April 1932 (*large areas degeneration present*)	March 1933: x-ray (800 r) to solitary lesion in lung: though asymptomatic it doubled in size in 4 mos.; July 1933 lobectomy (*cells swollen, more atypical*)	complete recovery NED in good health, died coronary disease 1956, 25 years after onset, at age of 80
2. Tavernier 1941-42 (410)	adult	hypernephroma with metastasis to humerus and supraclavicular lymphadenopathy	nephrectomy 20 days after resection	humeral metastasis resected; x-ray to supraclavicular region, lesion subsided	gained over 25 lbs., NED, well some mos. later
3. Tinney & McDonald 1945 (415)	F 39	carcinoma	nephrectomy	lung metastasis apparent 2 years after nephrectomy; left pneumonectomy	NED, well 4 years after pneumonectomy
4. Stortebacker 1951 (396)	adult	hypernephroma	nephrectomy	brain metastases removed surgically	NED 14 years after neurosurgery
5. Nesbit 1953 (245; 305; 308)	M 4	Wilms' tumor	nephrectomy, well next 17 years	asymptomatic lung metastasis (8 cm.) in rt. lower lobe found at physical examination for military service (therefore rejected); segmented resection of lesion as it appeared to be a tuberculoma (borders so distinct) pathologist reported it to be metastatic Wilms' tumor	complete recovery, married, son born 2 yrs. later; alive and well 1971, 37 yrs. after onset and 20 yrs. after resection of metastases

6. Straus 1956 (397)	adult	hypernephroma (weighed 1500 gm.)	nephrectomy	liver metastasis; left hepatic lobectomy	NED, well 5 yrs. after hepatic surgery, 10 yrs. after nephrectomy
7. Strieder 1956 (398)	M 62	renal carcinoma	nephrectomy	solitary lung metastasis, resected	NED, well 8 yrs. after resection
8. Strieder 1956 (398)	M 53	renal carcinoma	nephrectomy	solitary lung metastasis, resected	NED, well 4½ yrs. after resection
9. Groves & Effler 1956 (168)	adult M	renal cell carcinoma	nephrectomy	lung metastasis, brain metastasis, 7 years after nephrectomy; both were removed	NED, well 5½ yrs. later, over 12½ yrs. after onset
10. Gale & Brooks 1957 (143)	child	Wilms' tumor	nephrectomy	lung metastasis; rt. upper lobectomy	alive 22 mos. after lobectomy
11. Lent 1960 (239)	M 2½	Wilms' tumor	nephrectomy June 1955	pulmonary metastasis appeared 2 mos. later; x-ray (3400 r); lobectomy 10 mos. after nephrectomy	well 7½ yrs.; January 1963: radiation-induced chondrosarcoma rt. 6th rib; radical surgery; November 1963 massive metastasis to D 4-7; decompressive laminectomy; x-ray to spine (1400 r); early 1964, paralysis; further x-ray no improvement; death March 1964, 9 yrs. after onset
12. Potampa 1961 (333)	M 62	hypernephroma	nephrectomy February 1954	metastatic lesions in lungs resected May and December 1954	resumed work, well April 1960: radical prostatectomy; recovered, well 1961, over 7 yrs. after onset

TABLE 5: METASTASES FROM RENAL CANCER (MOSTLY PULMONARY), SUCCESSFULLY TREATED BY SURGERY: 34 CASES

Author Date Published (References)	Sex Age	Histological Diagnosis	Treatment of Primary	Treatment of Metastases	End Result Years Traced
13. Albers 1961 (8; 308; 434)	M 6	Wilms' tumor 15 x 9 cm. (child fell on lt. side just prior to onset)	lt. nephrectomy March 1953 (large area hemorrhage, and some necrosis); x-ray, 4600 r in 10 mos.	25 mos. after nephrectomy, wedge resection lung metastasis April 1954, shortly after it became apparent; intermittent fever to 103° F., wbc 24,000	complete recovery, grew, developed normally; had asthma in later yrs. NED 1971, 18 yrs. after onset
14. Soper 1961 (388)	M 3	Wilms' tumor 18 x 11 x 8 cm.	nephrectomy, growth completely replaced kidney, weighed 1080 gr.; post-operative x-ray	single coin lesion lower rt. lung resected 8 mos. after nephrectomy	NED 20 mos. later
15. Samellas 1961, 1963 (366; 367)	M 37	renal carcinoma with solitary pulmonary metastasis	nephrectomy	resection pulmonary metastasis	apparent cure, well 10 yrs. after onset, 7 yrs. after resection
16. White & Krivit 1962 (308; 439a)	M 21 mos.	Wilms' tumor	nephrectomy October 1950; post-operative x-ray, 2000 r	pulmonary metastases in lt. 4th intercostal space 12 mos. later; 2 nodules resected November 1951	NED September 1971, 21 yrs. after onset
17. Howard 1965 (188)	F 3½	Wilms' tumor	left nephrectomy September 1957	2 metastases lt. lung 17 mos. later 1 disappeared after dactinomycin other increased, then stationary; more dactinomycin, no change; rt. upper lobectomy, August 1959; 1 *lesion completely replaced by macrophages, appeared as a yellow plaque under pleura, other appeared "very attenuated"*; quite marked pleural infection postoperatively	complete recovery NED 1971, 14 yrs. after onset
18. Howard 1965 (188)	M 13 mos.	Wilms' tumor	rt. nephrectomy October 1958	4 mos. later multiple bilateral pulmonary metastases; x-ray caused those in lt. lung to disappear, those in rt. persisted; wedge resection of 2 lesions in lt. upper lobe; 1 mo. later lesion in rt. upper lobe resected	remained well 4 yrs., then died uremia during severe pneumonia; autopsy showed marked radiation nephritis in lt. kidney, no evidence of tumor

19.	Howard 1965 (188)	M 3	Wilms' tumor	rt. nephrectomy January 1958	lt. upper lobectomy for pulmonary metastases December 1958	complete recovery, alive and well, NED August 1971, over 3½ yrs. after onset
20.	Howard 1965 (188)	M 3	Wilms' tumor	Actinomycin D caused aplastic anemia; lt. nephrectomy March 1959	segmental resection metastasis upper lobe rt. lung December 1959	uneventful recovery, NED; alive and well, 1971, 12 yrs. after onset
21.	Gans et al. 1966 (145; 308)	M 6	Wilms' tumor with pulmonary metastases	lt. nephrectomy June 1961	x-ray to lungs November 1961; wedge resection lung metastases; chemotherapy; June 1962, wedge resection B6, rt. lower lobe; July 1962, rt. subtotal hepatic lobectomy for metastasis	complete recovery; NED, very well 1966, 5 yrs. after onset
22.	Fernbach & Martyn 1966 (127; 308)	F 6½	Wilms' tumor	lt. nephrectomy 3 courses dactinomycin	lung metastases responded poorly to radiation; resected 24 wks. after nephrectomy	alive and well but x-ray caused considerable deformity rt. chest, hypoplasia of breast; NED 1971, 12½ yrs. after onset
23.	Cliffton & Pool 1967 (79)	? 1	Wilms' tumor with pulmonary metastasis	nephrectomy December 29, 1958; x-ray (3000 r)	pulmonary metastasis to R.L.Q. October 1959, given 1000 r x-ray; lobectomy; Act. KS4 July 1960 January 1961	alive and well September 1966, 8 yrs. after onset
24.	Riches 1967 (216, p. 505)	M 65	low grade hypernephroma rt. kidney metastasis to lt. 7th rib	nephrectomy	excision of metastasis	complete recovery; lived 7½ yrs., NED at death, cerebral hemorrhage

TABLE 5: METASTASES FROM RENAL CANCER (MOSTLY PULMONARY), SUCCESSFULLY TREATED BY SURGERY: 34 CASES

Author Date Published (References)	Sex Age	Histological Diagnosis	Treatment of Primary	Treatment of Metastases	End Result Years Traced
25. Cliffton & Pool 1967 (79)	? 7	Wilms' tumor with multiple bilateral pulmonary metastases	nephrectomy August 1959 in Greece, x-ray 2650 r in Stockholm	multiple bilateral metastases December 1959; 1259 r x-ray January 1960; segmental resection August 1960; dactinomycin, September 1960, November 1960, March 1961, September 1961	normal growth, NED, alive and well 1967, 8 yrs. after onset
26. Cliffton & Pool 1967 (79)	? 5	Wilms' tumor with bilateral pulmonary metastasis	nephrectomy April 1964, x-ray 3,100 r, actinomycin D	bilateral pulmonary metastasis September 1964; x-ray 1588 r October 1964, dactinomycin January 1965, February 1965, April 1965; biopsies, rt. lung 3 wedges, lt. lung 4 wedges (only 1 lesion Wilms') actinomycin D at intervals for 2 yrs. (scapular lesion 1966)	alive April 1967 over 3 yrs. after onset
27. Cliffton & Pool 1967 (79)	? 8	Wilms' tumor with pulmonary metastasis	nephrectomy March 1963	pulmonary metastasis lt. lower lobe July 1963; triple chemotherapy and vincristine July 1963 - August 1965; wedge resection October 8, 1965; triple chemotherapy October 1965 - August 1967	alive August 1967 over 4 yrs. after onset
28. Westra 1967 (437)	? child	nephrectomy post-operative radiation	lung metastases 10 mos. after nephrectomy	resection of pulmonary metastases	alive and well 1967, 11 yrs. fater onset
29. Wedemeyer 1968 (308; 434)	M 26 mos.	Wilms' tumor, metastases to rt. lung, seen 10 mos. after nephrectomy	lt. nephrectomy	1 cm. nodule rt. lower lobe resected; October 1962, 6 cm. nodule removed by resection of apical and posterior segment rt. upper lobe; February 1963, small nodule in incision line, large mass in hilus, hepatomegaly; cobalt, 3000 r (t/d); some regression; thoracotomy April 1963 6 cm. mass on anterior rt. pericardium and rt. diaphragm nodules also excised from wall of vena cava, rt. lower lobe of liver and old incision	liver scan became normal; some residual changes in rt. costophrenic angle and chest deformity due to resection of 3 ribs; complete recovery, NED 1971, over 10 yrs. after onset
30. Wedemeyer 1968 (308; 434)	M 10 mos.	Wilms' tumor grapefruit-sized subiphoid mass apparent 8 mos. after nephrectomy, also lesion in lt. hilus	nephrectomy; resected abdominal nodes free of tumor	March 1965, several large metastatic nodules removed by lt. hepatic lobectomy; 5 day course dactinomycin; cobalt to lungs, 1400 r (t/d) and lt. upper abdomen, 3000 r (t/d)	complete recovery, well 1971, 7 yrs. after onset

31. Wedemeyer 1968 (308; 434)	M 5	Wilms' tumor, multiple metastases which increased in size prior to radiation; also liver metastases (8 cm.)	June 1961: left nephrectomy; post-operative cobalt (2150 r t/d)	June 1961: cobalt to lungs 1130-1520 r (t/d); complete regression; October 1961, 5 FU for liver metastasis, caused decrease in size, cobalt 4600 r (t/d) to liver, improved; June 1962 further lung lesions rt. lower lobe resected; July 1962 3 cm nodule on liver excised by rt. hepatic lobectomy; September 1962 metastases throughout lungs; 3 wk. course methotrexate, chlorambucil, dactinomycin; complete regression all lesions	complete recovery, NED 1971, 10 yrs. after onset
32. Kaufman 1968 (208)	? 1	renal cell carcinoma in solitary kidney with solitary pulmonary metastasis	resection of tumor	lobectomy for metastatic nodule in lung	complete recovery; NED
33. Taylor et al. 1969 (410a)	? child	Wilms' tumor	nephrectomy	liver metastases hepatic resection, x-ray dactinomycin	severe chronic hepatic impairment due to inadequate liver regeneration, hepatic fibrosis; alive NED 1969, 4½ yrs. after onset
34. Fernbach (personal communications) (308)	F 3 3/4	Wilms' tumor (mother x-rayed during pregnancy to see if twins were expected)	September 1967: surgical exploration; tumor removed intact; post-operative radiation to tumor bed	solitary lung metastasis November 1967; disappeared after 1 month of dactinomycin, but multiple nodules then appeared in both lungs; vincristine; in 1 month chest entirely clear; dactinomycin alternated with vincristine at monthly intervals to January 1968; December 1968 metastasis in rt. lower lobe removed by wedge resection; well until April 1970 then hilar node removed at thoracotomy, chemotherapy resumed; well 4 mos. then another solitary lesion in lt. lower lobe removed at thoracotomy, x-ray to another lesion in lower mediastinum	well September 1971, 13 mos. later, over 4 yrs. after onset

TABLE 6: RENAL CANCER WITH CONCURRENT INFECTION, FEVER, INFLAMMATION OR LEUKOCYTOSIS: 29 CASES

Author Date Published (Reference)	Age Sex	Histologic Diagnosis Extent of Disease	Treatment of Primary	Treatment of Metastases or Recurrence	Infection, Fever, Leukocytosis or Inflammation	End Result Years Traced After Onset
1. Abbe 1894, 1912 (1, 2)	F 14 mos.	massive Wilms' tumor (weighed 7½ lbs.)	nephrectomy, 1892 (child weighed only 15 lbs. after surgery)	untreated	fever 105°F. after surgery; hot water bottles; hot coffee enemas	complete recovery, traced well 1912, 20 years after onset
2. Most 1931 (291)	M 44	inoperable hypernephroma (then called sarcoma) with metastases to femur; onset August 1926; pathologic fracture femur, 1927	exploratory operation on left kidney May 1927; condition regarded as inflammatory; 2nd exploratory July 1928, portions of renal tumor removed	femur explored, November 1927 no tumor found, Staph. albus present; limb amputated December 3, 1927; 2nd amputation January 1928, revealing area of former metastases; hip joint disarticulation June 1928, thermocautery applied	post-operative high fever (septic) requiring prolonged treatment for 3 mos.; nonhemolytic, strep. and staph. infection of femoral lesion; fever subsided after amputation, further infection, December 24, 1927, sudden chill, wound septic; process continued after 2nd amputation	following disarticulation and cessation of sepsis, kidney pains recurred; death shortly after partial removal of renal tumor, almost 2 years after onset; *(Most believed the femoral metastasis had been completely absorbed during the septic process.)*
3. Potts 1932 (334)	M adult	squamous cell carcinoma kidney with leukoplakia of renal pelvis subsequent to renal stone (large number epithelial pearls throughout mass)	removal of stone size of horse chestnut; nephrectomy	untreated	concurrent purulent infection when stone was removed; fistula did not heal; chronic pyelitis next 4 3/4 years, fistula drained pus, urine	death 1931, about 5 years after onset
4. Pohle & Ritchie 1935 (330)	M 10 mos.	Wilms' tumor filling half of abdomen, very vascular in extremely poor condition	explored; x-ray, 50 r daily for 6 days March 1931; more x-ray (750r in 3 mos) growth regressed 50%; x-ray July-Sept. 1931, residual mass barely palpable; further x-ray July 1932, Jan. 1933-1934		Severe respiratory infection prevented surgery January 1932.	When re-explored tumor was found to have regressed from kidney but a remnant 4 cm. in diameter extended along vessels; alive and well November 1934, over 3½ years after onset. (Only 3 other known cases beside this one known to have survived after radiation alone.)

5. Barney & Churchill 1939, 1944 (23, 24)	F 55	adenocarcinoma kidney, onset early 1931; metastasis apparent in left lung November 1931	left nephrectomy April 1932; *(large areas of degeneration present)*	x-ray (800 r) to solitary lesion in lung; it doubled in size, though asymptomatic, March to July 1933; then lobectomy (cells swollen, more atypical)	concurrent t.b. right lung, night sweats, evening temperatures, wbc 11,500 prior to nephrectomy; after lobectomy pneumothorax, fluid in lung	complete recovery NED; died coronary disease 1956 over 25 years after onset, at age of 80
6. Dean 1941 (97)	child 2 (at onset)	Wilms' tumor diagnosed as pyelitis, 7 mos. later hematuria, mass; huge blood clots passed	x-ray (1 small dose) 11 mos. after onset some regression then grew rapidly; further x-ray for 5 mos. with few interruptions		pyelitis	shortly after 2nd x-ray growth began to shrink, complete regression, NED over 4 years after onset
7. Bandler & Roen 1946 (22)	M 47	January 1943, solitary testicular metastasis simulating primary tumor (antedating evidence of hypernephroma); 10-15 lb. weight loss; April 1945 gross hematuria, severe flank pain; also diabetes	right nephrectomy 1945 *(growth contained large fibrous bands)*	January 1943, orchiectomy; testis twice normal size thick pus evacuated, scrotal sac drained	concurrent E. coli in urine; testicular metastases infected by E. coli; thick yellow-green pus; after nephrectomy considerable sanguineous wound drainage requiring blood transfusion	NED after orchiectomy for 2 1/4 years; complete recovery after nephrectomy. NED 1946, 3½ years after orchiectomy, 14 mos. after nephrectomy
8. Nofsinger & Vinson 1942 (312)	M adult	hypernephroma right kidney, metastases simulating bronchial carcinoma in right lung	untreated	large pieces ulcerated, pedunculated tumor in bronchus to lower lobe removed twice via bronchoscope: *necrotic material, ill-defined degenerating cells*	concurrent influenza, purulent sputum, wheezing	3 mos. after 2nd bronchoscopy, asymptomatic; end result unknown
9. Sabadini, 1946-47 (364)	M 10 (at onset)	1925 tumor left hypochrondrium so large he had to sleep on right side; 1st pain, hematuria 1941; 2nd episode 1944; 3rd, 1945; enormous renal carcinoma by 1945	explored 1945; cystic mass size of adult head, covered with varicosities, very adherent, considerable thick black fluid evacuated, *large areas calcification*, large portion massive growth removed; 5 days later nephrectomy; 2 cycles x-ray		rather severe malaria while growth remained quiescent; fever until 6 days after nephrectomy	in excellent health 1947, 22 years after onset, 2 years after nephrectomy

TABLE 6: RENAL CANCER WITH CONCURRENT INFECTION, FEVER, INFLAMMATION OR LEUKOCYTOSIS: 29 CASES

Author Date Published (Reference)	Age Sex Sex	Histologic Diagnosis Extent of Disease	Treatment of Primary	Treatment of Metastases or Recurrence	Infection, Fever, Leukocytosis or Inflammation	End Result, Years Traced After Onset
10. Burgess 1947 (64)	F 3	Wilms' tumor apparent immediately after severe fall February 1943; extremely ill	February 1943 explored, large area of hemorrhage in tumor; transfusion, 11 days later nephrectomy; x-ray begun a week later		fever (103°F), nausea vomiting; lymph nodes showed marked rather bizarre hyperplasia (proliferation of RE cells, differentiation into macrophages)	complete recovery, well; intestinal obstruction 1960; abdomen explored; NED, entirely well 1968, 25 years after onset
11. Gahagan & Yeargood 1949 (142)	F 7 mos. Negro	Wilms' tumor large	left nephrectomy May 1941, then x-ray		high fever for 1 week prior to surgery	complete recovery, well, NED over 6 years later
12. Gahagan & Yeargood 1949 (142)	F 2 Negro	extensive Wilms' tumor involving entire left abdomen and lumbar region from costal margin to superior iliac spine, edema of ankles	x-ray for 12 days discontinued due to fever, leukopenia, nausea, emesis; left nephrectomy, further x-ray		fever during radiation	complete recovery, well NED 5½ years after surgery
13. Miller 1949 (282)	M Adult	extensive carcinoma rt. kidney, weight loss, acutely ill, hematuria, pain	transfusion, preoperative x-ray (7500 r); hematuria subsided, gained 15 lbs.; 2nd transfusion, rt. nephrectomy 11 mos. after radiation (growth about 12 cm in diameter)		leukocytosis (11,500) prior to radiation; further leukocytosis 6 mos. after radiation (15,000) with occasional pus cells in urine	symptoms subsided after radiation, gained 16 lbs., well 6 mos., symptoms then recurred; gained weight, NED after nephrectomy; entirely well 6 yrs. later, weight 182 lbs. in 1949
14. Levant & Feldman 1952 (240)	M 7	tremendous Wilms' tumor, onset of pain immediately after fall, acutely ill; (traumatic rupture of tumor) 1945	explored 3 days later, biopsy, mass extended to diaphragm, so no attempt at removal; x-ray (800r) then nephrectomy and further x-ray		fever to 101.4°F WBC 26,700 as a result of injury	prompt response to x-ray, uneventful recovery; alive and well 5 years later, NED

15. Livermore 1953 (245)	F 37	extensive Wilms' tumor	explored, biopsy, abscess drained, x-ray (4500 r) begun after 5 mos'. suppuration; satisfactory response; nephrectomy 6 weeks after x-ray		fever without chills due to perirenal abscess, also increase in renal colic, prior to exploratory operation; mucopurulent discharge for 5 mos. after surgery; chronic cystitis	gained 15 lbs. in 10 mos. after nephrectomy; excellent health thereafter; alive and well 1952, 14 years after onset
16. Arcomano 1958 (13, 119)	M 37	extensive hypernephroma (6 x 10 x 6 cm.) multiple bilateral pulmonary metastases	nephrectomy January 1955	pulmonary metastases untreated; craniotomy, surgical removal of brain metastases 6 weeks later	discharging fistula in nephrectomy scar	metastases in lungs disappeared in 8 mos., asymptomatic, well 20 mos. then brain metastases; died further cerebral involvement October 1958, nearly 5 years after onset
17. Hallahan 1959 (119, 174)	M 75	large adenocarcinoma on left kidney, 5 or more pulmonary metastases in perirenal fat	February 1956 nephrectomy, excision perirenal metastasis	transfusion postoperatively oral iron 6 weeks	tracheobronchitis, penicillin given	lung lesions disappeared in 12 mos. after tracheobronchitis, well until death, congestive heart failure, due to arteriosclerotic, hypertensive cardiovascular disease, October 1958, over 2½ years after onset
18. Buehler 1960 (59, 119)	M 59	extensive clear cell carcinoma left kidney bilateral pulmonary metastases onset 1954, 5 lb. weight loss in 4 years (also had scrotal hernia)	November 1958 left nephrectomy (15 x 30 cm. mass) extended to caval and aortic areas, involved renal vein	untreated	postoperative staphylococcus infection after nephrectomy and after hernia surgery, latter cleared very slowly	gained 20 lbs. in 10 mos.; pulmonary metastases almost gone by September 1959; inguinal herniorraphy performed; complete recovery, all metastases disappeared; well, NED 5 years after onset
19. Kolar 1961 Jakoubkova 1965 (198, 212; 308)	M 55	advanced hypernephroma; multiple bilateral pulmonary metastases; onset November 1958	right nephrectomy April 1959, condition then deteriorated	iron, Vitamin B complex	hematoma in wound suppurated, 2 fistulae discharged pus; antibiotics given, febrile 4 weeks (38.3°C); 1 fistula suppurated for 6 months	4 mos. after nephrectomy definite improvements; 10 lb. weight gain; all but largest lung lesion gone in 2 mos., this disappeared several mos. later; gained over 34 lbs.; NED 1971, over 12 years after onset

TABLE 6: RENAL CANCER WITH CONCURRENT INFECTION, FEVER, INFLAMMATION OR LEUKOCYTOSIS

Author Date Published (Reference)	Age Sex	Histologic Diagnosis Extent of Disease	Treatment of Primary	Treatment of Metastases or Recurrence	Infection, Fever, Leukocytosis or Inflammation	End Result Years Traced After Onset
20. Albers 1961 (8; 308)	M 6	Wilms' tumor 15 x 9 cm. (patient fell on left side 6 weeks prior to admission)	left nephrectomy March 1953 (large area of hemorrhage, one of necrosis); x-ray (4600 r in 4 months)	wedge excision of pulmonary metastasis April 1954 shortly after it was first seen	intermittent fever to 103°F; wbc 24,000; had asthma in later years	complete recovery grew and developed normally; well, NED 1971, 18 years after onset
21. H. C. Miller 1962 (285; 308)	M 57	extensive hypernephroma, bilateral pulmonary metastases (some 6 cm. in diameter)	right nephrectomy May 1959; marked necrosis, aggregations of lymphocytes	untreated	cough, sore throat, fever, generalized malaise; antibiotics given (7 weeks prior to nephrectomy); lymphocytic infiltration present at nephrectomy	extensive metastases in both lungs disappeared in 6 mos. alive and well 1970, over 10½ years after onset
22. Prentiss 1962 (308; 335)	F 63	extensive hypernephroma, grade IV, multiple bilateral pulmonary metastases	right nephrectomy 1947 (growth extended into pedicle and renal vein)	untreated	concurrent pyuria, sulfathiozole given	metastases still present 3 mos. after nephrectomy, chest entirely clear 10 mos. later; NED in good health 1971, 24 years after onset, at 87
23. Brocks 1964 (55)	M 43	hypernephroma left kidney, 1954 right kidney, 1962	December 1957 left nephrectomy; February 1962: encapsulated lesion in right kidney (5 x 6 x 5 cm.) excised, contained *necrotic tissue, hemorrhagic cysts*		postoperative perirenal infection after 2nd operation; finally cleared with antibiotics; recurrent pyelonephritis November 1962	recovered, lived normal life, NED; died June 1963 cerebral hemorrhage 8½ years after onset of 1st, 1½ years after onset of 2nd hypernephroma
24. Gonick & Jackiw 1964 (154)	M 58	large fungating clear cell adenocarcinoma, metastases in lower lobe and lingular of left lung, possible lesions in right lung	right nephrectomy	left thoracotomy October 1950; resection of lingular and 3 metastases from left lung; 2 biopsies upper lobe bronchus negative: *inflammatory*	wbc 10,600, fever 99°-100°F for 2 weeks after thoracotomy; further fever, chills, night sweats, productive cough 1957 (consolidation right upper lobe, hilar mass right side); antibiotics; 4 mos. later hemoptysis, 15 lb. weight loss; wbc 11,300	suspected nodules in right lung more definite after thoracotomy, then regressed entirely by August 1951; 1956, nodular lesion in different area right lung; death 9 years after onset, 8 years after nephrectomy (extensive metastases right lung, chest wall)

TABLE 6: RENAL CANCER WITH CONCURRENT INFECTION, FEVER, INFLAMMATION OR LEUKOCYTOSIS:

25. Howard 1965 (188; 308)	F 3½	Wilms tumor	lt. nephrectomy September 1957	2 metastases to lt. lung 17 mos. later; 1 disappeared after dactinomycin, other increased; further dactinomycin caused no change; lobectomy August 1959	quite marked pleural infection following lobectomy	complete recovery NED 1971, 14 yrs. after onset
26. Markewitz 1967 (268)	M 53	large hypernephroma; diffuse pulmonary metastases; onset June 1964	nephrectomy; *"tumor centrally necrotic, numerous intermingled leukocytes around and within tumor cells."*	recurrence in flank biopsied	fever daily for 4 weeks after nephrectomy	within 4 wks after nephrectomy, during febrile period, lung metastases began to regress, dramatic improvement, 30 lb. weight gain, cough ceased; very rapid deterioration after biopsy of recurrence; death a week later widespread metastases (only 2 in lungs), 18 months after onset. Autopsy: *"focal infiltration with lymphocytes, plasma cells, portions wholly necrotic suggestive of immunologic phenomenon"*
27. Boyer 1968 (50, 308)	M 21	large Wilms' tumor rt. kidney multiple bilateral pulmonary metastases, diffuse liver metastases (extreme rt. flank pain, rt. chest pain, 15-20 lb. wt. loss; onset August 1964)	dactinomycin prior to x-ray (2950 r in 26 days); further dactinomycin 2 weeks after last x-ray; laparotomy, necrotic remains of tumor and kidney excised, liver explored, revealing *multiple circumscribed scarred areas: healed metastases*	dactinomycin and x-ray to upper ½ of rt. lung, 1200 r in 8 days; entire lt. lung then given 1200 r in 8 days	rt. pleural effusion, atypical pneumonia, August 1964, prior to any treatment or diagnosis; severe rt. flank pain and rt. chest pain slowly abated, chest films almost cleared, then recurred	rapid regression of symptoms due to primary; pulmonary nodules increased except for those in lower rt. lung which had been irradiated by rt. flank port, these had disappeared; all other rt. lung nodules disappeared in 8 days during radiation; those in lt. lung continued to grow despite further dactinomycin; these disappeared after x-ray; NED 1968, 3½ yrs. after onset

28. Robinson 1969 (352)	M 70	renal cell carcinoma rt. kidney 10 cm. in diameter with abdominal lymph node metastases, 30 lb. wt. loss, anemia; by Jan. 1967 metastases to lungs, liver, brain; (onset Jan. 1964; by Jan. 1967 gross hematuria)	refused surgery for 3 yrs, given ferrous sulphate for anemia (300 mg. daily); nephrectomy 1967 tumor weighed 394 g.	none	persistent pyelonephritis (renal sepsis); evidence of marked chronic inflammation in renal parenchyma at surgery; cerebrovascular accident April 1965 with residual hemiparesis, generalized muscle weakness	in the 13 mos. following stroke, gained 40 lbs. lung lesions disappeared, remarkably well; condition then declined, lost 30 lbs. disease progressed after nephrectomy; further lung, liver metastases; death July 14, 1967, 3½ yrs. after onset; autopsy; metastases to lungs, mediastinum, liver, brain
29. Ridings 1971 (350)	M 36	inoperable adenocarcinoma upper half rt. kidney, multiple metastases to lungs; 45 lb. wt. loss; onset July 1967	October 1967: cobalt (60,500 rads); well tolerated; lesion regressed 50% in 2½ mos.; rt. nephrectomy April 1968 also gastric resection for ulcer; *tumor filled with reddish brown semi-liquid necrotic material*		concurrent peptic ulcer of 9 yrs. duration; leukocytosis (15,300 wbc; remained at 11,200 after cobalt); postoperative course stormy, pneumonitis; fever 102°F. from fistula prior to colectomy	some lung lesions increased after radiation of primary; all then disappeared in 2½ mos., primary 50% smaller, but large duodenal ulcer required subtotal gastric resection, tube duodenostomy; complete recovery, well 7 mos., then fistula in rt. hepatic flexure; colectomy; gained 45 lbs., well, NED over 3 yrs. after onset

TABLE 7: RENAL CANCER TREATED BY IMMUNOADJUVANTS (BACTERIAL TOXINS OR SERUMS): 14 CASES

Author Date Published (References)	Sex Age	Histologic Diagnosis Extent of Disease	Treatment Other Than Immunotherapy	Type of Toxins or Serum Technique Reactions	Immediate and Final Results Years Traced
1. W.B. Coley (84)	child 5	very large Wilms' tumor	transverse peritoneal nephrectomy 1898	1898 Coley toxins (Buxton VI) preoperatively for a short time, no postoperative toxins	no apparent effect from this brief course; metastases developed, death within a year
2. W.B. Coley 1914, 1935 (82, 83, 84)	M 1½	large Wilms' tumor (operable); onset 6 mos. after falling downstairs; child weighed only 21 lbs.	nephrectomy	September 1905 Coley toxins (Buxton VI) given at intervals for 2½ years, 0.5-6 minims; reactions averaged 100-101°F, maximum 105°F; final course 1910, 5 years after surgery (given by family physician throughout)	complete recovery, normal growth, 5'11", 170 lbs. by 1933; active life; January 1955 operated for polyps and diverticulitis; died January 20, 1954, heart failure, acute pancreatitis, 59 years after onset
3. W.B. Coley 1935 (84)	child	Wilms' tumor	nephrectomy	1930: Coley toxins (Parke Davis XIII) begun shortly after nephrectomy by Coley, continued by family physician (not aggressively administered)	recurrence in a few mos.; death within a year
4. W.B. Coley (unpublished) (85, 277)	M 39	extensive inoperable recurrent carcinoma left kidney onset early 1905; recurrence October 1905; 16 lb. weight loss; large recurrent mass adherent to cicatrix extended from costal margin to within 3 cm. of crest of ilium, metastasis just above crest of ilium	nephrectomy May 1905	September 28, 1908 Coley toxins (Tracy XI): 26 in 49 days, 1/4 to 8½ minims in buttocks or pectoral muscles; only 4 marked reactions (103°-104.6°F)	no improvement was noted; death February 1909, 4 years after onset
5. R.M. Green 1911 (164)	M 35	inoperable extensive hypernephroma; onset August 1907 "soreness, weight loss"	exploratory operation November 2, 1907; large sloughing tumor filling whole flank, partly removed	November 23, 1907 Coley toxins (Tracy XI) 10 subcutaneous injections in 10 days, little reaction	no apparent benefit, death January 1908, 5 mos. after onset

TABLE 7: RENAL CANCER TREATED BY IMMUNOADJUVANTS (BACTERIAL TOXINS OR SERUMS): 14 CASES					
6. Leach (unpublished) (85)	M 43	twice recurrent inoperable hypernephroma. 40 lb. weight loss in 6 mos. onset November 1907	explored May 30, 1908; nephrectomy (tumor weighed 13½ lbs.); recurrence in omental hernia removed with whole omentum up to stomach; June 1910 explored, inoperable: irregular recurrent growth involved so much of intestines	July 1910: Coley toxins (Tracy XI) 41 in 60 days, marked reactions several times	complete regression gained 40 lbs., and regained former strength; entirely well, NED; 1916, 9 years after onset
7. W.B. Coley 1914 (83-85)	F 37	huge recurrent inoperable hypernephroma, onset 1908; pain, episodes of hematuria next 3 years	explored February 1912, biopsied Mar. 1912; nephrectomy	June 13, 1912: Coley toxins (Parke Davis XII) administered by Connell in Sheffield, England	Complete regression, regained former weight and health; in excellent condition, NED 1926, 18 years ter onset
8. Harmer 1915 (179)	M 40	inoperable hypernephroma, with concurrent perinephritic abscess	May 25, 1913, abscess incised, 10 oz. pus evacuated; tumor mass size of grapefruit biopsied, no attempt at removal	June 15, 1913: Coley toxins (Tracy XI) given i.m., maximum dose 1 cc. reactions often severe	sinus continued to discharge for 6 mos. tumor regressed, 50 lb. weight gain, small mass remained (believed to be fibrous tissue or inflammatory) not traced subsequently
9. W.B. Coley 1914, 1935 Nauts 1953, 1959 (83, 84, 300, 301)	F 27	extensive inoperable hypernephroma involving retroperitoneal lymph nodes, practically moribund (onset early 1912)	explored, biopsy of large retroperitoneal mass, as well as large tumor involving lower pole of kidney; sinus developed in loin incision, condition absolutely hopeless	September 21, 1912 Coley Toxins (Tracy XI) given by McDonald for 2 mos. i.m. in buttocks marked febrile reactions (to 105°F)	immediate improvement, marked decrease in size, almost complete regression after 18 injections; rapid weight gain (20 lbs. in 4 mos., 32 lbs. in 9 mos.); excellent health; in old age had chronic constipation, influenza several times; cerebrovascular accident, heart attack 1963; died November 1966, 54½ years after onset

10. W.B. Coley 1935 (84)	M 44	immense adenocarcinoma right kidney, 55 lb. weight loss (operable)	nephrectomy by Barringer December 1928; stormy postoperative course due to shock, (operation very difficult due to size of tumor (1022 gm.); x-ray (2) postoperatively	January 26, 1929: Coley toxins (Parke Davis XIII); 27 i.m. in 3 mos., maximum dose 10 minims, maximum febrile reaction 101°F.	complete recovery, NED; heart attack 1935; prostatectomy 1940; worked until 1944, then coronary thrombosis; died July 1948, 2nd coronary, 20 years after onset
11. Johnston 1962 (205)	M 44	hypernephroma, bilateral pulmonary and pelvic metastases	nephrectomy 5 mos. after onset	Coley toxins (Johnston XV) 55 i.v. in 6 mos.	disease progressed, further metastases, no improvement, death 11 mos. after onset
12. Lageze 1960 (232)	M 58	hypernephroma, bilateral pulmonary metastases, 12 lb. weight loss (onset May 1958)	nephrectomy August 1958; hydrocortanyl daily for 3-4 mos. during which metastases increased (20 mg. at first then 10 mg. daily)	January 1959: Trypanosoma cruzi injections given daily for 3 mos.	asymptomatic, in excellent condition, gained 24 lbs.; metastases did not begin to regress until June 1959, complete disappearance by September 1959; well, NED 1960, 2 years after onset
13. Tuffier 1910 (417)	F 53	recurrent inoperable "cylinder cell epithelioma" left kidney, widespread lymph node metastases, cachexia	nephrectomy; (tumor size of orange, *areas of hemorrhage);* metastases not removed	November 1904 injections Borrel's serum (sheep inoculated with breast cancer tissue); violent general reaction each time (to 102.2° F); leukocytosis (20,000 wbc, 84% polys) injections given for 6 mos.	general condition much improved but nodes remained palpable June 1905; condition stationary next few mos., then regained appetite, former weight, NED over 6 years after onset
14. A. Wilson 1925 (442)	M 56	recurrent carcinoma left kidney, metastases to axillae, groin, scrotum (also had papilloma or villous carcinoma of bladder) 8 episodes hematuria 1907-1909; kidney cancer onset April 1911, of rapid growth, 70 lb. weight loss by mid-1912	bladder cancer treated by x-ray for some mos., hemorrhages continued despite radium (5) 1910-1911; kidney cancer removed surgically April 1911; x-ray June 1911 (24)	May 1911, 6 doses horse serum in 6 weeks, no benefit, condition deteriorated, bedridden; August 24, 1912; goat serum 16 in 5 mos. i.m. in buttocks, marked reactions (to 102°F), malaise, erythema	temperature had been elevated (100°-102°F) for 1 year, fell to normal after 2nd goat serum injection; within 8 weeks metastases decreased, disappeared 2 mos. later; appetite increased; April 1913, 3 mos. after last dose, passed more villous tumor (from bladder?) right kidney metastasis, death June 1913, over 2 years after onset of renal cancer, 6 years after onset of bladder cancer

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