"A CLINICAL STUDY OF WILMS' TUMOUR"
(NEPHROBLASTOMA)

IN
KENYATTA NATIONAL HOSPITAL

DR. GATHAIYA JUMBI

THIS STUDY WAS SUBMITTED TO THE UNIVERSITY OF NAIROBI AS PART OF THE FULFILMENT OF THE AWARD OF THE DEGREE OF MASTER OF MEDICINE (M. Med.) IN SURGERY

1980
DECLARATION

This study entitled "A CLINICAL STUDY OF WILMS' TUMOUR (NEPHROBLASTOMA) IN KENYATTA NATIONAL HOSPITAL" is my original work and it has neither been published nor submitted to any other university.

(DR. G. JUMBI)

This work was presented for the Examination with my approval.

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ACKNOWLEDGEMENT

I have great pleasure in extending my gratitude and sincere thanks to Dr. I.S. Bal and Professor N.E. Awori for their guidance and supervision of this study.

I also wish to express my many thanks to Dr. J.M. Kyambi, Professor E.G. Kasili, Dr. J.N. Onyango, Dr. M.S. Abdula and all the Paediatric Consultants of K.N.H. for not objecting to my using their patients for this study and for the general tuition they have rendered to me.

Many thanks too to Professor A.K. Kung'u and Professor D.G. Gatei for allowing me to consult the Kenya Cancer Registry, for reviewing my initial protocol of this study, and also for the specialised services they provided particularly on cytology of the urine sediment.

May I also take this opportunity to thank Professor L.R. Whittaker and Dr. N. Adamali for the help they gave me on the radiological data.
I deeply appreciate the technological work on urine cytology done by Mrs. R.N. Muriuki and Mrs. S. Mbugua.

I cannot forget to thank Mr. M.F. Muhinja, Mr. N.J. Muriithi, Mr. J.H. Kirika and Mrs. R.W. Chiuri for their concern in making sure that the records were available to me.

I am extremely grateful to Mrs. F.M. Maina for her secretarial services. She was patient and without the sacrifice she made on her own free time this dissertation would not have been ready in time.
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INTRODUCTION
INTRODUCTION

Wilms' tumour or nephroblastoma is also referred to by many other names such as embryonal adenomyosarcoma and mixed embryonal tumour of the kidney. It constitutes 20 - 25% of all malignant neoplasms of childhood. The tumour derives its name from Max Wilms who in 1899 gave a clear description of the special nature of this tumour. As in many other entities adequate credition for description of this renal blastema prior to those of Wilms' was not considered, particularly with reference to the work done by Birch-Hischfeld and Perthes who emphasised the special nature of mixed embryonal renal tumours in children. The uncertainty in its aetiology; its bizarre pathological nature and the wide diversity in its management has been a centre of controversy and interest among the clinicians and pathologists all over the world. Wilms' tumour is basically composed of both epithelial and mesodermal elements. The epithelial elements may be undifferentiated or on occasions might show features of acinar and tubular structures. The mesodermal elements include muscle, connective tissue, bone, cartilage and even neuronal
tissues. The frequent association with many congenital abnormalities has led to the conclusion that either a single genetic factor is responsible or the congenital abnormalities predispose to the development of Wilms' tumour.

Kenyatta National Hospital (K.N.H.) in Nairobi is the central referal hospital in Kenya and some adjoining countries. It receives the blunt of work in any field of medicine. This important fact of centralization of cases led to the interest in the present study. Special emphasis has been given to the clinical presentation and modalities of treatment of Wilms' tumour.
MATERIALS

&

METHODS
This was a clinical study on Wilm's tumour. It was partly retrospective and partly prospective. It was conducted in Kenyatta National Hospital (K.N.H) in Nairobi, Kenya. The study covered a ten year period between 1970 and 1979. The period between 1970 and 1978 was covered retrospectively and 1979 was covered prospectively. Materials for the retrospective study were collected from the various hospital records which included the ward admission registers, the central records office, the theatre registers, the Kenya Cancer Registry and the radiology department. The cases for the prospective study were selected from the general surgical wards and the general paediatric wards in The data collected included the following features of Wilm's tumour; epidemiology (overall incidence and distribution in age, sex, tribes and geography), clinical presentation, laboratory and radiological investigations, gross pathology, management and prognosis. The data for each case was recorded in a proforma, a copy of which is attached on page 8.

**EPIDEMIOLOGY:**

A statistical data on the overall occurrence was recorded. Apart from the age, sex and tribe of each patient, an attempt was made to establish the administrative district from which each case was referred.
CLINICAL PRESENTATION:

The major symptoms and signs were recorded. Those which were specifically looked for were; abdominal mass, haematuria, weight loss (or poor weight gain), anaemia and fever. The duration of the major symptom at presentation was also noted. Any concurrent infection was noted too.

LABORATORY AND RADIOLOGICAL INVESTIGATIONS:

Particular attention was paid to the results of the following investigations; microscopic analysis of urine for haematuria, blood urea (or BUN), electrolytes, haemoglobin levels, excretory pyelograms, histology and urinary vinyl madelic acid (V.M.A.).

GROSS PATHOLOGY AND TUMOUR STAGING:

In this aspect of the study of Wilm's tumour, the side affected, and the other organs involved by either distant metastases or by local extension of the primary tumour, were studied. The surgeon's report on the stage of the tumour at laparatomy was noted. If the stage was not explicitly stated by the surgeon, an attempt to stage the tumour from the operation notes was made. Unclear operation notes were disregarded and in such circumstances the stage of the tumour was never established.

TREATMENT:

Details of the various modalities of treatment of Wilm's tumour (Surgery, Chemotherapy and Radiotherapy)
were recorded in each case. The precise surgical procedure done was noted. Completeness of the removal of tumour tissue and any rupture of the tumour during the operation was noted in each case. In inoperable cases, the exact reason for inoperability was established. In chemotherapy, the various drug combinations, the doses and number of courses used in each case were investigated. Attention was paid to completeness of the whole chemotherapy course as prescribed. Similar details were studied for radiotherapy treatment (i.e. type of radiotherapy, dose and completeness of all the prescribed courses).

PROGNOSIS:

In the study of prognosis of Wilm's tumour, a careful follow up of all the cases was done with special emphasis on the following parameters of prognosis.

1) "Cure" rate
2) Survival rate
3) Recurrence rate
4) Mortality rate

1) "Cure Rate.
"Cure" in Wilm's tumour is defined as absence of any evidence of disease after a period of time equal to the arithmetic sum of the age of the patient at onset of the disease added to nine months. However, cases with a disease free survival of two years were considered cured.
2) Survival Rate:

For the purpose of this study, survival time was the time interval between the onset of symptoms and the last time the patient was seen. In this respect, it did not matter whether the patient was last seen at the time of death, or had simply "defaulted" from the follow-up clinic, or the patient was alive and well at the time of the end of the study period. A patient was considered a "defaulter" if he had not shown up in the follow-up clinic for a period of three or more months following the date of the last appointment. If the date of the last appointment was not explicitly stated, the time when the next treatment was due was taken to be the appointment date. If the child had completed treatment, an arbitrary appointment after three months was assumed.

3) Recurrence Rate:

A recurrence was a case whose major symptoms and signs (e.g. abdominal mass) disappeared with treatment and sometimes later the same case showed evidence of disease by re-appearance of a major symptom or sign.

4) Mortality Rate:

Definite documentation of death was essential in this aspect of the study. In addition to a statistical data on the number of cases of death, the causes of death were studied. Among the causes
specifically looked for were: advanced cancer, bone marrow depression (by anti-cancer treatment), concurrent life threatening infections (due to immunosuppression), and renal failure. The possibility of a pheochromocytoma in cases which had cardiac arrest during surgery was investigated.

On the basis of this clinical study of Wilm's tumour the observations were analysed to establish the various features of Wilm's tumour.
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abd. mass</td>
<td>1. Abd. mass</td>
<td>1. Haematuria</td>
</tr>
<tr>
<td>3. Haematuria</td>
<td>3. Haematuria</td>
<td>3. Tomography</td>
</tr>
<tr>
<td>5. Anaemia</td>
<td>5. Angiography</td>
<td>6. Ultra sound</td>
</tr>
<tr>
<td>6. B/P</td>
<td></td>
<td>7. Scanning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. Laparotomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9. Haemogram</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10. Alpha-fetal protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11. U/E</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12. Cytology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13. Weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14. Others</td>
</tr>
</tbody>
</table>
OBSERVATIONS

The main features established by the observations were: the occurrence in K.N.H., age distribution, sex distribution, geographical distribution in Kenya, tribal distribution in Kenya, symptoms and signs, investigations, gross pathology, treatment and prognosis.

In many cases, especially in the retrospective study group the record lacked in details and documentation. Only 48 cases had sufficiently reliable and complete data for analysis. Most of the observations were based on these 48 cases.

OCCURRENCE:

There were a total of 107 cases of Wilm's tumour recorded in Kenyatta National Hospital between the years 1970 and 1979 inclusive. This gives an average occurrence of 10.7 cases per year. The lowest occurrence was in 1975 (3 cases) and the highest was in 1977 (18 cases).

SEX DISTRIBUTION:

There were 66 males (62%) and 41 females (38%). The male:female ratio was approximately 3:2.
AGE DISTRIBUTION:

The age distribution is shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>THE AGE DISTRIBUTION</th>
<th>(WILM'S TUMOUR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
</tr>
<tr>
<td>0 - 2 years</td>
<td>18</td>
</tr>
<tr>
<td>2 - 4 years</td>
<td>14</td>
</tr>
<tr>
<td>4 - 6 years</td>
<td>6</td>
</tr>
<tr>
<td>6 - 8 years</td>
<td>4</td>
</tr>
<tr>
<td>8 - 10 years</td>
<td>3</td>
</tr>
<tr>
<td>10 - 12 years</td>
<td>2</td>
</tr>
<tr>
<td>Above 12 years</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
</tr>
</tbody>
</table>

The youngest child was five months old & the oldest was sixteen years of age. The peak incidence was among children in the age group 0 - 2 years. There was only one case above twelve years of age. Two thirds of the cases (66.67%) were under four years of age and three quarters (79.16%) were under six years of age.

GEOGRAPHICAL DISTRIBUTION:

Geographical distribution was very uneven. Most cases were from Central Province (represented by Murang'a, Kiambu, Nyeri, Kirinyaga and Nyandarua Districts). Over half the cases came from this province and Nairobi City. Table 2 shows the distribution according to the
administrative districts of Kenya.

Table 2

GEOGRAPHICAL DISTRIBUTION
(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th></th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murang'a</td>
<td>7</td>
<td>14.58</td>
</tr>
<tr>
<td>Kiambu</td>
<td>6</td>
<td>12.50</td>
</tr>
<tr>
<td>Nyeri</td>
<td>5</td>
<td>10.41</td>
</tr>
<tr>
<td>Nairobi</td>
<td>5</td>
<td>10.41</td>
</tr>
<tr>
<td>Nakuru</td>
<td>6</td>
<td>12.50</td>
</tr>
<tr>
<td>Meru</td>
<td>4</td>
<td>8.33</td>
</tr>
<tr>
<td>Kisumu</td>
<td>3</td>
<td>6.25</td>
</tr>
<tr>
<td>Others</td>
<td>12</td>
<td>25.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

The other districts contributing were: Kakamega (2 cases), Kisii (2 cases), Machakos (2 cases), Kirinyaga (1 case), Nyandarua (1 case), Embu (1 case), Kitale (1 case), South Nyanza (1 case) and Naivasha (1 case).

TRIBAL DISTRIBUTION:

All major tribal groups in Kenya were involved by Wilm's tumour. All the cases were Kenyans and they were all black (negroid). Two cases did not have their tribes specified. Table 3 shows tribal distribution.
Table 3

TRIBAL DISTRIBUTION
(WILM'S TUMOUR, KENYA)

<table>
<thead>
<tr>
<th>Tribe</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kikuyu</td>
<td>16</td>
<td>33.33</td>
</tr>
<tr>
<td>Luo</td>
<td>7</td>
<td>14.58</td>
</tr>
<tr>
<td>Kalenjin</td>
<td>6</td>
<td>12.50</td>
</tr>
<tr>
<td>Meru</td>
<td>4</td>
<td>8.33</td>
</tr>
<tr>
<td>Kamba</td>
<td>4</td>
<td>8.33</td>
</tr>
<tr>
<td>Luhya</td>
<td>3</td>
<td>6.25</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>10.42</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

The Kikuyu tribe formed one third of the total number (33.33%). Between them, the Kikuyu, the Luo and the Kalenjin tribes had over 60% (29 cases) of the total number. The other tribes, represented by one each were Kisii, Embu, Digo and Turkana.

SYMPTOMS:

The main symptoms are summarised in Table 4.

Table 4

THE MAIN SYMPTOMS
(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal mass</td>
<td>48</td>
<td>100.00</td>
</tr>
<tr>
<td>Fever</td>
<td>14</td>
<td>29.17</td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>8</td>
<td>16.67</td>
</tr>
<tr>
<td>Haematuria</td>
<td>1</td>
<td>2.08</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>10.42</td>
</tr>
</tbody>
</table>
Virtually all the cases presented with abdominal mass. All the cases which presented with fever, with exception of two cases, had a concurrent infection. The two exceptions had pyrexia of unknown origin (P.U.O.), presumably due to the tumour itself. The various concurrent infections are shown in Table 5. Other symptoms were: abdominal pain, lump on the leg (fibular metastases), fits (due to brain metastases) bilateral leg oedema (due to hypoproteinaemia), rectal prolapse (due to debilitation) and unexplained generalised lymphadenopathy. The average duration of main symptom (abdominal mass) before presentation was three and a half months. There was one case with a history of one year.

Table 5

CONCURRENT INFECTIONS AMONG CASES WITH WILM'S TUMOUR

<table>
<thead>
<tr>
<th></th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopneumonia</td>
<td>3</td>
<td>6.25</td>
</tr>
<tr>
<td>Diarrhoea and vomiting</td>
<td>3</td>
<td>6.25</td>
</tr>
<tr>
<td>Measles</td>
<td>2</td>
<td>4.17</td>
</tr>
<tr>
<td>URTI</td>
<td>1</td>
<td>2.08</td>
</tr>
<tr>
<td>Thrush</td>
<td>1</td>
<td>2.08</td>
</tr>
<tr>
<td>S. Typhimurium</td>
<td>2</td>
<td>4.16</td>
</tr>
</tbody>
</table>
CLINICAL SIGNS:

The main clinical signs are summarised in Table 6.

Table 6

<table>
<thead>
<tr>
<th>THE MAIN CLINICAL SIGNS</th>
<th>(WILM'S TUMOUR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal mass</td>
<td>48</td>
</tr>
<tr>
<td>Fever</td>
<td>14</td>
</tr>
<tr>
<td>Palour</td>
<td>5</td>
</tr>
<tr>
<td>Muscle wasting</td>
<td>4</td>
</tr>
<tr>
<td>Ascites</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
</tr>
</tbody>
</table>

All the cases had a palpable abdominal mass. As explained above in the section of symptoms, the cases which presented with fever had intercurrent infections (shown in Table 5) with exception of two cases which had P.U.O. Other clinical signs seen were gross haematuria, abdominal tenderness, pleural effusion (due to chest metastases), bilateral leg oedema (due to hypo-proteinaemia) generalised epileptic fits (due to brain metastases), rectal prolapse (due to debilitation) and unexplained generalised hymphadenopathy. It is noteworthy that only one case presented with gross haematuria.

LABORATORY AND RADIOLOGICAL INVESTIGATIONS:

The main relevant investigations carried out were urine microscopy, blood urea, serum electrolytes,
haemoglobin estimations, I.V.P. and biopsy. Microscopic haematuria was considered a positive evidence of a renal tumour. Haemoglobin level of less than 10 gm per 100 ml was considered significant. The other investigations (blood urea and electrolytes, I.V.P. and biopsy) were interpreted objectively based on the normal values, radiologist's report and pathologist's report respectively. Table 7 shows the main laboratory radiological investigations and the corresponding number of positive cases for each investigation.

Table 7:

THE MAIN LABORATORY AND RADIOLOGICAL INVESTIGATIONS

(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th>Investigation</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine microscopy</td>
<td>5</td>
<td>10.42</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>23</td>
<td>47.91</td>
</tr>
<tr>
<td>Urea and Electrolytes</td>
<td>2</td>
<td>4.17</td>
</tr>
<tr>
<td>I.V.P.</td>
<td>47</td>
<td>97.91</td>
</tr>
<tr>
<td>Histology (biopsy/ nephrectomy)</td>
<td>48</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Wedge biopsy (without nephrectomy) was done in 7 cases. The following investigations were also done
but in only a few cases: Urinary Vinyl Mandelic acid - V.M.A. (9 cases), renal angiography (1 case), Ultrasound studies (1 case), bone marrow (2 cases) and cytology of urine sediment (9 cases). Both the renal angiography and the ultrasound studies were done on the same patient. Both investigations showed evidence of a renal mass. One of the two bone marrow aspirates showed tumour cells. Of the 9 cases subjected to cytology of urine sediment, one showed suspicious cells but none was diagnostic.

GROSS PATHOLOGY & TUMOUR STAGING:

By the time of laparatomy, in nearly all the cases, the tumour involved the whole of the kidney making it impossible to tell which pole was affected primarily. The main features of gross morbid anatomy analysed were: the degree of spread (staging), the frequency of affection of each kidney (laterality), the pattern of metastases and the associated abnormalities.

1) Tumour Staging:

The number of cases in each stage are shown in Table 8.
### Table 8: The Number of Cases in Each Stage (Wilm's Tumour)

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>8</td>
<td>16.67</td>
</tr>
<tr>
<td>Stage II</td>
<td>7</td>
<td>14.58</td>
</tr>
<tr>
<td>Stage III</td>
<td>8</td>
<td>16.67</td>
</tr>
<tr>
<td>Stage IV</td>
<td>17</td>
<td>35.42</td>
</tr>
<tr>
<td>Stage V</td>
<td>3</td>
<td>6.25</td>
</tr>
<tr>
<td>Unspecified</td>
<td>5</td>
<td>10.42</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

The staging used here is that recommended by National Wilm's Tumour Study group (N.W.T.S.), U.S.A. (D'Angio G.J.).

**Stage I**: The tumour is limited to the kidney. The capsule is intact without any tumour infiltration. The tumour is completely resectable.

**Stage II**: The tumour is limited to the kidney. The capsule is infiltrated with tumour. Renal vessels and inferior vena cava may be involved. Tumour is completely resectable.
Stage III: Tumour beyond the kidney but within abdomen with exception of the liver involvement. Any intra-operative rupture of tumour. Tumour is not completely resectable.

Stage IV: Tumour with a haematogenous metastases including all cases of liver involvement. The tumour is not completely resectable.

Stage V: Bilateral renal involvement.

Table 8 shows that 58.34% of the cases were too advanced for complete resection (stages III, IV and V). In fact, 2 cases of stage IV tumour turned out to be inoperable.

2) Laterality:

The left kidney was more frequently affected than the right (25 cases and 20 cases respectively). There were 3 cases of bilateral tumours. Two of these 3 cases presented with bilateral tumours synchronously. The third case presented first with a right side tumour and the left side tumour showed three months later as a "recurrence" (i.e. metachronously).

3) Metastases:

There were 6 cases (12.50%) with chest metastases, 3 cases (6.25%) with liver
metastases, another 3 cases (6.25%) with metastases to bone and one case to the brain. The spleen was locally infiltrated in one case of a left side Wilm's tumour. The bone metastases involved the femur, the fibula and the spine (L3). This last case (with spine metastases) was the same case with brain metastases. This uniquely spreading tumour occurred in the oldest patient (sixteen years) and the only case above twelve years of age. This boy had chest metastases as well. This case was also resistant to all forms of treatment (recurred) and the patient died of advanced cancer after one year.

4) Associated Abnormalities:

In one case of left side Wilm's tumour, there was an associated incomplete epispadius. In this same case renal failure occurred eventually. In another case of right side tumour, there was an associated multicystic kidney.

TREATMENT:

The principle of combined modality treatment (surgery, chemotherapy and radiotherapy) was adopted except in a few cases where the three modalities were
not applicable. Table 9 shows how these modalities were combined in the treatment regimes.

Table 9:

THE NUMBER OF CASES TREATED BY EACH COMBINATION OF MODALITIES

(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th>Combination</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three modality combination (surgery, chemotherapy and radiotherapy)</td>
<td>39</td>
<td>81.25</td>
</tr>
<tr>
<td>Two modality combination (chemotherapy &amp; radiotherapy)</td>
<td>5</td>
<td>10.42</td>
</tr>
<tr>
<td>Single modality (Nephrectomy)</td>
<td>2</td>
<td>4.17</td>
</tr>
<tr>
<td>Palliation treatment</td>
<td>2</td>
<td>4.17</td>
</tr>
</tbody>
</table>

1) Surgical Management:

A total of 41 cases were treated by surgery, either as the only modality of treatment (2 cases) or as one of the three modality combination with chemotherapy and radiotherapy (39 cases). 7 cases did not have nephrectomy. Two of these were inoperable, two were bilateral tumours, two were treated by palliation and one refused to consent for nephrectomy. The therapeutic surgical procedure used was radical nephrectomy which included removal of as much of the ureter as possible. Any
resectable tumour in the abdomen was also removed. In 3 cases splenectomy had to be done. In one of these the spleen was locally infiltrated by a left side tumour and in another case the spleen was accidentally injured during the operation. It was never clear to me why the third spleen was removed. None of the metastatic deposits was subjected to surgical treatment other than biopsy. The two cases "treated" by nephrectomy alone were in fact operative deaths. They had been scheduled for post-operative chemotherapy and radiotherapy. These two cases had no pre-operative anti-cancer treatment of any kind.

2) Chemotherapy:

A total of 44 cases received chemotherapy treatment either as one of a two modality combination with radiotherapy (5 cases) or as one of a three modality combination with surgery and radiotherapy (39 cases). Of these 39 cases which had surgical treatment, 32 cases received post-operative chemotherapy and 2 cases received both pre-operative and post-operative chemotherapy. 4 cases did not have chemotherapy. Two of these four were the operative death cases and the other two cases had only palliative treatment. The operative death cases had been
scheduled for post-operative chemotherapy (and radiotherapy too).

Patients who received chemotherapy treatment fell into three groups. These chemotherapy groups were independent of the modality combination groups shown in Table 9 (Page 20). Group I cases had a three drug combination regime consisting of Actinomycin D, Vincristine and Cyclophosphamide. Often Actinomycin D was alternated with Adriamycin. Group II cases had a two drug combination consisting of Actinomycin D and either Vincristine or Cyclophosphamide. Group III cases had a single drug regime with Actinomycin D only. Table 10 shows the number of cases in each chemotherapy group.

Table 10:

THE NUMBER OF CASES TREATED BY EACH CHEMOTHERAPY REGIME

(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th></th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (Three Drug Combination)</td>
<td>32</td>
<td>72.72</td>
</tr>
<tr>
<td>Group II (Two drug Combination)</td>
<td>2</td>
<td>4.55</td>
</tr>
<tr>
<td>Group III (Single drug Regime)</td>
<td>10</td>
<td>22.73</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Among the 32 cases in chemotherapy group I (three drug regime), 27 cases were treated with all the three modalities (surgery, chemotherapy and radiotherapy) and 3 cases received a two modality treatment with radiotherapy and chemotherapy only. In the chemotherapy group II (two-drug regime), both cases were treated by all the three modalities. In the chemotherapy group III (10 cases), 8 cases received a three modality treatment and the other two cases received a two modality treatment with radiotherapy and chemotherapy.

The protocol of drug administration was as follows:

1) **Induction Course** (Actinomycin D or Adriamycin + Vincristine + Cyclophosphamide)

A total of 6 courses of each drug was given at intervals of one week. Each course consisted of a single injection of each drug. Adriamycin was alternated with Actinomycin D.

2) **Maintenance Course** (Same drugs as for induction course were used).

In the first four months, 4 courses were given at intervals of one month. In the next one year, 4 courses were given at intervals of three months. A course consisted of a single injection of each drug. During the maintenance therapy Actinomycin D was alternated with Adriamycin. (A complete treatment should last for 16½ months).
The above protocol of drug administration applied mainly to a triple therapy (Group I cases with three drug combination) regime which became fully and solely adopted in the second part of the study period. The cases which were treated with a single drug regime (Actinomycin D) received 6 courses at intervals of one month. However, unlike in triple therapy, a course consisted of five daily injections of Actinomycin D.

Drug dosages were calculated as follows:

- Actinomycin D: 0.5 mg/m²
- Cyclophosphamide: 450 mg/m²
- Vincristine: 1.5 mg/m²
- Adriamycin: 60 mg/m²

All the drugs were given by intravenous route.

Recurrences were treated exactly as if they were fresh cases by a new induction course followed by a maintenance course.

3) Radiotherapy:

A total of 44 cases received radiotherapy treatment either as one of a two modality combination with chemotherapy (5 cases), or as one of a three modality combination with surgery and chemotherapy (39 cases). All except the 5 cases which did not have surgery, received postoperative radiotherapy. 4 cases did not have radiotherapy treatment. Two of these four were the operative death cases scheduled for postoperative radiotherapy and chemotherapy, and the
other two were the ones treated by palliation only.

Radiotherapy was administered in form of deep x-ray therapy from a sealed cobalt (Co$^{60}$) unit. The total dose given by a protracted fractionation technique with the whole course lasting for about four weeks. The tumour dose (total dose) was calculated according to the age of the patient but adjustment of dose for disseminated disease was individualised.

PROGNOSIS:

The prognostic parameters used were: "cure rate, survival rate, recurrence rate and mortality rate. Table 11 shows the general situation on follow-up at the end of the study period.

Table 11:

THE RESULTS OF FOLLOW UP AT THE END OF THE STUDY PERIOD (WILM'S TUMOUR)

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive (surviving)</td>
<td>12</td>
<td>25.00</td>
</tr>
<tr>
<td>Cured</td>
<td>5</td>
<td>10.42</td>
</tr>
<tr>
<td>Recurrences</td>
<td>16</td>
<td>33.33</td>
</tr>
<tr>
<td>Defaulters</td>
<td>25</td>
<td>52.08</td>
</tr>
<tr>
<td>Dead</td>
<td>11</td>
<td>22.91</td>
</tr>
</tbody>
</table>
1) **Cure Rate:**

Only five cases were considered cured (10.43%). These cases had a disease free survival of two years or more. Three of these five cases had no evidence of disease at the projected time of cure (i.e. age at onset added to nine months).

Two of these are alive and well. The other three defaulted from the follow-up clinic. These three had completed their treatment. It was observed that all the five cured cases were under two years of age. All the cured cases were treated with all the three modalities (surgery, chemotherapy and radiotherapy) and they all completed the prescribed treatment in each modality. It was also noted that four of these cases had a three drug combination chemotherapy (chemotherapy group I) and the other one had a single drug regime chemotherapy (chemotherapy group III). Two cases had a stage I tumour, two had a stage III tumour and one case was unspecified as far as staging was concerned.

2) **Survival Rate:**

In general survival rate was very poor. Table 12 shows the survival rates for various years.
Table 12:

THE SURVIVAL RATES
(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th>Survival Time</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr. survival</td>
<td>10</td>
<td>20.83</td>
</tr>
<tr>
<td>2 yr. survival</td>
<td>5</td>
<td>10.42</td>
</tr>
<tr>
<td>3 yr. survival</td>
<td>3</td>
<td>6.25</td>
</tr>
<tr>
<td>4 yr. survival</td>
<td>1</td>
<td>2.08</td>
</tr>
<tr>
<td>5 yr. survival</td>
<td>0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Up to the end of the study period, there was no five year survivor. The longest survival was four years. Some of the factors which influence survival were analysed. These included the methods of treatment, the age at onset of the disease and the stage of the tumour. Table 13 shows the number of survivors at various years for the cases treated with a three modality combination as compared to those treated with a two modality combination.
Table 13:

SURVIVAL FOR CASES TREATED WITH DIFFERENT COMBINATIONS OF MODALITIES

(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th></th>
<th>NO. OF SURVIVORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 yr.</td>
</tr>
<tr>
<td>Three modality</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td></td>
</tr>
<tr>
<td>(surgery, chemotherapy and radiotherapy)</td>
<td>8</td>
</tr>
<tr>
<td>Two modality</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td></td>
</tr>
<tr>
<td>(Chemotherapy and radiotherapy)</td>
<td>2</td>
</tr>
</tbody>
</table>

All the survivors who survived for two years or longer were in three modality combination group. The two cases in the two modality group which survived one year were in fact cases of bilateral Wilm's tumour which never had nephrectomy. To elaborate further on the effect of treatment on survival, the various chemotherapy regimes (chemotherapy groups) were compared. In this exercise only cases treated with all the three modalities (surgery, chemotherapy and radiotherapy) were considered. By choosing cases treated with only one combination of modalities, the only variable left was the drug combinations. This enabled a more controlled comparison. Analysis of relationship between survival rate and the method of treatment showed that a combined three modality approach
was associated with better survival but no demonstrable correlation was shown between survival and the different chemotherapy drug combinations used in this study.

The influence of age on survival was shown by comparing the number of survivors for the different age groups. Table 14 shows the survival rates for different groups.

Table 14:

SURVIVAL FOR DIFFERENT AGE GROUPS
(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th></th>
<th>NO OF SURVIVORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 yr</td>
</tr>
<tr>
<td>0 - 2 years</td>
<td>4</td>
</tr>
<tr>
<td>2 - 4 years</td>
<td>3</td>
</tr>
<tr>
<td>4 - 6 years</td>
<td>1</td>
</tr>
<tr>
<td>Over 6 years</td>
<td>2</td>
</tr>
</tbody>
</table>

There was no five year survivor. The younger children showed a longer survival than the older ones. Survival rates were shown to decrease with increasing age. The age of four years appeared a critical one. It was observed that even within the age groups under four years, the very young children (0 - 2 years) exhibited a markedly superior performance than those in the age group of 2 - 4 years.
No correlation was shown between survival and tumour stage. Indeed the sole four year survivor and two of the only 3 cases with a three year survival had a stage III tumour.

No attempt was made to correlate survival rates with histological grading because details of the precise histological types were not included in the pathologist's histology report.

3) Recurrent rate:

There were a total of 16 cases (33.3%) of recurrence. A "recurrence" was defined as a case whose major signs and symptoms disappeared with treatment and sometimes later the same case showed evidence of disease by re-appearance of a major symptom or sign. On the average recurrence occurred after three and a half months. Some factors which influence recurrence were investigated. These were the stage of tumour and the methods of treatment. Table 15 shows the recurrence rates for cases with different stages of the tumour.
Table 15

RECURRENT Rates FOR CASES
WITH DIFFERENT STAGES OF TUMOUR
(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Recurrence</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>12.50</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>28.57</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>37.50</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td>47.06</td>
</tr>
<tr>
<td>V</td>
<td>2</td>
<td>66.67</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>33.3</td>
</tr>
</tbody>
</table>

It was observed that there was a peak in recurrence for stage IV tumour. There was no correlation between recurrence rate and the methods used in treatment. Relationship between recurrence and histological grading was not done because the precise histological details were not included in the pathologist's histological report.

4) Mortality Rate:

There were 11 cases of death. Table 16 shows the causes of death.
Table 16

THE CAUSES OF DEATH

(WILM'S TUMOUR)

<table>
<thead>
<tr>
<th></th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced cancer</td>
<td>6</td>
<td>54.55</td>
</tr>
<tr>
<td>Operative deaths</td>
<td>3</td>
<td>27.27</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
<td>9.09</td>
</tr>
<tr>
<td>Not established</td>
<td>1</td>
<td>9.09</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>11</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

A death was considered to be due to advanced cancer if, in a stage III, IV or V case, there was no other obvious cause of death. Operative deaths were those who died either on the theatre table or died within twenty four hours of operation. The time interval between presentation and death ranged between three months and one and a half years with an average of eight months. Apart from the operative deaths, all other deaths occurred during a recurrent attack of the disease. None of the operative death cases had a pheochromocytoma. It was observed that all the three had a haemoglobin of less than 10 gm per 100 ml at the time of surgery.
DISCUSSIONS
DISCUSSION

In 1899, Max Wilms of Leipsig, a professor of surgery in Heidelberg, Germany published the initial work of this tumour which earned him the eponymic designation. However, a lot of work on the biological nature and pathological behaviour of mixed embryonic renal tumours in childhood had been done by Birch-Hirschfeld and Perthes whose materials Professor Wilm's published. (Bailey & Love, Thomasson & Ravitch).

Wilm's tumour comprises 0.1% of all cancers and 20 - 25% of all childhood cancers. It is the commonest malignant renal tumour in children. Among all the childhood tumours, it is second only to neuroblastoma. In Kenya, Wilm's tumour is in fact the commonest malignant renal tumour. (Awori N.E.).

AETIOLOGY:

Like in all neoplastic diseases the exact carcinogen and the exact mechanism of carcinogenesis in Wilm's tumour is unknown. Aetiologically, two types of Wilm's tumour are recognised - a familial form and a sporadic form. (Rudiger H.W.; Maurer H.S. et al).

Familial Form of Wilm's Tumour:

Evidence of genetic cause of this form of Wilm's tumour is rapidly accumulating. The familial
tendency is as high as 33%. (Maurer H.S. et al). This figure is probably too high for a mere statistical chance. Furthermore, this form of Wilm's tumour is commoner among identical twins. It has been reported in three successive generations among siblings which had aniridia as well. (Maurer H.S. et al). Wilm's tumour has also been reported in a mother and a son (Tebbi K. & Cross S.). A stronger genetic evidence is shown by the frequent occurrence of Wilm's tumour among patients with certain conditions or syndromes known to have some genetic or chromosomal disorders. The commonest is aniridia which produces the aniridia - Wilm's tumour syndrome. Aniridia occurs in between 1.1% to 1.4% of all Wilm's tumour cases. (Maurer H.S. et al). The others are: hemihypertrophy, mental retardation and ambiguous genitalia. (Richard V.M. et al). A more objective evidence of genetic actiology has come from chromosomal studies of Wilm's tumour patients. In one study the karyotypes of nephroblastoma cells were compared with karyotypes of normal cells from the same kidney. All the nephroblastoma cells were found to be hyperdiploid with a mean of 55 chromosomes. The normal cells had a normal number of chromosomes. Most abnormalities were in chromosomes in group C, D and G. Deletion was the most prominent defect. Marker chromosomes coincided with those found in other childhood tumours. (Robinson K.M.). In another chromosomal study, translocation defects were shown
in the chromosomes of groups B and C. (Maurer H.S.). In yet another study, a case of Wilm's tumour with hypospadius and bilateral cryptorchidism was found to be a mosaic of 46XY/48XXYY. (Ballesta M. & Cruz M.). Another chromosomal aberration demonstrated in another study was deletion of chromosome 11. (Ricard V.M. et al). Nephroblastomatosis is frequently associated with trisomy 18 and it is also associated even more frequently with Wilm's tumour. (Stambolis C.). There is little doubt that genes play a key role in causation of this form of Wilm's tumour. Observations have shown that if the genetic theory is correct, at least two gene abnormalities are necessary for one to develop Wilm's tumour. (Cotlier et al, Tebbi K. & Cross S.). One abnormality must be inherited from one parent. The other abnormality is an acquired mutation. It is not known for certain whether the mutation occurs in the same gene as the inherited abnormality or whether it occurs in a separate gene. The first gene abnormality is said to be closely linked to aniridia and this is inherited. The second gene abnormality is closely associated with hemihypertrophy. A combination of these two conditions in the same child poses a very high likelihood to develop Wilm's tumour. (Maurer H.S.). Genetic studies on HLA locus proved that at least these abnormal genes were not situated in the HLA segment. (Majsky A. et al). Incidentally, the
inheritance appears dominant. (Brown).

Sporadic Form of Wilm's Tumour:

Studies on aetiology of this form of Wilm's tumour have not been as encouraging as those of the familial form. (Jaffe N. et al). It has been suggested that like in the familial form two gene abnormalities are also necessary in order to develop this form of Wilm's tumour. The only difference with the aetiology of the familial form is that both gene abnormalities occur by two successive mutations. The first mutation which is analogous to the inherited abnormality in the familial form must occur very early - probably in the germinal cell. The second abnormality is said to occur in the somatic cell.

The familial form of disease is therefore partly inherited and partly environmental while the sporadic form is wholly environmental. However, one cannot rule out genetic factors in general oncology. Some individuals have an increased susceptibility to develop tumours with relatively low doses of carcinogens. Such individuals may not have any genetic relationship at all. There is a general concept that even in the non-hereditary neoplastic diseases there is an inherent genetic susceptibility. After all, some cancers are limited to some species only. Such genetic susceptibility may lack adequate expressivity to show any hereditary
pattern within the genetic tree of an individual. This susceptibility may render the genes more easily mutated by ordinary doses of carcinogens. Even though the ordinary doses of natural carcinogens are fairly random, only patients with this susceptibility get the necessary mutations to cause disease. The role of abnormal genes in causation of sporadic form of the disease cannot therefore be completely excluded.

No carcinogens have so far been shown to cause human Wilms' tumour. However, chemical carcinogens e.g. Cycasin have been used successfully to induce Wilms' tumour in animals. (Wistar rats). (Gusek W.) Bovin reported a case of metanephric adenoma with persistent immature glomeruli in a child whose mother had severe aspirin poisoning during pregnancy while trying to commit suicide. (Bove K.E. et al). These renal blastema disorders have a high association with Wilms' tumour (Bolande). Attempts to isolate any viruses in Wilms' tumour patients have been unsuccessful. The BKV virus, a known oncogenic virus which is usually recoverable from human urine has been particularly investigated but no association was found. (Jaffe N. et al; Wold W.S. et al; Peebles P.T. et al). No specific studies on aetiology were done in the present study.
OCCURRENCE:

The overall incidence of Wilm's tumour is about 1:200,000 - 1:250,000. The National Wilm's Tumour Study group (NWTS) reported an annual occurrence of 450 cases in United States of America (U.S.A.). (D'Anglo J.G. et al). This incidence is less than the overall incidence. However, Wilm's tumour has a remarkably evenly distributed cosmopolitan occurrence. Loeffler contends that the geographical distribution is so even that the recorded incidence of Wilm's tumour can be used as a parameter to assess the completeness of any country's cancer registry. (Loeffler). A study done in Erie county (New York, U.S.A.) reported a slightly higher incidence among negro children. (Mauric & Griffel). In South Africa, one study showed a slight predominance among white girls (Kaschula R.O. et al). Despite these studies, the general racial as well as sex distribution is usually uniform.

The average annual occurrence of Wilm's tumour in our hospital (K.N.H.) was 10.7 cases (see page 9). It is not possible to define the exact population served by this hospital. It was therefore not possible to establish the exact incidence. Theoretically, K.N.H. is supposed to serve the whole nation of about 15 million
people but inaccessability to the hospital makes it impossible for the hospital to serve every part of the country equally. Therefore, the occurrence in this hospital cannot be taken as the national occurrence. We also know that some provincial hospitals handle some cases of Wilm's tumour. The calculated theoretical incidence based on this study was 1:1,500,000. This is about 1/6 of the expected incidence (1:250,000) for Kenya. This incidence is far from accurate and this is because K.N.H. does not receive all the cases.

Based on this predicted general incidence, it seems that K.N.H. receives only 1/6 of the total cases of Wilm's tumour.

Sex Distribution:

There were 66 males and 41 females giving a male:female ratio of approximately 3:2 (see page 9). This is unusual. In fact, there is usually an insignificant female preponderance. (Kaschula R.O. et al). The population structure could not explain this male preponderance in K.N.H.

Age Distribution:

The mean age at diagnosis is generally 3.87 years. (Mauric & Griffel). The range includes all phases of childhood and young adults. The peak incidence is between three and four years. The main age group affected is 0 - 7 years which
includes 80% - 90% of cases. (Kaschula R.O. et al; Shah K. et al; Harrison M.R.). In one series there were five cases between 15 - 18 years of age. (Shah K. et al). Older cases have been reported. Bard reported a case of twenty four. (Bard R.H. et al).

In this study the mean age at diagnosis was 2½ years (see Table 1, page 10). The peak incidence was 2 years of age. The main age group affected was 0 - 6 years which comprised 80% of the cases. The youngest child was 5 months and the oldest was sixteen years old. The age incidence was in general very normal in distribution.

Geographical Distribution:

In this study, the geographical distribution was uneven (See Table 2, page 11). This is contrary to the expected distribution. 50 - 60% came from the Central Province of Kenya and Nairobi City. Among these, 27.08% came from Murang'a and Kiambu Districts. A significant number came from Nakuru (12.50%). Kenyatta National Hospital is situated in Nairobi City which is adjacent to the Central Province of Kenya. These are some of the most populous areas in Kenya. The increased occurrence of Wilm's tumour in these areas is biased. It does not represent the true picture.
It is almost certain that this increased occurrence is due to the ease with which the people in these areas reach to Kenyatta National Hospital. Probably the medical services around this capital city are better too and medical awareness is correspondingly greater. Nakuru town is a provincial headquarters with a good provincial hospital. It is also in a rich populous area. It has a very good direct road communication with Nairobi. Most of the cases from Nakuru were in fact transferred from the provincial hospital. Most likely the increased occurrence in Nakuru has the same explanation as that in Nairobi and Central Province. The true geographical distribution in Kenya can only be established by grass-root surveys at the district and provincial levels.

Tribal Distribution:

In this study there was an apparent increase among the Kikuyu tribe. 33.3% were of Kikuyu tribe, 14.50% were Luos and 12.50% were Kalenjins (see Table 3 page 12). The Kikuyus live in the Central Province around Nairobi City where the Kenyatta National Hospital is situated. This is probably one of the reasons for the increased occurrence among the Kikuyus. The major tribes in Kenya include
the Kikuyu, the Luo, the Luhya, the Kalenjin, the Kamba, the Meru, the Kisii, the Embu and the Taita. The occurrence of Wilm's tumour seems to correspond fairly well with the relative size of each tribe. However, there was a marked relatively lowered occurrence among the Luhya tribe. This was also noted by Awori. (Awori N.E.).

PATHOLOGY:

Gross Appearance:

The tumours are usually very large often involving the whole kidney. The usual surgical specimen weighs about one kilogram or more. Any pole can be primarily affected but the commonest is the upper pole. The lower pole is next in the frequency of involvement. The middle segment is the least commonly affected as the primary site. The tumours are usually spherical and encapsulated. The cut surface may be cystic, haemorrhagic, solid, gelatinous or variegated with all the above. In advanced cases, the tumour may have infiltrated through the capsule and may even have spread into the peritoneal cavity with a haemorrhagic ascites. The renal vessels and even the inferior vena cava may be infiltrated. Nodes at the hilum and para-aortic nodes may be involved too. In still more advanced cases involvement of the adjacent abdominal viscera
(peritoneum, omentum, the liver, the spleen and the colon) may occur. An associated renal abnormality may be found e.g. polycystic disease, nephroblastomatosis and multilocular cyst of the kidney. Bilateral lesions occur. In this study, the tumours were probably larger than average. Tumours of up to 1.5 kgm were not uncommon at surgery. 58.34% of the cases had stage III or more disease. (See Table 8, page 17 ).

Bilateral Wilm's Tumour:

Between 1.5% - 13% of cases are bilateral. (Garrett R.A. et al). Bilateral tumours are commoner in the familial form of Wilm's tumour. (Maurer H.S.). Associated abnormalities such as nephroblastomatosis and polycystic disease are likely to be seen in bilateral tumours. Theoretically bilateral tumours can occur either through metastases or as a result of multicentric origin. Most of them have no demonstrable lung metastases and there is no direct tumour continuity between the two sides. Bilaterality is therefore more likely to be caused by a multicentric origin rather than by metastases. (Guilio J.). Bilateral tumours can present either synchronously or consecutively. In the latter, the second tumour appears during the course of treatment of the first tumour and it is often mislabelled a
"recurrence" on the opposite kidney. In one series there were 5 cases reported. Among these five, two presented synchronously and three were metachronous. (Garrett R.A. and Donohue J.P.).

In the present study, bilateral tumours were in 3 cases (6.25%). This is in accordance with their general incidence (1.5% - 13%).

Extra-renal Wilm's Tumour:

Eleven cases of extra-renal Wilm's tumour have been reported in the literature. (Madant F. et al). In one series of literature review, 4 cases out of 9 occurred in association with a teratoma. (Akhtar M. et al). Three cases of groin lesions have been reported. (Madant F. et al; Harm D. & Lohr J.). One tumour involved the chest wall. According to the present review of extra-renal tumours it is concluded that the commonest sites of occurrence of extra-renal Wilm's tumour is in association with a teratoma and in the groin. Those which are not associated with teratomas are postulated to arise from heterotopic renal blastema cell rests. (Akhtar M. et al; Harm D. & Lohr J.). In a study of mesenchymal tumours of anterior mediastinum and the lungs, Dehner L.P. et al demonstrated a tumour which was indistinguishable from Wilm's tumour in histology. (Dehner L.P. et al).
No case of extra-renal Wilm's tumour has been described in our hospital so far.

Microscopic Appearance:

Like all mixed embryonal tumours, the histology of Wilm's tumour is extremely variable both in its cell types and the degree of differentiation of each type. The essential feature in the histology is evidence of nephrogenic tissue as shown by attempts of glomerulo-tubular formation and presence of renal blastema cells. The latter (renal blastema cells) are represented by spindle blast cells in the stroma. However, very anaplastic tumours may not show any evidence of glomerulo-tubular formation and the only evidence of their nephrogenic nature is their anatomical location.

There is a group of "nephroblastomas" which have an atypical histological pattern. These fall broadly into two sub-groups - the "epithelial nephroblastomas" and the "exclusively sarcomatous nephroblastomas".

"Epithelial Nephroblastomas"

Epithelial nephroblastomas include cystic nephromas, polycystic nephroblastomas (also called benign multilocular cystic nephroma), cystic
partially differentiated nephroblastoma, well differentiated epithelial nephroblastomas and tubular nephroblastomas. Characteristically, their cysts are lined by an epithelium. These tumours are most likely well differentiated nephroblastomas and not renal dysplasias. (Guillerimo E. et al). Multilocular cystic nephromas with metanephric blastema cells and striated musculature elements should be regarded as Wilm's tumour. (Stambolis & Havers). Some observers have proposed that some epithelial nephroblastomas such as cystic partially differentiated nephroblastoma should be viewed as different clinical entities due to their relatively benign course. (Vijay et al). However, these tumours contain renal blastema cells in the stroma between the epithelial lined cysts. It therefore seems quite in order to consider them as Wilm's tumour on this histological ground. Some typical nephroblastomas especially the well differentiated types have a demonstrably relatively much better prognosis than the more anaplastic tumours. The relatively benign course of the epithelial nephroblastomas is probably not enough to exclude them from the general group of Wilm's tumour.

Epithelial nephroblastomas are characterised
by epithelial lined cysts. They have to be distinguished from nephroblastomas occurring in a cystic disease of the kidney. Association of polycystic disease and multilocular kidney cyst with typical Wilm's tumour happens occasionally. (Redman J.F. and Harper D.L.).

"Exclusively Sarcomatous Nephroblastomas"

   Exclusively sarcomatous nephroblastomas are probably a genuinely different clinical entity from Wilm's tumour. These tumours are normally included as variants of Wilm's tumour with a typical histology. A few authors have shown features which sharply contrast with classical Wilm's tumour. The histology consists of exclusively sarcomatous spindle celled tumour. It has a very high predilection to bone metastases when compared with Wilm's tumour. In one series 7/9 cases had bone metastases (cf 3.7% in Wilm's) and these same number of cases showed recurrences (cf with 50% of Wilm's). (Morgan E. et al). The survival rate of this type of tumour is also very low compared with Wilm's tumour. (Beckwith J.B. and Palmer N.F.).

   The type of histological appearance has a lot of bearing on prognosis. Tumour grading in Wilm's tumour is based on various histological patterns. No single grading system has received a concensus for standard use. Handwick and Stevens
grading has five histological types (Bolkenius M. et al). Sandstedt and Jereb grading has four histological types while Bodian and Rigby grading has seven types. Handwick and Stevens based their grading on the overall differentiation of all tissue elements. In Sandstedt and Jereb's grading the least differentiated tissue element was used. In practice however, most centres group Wilm's tumours into three groups: the well differentiated, the poorly differentiated and anaplastic types.

**Metastases in Wilm's Tumour:**

Wilm's tumour spreads both by direct infiltration and by metastases. The main routes of spread are haematogenous and permeation along the veins. Haematogenous spread commonly occurs in the lungs. 25 - 50% of cases have haematogenous spread at diagnosis. (Mauric and Griffel; Brenn and Rector). The lung metastases contributes to most of these haematogenous spread. (Kaschula R.O. et al). Liver metastases are uncommon while bone and brain metastases are very rare. (Gudjahr P.; Benz G. et al; Morgan E et al). Lymphatic spread involves the lymphnodes of the hilum of the kidney (pedicle of kidney) and the para-aortic lymphnodes. Malignant renal tumours characteristically spread directly
along the renal vein and the Wilm's tumour is no exception. The spread may reach to the vena cava and the heart. (Bryant J. and Vuckovic G.). Transcoelomic spread may occur if the tumour infiltrates beyond the confines of the kidney capsule. Direct infiltration into adjacent viscera occurs in advanced cases. The peritoneum, the liver, the spleen, the tail of pancreas and the colon can be affected by direct infiltration.

The usual rate of bone metastases is about 3.7%. (Gudjahr P.; Benz G. et al). Atypical nephroblastomas with an unusually high rate bone metastases have been reported. These tumours are mainly sarcomatous in histology. In one series 7/9 cases had bone metastases. (Morgan E. et al). "Clear cell" sarcomas too had a high metastases rate to the bone. (Beckwith J.B. and Palmer N.F.). A suggestion that these sarcomatous tumour are probably a separate clinical entity has been proposed. (Morgan E. et al). The histology and clinical course resembles that of primary renal sarcomas. This sarcomatous Wilm's tumour constitutes 2.3% of renal tumours. (Marsden H.B.).

About twelve cases of heart involvement have been reported. The main route of spread to the heart is along the renal vein and inferior
vena cava. Autopsy reports of metastatic deposits in the myocardium have been published. (Bryant J. Vuckovic G.). A tumour causing a complete obstruction of the inferior vena cava and demonstrable collaterals to the heart was reported by Vaughan. (Vaughan et al). This tumour extended right into the right atrium. Cases with atrial extensions of the tumour can present primarily with cardiac symptoms. In a review of 8 cases, with heart involvement, four cases presented primarily with cardiac symptoms without any reference to the abdominal symptoms. (Slovis T.L. et al). Heart involvement is very rare. Nevertheless any clinical evidence of cardiac dysfunction in a case suspected of Wilm's tumour calls for a complete cardiological investigation. It is recommended that because of the rarity of heart involvement only the non-invasive investigations should be used initially. These include echocardiograms and electrocardiogram. Many centres do routine inferior vena cavograms. (Slovis T.L. et al).

Cases of brain metastases are very rare.

In the present study, the overall rate of metastases (haematogenous) at diagnosis was 25%. This is as expected. However, the rate of bone
metastases was more than usual (6.25% cf 3.7%). It equaled that of liver metastases. As expected, most metastases occurred in the lungs (12.50%). (see page 18).

**Conditions Frequently Associated with Wilm's Tumour:**

The following conditions are found in association with Wilm's tumour with remarkable frequency: nephroblastomatosis, nodular renal blastema, persistent renal blastema (Kumar M. et al), aniridia, hemi-hypertrophy, mental retardation (Cotlier E. et al), ambiguous genitalia (Ballesta F. & Cruz M.), congenital cataracts, renal as well as extra-renal hamartomas, visceromegaly, multilocular cystic disease of the kidney, cardiac anomalies, neurofibromatosis (Stay E.J. et al), Beckwith-Wiendeman syndrome (Brown N.G. and Goldie D.J.), adreno-cortical tumours (Muller S. et al), Klippel - Trenauny syndrome, splenic agenesis, Trisomy 18 fetal gigantism and macroglossia (de Chadarevian).

The commonest associations are aniridia and hemi-hypertrophy which occur in 1.1% - 1.4% of all Wilm's tumours, and nephroblastomatosis or one of its variants (see page 19) which occur in as high as 50% of cases. (Bolande).

The only associated abnormalities encountered in this study were epispadius (one case) and multicystic
Experimental Wilm's Tumour:

Tumour models of Wilm's tumour are frequently used for experimental work. Real human Wilm's tumour cell cultures are probably the best specimens produced so far. Such cell cultures have been grown in soft agar for over two years. They still retain their human chromosomal make up and enzyme studies show human identity. They are available from American Type Culture Collection, Rockville, Maryland (Peebles et al).

Animal model Wilm's tumours include Murine Wilm's tumour (West C.R. et al) and cycasin induced Wistar rat Wilms tumour. (Gusek W.). Studies using the cultured Wilm's tumour cells have almost excluded any of the known viruses as the aetiological cause. Murine Wilm's tumour showed a lowered rate of metastases under high CO₂ concentrations (55% and 76%). Cycasin induced Wistar rat Wilm's tumours are usually bilateral. This experimental animal model inducable Wilm's tumour imply that Wilm's tumour is probably not a dysontogenetically produced tumour since it can be induced in normal Wistar rat kidneys. (Gusek W.).
CLINICAL FEATURES:

Clinical diagnosis of Wilm's tumour is fairly straightforward. The differential diagnosis is lengthy but the rarity of all other conditions excludes them from clinical impressions. The peak incidence occurs between 3 - 4 years of age. 80% - 90% of cases present before seven years of age. (Mauric & Griffel, Kaschula R.O. et al, Brenner & Rector). Only about 150 cases have been reported in adults. (Shah K et al, Garrett R.A., Bard R.H.). Both males and females are affected equally. (Kaschula et al). The disease is evenly cosmopolitan and all races are equally affected too. The main presenting features are abdominal mass, haematuria, hypertension, fever and symptoms and signs due to concurrent infections. Other clinical features are related to local extensions and metastases. Pulmonary metastases may cause cough, haemoptysis, pleural effusions and breathlessness. Liver metastases may be palpable clinically. Local extensions along the renal vein and vena cava may reach the heart and present with cardiac symptoms. (Bryant J., Slovis T.L. et al, Vuckovic G., Vaughan et al). Extra renal tumours present with unique symptoms and signs related to their specific locations. Usually they are found among intra-abdominal teratomas and these present as "non-renal"
abdominal masses too. The next commonest presentation of extra-renal Wilm's tumour is a groin tumour. (Akhtar M. et al; Madant F. et al, Harr D. & Lohr J.). Bilateral tumours may present with bilateral masses. Symptoms and signs due to other associated abnormalities can also be elicited.

Abdominal Mass:

Nearly all cases present with an abdominal mass which is situated characteristically over the upper quadrant of the side affected. (De Lamerens S.A.). All intra-renal masses in children are nearly always Wilm's tumours. Therefore, all renal masses in children should be labelled as Wilm's tumours until they are proved otherwise. (Aubert J. et al). Over 90% of the cases of Wilm's tumour present with abdominal mass. The usual history is that the mother felt a mass when bathing the child. The rest of the cases are discovered by the physician when a patient comes to the hospital for another ailment which may or may not bear any relationship to Wilm's tumour. A full detailed physical examination will pick up nearly all the cases. Bilateral Wilm's tumours which represent 2% - 10% of all cases often present with bilateral masses synchronously (65%) but in many cases the second tumour presents later within the course of the
treatment. The intravenous pyelogram will pick a considerable number of the unpalpable second tumour of the bilateral cases. Attention should therefore be paid to the pyelogram of the clinically normal side. This will also ensure that the other kidney is actually present and functioning. The main differential diagnosis of renal and peri-renal masses are neuroblastoma, hydronephrosis, Wilms' tumour, pheochromocytoma, multilocular cyst, polycystic kidney, renal vein thrombosis, renal hamartoma, nephroblastomatosis and other renal blastema dysplasias, Burkitt's lymphoma, adenocarcinoma, transitional cell tumours, sarcomas, teratomas, adenomas, haemangiomias and lipomatosis. (AllenR.G.). True renal masses are usually due to hydronephrosis and Wilms' tumour. In one study 56/133 were due to hydronephrosis and 48/133 were due to Wilms' tumour. (Kelalis P.P.) Quite often the hydronephrosis is due to posterior urethral valves.

Very advanced tumours, especially in babies may not be easily localised as renal masses. In these cases other non-renal abdominal masses may have to be considered in the differential diagnosis of Wilms' tumour. Liver masses can also mimic right renal masses. The usual liver masses in children are haemangiomia, lymphangiomias, sub-capsular haematomas, hepatoblastomas, hepatocellular
carcinoma and cysts in the liver. Gall bladder masses are often associated with jaundice and are due to biliary atresia or biliary obstruction. Large spleens can be confused for a left renal mass. They are due to various haematological disorders, reticulo-endothelial diseases and chronic infections. Pancreatic tumours are usually cysts, often associated with mucoviscoidosis and other "cystic" diseases of pancreas. Enlarged lymphnodes of palpable sizes are usually due to tuberculosis or Burkitt's lymphoma. Gastro-intestinal masses are usually due to muconeum ileus, muconeum pseudocyst, duplication cysts, intussusceptions and ascaris lumbricoides which may form a "ball of worms" in severe infections. Finally, abdominal masses arising from pelvic viscera include ovarian cysts and tumours, teratomas and hydrocolpos. Bladder masses other than a distended bladder are unusual in children. (Allen R.G.).

All cases in this study presented with an abdominal mass. (See Table 4 and Table 6).

Haematuria:

Haematuria is due to leakage of blood elements into the collecting system of the kidney. It usually denotes erosion into the renal pelvis but this is not necessarily so. Frank haematuria is very unusual but microscopic haematuria is quite common. In one series 50% of cases had
microscopic haematuria. (Kelalis P.P.). Usually only less than 10% show microscopic haematuria at diagnosis. (Brenner and Rector). Other causes of haematuria are adenocarcinomas, transitional cell tumours, nephritis, pyelonephritis nephrolithiasis, hypertension, ureterolithiasis, bladder tumours, bladder stones, cystitis, urethral stones and trauma to the whole of the urinary tract.

In this study 5 cases had microscopic haematuria. Only one case had frank haematuria. (See Table 4 and Table 7). This is as expected.

Hypertension:

The exact mechanism of causation hypertension is not fully established. Some tumours certainly secrete rennin. (Sheth K.J. et al). In such tumours the hypertension is caused through the rennin-angiotensin-aldosterone mechanisms. Such tumours present very early due to their physiologic symptoms. One tumour presented with unexplained polyuria, polydipsia and hyponatremia. Catecholamines were also raised. There was an occult tumour revealed by an intravenous pyelogram. It was cured by surgery (nephrectomy). (Sheth K.J. et al). Tumours which secrete rennin arise from near the juxtaglomerular apparatus and they may well be juxtaglomerular apparatus cell tumours. May be they are the malignant counterparts of haemangiopericytomas
Rennin producing tumours are very rare. On the other hand, hypertension is fairly common. In one series 30/36 cases had hypertension and in another 29/40 cases. (Kelalis P.P.). It is evident that rennin cannot explain the high occurrence of hypertension in Wilm's tumour. In those cases where rennin is markedly raised, its diagnostic as well as therapeutic monitoring values can be of some benefit. Probably the exact frequency of hypertension is even more than casual surveys show. The exercise of taking blood pressures from very young children using the usual clinical apparatus is certainly subject to fairly gross errors. Subjectivity is high in both the sphygmomanometer and the flush methods. Objective methods such as the arterial catheters are probably too traumatic for routine use.

Fever and Concurrent Infections:

A low grade pyrexia without any evidence of infection is common in Wilm's tumour. It is due to the tumour itself and after many investigations it gains the expression P.U.O. (Pyrexia of Unknown Origin). However, patients with Wilm's tumour are very prone to infections. Demonstrable suppression of immunocompetence has been shown among Wilm's tumour patients by mixed lymphocyte culture techniques. (Kelalis P.P.). Both the cellular as well as humoral immunity systems are
suppressed. Cytostatic treatment reduces this immuno-competence further. It also makes malnutrition worse. (Kaschula R.O. et al). The whole set up creates a very good environment for infections. Indeed infections are a major cause of death among Wilm's tumour patients. In this series fever was present in 29.17% of cases. Of these, 25% had infections but 4.17% had no demonstrable infection. (See Tables 4, 5 and 6, pages 12, 13, 14 respectively).

Other Symptoms and Signs:

Symptoms and signs due to metastatic disease are usually related to pulmonary and liver metastases. Bone and brain metastases are rare. Local extensions into the heart along the renal vein and the inferior vena cava may cause cardiac symptoms without the usual abdominal symptoms. (Slovis T.L. et al).

Finally symptoms and signs due to associated abnormalities include aniridia, hemihypertrophy, ambiguous genitalia, mental retardation, congenital cataracts, cardiac abnormalities, neurofibromatosis, foetal gigantism and macroglosia.

The symptomatology and clinical signs of Wilm's tumour in this study correlates well with the usual picture. (See Tables 4, 5 and 6). However, patients came at fairly advanced stage of the disease. 58.34% of the cases had tumours at stage III or more, 25% had signs of metastatic disease at presentation and 8.33% had ascites.
A good number of cases are first seen in a health centre. The chain of referrals in Kenya Health Services structure is through a district hospital and a provincial hospital to Kenyatta National Hospital. Casual observations shows that this chain of referrals may take as long as two months. There may be loss of time before the condition is recognized at health centre level where the work load may rob from the Clinical Officer, the patience to do a thorough clinical examination. While these two reasons cannot explain all the delay, there is a need to emphasize the need to handle suspected cases of Wilm's tumour with some urgency. This should be done in the peripheral service centres.

LABORATORY AND RADIOLOGICAL INVESTIGATIONS:

The aims in the work up of a patient suspected to have Wilm's tumour are:-

1) to confirm the clinical diagnosis
2) to assess the extent of the disease pre-operatively
3) to assess the general condition of the patient with regards to his fitness to stand the various treatment procedures, e.g. surgery
4) to obtain a baseline data which will be used later to monitor the progress of the disease.
In most cases, the clinical diagnosis is easily confirmed by urine microscopy, IVP, plain abdominal radiograph and urinary VMA. The VMA helps to rule out the other two most important tumours - the neuroblastoma and pheochromocytoma. (De Lamerens). Doubtful cases may require renal arteriogram and ultrasound studies. Some centres perform routine inferior vena cavograms.

Routine pre-operative assessment of disease extent is usually done by clinical evaluation, chest radiograph, electrocardiogram and in some centres inferior vena cavogram. (Kelalis). The other investigations which can be used to assess the extent of disease when indicated by the clinical evaluation are chest tomograms, bone marrow examination and scans of the liver, bone and the brain. Echocardiograms can also be used when indicated by any heart symptoms and signs.

Assessment of the general condition and fitness of the patient is normally done by clinical evaluation, radiological, biochemical and haematological tests. Clinical evidence of renal, liver and pulmonary compromise, haemopoietic insufficiency (anaemia) and malnutrition should be sought for. The same organs should be evaluated by biochemical tests, haematological tests and radiological tests. Precisely these tests include: renal function tests (blood urea, electrolytes, serum creatinine, and
clearance tests); liver function tests (serum bilirubin, alkaline phosphatase, prothrombin time and serum proteins), haematological tests (haemoglobin, white blood cells count, red blood cells count and platelet counts); and radiological tests of function such as the IVP.

Baseline data to monitor the treatment and disease progress must include quantitatively measurable indices. The usual monitoring data consists of: any clinical landmarks e.g. palpable tumours; any radiological landmarks e.g. demonstrable deposits and the size of the kidney in the nephrogram of IVP; all the haematological indices such as haemoglobin levels and cell counts; and functional biochemical indices such as renal function tests and liver function tests. Any identifiable tumour marker is maximally exploited. Only rennin has been used to monitor treatment but renning producing tumours are very few and its routine use is not established anyway.

A good tumour marker should be reliable, specific, reproducible, sensitive and easily measured quantitatively. Such a tumour marker would be the ideal index for monitoring treatment. A classical example is the HCG (Human Chorionic Gonadotrophin) of trophoblastic tumours. No such a good tumour marker has been discovered for Wilm's
tumour. A number of substances produced by Wilm's tumour have been investigated in hope of finding a good tumour marker. These include rennin (Sheth K.J. et al, Mast G.J. et al), erythropoietin (Slee P.H. et al), onco-neural proteins (Zeltzer P.M. and Seeger R.C.), alpha-foetal proteins (Brown N.J. and Goldie D.J.), thymidine phosphorylase (Pauly J.L. et al), tumour associated antigen (Burtin), glycosaminoglycan (Hopwood J.J. and Dorfurann A), carcino-embryonic antigen and alpha-2H-isoferritin (Buffe D. et al). Many of these are positive in Wilm's tumour but they lack specificity and sensitivity. Onco-neural antigens occur in neuroblastomas, thymidine phosphorylase occurs in lymphomas and leukaemias, alpha-foetal proteins occur in many gastro-intestinal, urogenital disorders and in normal babies. Carcino-embryonic and alpha-2H-isoferritin have similar distributions. An ideal tumour marker for Wilm's tumour awaits to be discovered.

Specific cytostatic agents with specific properties and specific complications should be monitored using these properties. Toxicity due to Adriamycin is best monitored by frequent electrocardiograms because of its cardiotoxic effects.
TREATMENT:

Today it is universally accepted that Wilm's tumour is a curable cancer. Successful treatment is a major challenge to the physicians. In all cases except those who come too late, the doctor's aim should be to cure. With proper modern methods of treatment, a long term survival is the usual expectation (80%). Even cases with advanced disease should enjoy a reasonable survival period with a carefully planned palliative treatment schedule. The recent long term survival in Wilm's tumour is founded from a multi-modality treatment approach with surgery, radiotherapy and chemotherapy. (Bolkenus M. et al, Jenkin). To effect these, maximum co-operation between surgeons, radiotherapists, pathologists, paediatricians and oncological physicians is essential. Successful treatment of Wilm's tumour is a big test of interdisciplinary consultations and co-operation. (Kasili E.G.).

The recent reduction in mortality due to malignant diseases among children is for the most part due to the advances made in the treatment of Wilm's tumour and childhood leukaemias. (Ericsson et al).

A complete treatment schedule for Wilm's tumour entails an exceptionally prolonged period of treatment (approximately 20 months) (Kasili E.G.). Realization of this fact and a full commitment by all the members of the "treatment teams" (surgeons,
Radiotherapists, pathologists, paediatricians and oncological physicians) is the key to a successful outcome. While each of the treatment team is responsible for carrying out its part of treatment, every member must genuinely bear the burden of looking after these patients during the whole period of treatment.

The treatment schedule should start with a careful assessment of each patient. (Kasili E.G.).

Assessment of Patients for Treatment:

The aim of assessment of a patient with Wilm's tumour is two-fold - to assess the general condition of the patient, and to assess the exact extent of the disease (stage). The exact therapeutic procedures will depend on this assessment. The initial assessment should be based on clinical examination, haematological, radiological and biochemical tests.

Inevitably, a final assessment of the exact extent of the disease is impossible until after surgery and a variable period of follow-up. The universal T.N.M. clinical staging of tumours has a lot of limitations when applied to Wilm's tumour because of the deep anatomical situation of the kidneys. With such a deeply situated tumour, the T.N.M. clinical staging cannot express the true extent of the disease with any accuracy. The more practical method of staging of Wilm's tumour is the one adopted by the National Wilm's Tumour Study (NWTS) group of the
United States of America. It is based on both the pre-operative assessment and the findings at laparotomy. (Jenkin).

**Stage I:** The tumour is limited to the kidney. The capsule is intact without any tumour infiltration. The tumour is completely resectable.

**Stage II:** The tumour is limited to the kidney. The capsule is infiltrated with tumour. Renal vessels and inferior vena cava may be involved. Tumour is completely resectable.

**Stage III:** Tumour beyond the kidney but within abdomen with exception of the liver involvement. Any intra-operative rupture of tumour. Tumour is not completely resectable.

**Stage IV:** Tumour with a haematogenous metastases including all cases of liver involvement. The tumour is not completely resectable.

**Stage V:** Bilateral renal involvement.

This clinical pathological assessment of the extent of the disease is essential in order to plan the exact therapeutic measures for each case. Treatment should include all the modalities in most of the early cases (stages I, II and III). A combined
modality approach is certainly superior to any one modality used alone. (Green D.M. and Jaffe N., Kasili E.G., Bollenius M. et al).

In stage IV cases, surgery and radiotherapy should be applied in limited amounts depending on each case. However, chemotherapy should be given aggressively. Non-curative tumour reducing operative are advocated whenever the tumour is resectable. (Kunze & Kaufmann). Cytostatic agents are more effective in small tumours than in large ones. For this reason every resectable tumour tissue should be removed prior to cytostatic treatment.

Treatment of stage V disease (bilateral tumour) should be individualised. Many therapeutic measures can be applied to each one of the involved kidneys. A common practice is to apply all the three modality approach to the more affected side and to avoid surgery on the better side. Very often surgery can be left out altogether. Whatever computations of the surgical procedures are used, bilateral total nephrectomy should be avoided until the last resort.

SURGICAL TREATMENT OF WILM'S TUMOUR:

No patient has survived without surgery which probably forms the cornerstone of the treatment of Wilm's tumour. Before the adoption of radiotherapy and chemotherapy the five year survival rate for surgically treated cases was 21%. Introduction of
Radiotherapy improved the five year survival to 50% and the recent advances in chemotherapy has raised the five year survival rate to 80%.

The aim of surgery is to remove as much resectable tumour tissue as possible. In localised disease (NWTS groups I, II and III) it takes the form of radical nephrectomy together with the removal of all the affected adjacent organs preferably en bloc. In stage IV disease, all resectable tumour tissue should be removed but radical operations are not recommended. In these cases the aim of surgery is to reduce the tumour size as much as possible in order to facilitate the action of the cytostatic agents on the remaining tumour tissue. (Kunze & Kaufamann). In stage V disease, the role of surgery ranges from no operation at all to bilateral total nephrectomy with renal transplantation. The precise surgical procedure done in each kidney with bilateral tumours is individualised.

Surgical resection is normally the first line of treatment. This enables an early laparotomy diagnosis, and prevents any chance of wrong diagnosis. It also establishes the final staging early and it is associated with very good end results. The place of pre-operative cytostatic treatment (radiotherapy and chemotherapy) is limited to a very small minority (less than 5%) with very large tumours and a poor general condition, usually
resulting from pulmonary metastases. (Harrison M.R., Jenkin R.D.T., Grosfield et al). Pre-operative treatment has increased operability rate for such large tumours. (Guilio J., Harrison M.R.). The disadvantage of pre-operative cytostatic treatment is wrong diagnosis which occurs in 2-10% of cases. (Guilio J, Jenkins R.D.T.).

Surgical treatment should be instituted as soon as a firm clinical diagnosis has been confirmed by other diagnostic methods. Further undue palpation should be avoided although no one has shown a difference in prognosis resulting from such palpation. Although an emergency laparatomy is not advisable most surgeons will treat a presumptive case of Wilm's tumour with considerable urgency. This urgency should however, allow all the confirmatory investigations to be done. Corrective measures to improve the general state of the patient should also be done before surgery. This may include blood transfusion.

A transperitoneal approach is advised in all cases of renal malignancy. It allows the surgeon to inspect the whole abdomen and therefore perform a visual staging of the tumour. A lumbar approach cannot achieve these important aspects of surgery of Wilm's tumour. Either a trans-abdominal incision or a thoraco-abdominal incision can be used depending on size and location of the tumour. In the trans-abdominal approach both transverse and para-median
incisions can be used. Once the abdomen is opened, a general laparatomy is carried out. Particular attention is paid to the renal vein and the inferior vena cava, the other kidney, the liver and the para-aortic nodes. The surgeon then makes a mental picture of the whole tumour mass which may include adjacent viscera. He then designs to remove the whole tumour mass en bloc. This design may involve pancreatic resections, gut resections and splenectomy. The surgical set up should therefore be ready for such procedures. If possible, resection should start with ligation of the renal vein beyond the limits of the visible tumour. Tumours involving the vena cava may pose problems and caval deposits may have to be left unresected particularly if the extent of involvement reaches the hepatic portions. Early ligation of the renal vein prevents tumour embolization theoretically. No such advantages have been proved though. (Lucian L. et al). In curative operations the tumour mass includes every involved tissue en bloc. If involved, it should include the kidney, the ureter, the peri-renal tissues, the tail of pancreas, the spleen, the colon, the psoas muscle and fascia, part of diaphragm and the adrenal gland. At the end of the resection, the surgeon maps the margins of the tumour bed with radio-dense silver clips. (Jenkin R.D.)

Block dissection of para-aortic nodes is unnecessary. It does not add to survival rate. In
fact, it is often associated with chyloous ascites due to damage caused to the major lymphatic chains. (Hertz J. et al). However, excision biopsy of separate involved nodes should be done. (Jenkins R.D.T.)

The surgeon's main contribution to the total management of Wilm's tumour is his accurate explicit description of the extent of tumour at laparotomy and how efficiently he removes all the resectable tumour tissue. It is on these factors that the subsequent treatment and its outcome will depend. Explicitly stated descriptions of the extent of the tumour enables the other members of the treatment team who are not in the surgical group to have a clear picture of the disease extent. (Lucian L. et al). Apart from observations on the extent of the disease, the tumour size is probably important. Very large tumours (bigger than 375 gm) have a poorer prognosis. On the other hand the consistency of the tumour, the polarity and the multicentricity have no bearing on the prognosis. Pre-operative rupture and vascular invasion have no effect on survival either. However, intra-operative rupture increases the rate of local recurrence and reduces the relapse free survival period. Early ligation of the renal vein and meticulous extirpation of disseminated abdominal tumour deposits did not alter the outcome either. The benefits of clearing the tumour from involved renal vein has not been established. (Lucian L. et al).
Inoperable Wilm's Tumour:

Most tumours are operable at the time of diagnosis. In one series 2/95 cases were not operable. (Jenkin R.D.T.). Pre-operative cytostatic treatment with radiotherapy and chemotherapy can turn out more operable cases. (Guilio J.). A biopsy is taken in all inoperable tumours in order to have histological diagnosis. Such tumours are usually so advanced that taking a biopsy from them does not amount to an intra-operative spillage of tumour as it would be the case with a stage I tumour. Thereafter the patient is likely to receive some cytostatic treatment. A "second look" operation after such a course has yielded an increased operability rate. (Crosfield et al). A pre-operative angiographic embolization of renal artery in large haemorrhagic tumours may reduce primary haemorrhage and increase operability rate. The other methods of controlling haemorrhage are by the control of thoracic aorta and pre-operative cytostatic therapy. (Harrison M.R.). In this series only two (approximately 4% of the cases were inoperable).

Surgery in bilateral Wilm's Tumour:

Bilateral Wilm's tumours (NWTS Stage V) pose special surgical problems. In a considerable number of cases one cannot resect as much tumour tissues as possible because this may amount to total bilateral nephrectomy. A renal transplant
would then have to be done. This kind of treatment should be left as a last resort only. (Ehrich and Godwin). In bilateral disease surgery is certainly not the cornerstone of treatment. Most cases are often managed without surgery. When surgery is done many computations of surgical procedures in both kidneys are possible. One kidney can be removed and the other left undisturbed, surgically. Partial bilateral nephrectomy is another possibility. Partial nephrectomy can be done in one kidney without any surgery on the other. Bilateral total nephrectomy should be avoided in the initial plan. (Ehlich and Godwin, Garrett R.A.). When total nephrectomy is done, renal transplant can be done either immediately (during the same operation) or at a later stage. In the latter case the patient is maintained on dialysis. In this series there were 3 cases (6.25%) of bilateral tumours. Two cases presented synchronously. They did not have any nephrectomy (had biopsy). The third case presented asynchronously. Nephrectomy had been done before the second tumour presented. The second tumour was treated by radiotherapy and chemotherapy only. (See page 18).

Surgery in Metastatic Wilm's Tumour:

Most metastases occur in the lungs and occasionally in the liver. Bone and brain metastases are rare.
A few tumours extend into the vena cava and the heart. (Abdelsayed M.A. et al). Pulmonary metastases which are limited are better treated by resection. Multiple metastases should be irradiated. Tomograms are necessary to establish the degree of pulmonary metastases. About 10 - 15% of all pulmonary metastases are limited enough for resection. Post irradiation pneumonitis is a grave complication of radiotherapy of lung deposits. Therefore all resectable lung deposits should be subjected to surgery. Once discovered these metastases should be resected without any pre-operative radiotherapy because apart from risking pneumonitis unnecessarily, such pre-operative treatment may reduce the tumour size and make it too small for easy recognition at surgery. However, very large tumours which cause a poor general state due to pressure symptoms may be irradiated to improve the general condition of the patient. Such tumours are likely to be so large that the fear of reducing them with radiotherapy to unrecognisable sizes at surgery does not apply. (Van Dongem J.A., Van Slooten E.A.). In all cases of pulmonary metastases chemotherapy is given in full doses. This takes care of the micro-metastases which might not be demonstrable radiologically.

Liver metastases are best treated by radiotherapy. Those deposits which are isolated and are resistant to radiotherapy and chemotherapy
can be resected. Liver resections have to be viewed within the general context of the patient. Probably only those cases which do not show evidence of disease elsewhere warrant liver resections. When any liver resection is done radiotherapy should not be given because it can induce a very intense toxic hepatitis in the regenerating liver. Any cytostatic agents should be withheld until the liver has healed completely. (Jenkin R.D.T.). Patients with liver metastases have disseminated disease by definition. They therefore need cytostatic treatment which is the backbone of treating disseminated disease. Any liver resection will deprive the patient of this other treatment of the disseminated micro-metastases. This is the rationale of not resecting the liver metastases during the initial laparatomy.

There is hardly any place for surgery in bone and brain metastases. Here radiotherapy is probably the treatment of choice. Very occasionally pathological fractures may call for surgical attention. These should be handled and treated as any other pathological fracture without any specific consideration to Wilm's tumour treatment.

Tumours involving the inferior vena cava may call for very delicate resections. Very high ones may require profound hypothermia and a cardio-pulmonary bypass. (Theman T. et al).
The adoption of routine radiotherapy in the treatment of Wilm's tumour raised the five year survival rate from 21% to 50%. (Jenkin R.D.T.). According to NWTS recommendation all cases except children below two years of age with stage I disease should get irradiation therapy. Children below two years of age with stage I disease have the same survival rate whether their treatment includes radiotherapy or not. (D'Angio G.J. et al). In one study conducted by NWTS, all cases of stage I disease had the same survival with or without radiotherapy regardless of their ages. (Jenkins R.D.T.). Disseminated disease is not a contra-indication to radiotherapy. Radiotherapy has a significant role in controlling the disease locally. (D'Angio G.J.). It increases the relapse free survival period and so it may prevent recurrence at the local tumour bed. However, radical radiotherapy should be avoided in palliated cases. (Cassady J.R. & Belli J.A.). Radiotherapy is probably the cornerstone in treatment of stage V (bilateral) tumours.

Deep x-ray therapy is the form of radiation therapy used. Either a high voltage source or a cobalt (Co$^{60}$) unit can be used. We use a cobalt unit in our hospital (K.N.H.). The routine procedure is post-operative radiotherapy. Only rarely is pre-operative radiotherapy done.
Pre-operative Radiotherapy:

Pre-operative radiotherapy should not be adopted for routine use. The society of International Paediatric Oncology (SIOP) contends that it has no added benefit on survival rate. (Lemerle M.D.).

However, in very large tumours many authors have claimed that pre-operative radiotherapy can make surgery easier and increase operability rate. (Harrison M.R.; Guilio J.). Cases treated by cytostatic agents (including radiotherapy) after having been passed as inoperable have turned operable during a "second look" laparatomy. (Crosfield et al). Despite its credit in making surgery easier, pre-operative radiotherapy does not add to the survival rate of these cases. Tumours whose resectability is improved by radiotherapy are anyway too large and too advanced for a long term survival. In many European centres, pre-operative irradiation is very frequently used. In 1971 and 1974, the SIOP group compared the advantages of pre-operative radiotherapy and post-operative radiotherapy. They found a reduced incidence of intra-operative rupture of tumour and also a reduction in relapse rate at the end of one year among the pre-operatively treated cases. However, there was no difference in survival. (Lemerle M.D.). The major disadvantage of pre-operative...
radiotherapy is wrong diagnosis which occurs in 2 - 10% of cases. (Jenkin R.D.T.). This disadvantage is certainly very real in early disease but it is exaggerated in very advanced disease. In early disease the tumours are anyway small and easily resectable without the need to resort to any pre-operative radiotherapy. In such tumours which are not very advanced pre-operative radiotherapy does not add any benefits to resectability. There is therefore no justification to risk wrong diagnosis in cases with early disease. On the other hand, in very advanced cases which require palliation rather than cure this disadvantage of wrong diagnosis is certainly exaggerated. In such cases, a pre-operative diagnosis of an intra-abdominal malignancy can be made by the clinician with an almost absolute confidence. Pre-operative radiotherapy cannot possibly add any harm to these cases and may well make a difference in resectability. As a matter of fact, it is in these very advanced tumours that pre-operative radiotherapy adds to the operability rate. Removal of tumour bulk improves palliation markedly. (Kunze and Kauffmann). It seems that the role of pre-operative radiotherapy should be limited to those cases which are deemed to require palliative treatment only. In such cases the major disadvantage due to wrong diagnosis is probably over emphasised at the expense
of possible palliative benefits of improving resectability.

Post-operative Radiotherapy:

Post-operative radiotherapy is the standard procedure in most centres. There is no doubt that post-operative radiotherapy is necessary. Treatment can start on the first post-operative day. This does not affect wound healing significantly. However, a delay of ten days does not affect the results of treatment either. (D'Angio G.J. et al). Surgery is a major trauma in these very sick children. A delay of ten days is probably good. It makes post-operative care easier and more successful. It also gives this very sick operated patients some greater comfort for at least ten days. Radiotherapy is also a fairly major trauma. A delay of ten days helps to space these two major traumatic methods of treatment. Since it does not affect the outcome of the treatment, there seems to be a good reason to delay the radiotherapy until the tenth day.

Slight variations in dosage and regimes occur from centre to centre. Usually the total dose is given in twenty fractionated doses over a period of about four weeks. A workable schedule is normally made in consultation with treatment schedules of the other modalities. A typical radiotherapy schedule is everyday from Monday to Friday with a weekend break. Toxic effects may warrant
modifications of dosage as well as schedule. Sometimes, very toxic cases may be put on off therapy schedules. The NWTS recommended the following dosage based on age:–

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 18 months</td>
<td>1800 - 3000 rads</td>
</tr>
<tr>
<td>19 months - 30 months</td>
<td>2400 - 3000 rads</td>
</tr>
<tr>
<td>31 months - 40 months</td>
<td>3000 - 3500 rads</td>
</tr>
<tr>
<td>Over 40 months</td>
<td>3500 - 4000 rads</td>
</tr>
</tbody>
</table>

Very young children (under two years of age) with stage I disease do not require radiotherapy. In the older children with stage I disease and all cases with stage II disease, only the tumour bed is irradiated. In stage III cases the whole peritoneal cavity from the domes of the diaphragm to the bottom of obturator foramina is irradiated ("abdominal bath"). In stage IV disease, the whole abdomen and the metastases are irradiated. Isolated lung metastases are best reserved for resection at a later date, but if they are multiple, the lungs should be included in the radiation therapy. Scattered metastases e.g., bone are irradiated locally. The necessity of mapping the tumour bed with silver clips at surgery is of paramount importance to the radiotherapists. Certain abdominal organs require deliberate protection during deep x-ray therapy in stages III, IV and V cases. Any remaining kidney tissue should be handled very delicately. It should not receive more than 1500 rads.
The gonads are very sensitive to irradiation. The contra-lateral ovary and both testis should be protected. The femoral heads can easily collapse with radiotherapy. They should not receive more than 2400 rads. The liver which is not the seat of a metastatic disease should be protected to receive not more 2400 rads too. These protective measures go a long way in prevention of post-irradiation nephritis, hypogonadism and liver damage. An operated liver must not receive any post-operative radiotherapy until it has fully regenerated because of the risk of toxic hepatitis in the regenerating liver. Surgical resection is therefore not advisable during the routine nephrectomy because post-operative radiotherapy is nearly always indicated. During surgery the liver metastases are only noted and the liver is included in the "abdominal bath" irradiation beam post-operatively. The whole width of the spine should be included into the field. This ensures that all the para-aortic nodes are covered and it also prevents post irradiation spinal deformities such as scoliosis, kyphosis, and vertebral body abnormalities. (Oliver J.H. et al).

Radiotherapy in Bilateral Wilm's Tumours:

Radiotherapy is probably the mainstay of treatment in stage V disease (bilateral tumours). The precise doses given to each kidney and the precise fraction of each kidney that require to be irradiated are highly individualised. They depend on the degree
of involvement in each kidney and also on the precise surgical procedure done if any. Some writers recommend a combined modality (surgery, radiotherapy and chemotherapy) on the more affected side and radical radiotherapy on the affected portion of the better side. (Marcia J.S. et al). Any residual renal tissue should not receive more than 1500 - 1800 rads.

Radiotherapy Treatment of Metastases:

Most metastases occur in the lungs. A multi-modality approach to pulmonary metastases can be used in their treatment. The main place for radiotherapy is in the treatment of multiple pulmonary metastases. Limited pulmonary deposits are better treated by resection. In very large pulmonary deposits causing pressure symptoms and a poor general condition there may be a place for pre-operative radiotherapy. Otherwise, pre-operative radiotherapy is unnecessary when surgery is contemplated. It is necessary to do tomograms to be certain that any pulmonary deposits are actually limited enough for surgery. According to NWTS, the dosage for pulmonary deposits is 1400 rads. After irradiation, it is necessary to follow these cases up with serial chest radiographs.
in order to detect recurrent tumours. The main complication of irradiation of the lungs is post irradiation pneumonitis which is responsible for considerable proportion of deaths. (Jenkin R.D.T.).

Liver metastases should be specifically looked for at the initial laparotomy. Radiotherapy is the treatment of choice. The liver should be included in the "abdominal bath" of the initial irradiation beam. The dosage for liver metastases is about 3000 rads. Thereafter, liver metastases should be followed up with palpation and liver scans. Resistant liver deposits which are isolated well enough call for surgical resection. Care should be taken not to combine surgery and radiotherapy synchronously to avoid toxic hepatitis in the regenerating liver. If surgery is done, irradiation should be deferred until the liver has regenerated fully. However, it is unlikely that radiotherapy will be indicated after surgical resection of liver metastases. Chemotherapy is given in full doses.

Bone and brain metastases are solely treated by radiotherapy and chemotherapy. The dosage for bone metastases is 3000 rads. Bone and brain metastases are very rare in Wilm's tumour. Pathological fractures are treated on their own right.
Complications of Radiotherapy in Wilms' Tumour:

Disturbances of haemopoiesis can occur during the course of the treatment due to bone marrow suppression. Gastro-intestinal upsets do occur during treatment too. The main post-irradiation syndromes commonly met with are: pneumonitis, nephritis, hepatitis and hypogonadism. Late effects are skeletal deformities such as vertebral body asymmetry, scoliosis, kyphosis and ilium hypoplasia (causes pelvic obliquity). Patients treated with radiotherapy show a 10% reduction in the length of vertebral column. (Kelalis). Other late effects of radiotherapy are flank atrophy, reduced compensatory renal growth, hypogonadism and chromosomal aberrations. (Miller R.C. et al; Cassady et al; Gudjar P. et al; Oliver J.H. et al).

Hypogonadism is certain to follow irradiation treatment of Wilms' tumour unless the ovaries are protected in female children. (Rezek A.A. et al). If the whole abdomen is to receive radiotherapy treatment, the contra-lateral ovary should be protected to prevent development of amenorrhoea. Testicular function is also affected but frank hypogonadism does not occur in males. In one study, testicular function of ten men and eight pre-pubertal boys who had been treated for Wilms' tumour with radiotherapy and chemotherapy was conducted. (Small doses of scattered irradiation
reach the testis during routine treatment of Wilm's tumours). The men showed an increased frequency of azospermia, oligospermia and elevated levels of follicle stimulating hormone. One man had a Leydig cell disfunctioning. Potency and libido were unimpaired. There were no demonstrable effects in pre-pubertal boys. Therefore, one of the late effects of radiotherapy in Wilm's tumour on the testis is disturbed spermatogenesis during adulthood caused by hormonal disfunction.

Musculo-skeletal deformities are the commonest and may cause enough morbidity to require an orthopaedic surgeon. Worse still these are permanent. (Oliver J.H. et al). Cases treated with more than 2000 rads show a 10% reduction in the length of the vertebral column. (Kelalis P.P.).

Normal compensatory renal growth is reduced in cases treated with radiotherapy. (Cassady J.R. et al). There is, however no significant reduction in routine renal function after five years when compared with normal controls with both kidneys. Clearance tests were reduced (85% of normal) but this does not produce any functional symptoms. (Gudjahr et al).

Chromosomal abnormalities are reported with a frequency which exceeds the normal. (Miller R.C. et al). Both stable and unstable aberrations have been claimed. The significance of these abnormalities
are not fully established. May be more abnormalities occur at the gene level. Oncogenic potentialities of such genetic disorders cannot be excluded. Reimer reported a case of carcinoma of breast in a 24 year old girl who had been treated for pulmonary metastases 15 years earlier. (Reimer R.R. et al).

Teft observed that 5% of cases treated with more than 1000 rads developed a tumour after two years. (Teft). Braun reported five cases of leukaemia in cured children who had been treated with deep x-ray therapy and Vincristine for Wilm's tumour. (Braun).

Patients who have been treated with cytostatic agents may have psychological problems peculiar to them. These are mainly related to fears of the cancer they had. Careful counselling can alleviate some of these psychological problems. (Kelalis; De Lamerens).

Paradoxically, it has been suggested that Actinomycin D reduces the risks of developing post-irradiation malignancy. (Jenkin R.D.T.; Kelalis P.P.).

**CHEMOTHERAPY IN WILMS' TUMOUR**

The recent advances in treatment of Wilm's tumour and indeed in general oncology are due to the development of cytostatic chemotherapy. Since it was adopted in the standard management of Wilm's
tumour the five year survival rate increased from 50% to 80%. (Jenkin R.D.T.).

In principle, chemotherapy treats the micro-metastases which are not emenable to either surgical resection or irradiation therapy. All cases with Wilm's tumour should receive some form of cytostatic chemotherapy. Although some observers have doubted its benefit in children with stage I disease, especially those below two years of age, there is as yet no adequate data to justify exclusion of chemotherapy from any patient with Wilm's tumour. (Green D.M., Jaffe N. and Rezek A.A.). Both pre-operative and post-operative chemotherapy can be given. Most centres adopt post-operative chemotherapy as the routine procedure.

Pre-operative Chemotherapy:

Pre-operative chemotherapy is not advised for routine treatment. However, some have argued that it has benefits of making surgery easier and it may convert inoperable tumours to operable ones. (Guilio J.; Harrison M.R.). Nevertheless, there are no conclusive reports to show that such an increase in operability rate has any effect on the long term survival. Certainly removal of tumour bulk in surgery improves palliation. In this sense a pre-operative chemotherapy which makes an unresectable tumour to be resectable has a role in
palliative treatment but it does not add to the survival rate. Like in pre-operative radiotherapy, the main disadvantage is wrong diagnosis which occurs in 2 - 10%. (Guilio J.; Jenkin R.D.T.). This possibility of wrong diagnosis is probably high enough to dissuade one from pre-operative treatment in cases with early tumours whose resectability is usually possible anyway. But in advanced tumours the risk of wrong diagnosis may not matter. In this very advanced tumours a pre-operative diagnosis of an intra-abdominal malignancy can be made by the clinician fairly certainly. These are the same cases whose tumours are difficult to resect and whose resectability may be increased by pre-operative chemotherapy. In such very advanced tumours the dangers of misdiagnosis are exaggerated. The differential diagnosis is almost certainly another very advanced intra-abdominal malignancy anyway. Pre-operative chemotherapy cannot possibly add any harm to such cases. On the contrary, it may contribute significantly to operability and by so doing contribute to better palliation. It is suggested here that the role of pre-operative chemotherapy is basically palliation mainly by improving the operability rate.

Post-operative Chemotherapy:

This is the standard procedure in most centres. It is advised whether a pre-operative
chemotherapy was given or not. The main cytotoxic drugs used for the treatment of Wilm's tumour are Actinomycin D (Dactinomycin), Vincristine, Cyclophosphamide and Adriamycin. Aclacinomycin A which is less cardiotoxic than the other anthracyclines (adriamycin and daunomycin) showed no tumour response. (Sakano T. et al). Other drugs which have also been used are the epipodophylotoxins VP 16 - 213 and VP 26. (Bleyer W.A. et al).

Methotrexate, Vindestine and 5-Fluorouracil have also been tested in experimental animal models of Wilm's tumour. (Santos E.S. et al). Similarly high carbon dioxide concentration has effected some reduction of metastatic rate in experimental tumours. (West C.R. et al).

A multiple drug combination treatment is much superior than any single drug treatment regimes. (Ericsson et al; Rezek A.A. et al; D'Angio J.G.; Kasili E. Santos E.S. et al). While there is ample evidence to prove the superiority of multiple drug chemotherapy over single drug chemotherapy, it is difficult to show for certain which combinations of the standard drugs is the best. Good results of up to a five year survival of 80% have been achieved by many different combinations. The more commonly used combinations are:

Actinomycin D + Vincristine + Cyclophosphamide + Adriamycin
Actinomycin D + Vincristine + Cyclophosphamide

Actinomycin D + Vincristine

Cyclophosphamide + Adriamycin (Kleinfeld H.)

Good results too used to be achieved with single drug treatment with Actinomycin D or Vincristine but certainly not as good as the modern results of multiple drug chemotherapy.

The chemotherapy schedule normally consists of an initial induction course followed by a prolonged maintenance course. (Kasili E.G.) The precise chemotherapy combination and schedule varies from centre to centre. In our hospital (K.N.H.) all the four main drugs are combined in the schedule (Actinomycin D + Vincristine + Cyclophosphamide and Adriamycin). This schedule was fully adopted in the latter half of the study period. The induction course takes six weeks and the maintenance course takes 1½ years. The drug dosages are shown on page 24.

Induction Course:

All the drugs are given together, through an intravenous route once a week for six weeks. If need be the induction course can be extended from six weeks to eight weeks. Induction course is completed in the wards.
Maintenance Course:

Maintenance course is given in two phases - a monthly maintenance phase and a three-monthly maintenance phase. The monthly maintenance phase takes the first six months after induction course. The three-monthly maintenance phase takes the whole of the year following the monthly maintenance phase. All the four drugs are used in each phase. In the monthly maintenance phase, all the drugs are given together by intravenous route once every month for four months. Adriamycin and Actinomycin D are given in alternate months. In the three-monthly maintenance phase, all the drugs are given together by an intravenous route once every three months for one year. Again adriamycin and Actinomycin D are alternated every three months. Patients are normally discharged from the wards at the induction course. They are reviewed in a follow-up clinic for maintenance. If need be they may be admitted for one day for administration of maintenance doses.

The whole treatment course takes 20 months. If recurrences occur they are treated by a fresh induction and follow-up. Appropriate measures to handle recurrences by the other modalities are also taken accordingly.
Almost any of these drug combinations have been used with good results. In one study, a combination of Cychophosphamide and Adriamycin achieved a remission rate of 83%. Adriamycin was given in one dose of $40 \text{mg/m}^2$ on Day 1 intravenously and Cychophosphamide was given in doses $200 \text{mg/m}^2$ orally on Day 3 and Day 6. The course was repeated after three weeks. (Kleinfelder H.).

The ideal length of time over which maintenance chemotherapy should be given is not established yet. This is unfortunate because cytotoxic drugs should not be given unnecessarily. They are expensive and dangerous and therefore they should be given for as short a time as it is necessary. The schedules used today are almost emphilical as far as the maintenance period is concerned. Their adoption is based on good end results and the past experiences. Other parameters to go by are the rapidity of response to treatment and behaviour of any tumour marker which may be present. (Cerny V.). Some observers suggest that equally good results can be achieved by shorter maintenance courses. (Jenkin R.D.T.).

Even though the ideal length of time for maintenance therapy is not established, haphazard administration of cytotoxic drugs without a disciplined schedule should be condemned. Each centre should adopt one drug administration
schedule incorporated in a carefully planned protocol of management. It should be the duty of every member of the "treatment teams" (surgeons, radiotherapists, paediatricians and oncological physicians) to ensure that he is fully familiar with the drug schedule which is adopted by his centre.

In this study, the multiple drug chemotherapy was not adopted in a standardised form until the latter part of the study period.

Complications of Chemotherapy in Wilm's Tumour:

Minor disturbance of bone marrow suppression is bound to occur with cytotoxic chemotherapy. Severe haemopoietic suppression that causes symptoms of anaemia, agranulocytosis and thrombocytopenia should call for revision of dosage or drug schedule. This may amount to withholding chemotherapy temporarily. The white blood cell count should not be kept below 2000 cells/cc. Similarly varying degrees of gastroenteritis and disturbances of other epithelial linings are expected. Again severe symptoms may call for revision of dosage and the schedule.

It is difficult to distinguish late complications of chemotherapy from those of radiotherapy in Wilm's tumour. Patients treated for Wilm's tumour with all the three modalities
(surgery, radiotherapy and chemotherapy) have a reduced compensatory renal growth of the remaining kidney. (Moskowitz P.S. and Donaldson S.S.). Most of the main drugs used in the treatment of Wilm's tumour have been shown to reduce this compensatory renal growth experimentally. Actinomycin D and Vincristine inhibit early compensatory renal growth and recovery occurs. Adriamycin inhibits this growth late and is prolonged. Actinomycin D inhibits the total body growth much more than that of the kidney. Vincristine does not inhibit the total body growth. Adriamycin inhibits both the total body growth and the renal growth equally. (Moskowitz P.S. and Donaldson S.S.). This reduction in compensatory renal growth does not affect the overall renal function tests. No abnormal findings were seen in such patients on blood urea, electrolytes, creatinine, proteins, and alkaline phosphatase after five years. However, clearance tests ranged from 75% - 85% of normal children with two kidneys. There were no clinical problems referable to this reduced clearance. Probably, these children differ functionally from normal children only in the amount of renal reserve. (Gudjahr et al).

Gonadal function is probably not affected by chemotherapy. The usual hypogonadism seen in
cases treated for Wilm's tumour is probably due to radiotherapy rather than chemotherapy. However, the contribution of chemotherapy to gonadal function cannot be excluded. (Shalel S.M. et al).

Chemotherapy causes chromosomal aberrations. (Miller R.C. et al). Cases treated with chemotherapy have an increased frequency of chromosomal aberrations. The significance of this is not fully established. Their potentiality for causation of other malignant diseases cannot be excluded. There was an increased frequency of leukaemia among cases treated with deep x-ray therapy and Vincristine. (Braun). Patients treated with cytostatic drugs suffer from psychological problems associated with fears of cancer and this may haunt them for a fairly long period after cure. Counselling should be part of treatment. (De Lamerens, Kelalis P.P.).

Paradoxically, it has been suggested that Actinomycin D reduces the risks of developing post irradiation malignancy. (Jenkin R.D.T.; Kelalis P.P.).

The Cytostatic Treatment of Wilm's Tumour and Cell proliferation Kinetics:

Wilm's tumour is a very fast growing tumour. On the average, the tumour doubling time is about
one week. For this reason most surgeons will treat a suspected case of Wilm's tumour with considerable urgency. (Jenkin R.D.T.). Willinow studied the cell proliferation Kinetics in a model tumour. (Willinow U.). His observations corresponded very well with the known clinical data. He used Wilm's tumour cells labelled with H\(^3\) and C\(^{14}\) which were incorporated in the thymidine base of the DNA. He achieved a cell labelling rate of 22.4\% - 46.3\%. The following were some of his observations:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cell cycle Time (Tc)</td>
<td>11.2 - 22.2 hours</td>
</tr>
<tr>
<td>D.N.A. Synthesis Time (Ts)</td>
<td>8.5 - 13.8 hours</td>
</tr>
<tr>
<td>Mitosis Time (Tw)</td>
<td>0.3 - 1.5 hours</td>
</tr>
<tr>
<td>Growth Time (Post-mitotic growth phase time (G_1)) + pre-mitotic growth phase time (G_2))</td>
<td>1.3 - 10.3 hours</td>
</tr>
<tr>
<td>Potential Tumour doubling Time (Td)</td>
<td>15.1 - 34.5 hours</td>
</tr>
<tr>
<td>Cytokinetic Therapy index</td>
<td>0.6 - 1</td>
</tr>
</tbody>
</table>

The sensitivity of a living cell to cytostatic agents (radiotherapy and chemotherapy) is different during each phase of the growth cycle. The most sensitive phases are the DNA synthesis phase, the pre-mitotic growth phase \(G_2\) and the mitosis phase. It follows that tumours with relatively long sensitive phases are likely to be more sensitive to cytostatic treatment. The fraction of the total cell cycle time (Tc) which is occupied by these sensitive
phases of the cell cycle (DNA Synthesis time (Ts) pre-mitotic growth phase time (G₂) and mitosis time (Tm)) is therefore a measure of sensitivity of a tumour to cytostatic agents. This fraction is the "Cytokinetic Therapy Index" (CTI).

\[
CTI = \frac{Ts + G_2 + Tm}{Tc}
\]

The nearer the CTI approximates 1, the more sensitive the tumour is to cytostatic agents such as radiotherapy and cytotoxic drugs. For Wilm's tumour it was 0.6 - 1. This is an extremely high sensitivity index and clinical evidence supports this. Studies of tumour proliferation kinetics can predict with reasonable accuracy which tumours will respond to cytostatic agents. Probably this could have a bearing on the planning of the treatment. May be patients with very low CTI do not benefit at all from cytostatic treatment since their tumours are not likely to respond to radiotherapy and chemotherapy. The unnecessary trauma caused by these cytostatic agents in these cases can probably be avoided by measurement of CTI. It is also probable that patients with a very high CTI receive superfluous cytostatic doses in these cases. These proposals by the author requires an overhaul on the treatment policy. It
is necessary to establish a scale in which the doses of cytostatic agents (radiotherapy and cytotoxic drugs) are calibrated against CTI. Such calibration involves a lot of emphilical research which has not yet been done. The ethical ground of withholding an established treatment with demonstrably good results on the bases of a theoretical superfluity based on CTI can pose acceptability problems. Technicalities of the measurements of CTI could also present difficulties in routine use. However, it seems emphilical to suggest that if some tumours are more sensitive than others, they should require less cytostatic doses of the same agents to effect cure. The CTI is probably the most sensitive index of predicting the sensitivity of a tumour to cytostatic agents. It appears that the only hope of attempting to establish the exact doses required to effect cure with minimum risks of either under treating or over treating each case lies in the further exploitation of CTI.

PROGNOSIS:

The time when a person can be regarded as cured from a malignant disease is difficult to define. In Wilm's tumour, a patient is considered
cured if there is no evidence of disease after a period of time equal to the arithmetic sum of the age of the patient at the onset of the disease added to nine months. This is just a working definition and it is in no way absolute. However, patients with a disease free survival of two years are often considered "cured".

Follow-up studies have shown that the two year survival rate is the same as the five year and the nine year survival rates. (Guilio J; Jenkin R.D.T., De Lamerens). Therefore, very few cases die after a disease free survival of two years. A disease free survival of two years is therefore the most appropriate "definition" of cure in Wilm's tumour.

The most important factor in the prognosis of Wilm's tumour is the method of treatment and the efficiency at which it is carried out. (Breslow N.E. et al). The other major prognostic indices are the histological grading of the tumour, the stage of the disease at diagnosis and the age of the patient at the onset of the disease.

A combined modality treatment with surgery, radiotherapy and chemotherapy is associated with the longest survival and the highest cure rates. Multiple drug chemotherapy, give longer survival rates than single drug chemotherapy regimes.
Maintained treatment with chemotherapy too appears to be superior to short courses, particularly in controlling recurrences. (Burgett and Gridwel). These facts were evident in this study. (See Table 13, page 28).

All the cases with two years survival or longer were treated with a multi-modality combination. They all completed their treatment too. Table 13 page 28.

The more anaplastic the tumour is, the poorer is the prognosis. (Beckwith J.P. and Palmer N.F.; Breslow N.E. et al; Kheir S. et al). Sarcomatous tumours have an equally poor prognosis. These tumours have a very high rate of metastases especially to bones. (Beckwith J.B. and Palmer N.F.). They also have a very high recurrence rate.

On the other hand, the well differentiated nephroblastomas and the "epithelial nephroblastomas" have the best prognosis. Some of these could probably be cured by surgery alone. (Vijay V. et al).

The younger children (below two years of age) have a better prognosis than older children. This point was confirmed in this series. (See Table 14, page 29). No case which presented after 4 years of age survived two years. Children under two years of age
of age had the best survival.

Long term survival is markedly influenced by the extent of the disease at diagnosis. The highest cure rates and the highest long term survival rates are found in cases with stage I disease. In one study, the nine year survival rates of the various stages were: 100% for stage I, 73% for stages II and III and 66% for stage IV. (De Lamerens). The usual two year survival rates are 90% for stage I, 80% for stage II, 60% for stage II and below 40% for stage IV. (Rezek A.A. et al). The long term survival rate for stage V tumours is variable but it does not exceed 50%. (Jenkin R.D.T.). In this series no correlation was shown between the stage of tumour and survival. Indeed, the sole four year survivor and two of the only three year survivors had a stage III tumour.

Other minor determinants of the length and quality of survival are intra-operative rupture, undue spillage of the tumour, and the gross size of the tumour. Tumours larger than 375 gm had a poorer prognosis than small ones. (Leap L. et al). Probably the tumour size is related to disease extent anyway and may be the tumour size per se is not the determinant parameter in survival. Liver involvement
carries a poor prognosis.

Pre-operative spontaneous rupture of the tumour, vascular invasion, lymphnode dissection, and early ligation of renal vein did not make a difference in the long term survival. Meticulous extirpation of tumour tissue in the abdomen and the renal vessels did not improve survival among the advanced cases either. (Leap, Lucian L. et al).

On the whole, the average two year survival rate for all cases is 80%. (Guilio J.). This is the same as the five year survival rate (Jenkin R.D.T.) and almost the same as the nine year survival rate (77%). (De Lamerens). It seems that very few patients die after a disease free survival of two years. This emphilical observation is probably a justification to consider all patients with a disease free survival of two years as "cured".

The favourable factors in Wilm's tumour are therefore efficient treatment, histologically well differentiated appearance, young age at onset of the disease (under two years) and early disease at diagnosis (Stage I, II and III). On the other hand, bad prognosis is related to inefficient undisciplined treatment, anaplasia, sarcomatous
predilection, advanced disease at diagnosis (stage IV) and late onset of the disease (above two years of age).

The main causes of morbidity and mortality are: advanced disease (usually in recurrent form), concurrent infections and direct or indirect complications of treatment (surgery, radiotherapy and chemotherapy). Advanced disease (stages IV and V) is associated with high morbidity due to inadequate remission and recurrences. In fact death may ensue before a remission but usually it is the recurrent disease that kills. The median survival is about 1½ to 2 years among cases with advanced tumours. (Kaschula R.O.; Mauric & Griffel).

The main infections that contribute most to morbidity and mortality are respiratory tract infections and gastro-enteritis of ineffective origin. Often patients succumb to a severe attack of bronchopneumonia. (Kaschula R.O.). Finally, the treatment procedures can cause considerable morbidity and mortality either directly or indirectly. The usual operative mortality rate is probably about 4%. This is due to inadequate pre-operative preparation or sheer surgical trauma in very unfit patients. The main direct complication of radiotherapy that may cause
severe morbidity and considerable mortality is post-irradiation pneumonitis. This may account for as many deaths as those due to advanced disease itself. (Jenkin R.D.T.). Chemotherapy causes morbidity mainly by its toxic effect on the haemopoietic system. All the treatment modalities can potentially result in renal compromise either by resecting too much renal tissue, undue aggressive irradiation of the residual renal tissue or by toxic effects of chemotherapy.

In our series it is probably too early to evaluate the outcome because standardized multiple drug chemotherapy which contributes much to survival rates was not fully adopted until the latter part of the study. It is certain, however, that the overall performance for the ten years of the study is far from satisfactory. Defaulting from the clinic was too much. 52.08% of the cases had disappeared without a trace by the end of the study period. (see Table 11). It is true that a few of these may have been attending clinics in the provincial hospitals but all the same, knowledge on their state of health was not available to the follow-up clinic of Kenyatta National Hospital. This makes the evaluation of treatment very unreliable. Of the remaining
49.92% whose follow-up was known 25.00% were alive and 22.91% had died. Among the living ones 10.42% were cured. (See Table 11, page 25). The overall two year survival rate was 10.42% and there was no five year survivor. The longest lone survivor had lived for almost 4½ years and was among those who were cured. These preliminary results do not evaluate the present protocol of management of Wilms' tumour in K.N.H. which was fully adopted in the latter part of the study only. A preliminary evaluation specific for the present protocol is needed before any conclusions on the results of the treatment can be drawn.
CONCLUSIONS
CONCLUSIONS

1) It was estimated that Kenyatta National Hospital (K.N.H.) receives only about 1/6 of the total number of the expected cases of Wilm's tumour in Kenya. The recurrence in K.N.H. cannot therefore be taken to represent the national incidence. The true national incidence can only be established by studies at both the district and provincial levels.

2) The peak incidence in Kenyatta National Hospital occurs two years earlier than expected. (1 - 2 years cf 3 - 4 years). No explanation to this was offered.

3) There was an unusually high male affection by the Wilm's tumour in this study. The male:female ratio was approximately 3:2. Normally sex distribution is uniform.

4) The seemingly increased occurrence of Wilm's tumour around Nairobi City and the Central Province of Kenya is false. It is a reflection of ease of accessability to Kenyatta National Hospital.
5) The apparent increased occurrence of Wilms' tumour among the major tribes is a reflection of the size of the tribe and not a true increased incidence. The geographical factor (nearness to Kenyatta National Hospital) compounds this apparent increase among the Kikuyu tribe. However, the occurrence among the Luhyas appears too low for the size of the tribe.

6) The bone metastases rate was higher than usual for Wilms' tumour in this study. It was 6.25% (cf 3.7%).

7) The true incidence of hypertension in Wilms' tumour is difficult to establish in infants without resorting to arterial cannula techniques.

8) No case of extra-renal Wilms' tumour has been described in K.N.H. so far. A search for extra-renal Wilms' tumour entails a high suspicion in teratomas and all bizarre groin tumours in children.

9) The cases in this series were on the average very advanced. Probably they
presented late. However some delays are also related to lack of recognition during the first visit of a child (inadequate physical examination) and also the referral to Kenyatta National Hospital may take too long. Peripheral health service centre staff should be made aware of the need to recognise the disease quickly and the need for urgent treatment.

10) A multi-modal treatment has the best results. Multiple drugs should be used too.

11) Probably all cases of Wilm's tumour with stage I disease including those above 2 years of age do not require radiotherapy. It does not seem to increase survival.

12) Radiotherapy should be delayed to the tenth day after surgery. This does not make a difference to the survival rate and it gives the patient more comfort during the early post-operative period.

13) Cases with a disease free survival of two years are probably cured. Thereafter,
deaths due to Wilm's tumour probably do not occur. The two year survival rate, the five year survival rate and the nine year survival rate are almost the same.

14) No correlation was established between the stage of tumour at diagnosis and survival, up to three years. Usually the cases with less advanced tumours have a higher long term survival rate.

15) Generally the results of treatment at Kenyatta National Hospital for the years 1970 - 1979 were far from satisfactory. During the initial period of the study period, treatment was not fully standardised especially the chemotherapy. The triple chemotherapy schedule was adopted for routine standard use during the latter part of the study period. The two year survival rate was 10.42% (cf 80%) and there was no five year survivor (cf 80%). The mortality rate in the first two years was unacceptably high. This implies that initial remission rate was very
poor. Recurrence rate was as expected (33.33% cf 14 - 50%). The results shown by this study are therefore not to be taken as the evaluation of the present protocol of management in Kenyatta National Hospital. However, with such a poor result background, there is an urgent need for a study for specific evaluation of our present protocol of management of Wilm's tumour.
BIBLIOGRAPHY
Abdelsayed, M. et al
Journ. of Urol. 120(2):153-158. 1978

Akhtar M. et al
Cancer 40(6): 3089-91. 1978

Allan R.G.

Allen A.C.
The Kidney

Askin F.B. et al
Lab. Invest. 38(3):381-82. 1978

Aubert J. et al
Eur. Urol. 4(4) 306-08. 1978

Awori N.E. et al

Bailey and Love
A short Practice of Surgery

Ballantine T.V. et al

Ballantine T.V. et al

Ballesta et al

Bard R.H.
Jour. of Urol. 121(5) 679-80. 1979

Braun
See Kelalis P.P.

Beckwith J.B. et al

Benz G. et al
Paed. Radiol. 6(4):233-4. 1978

Bleyer W.A.

See Kelalis P.P.

Bolande

Bolkenius M. et al
Abs. Z. Kinderchir. 24(4): 322-331. 1978

Bove K.E. et al

Bove K.E. et al

Brenner & Rector
The Kidney

Breslow N.E. et al
Cancer. 44(4): 1577-89. 1978

Brinton
See Allen A.C.

Brown et al
Arch. Dis. of Chil. 53(5):435. 1973

Bryant J. et al
Buffe D. et al
Burgett & Gridwel
Burtin
Cassady J.R. et al
Cassady J.R. et al
Cerny V.
Cooke
Cotlier E. et al
D'Angio G.J. et al
D'Angio G.J. et al
Danguar et al
Danguar et al
de Chadarevian et al
De Lamerens S.A.
Ehrich & Godwin
Ericsson J.L. et al
Fu et al.
Futtrell J.W. et al
Gallo J.E.
Garrett R.A. et al
Gordon
Green D.M. et al
Griffcl et al
Grosfield et al
Gudjar P. et al
Guilio J.D. et al
Guillermo E. et al

See Kelalis P.P.
See Kelalis P.P.
See Allen et al
Cancer. 38(2). 1977
Cancer. 39(3). 1978
Cancer. 39(5): 2294-305. 1977
See Kelalis
See Kelalis P.P.
Cancer. 41(4):1565-70. 1978
Jour. of Urol. 120(5):586-88. 1978
See Allen A.C.
Cancer. 44(1): 52-57. 1979
40(6): 3140-5. 1977
J. of Paed. Surg. 13(3)
Abs. Therapiewoche. 28(21): 243-50. 1978
Cancer. e9(3). 1977
Harrison J.H. Diseases of the Kidney
Hollman See Kelalis P.P.
Hou See Kelalis P.P.
Kasili E.G. Unpublished. Protocol of Chemotherapy of solid tumours in Kenyatta National Hospital (Revised, 1979)
Kelalis P.P. Clinical Paediatric Urology
Kleinfelder H. Abs. Therapiewoche. 28(48): 9248
Kumar et al Jour. Paed. Surg. 13(3)
Loeffler Personal communication during tuitorial
Looney W.B. et al Cancer. 43(4)
Marsden H.B. Cancer. 42(4)
Maurer H.S. et al 43(1): 205-208. 1979
Miller & Frauma See Kelalis P.P.
Murphy & Mostofi See Brenner & Rector
Priestley See Allen A.C.
Redman J.F. et al Jour. of Urol. 120(3): 356-57. 1978
Robinson K.M. Jour. of Anat. 126(3): 672-673. 1978
Santos E.S. et al

Shalel S.M. et al

Shah K. et al
Jour. of Urol. 121(3):365-366. 1978

Shende A. et al

Sheth K.J. et al
Jour. of Paed. 92(6): 921-924. 1978

Shils M.E. et al

Slee P.H. et al

Slovis T.L. et al
Am. J. of Roentol. 131(2): 263-266. 1978

Stambolis C. et al.

Tebbi K. et al

Teft
See Kelalis P.P.

Telander R.L. et al

Theman T. et al

Thomasson et al
See Allen A.C.

Van Dongen et al

Vaughan E.D. et al
Jour. of Urol. 117(4): 530-33. 1978

Vaughan E.D. et al
Jour. of Urol. 118(6)

Vijay V. et al
Cancer. 40(2): 789-802. 1977

West. C.R. et al

Wold W.D. et al

Wolff O.H. et al
Wood et al
Willinow U.
Zeltier P.M. et al

See Allen A.C.