Papers and Originals

Natural History and Treatment of Wilms's Tumour : An Analysis of 335 Cases Occurring in England and Wales 1962-6

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British Medical Journal, 1970, 4, 195-200

Summary: Hospital records and other data relating to Wilms's tumour were analysed to elucidate both the natural history of the disease and the effects of treatment, with special reference to actinomycin D. The age of maximum incidence was about 18 months; left-sided tumours were significantly more common than right-sided ones.

Prognosis was related to stage of the disease at the initial operation and to the occurrence of metastasis. The three-year survival rate for cases having a nephrectomy was 35%; no child who did not have a nephrectomy survived.

Recurrence of the tumour was observed in two-thirds of the cases, almost always within two years of the initial treatment, irrespective of the child's age. The three-year survival rate for this group was 11%.

The effects of radiotherapy and chemotherapy are considered in detail. Very little improvement in survival rate could be ascribed to actinomycin D. The reasons for this and for the variations found in earlier reports on selected cases are possibly the addition of other components of treatment and differences in drug regimens. The findings suggest the need for controlled clinical trials.

Introduction

For some years the Oxford Survey of Childhood Cancers has been collecting data on all cases of children certified as dying from cancer and also cases notified to registries in England and Wales who have survived. These data have made it possible to study individual diseases, first from the point of view of their natural history, and, secondly, in order to assess the effectiveness of different treatments. The present study, which is probably unique in that every case, including untreated and coroners' cases, is included, is based on 335 cases of Wilms's tumour, and is thought to comprise all the children in England and Wales under the age of 10 years who were diagnosed during the five-year period 1962-6. No case without histological confirmation has been included. The information required for the dead children was obtained from the hospital notes, while for most of the surviving children the general practitioners interviewed the mothers and loaned to us the relevant hospital letters. Consultants were asked to supply the necessary details for the remainder. On checking the records against the death certificates the inaccuracy of the latter was found to be about 8%. Nineteen cases certified as Wilms's tumour had to be discarded—two-thirds because the necropsy findings did not confirm the death certificate diagnosis, and one-third on account of copying errors owing to the similarity of the words "neuroblastoma" and "nephroblastoma."

Natural History

The incidence of nephroblastoma was about 13% of all children under 15 years suffering from cancers other than

leukaemia during this period, a figure which is similar to those published from Great Ormond Street (Riches, 1964), Manchester (Pearson and Steward, 1969), and the California Tumour Registry (Platt and Linden, 1964).

There were more boys than girls (184 boys, 151 girls; ratio 1.2:1) (Fig. 1) and more left-sided than right-sided tumours (185 left, 139 right; ratio 1.3:1; also nine bilateral cases). A significant excess of left-sided tumours was found at the 2% level and was confined to cases without extrarenal spread. Half of the tumours presented before the age of 3 years, the peak incidence being at 18 months. The total sample could be divided into three almost equal age groups, 119 under 2 years at diagnosis, 115 aged 2 or 3, and 100 over 4 years (no record of one). These figures are similar to those in other published series (Collins, 1955; Young and Williams, 1969). The Registrar General's figures for deaths from Wilms's tumour in children under 10 for the period 1940-68 showed only a slight preponderance of boys, 876 male deaths as compared with 850 female deaths. This is a lower sex ratio than that found in our series; the period covered by the present study is atypical in this respect.

The modal age of cases arising spontaneously is consistent with Stewart and Kneale's (1970) finding that for tumours which were probably caused by obstetric radiography, and therefore initiated during the third trimester (radiogenic cases), the commonest latent period or interval from initiation to the onset of symptoms was 12 to 36 months.

Congenital tumours occurred in 10 children, six of whom have survived for three years or more without developing signs of further disease. All 10 underwent nephrectomy, and the four deaths occurred within the first month with no evidence of spread beyond the primary site. The absence of metastases in any of this group, together with the unusually high survival rate, raises the possibility that the tumours were fetal mesenchymal hamartomas (Wigger, 1969).

The nine bilateral cases have been classified in a way modified from that suggested by Scott (1955): found

FIG. 1.—Wilms's tumour in England and Wales 1962-6: sex related to age at diagnosis.

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primarily at necropsy, 2 cases; found at first operation, 5 cases (one of these has survived over four years without recurrence, the other four have died); and unilateral at first operation with second tumour found later, 2 cases.

The 241 cases for which the sibship was known included nine boy twins and two girl twins. There was one pair of identical male twins, of whom one died and the other has survived without recurrence for at least four years after his treatment at the age of 1 year.

The incidence of congenital defects was similar to that already described by Barber and Spiers (1964). The defects found in the present series are summarized in Table I.

TABLE I.—*Congenital Defects Associated with Wilms's Tumour*

	Male	Female	Total
Genitourinary—hypospadias, duplex kidney, and polycystic disease	4	3	7
Hemihypertrophy	2	3	5
Aniridia	—	1	1
Other	4	3	7
Total	10	10	20

Aniridia occurred in one child only (cf. an incidence of 1:73 reported by Miller (1968) for children with Wilms's tumours). She was a mentally retarded child with bilateral aniridia and lens opacities. The nephroblastoma, diagnosed at the age of 10 months, was treated by nephrectomy, but the patient died four months later.

History and Presenting Symptoms

The duration of symptoms was known in 207 of the fatal cases and in 83 of the survivors. One-third of the whole series were admitted within a week and two-thirds within a month. No correlation between the length of history and the extent of the disease was found.

Among the 98 cases (one-third of the whole) with symptoms lasting a month or more before treatment was instituted a delay of up to four weeks occurred in 18 cases after a doctor had been consulted before laparotomy was done. Eleven of these presented with haematuria and were kept under observation as probably having acute nephritis; one was found to have a duplex kidney and not investigated further; and the other six were given provisional diagnoses of "enlarged spleen" (three cases), convulsions, obscure abdominal pain, and umbilical hernia. The remaining 80

FIG. 2.—Recurrence in Wilms's tumour. For the explanation of "periods of risk" see text.

cases with a long history had increasing abdominal distension, pain, malaise, or vomiting, and the history often ended with a sudden crisis of pain, distension, or haematuria which brought them quickly to hospital. There seems therefore little reason to suppose that more could be done to hasten the admission to hospital of children with nephroblastomas.

In most cases an abdominal mass was palpable on admission and treatment was promptly instituted. Abdominal pain was present in one-third of the cases. Haematuria and general symptoms (pyrexia, lassitude, anorexia) each occurred in about one-quarter of the cases. Eighteen children gave a history of abdominal symptoms following an injury, eight were admitted as acute abdominal emergencies, and five had no symptoms at all, the tumour being discovered by the doctor examining the child for an unconnected symptom.

Recurrence of Tumour

The term "recurrence" will be taken to mean a re-appearance of neoplastic tissue either locally or outside the abdomen after removal of the primary tumour. Two hundred and thirty-two children thought to be tumour-free after nephrectomy have been followed up until death or for a survival period usually exceeding three years. The interval to recurrence or last follow-up is plotted against age at diagnosis for these children (Fig 2). A recurrence was observed in 156 cases (67%), of whom 141 have died (three of them after surviving three years). The three-year survival rate for these cases was 12%. No recurrence has been observed in 76 cases, all of whom have survived.

The length of the so-called "period of risk"—that is, the period beyond which recurrence of the disease is unlikely—has been discussed by many authors, including Collins *et al.* (1956) and Platt and Linden (1964). Collins suggested that the period of risk was the age of the child plus nine months, on the grounds that the original tumour probably started close to the time of conception and any recurrence might be expected to have the same growth rate. In Fig. 2 the period of risk postulated by this rule is marked off by the diagonal line. If, however, it is postulated that the period of risk is usually two years, irrespective of the age of the child, the period is delimited by the horizontal line. In four cases the interval to recurrence exceeded the period given by the latter rule; of these, three occurred within 28 months of diagnosis. Two of the four also exceeded the period given by Collins, but since both had bilateral tumours it is probable that these "recurrences" were in fact new tumours. One child, after a nephrec-

FIG. 3.—Survival after recurrence in Wilms's tumour. The vertical lines show the length of time between the occurrence of metastases, indicated by ●, and the time of latest follow-up at which the child was alive, indicated by ○.

TABLE II.—*Wilms's Tumour—Metastases in Survivors*

	Treatment	*Stage	Age at Diagnosis (Months)	Age at Recurrence (Months)	Follow-up After Recurrence (Months)
<i>Metastases Appearing after First Treatment</i>					
<i>Lungs:</i>					
Bilateral and multiple	Actinomycin	A	23	33	34
Left midzone. Solitary	Vincristine. XRT	A	25	32	30
Bilateral. 2 Deposits	2 Lobectomies. Actinomycin	A	42	46	35
? Site. Solitary	Lobectomy. Cyclophosphamide	A	48	57	43
Right side. 3 deposits	Excision. Vincristine. Actinomycin	A	61	68	26
Bilateral and multiple	XRT only	A	62	68	76
R.U.L. Solitary	XRT only	A	69	79	43
Right side. Multiple	Excision. XRT. Actinomycin	A	70	76	37
Right apex. Solitary	Lobectomy. Actinomycin	B	42	61	73
R.L.L. Solitary	Wedge resection. Actinomycin	B	55	59	37
L.U.L. Ant. mediastinum	XRT. Actinomycin	B	88	106	25
L.L.L. Solitary	Lobectomy	C	26	36	38
<i>Abdomen:</i>					
Opposite kidney	Excision. Actinomycin	A	13	38	24
Opposite kidney	XRT. Actinomycin	A	41	56	49
Liver	L. hepatic lobectomy	B	28	48	28
<i>Metastases Present at First Treatment</i>					
<i>Lungs:</i>					
R.U.L. Solitary	Excision. XRT	A	61	61	51
Bilateral and multiple	XRT. Actinomycin. Cyclophosphamide	C	91	91	41
Bilateral and multiple	XRT. Actinomycin	—	72	72	36

R.U.L. = Right upper lobe. L.L.L. = Left lower lobe, etc. XRT = Radiotherapy. *See "Prognostic Factors" for definition.

tomy at 13 months, was found to have a tumour in her remaining kidney 25 months subsequently. The second child had a right nephrectomy and left heminephrectomy for bilateral tumours when 23 months old. A tumour developed 53 months later in the remaining kidney tissue.

The pattern of recurrence times strongly suggests that beyond two years the chance of recurrence is very small, and that the two-year rule is more useful from a practical point of view than that suggested by Collins. One may in fact question the application of Collins's rule to a tumour where the recurrence takes the form of a metastasis, since the assumptions of similar growth rates and known time of initiation do not apply to this situation.

Only 2 of the 141 fatal cases lived more than two years from the time of recurrence. This suggests that the 15 who have survived longer than this have been successfully treated for their recurrences and are cured.

Details of these 15 and also of three surviving children who presented with metastases are given in Table II. The interval to recurrence and length of subsequent follow-up are shown in Fig. 3.

Sites of Metastases

Analysis of the site of metastasis diagnosed before death or found at necropsy has been attempted, but is only approximate, for in some children neither the sites nor their full extent were known.

(a) *Pulmonary Metastases.*—In a total of 105 children lung deposits only were detected. A further 30 cases in which the intrathoracic metastases were part of widespread disease are considered under (c). The most striking feature of the lung

FIG. 4.—Frequency of metastases in Wilms's tumour related to age at diagnosis.

metastases was the rise in incidence and proportionate survival with increasing age of the children. The relative incidence and three-year survival of children with metastases in the lung and elsewhere is shown in Fig. 4.

(b) *Abdominal recurrence* (as distinct from extracapsular spread of the tumour) occurred in 53 cases and was characterized by being found almost equally in all age groups and carrying a mortality of 90% at all ages.

(c) *Metastases in multiple sites* were found in 46 cases, all of which were fatal.

Varying and unpredictable combinations of sites occurred, though in more than half the cases the sites involved were lungs and intra-abdominal structures, including the liver. In two cases a bone metastasis (skull and zygoma) was the first sign of reappearance of active disease, but in these and in all other cases with bony deposits other organs were subsequently affected. Bones involved were ribs, pelvis, spine, skull, and zygoma. Two children born with hydrocephalus died within the first year and were found to have Wilms's tumours with intracranial deposits.

Prognostic Factors

Of the total of 335 cases, 107 (32%) were alive three years after diagnosis. (The four surviving cases with periods of follow-up between 30 and 35 months have been counted as three-year survivors.) The survival curve for intervals up to three years—that is, the proportion of cases still alive at each time—is shown in Fig. 5. Most of the deaths occurred within two years of diagnosis. There is no difference between the sexes as regards survival.

The extent of abdominal spread was classified according to

FIG. 5.—Survival curve for 335 cases of Wilms's tumour diagnosed in England and Wales 1962-6.

the following scheme: stage A, tumour encapsulated with no extension of the tumour outside the capsule, though the renal parenchyma may be involved; stage B, adherence to surrounding structures, but no invasion; and stage C, intra-abdominal spread outside the kidney, or rupture of tumour during removal. These three stages are modified from stages I, II, and III of Garcia *et al.* (1963), who found that they were of considerable prognostic significance.

The three-year survival rates for each stage, each age-group, and also according to the presence or absence of metastases at the time of operation and later are shown in Table III. Each of these factors is strongly related to the probability of survival. About two-thirds of stage A cases, but very few stage C cases survive; older children have a worse prognosis than younger ones; only a small proportion of cases with metastases survive, and this is true whether the metastases were discovered at the time of operation or later. These three factors, however, are closely interrelated, and a more detailed examination of the data is needed to elucidate their separate effects. The proportion of cases with metastases increases with the extent of abdominal spread (Table IV). Within the stage A group age is related to the occurrence of metastases and to survival. In this group the proportion of cases with metastases is 26% for those under 2 years, 46% for those aged 2 and 3 years, and 74% for those aged 4 years or more. The overall survival rate for these cases is 26%, whereas the rate for stage A cases without metastases is 100%. This accounts for the relationship of age to survival in this group shown in Table V, which also shows that the older children are more likely to be stage B and C and hence to have a worse prognosis.

The chance of survival therefore depends on the stage of the tumour at diagnosis, and on whether or not metastases occur. The relationship of survival to age arises from the fact that older children are more likely to have tumours at a more advanced stage and are more likely to show metastatic involvement even with localized tumours.

Initial Treatment

Among the 304 children subjected to nephrectomy (90% of the cases) the overall three-year survival rate was 35%: no patient who did not have a nephrectomy survived. Assessment of the effect of adding radiotherapy and chemotherapy to nephrectomy is difficult, since the groups of cases receiving different treatment combinations are not comparable. Furthermore, factors of known clinical significance, such as histological grade and size of tumour, which were not known,

TABLE III.—Three-year Survival Rates for Wilms's Tumour by Stage, Age at Diagnosis, and Occurrence of Metastases. Cases where the necessary data are not available are omitted from this table

	No. of Cases	No. Alive at 3 Years	3-Year Survival Rate (%)
All cases	335	107	32
Stage			
A	121	78	64
B	30	9	30
C	125	8	6
Age at diagnosis in years			
0-1	119	49	41
2-3	115	32	28
4-9	100	26	26
Metastases:			
Present at operation	35	3	9
Found later	158	18	11
All cases with metastases*	208	21	10
None found	83	76†	92†

*Includes cases where time of detection was not recorded. †The seven children without metastases who died were those who did not have a nephrectomy. If these are excluded the survival rate for cases with no metastases is 100%.

TABLE IV.—Frequency of Metastases in Wilms's Tumour Detected at Operation or Later, Related to Stage

	Stage A		Stage B		Stage C	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
Distant metastases present:						
At operation	5	4	3	10	16	13
Later	46	38	20	67	80	64
All cases with metastases*	53	44	24	80	103	82
None found	64	53	5	17	5	4
Data not available	4	3	1	3	17	14
All cases	121	100	30	100	125	100

*Includes cases where the time of detection was not recorded.

are omitted from the analysis. In the following analyses the cases have been divided into small relatively homogeneous subgroups and the treatments compared on a standardized basis, though this certainly does not overcome all the difficulties. The three-year survival rates for cases treated with and without radiotherapy are shown separately for each stage in Table VI. The striking difference in survival between cases receiving preoperative radiotherapy only and those receiving preoperative and postoperative radiotherapy is probably explained by the fact that the latter group consists largely of advanced cases in which extracapsular spread had not been eradicated by the preoperative radiotherapy. The survival rate for all cases treated by preoperative irradiation, combining the groups with and without a postoperative course, is seen to be similar to that for cases receiving only postoperative radiotherapy, and rather worse than for those receiving none. The cases receiving no radiotherapy fall into two distinct groups:

TABLE V.—Three-year Survival Rates in Wilms's Tumour Related to Stage and Age

Age at Diagnosis (years)	Stage A			Stage B			Stage C			All Cases		
	No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors	
		No.	%		No.	%		No.	%		No.	%
0-1	54	41	76	7	1	14	36	2	6	119	49	41
2-3	39	23	59	9	3	33	47	3	6	115	32	28
4-9	28	14	50	14	5	36	42	3	7	100	26	26
All ages	121	78	64	30	9	30	125	8	6	335	107	32

Cases for which the staging or age is not available are included in "All Cases."

TABLE VI.—Three-year Survival Rates in Wilms's Tumour Treated by Nephrectomy with and without Radiotherapy

Radiotherapy	Stage A			Stage B			Stage C			All Cases		
	No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors	
		No.	%		No.	%		No.	%		No.	%
None	19	15	79	5	1	20	18	2	11	43	18	42
Preoperative	18	10	56	12	3	25	7	0	0	40	13	33
With postop.	6	2	33	5	1	20	6	0	0	17	3	18
Without postop.	12	8	67	7	2	29	1	0	0	23	10	43
Postoperative*	83	52	63	13	5	38	100	6	6	214	70	33
With chemotherapy	28	20	71	7	3	43	48	5	10	86	30	35
Without chemotherapy	55	32	58	6	2	33	51	1	2	123	36	29

*Excludes cases which also had preoperative radiotherapy, and includes cases where chemotherapy data were not available. Cases for which the staging is not available are included in "All Cases."

TABLE VII.—*Three-year Survival Rates for Wilms's Tumour Treated by Nephrectomy with and without Chemotherapy*

Chemotherapy	Stage A			Stage B			Stage C			All Cases		
	No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors	
		No.	%		No.	%		No.	%		No.	%
Actinomycin	42	29	69	12	4	33	54	7	13	112	42	38
Other chemotherapy .. .	2	1	50	2	1	50	5	0	0	9	2	22
No chemotherapy .. .	76	47	62	16	4	25	65	1	2	171	53	31

Cases for which staging is not available are included in "All Cases."

TABLE VIII.—*Three-year Survival Rates in Wilms's Tumour for Cases with Recurrence*

Interval to Recurrence after Nephrectomy	Stage A			Stage B			Stage C			All Cases		
	No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors	
		No.	%		No.	%		No.	%		No.	%
1-5 months	15	1	7	9	1	11	55	0	0	83	2	2
6-30 months* .. .	31	11	35	11	3	27	25	2	8	73	16	22
All recurrences .. .	46	12	26	20	4	20	80	2	3	156	18	12

*1 recurrence at 53 months is also included.

Cases for which staging is not available are included in "All Cases."

TABLE IX.—*Three-year Survival Rates in Wilms's Tumour after Treatment to Metastases*

Metastases Treatment Includes	Lungs			Abdomen			Other & Multiple			All Sites		
	No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors		No. of Cases	3-year Survivors	
		No.	%		No.	%		No.	%		No.	%
Chemotherapy .. .	60	11	18	13	3	23	14	0	0	88	14	16
+ Surgery ± radiotherapy .. .	17	7	41	5	1	20	1	0	0	23	8	35
+ Radiotherapy .. .	29	4	14	2	2	100	4	0	0	35	6	17
Only chemotherapy .. .	14	0	0	6	0	0	9	0	0	30	0	0
No chemotherapy .. .	19	4	21	10	2	20	6	0	0	35	6	17
+ Surgery ± radiotherapy .. .	2	2	100	5	1	20	2	0	0	9	3	33
+ Radiotherapy .. .	17	2	12	5	1	20	4	0	0	26	3	12
Untreated Metastases .. .	25	0	0	30	0	0	26	0	0	83	0	0
All cases .. .	105	16	15	53	5	9	46	0	0	208	21	10

Five cases where data on treatment or site are not available are included in the totals.

19 stage A cases, considered to be of such good prognosis that irradiation was not required, had a survival rate of 80%; whereas 23 stage B and C cases, of whom 11 died post-operatively and many of the remainder were too ill for further treatment, had a survival rate of only 13%.

The right-hand column of Table VI shows the survival rates standardized for age and stage of disease. This allows comparisons between treatments to be made, taking into account the importance of these prognostic factors. From this it would appear that the results of postoperative radiotherapy are rather better than those of preoperative, and that the addition of chemotherapy improves the survival rate still further.

Among the stage B cases—that is, those with local adherence—12 out of 30 (40%) received preoperative radiotherapy compared with 15% of stage A and 6% of stage C cases. The poor prognosis for stage B cases holds both for patients who had preoperative radiotherapy, which probably caused the adherence, and for those who did not.

The three-year survival rates for patients receiving and not receiving chemotherapy as part of their initial treatment are shown in Table VII. Of the 121 cases stated to have received chemotherapy, all except nine had actinomycin. For stage A and B cases the patients treated with actinomycin did rather better than those not so treated. For stage C cases the difference is much more pronounced: 7 out of 54 cases treated by actinomycin survived to three years, but only 1 out of 65 who received no chemotherapy. For cases receiving actinomycin the survival rate was 38%, compared with 31% for those who had no initial chemotherapy. When these figures are standardized to allow for the difference in the types of case treated the figures become 40% and 29% respectively. Actinomycin appears to be particularly effective in treating the stage C cases.

Of the eight stage C cases who survived for three years or more, seven received actinomycin and five postoperative radiotherapy. At operation five of the eight were found to have tumour in the inferior vena cava or renal vein, while the

other three had infiltration of tissues around the kidney. Three of the children developed pulmonary metastases: one died more than three years later, but the other two were apparently successfully treated.

Possibly some of the successes in cases treated with actinomycin are in fact due to other aspects of the treatment they received. For example, among stage A and B cases in which a recurrence was observed 14 out of 28 (50%) had surgery for the recurrence, whereas for cases not initially given chemotherapy the corresponding figure was only 4 out of 46 (9%). On the other hand, the explanation of this difference might be that metastases occurring in actinomycin-treated cases are more amenable to surgical treatment. Again, the (standardized) survival rate for teaching and children's hospitals is considerably better than that for other hospitals for cases treated with actinomycin and rather better for cases not so treated. It may be that actinomycin was used in more effective dosages in the former.

Rates of recurrence are consistent with reports that actinomycin has an inhibiting effect on metastatic growth, but our results could easily be attributed to chance.

Treatment to Metastases

Eighteen children in whom metastases were detected after the initial treatment were still alive three years after the original diagnosis (three of these subsequently died). Three additional cases with metastases at the time of diagnosis have also survived. The results shown in Table VIII suggest that recurrences for stage A and B cases have a better prognosis than those for stage C. This table also shows that the proportion of late recurrences is smallest for stage C, larger for B, and largest for A. This implies that localized cases are likely to be at risk of recurrence for a longer period than non-localized ones. Cases with late recurrences, however, have a better prognosis than those recurring early.

The results of treatment to metastases are summarized in

Table IX; it is difficult to draw any conclusions about the effect of individual components of treatment. The most effective treatment appears to have been surgery. The additional benefits of radiotherapy and chemotherapy are hard to assess because of the small numbers of cases and possible effects of selection. Radiotherapy alone was effective, though in a smaller proportion of cases; chemotherapy alone was never successful.

Discussion

Recent papers on the treatment of Wilms's tumour have presented apparently conflicting evidence on the efficacy of actinomycin. Several papers have presented series in which the proportion of successes, usually defined as survival for two years, is greater for cases treated with actinomycin than for cases not given the drug. These rates range from 67 to 92% (Howard, 1965; Farber, 1966; Fernbach and Martyn, 1966; Burgert and Glidewell, 1967). Other authors quote rates from 29 to 63% and state that these are similar to those for their comparison series not given actinomycin (Sukarochana and Kiesewetter, 1966; Maier and Harshaw, 1967; Stone and Williams, 1969).

In the present series the overall three-year survival rate for cases treated with actinomycin was 38%. Three possible explanations for these conflicting reports should be considered: (a) differences in selection of cases, (b) the effects of other components of the treatment, and (c) differences in dose regimens.

(a) Not all assessments of actinomycin have made proper allowance for factors of known prognostic significance. We feel that the weight of evidence from the papers cited is that actinomycin does improve prognosis, but the information available in published series is usually inadequate for rigorous analyses to be made and varying degrees of case selection may have occurred.

(b) The effects of the other components of treatment are even more difficult to analyse. Most assessments of actinomycin have been made largely with cases treated in earlier years as a comparison series, where both initial treatment and treatment to metastases may have been different.

(c) Burgert and Glidewell (1967) suggested that better results are obtained if treatment with actinomycin is begun at the time of operation rather than later, but it is not clear that the groups of cases on which they base this conclusion are comparable. It has also been suggested that results are improved by giving repeated courses. The best evidence for this is provided by Wolff *et al.* (1968), who found a statistically significant reduction in metastases when comparing this type of therapy against a single course in a controlled trial.

Actinomycin did not become generally available in this country until 1965, and it may be that its value cannot be properly assessed until more evidence has been accumulated on cases in which adequate dosage regimens have been used.

The present series includes 34 children who received actinomycin as part of their initial treatment in 1966. One child received two courses and the others one course only. The injections were started before operation in nine cases, at operation in seven, and postoperatively in 15 (for three cases no records are available).

We conclude that each of the factors (a), (b), and (c) may be contributing towards the different success rates quoted for actinomycin and that, in particular, the relatively disappointing results in the present series could be due to the fact that the cases were completely unselected and possibly that optimum drug schedules were not used. It would appear that, even admitting the practical difficulties, these questions can be elucidated only by carrying out a controlled trial, in which other drugs, such as vincristine, might also be included. The evidence in favour of actinomycin is such that it seems ethically impossible to withhold it at this stage, but we suggest that further trials similar to that of Wolff *et al.* (1968) should be carried out to evaluate various different drug schedules, with a sufficiently long follow-up to ensure that recurrences are being prevented and not simply postponed.

The Oxford Survey of Childhood Cancers is supported by grants from the U.S. Public Health Service (Grant No. CA-05392), the Medical Research Council (Grant No. G.964/230/C), and the Cancer Campaign for Research. Our thanks are due to the many doctors and social workers, and in particular to the medical officers of health and public health departments and the records departments of hospitals, who have supplied us with the data. We are grateful to Mrs. J. Lay, of the Atlas Laboratory, Chilton, for assistance in programming the computer tabulations. Finally, we acknowledge our indebtedness to the Director of the Survey, Dr. A. M. Stewart, for her help in enabling us to assemble the necessary records and for her constant encouragement.

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