PAPERS AND ORIGINALS

Neuroblastoma, Its Natural History and Prognosis: A Study of 487 Cases

L. M. KINNIER WILSON, G. J. DRAPER

British Medical Journal, 1974, 3, 301-307

Summary

The natural history of neuroblastoma and factors affecting survival for this disease were studied in an unselected group of children notified to cancer registries in Britain during 1962-7. The three-year survival rate based on 487 cases was 23%; many of the cases were followed up for more than five years, and this made it possible to calculate long-term survival and recurrence rates. There were only five deaths among 110 cases followed for more than three years, 64 of the survivors having been followed for more than five years. Factors affecting the prognosis included age at diagnosis, site, histological grade at diagnosis, and the sex of the child. The interrelationship between these factors together with their effect on prognosis were analysed, and in particular we attempted to elucidate factors which might explain our observation that girls have a significantly better survival rate than boys. Direct histological evidence and also the analyses of survival and recurrence rates seem to support the suggestion that the likelihood of maturation for this tumour is greater for girls than for boys.

Introduction

The data on which this study was based were collected as part of the Oxford survey of childhood cancers, which receives notifications of cases through both cancer registrations and death certificates for children with neoplastic disease in England, Scotland, and Wales. For each child notified to the survey further information covering both clinical and epidemiological factors is collected from the parents and from hospital and general practitioner records.

We present here the results of a study of cases of neuroblastoma occurring during the years 1962-7 in children below the age of 15 at the time of diagnosis. The data presented are largely concerned with the natural history of the disease, factors of prognostic interest, survival times, and recurrence of the disease. In a subsequent paper we hope to present also some data on incidence rates and epidemiology for this tumour.

Originally 639 cases were included in this study, 539 of these having been notified to cancer registries and the remainder included only because we had received a death certificate. Histological confirmation was available for 487 of the cases notified to the cancer registries; the analysis relating to prognosis and survival was confined to these cases. In studying certain aspects of neuroblastoma, however—for example, the nature of the presenting symptoms, the delays between onset and medical examination, and delay in treatment —data on all 639 cases were used.

Natural History

AGE AND SEX

In this series 41% of the patients were below 2 years of age and 91% below 10 years (see table I). These figures are roughly comparable with those of Breslov and McCann (1971), Stella *et al.* (1970), Gross *et al.* (1959), and de Lorimier *et al.* (1969). The ratio of male to female for the cases presented here was 1·22:1. This may be compared to ratios of 1·29:1 for the cases of Stella *et al.*, and 1·26:1 for those of de Lorimier *et al.* The number of cases in each age group are given separately for the two sexes in table IV. In the present series the sex ratio was closer to unity for the children diagnosed early in life than it was for those diagnosed later.

HISTOLOGY

The histological details for this report were obtained from the pathological descriptions of biopsy and operation specimens and post-mortem material included in hospital notes. (In many

Research Department, Marie Curie Memorial Foundation
L. M. KINNIER WILSON, B.M., B.CH., Head of Epidemiology Unit

Department of Social Medicine, Oxford University, Oxford
G. J. DRAPER, M.A., Lecturer in Medical Statistics

TABLE I—*Numbers of Cases, Survivors, and Survival Rates in Various Categories*

	Cases No.	Cases % of total	Surviving to 3 years No.	Surviving to 3 years Rate %
Total	487	(100)	114	(23·4)
Site:				
Adrenals	112	23·0	12	10·7
Abdomen	155	31·8	27	17·4
Pelvis	32	6·6	12	37·5
Thorax	58	11·9	19	32·8
Thoracic ganglia	22	4·5	14	63·6
Liver	19	3·9	11	57·9
Other	89	18·3	19	21·3
Histology:				
Undifferentiated	140	28·7	15	10·7
Early differentiated	103	21·1	21	20·4
Unspecified	195	40·0	47	24·1
Ganglioneuroblastoma	36	7·4	22	61·1
Ganglioneuroma	13	2·7	9	69·2
Stage:				
I	83	17·0	49	59·0
II	47	9·7	22	46·8
III	31	6·4	6	19·4
IV	160	32·9	8	5·0
IV-S	39	8·0	19	48·7
Unknown	127	26·1	10	7·9
No. of deposits:				
1	199	40·9	83	41·7
2	134	27·5	25	18·7
⩾3	115	23·6	5	4·3
Unknown and multiple	39	(8·0	1	2·6
Age:				
0-11 months	121	24·8	59	48·8
12-23 months	79	16·2	19	24·1
2-4 years	149	30·6	15	10·1
5-9 years	92	18·9	15	16·3
10-14 years	46	(9·4	6	13·0
Sex:				
Male	268	55·0	48	17·9
Female	219	45·0	66	30·1

cases no detailed description was given, only a summary of the findings—for example, "typical of neuroblastoma." These cases were grouped together as "pathology with unspecified differentiation" and were more likely to be similar to the early differentiated group than to the completely undifferentiated group). In classifying the histological findings we followed Willis's (Willis, 1962) description, and there were five main categories: (*a*) the undifferentiated round cell malignant tumours consisting of sheets of small round cells devoid of arrangement or differentiation; (*b*) the early differentiated group showing rosette-like clusters of cells around a central area of fine fibres which are the young axons; (*c*) the unspecified group; (*d*) the ganglioneuroblastomas showing further differentiation with recognizable young nerve cells and continued outgrowths of their axons to form bunches of non-medullated fibres; and (*e*) the mature ganglioneuromas consisting entirely of mature nerve cells and fibres.

Of the total 639 cases in the series 572 had positive histological confirmation, and of the 539 notified to the national cancer registries 487 had such confirmation. The remainder were diagnosed as neuroblastoma on clinical, radiological, and chemical evidence without histology.

The analyses presented below which relate to survival are based on the 487 histologically confirmed cases, the histological category used being the earliest one which was available to us, usually that obtained at the time of first treatment. The number and percentage of cases in each histological group is given in table I.

SITES

For each case the sites at which tumour deposits were found at the time of treatment, at a later recurrence, and at the time of death were recorded. Tumour deposits found within one month of the start of treatment were recorded as having been present from the time of treatment. The "site" used in the analysis was the site at which the main tumour deposit was found; in some cases with the records available it was impossible to determine the primary site.

The distribution of these sites was as shown in table I. "Abdomen" included retroperitoneal tumours and those arising from the lumbar sympathetic chain and associated ganglia. The thoracic sites were subdivided into two groups: those tumours which were described during surgery as arising from the ganglia and were therefore presumably earlier tumours and the rest of the thoracic tumours whose origin were not so clearly definable. Cervical and intracranial tumours were included among "other" as the numbers were very small. Also included in this group were cases with multiple deposits and some for which records were incomplete. Neuroblastomas apparently arising in the liver formed an interesting group; only cases where the liver was the single presenting site at the time of diagnosis were classified under "liver." Many of these patients had exploratory laparotomies and no primary deposit was found, and in some the liver was the only site ever found though in others later and widespread disease became evident. A possible explanation of these tumours has been given by D'Angio *et al.* (1971), who suggested that they arise from abnormal distribution of neural crest cells. Alternatively the primary deposits may have been so small as to be comparable to in situ tumours (Beckwith and Perrin, 1963).

STAGE

As far as possible we used the staging method suggested by Evans *et al.* (1971). This is briefly as follows: stage I, tumour confined to the organ or structure of origin; stage II, tumour extending in continuity beyond the organ or structure of origin, but not crossing the midline, and regional lymph nodes on the homolateral side may be involved; stage III, tumour extending in continuity beyond the midline, and regional nodes may be involved bilaterally; stage IV, remote disease involving skeleton, organs, soft tissue, or distant lymph nodes; stage IV-S, cases who would be otherwise in stage I or II but who have remote disease confined only to one or more of the following sites: liver, skin, or bone marrow without bony metastases.

The numbers of cases classified as being in each of these stages are shown in table I. The cases where the only deposits found were in the liver were placed in the IV-S category, on the assumption that there was a hidden primary tumour elsewhere which had not been discovered at diagnosis.

NUMBER OF DEPOSITS

The "number of deposits," as used in the analysis below, is the number of sites initially affected and includes the primary. This provides an alternative to the staging method in describing the extent of spread of the disease and is also found to be of prognostic significance.

HISTORY

One of the characteristics of neuroblastoma is the vagueness of the symptoms, which may often lead to a delay in diagnosis. Only 7% of cases were treated within one week and only 32% within a month from the onset of the first symptom. In 35% of the cases there was a delay of between one and three months between the first symptom and the start of treatment. These figures are in marked contrast to those which were found in our report on the natural history of Wilms's tumour (Ledlie *et al.*, 1970), where one third of the whole series was admitted to hospital and received treatment within a week of the onset of the first symptom and two thirds within a month. The total length of time between the first symptom and treatment in the present series is shown in table II. Also shown is the delay between first symptom and first clinical examination and between this examination and treatment, indicating that the delay is usually in diagnosis. The longest period between onset of

symptoms and treatment was two years where the patient had a single superficial lump on the back, which when ultimately biopsied proved to be metastatic neuroblastoma, and an adrenal tumour was found.

TABLE II—*Proportions of Patients Experiencing Delays of Various Types*

Length of Delay	% of Cases with Stated Delay: between First Symptom and First Clinical Examination	between First Clinical Examination and Treatment	between First Symptom and Treatment
<1 week	31	13	7
1 week—	16	14	8
2 weeks—	12	18	17
1 month—	12	28	35
3 months—	3	12	16
6 months—	0	5	6
9 months—	0	2	3
⩾1 year	1	2	4
No record or not applicable	25	5	5

SYMPTOMS

As is to be expected in a tumour which may arise in a variety of sites there was a very wide variety of presenting symptoms. Up to three symptoms were recorded for each case. The findings, expressed as the percentage of cases reporting each symptom within each sex and each age group, are presented in table III for the original group of 639 cases.

Abdominal swelling was most commonly a symptom in the youngest age group and its frequency decreased with increasing age. The same relationship may be seen to a less extent in respiratory symptoms of breathlessness and stridor. Conversely, pain was a relatively uncommon symptom in very young children and was more often reported by older children though this was presumably partly due to the greater ease in eliciting this symptom from them. Symptoms related to nerve involvement were also more often reported for older children. There was little difference between the two sexes in the type of symptom reported. The figures reflect the frequent incidence of abdominal tumours (of the adrenal, abdominal sympathetic ganglia, and liver) and thoracic tumours in the youngest age groups, while tumours occurring in the spinal canal and in the brain were more frequent among older children.

Analysis of Survival Rates

For the 487 registered and histologically confirmed cases survival rates were calculated for each sex and age group and also for the various categories in each of the classifications described above. The effects of various combinations of factors on the survival rates were analysed, and we tried to determine the main factors influencing survival.

First, the proportions of survivors at various periods after treatment were calculated for the total 487 cases and for various subgroups. Secondly, the proportion of survivors at three years after treatment was calculated for each site, histological category, stage, number of deposits, age group and sex, and for various combinations of these factors. We tried in this way to determine factors of prognostic significance and their interrelationships.

Since the data available to us were not from controlled studies we made no attempt to analyse the effects of treatment. A wide variety of combinations of surgery, radiotherapy, and chemotherapy were used for the cases in this series. The choice would in many cases have been determined by the course of the disease and in such circumstances there is little hope of making any proper assessment of the effect of treatment on survival.

SURVIVAL CURVES

The survival curve for the complete series is shown in fig. 1. It can be seen that the survival rate three years after diagnosis was 23%. Most of the deaths had occurred within two years and well over half occurred within six months. The survival curves for the youngest and oldest age groups are given in fig. 2. There

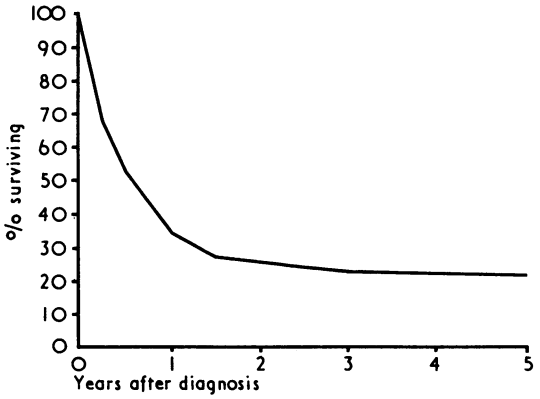

FIG. 1—Survival curve for 487 registered cases of neuroblastoma.

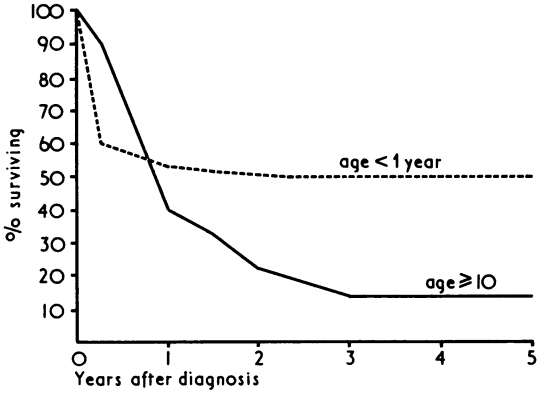

FIG. 2—Survival curves for youngest and oldest age groups of children with neuroblastoma.

TABLE III—*Percentage of Patients Reporting Various Symptoms by sex and age groups*

Age (Years)	No. of Cases	% Reporting each Symptom: Abdominal Swelling	Febrile Illness	Malaise	Pain	Genito-urinary	Respiratory	Swelling other than Abdominal	Nerve Involvement	Other
Total:	639	35	10	31	39	24	6	32	17	7
Sex Male	357	33	9	30	41	24	4	33	18	7
Sex Female	282	38	11	33	37	24	8	31	16	7
Age Group <1	152	44	9	15	7	30	11	30	8	7
Age Group 1	118	43	11	48	12	19	6	38	12	6
Age Group 2-4	201	39	8	43	52	27	3	29	20	9
Age Group 5-9	111	19	12	23	72	19	5	34	25	2
Age Group 10-14	57	14	12	18	75	21	4	37	26	11

were very large differences in the nature of the survival curves for these two age groups. The other age groups showed a pattern intermediate between that of the youngest and oldest groups: with increasing age the proportion of survivors decreased, but death took longer to occur. The youngest group, those below 1 year of age at the time of treatment, had a 49% three-year survival rate whereas for the oldest group, aged 10-14 years, the corresponding figure was only 13%. Many of the deaths in the youngest age group occurred within one month of treatment, but hardly any deaths were observed in this period for the oldest group.

FACTORS AFFECTING THE THREE-YEAR SURVIVAL RATES

A total of 110 cases were followed up and alive three years after diagnosis; a further four cases were known to be alive for at least two years and for the purpose of the following analysis it was assumed that they survived three years. This total of 114 survivors gave an overall three-year survival rate of 23·4%. Of the 110 cases known to be alive at three years, five died subsequently. A further two have disease still present and are deteriorating; two have no tumour present but have residual effects, loss of vision, and paraparesis; one has no residual tumour but developed a second neoplasm, a basal cell carcinoma. Sixty-four patients are known to have survived for more than five years after diagnosis, and no death has been observed at an interval greater than this.

The three-year survival rate was taken as a measure of outcome and related to various factors, some of which seem to bear no relation to prognosis and are not discussed here. These include the delays from first symptom to examination and from examination to treatment. The type of symptom reported also seemed to be unrelated to prognosis except that cases with "malaise" seemed to have a particularly poor prognosis. This generalized symptom might have been related to the presence of widespread disease. Increasing numbers of symptoms were associated with poorer prognosis. Moreover, though the number of symptoms was to some extent related to the number of deposits the prognosis was worse for cases with greater numbers of symptoms even when due allowance was made for differences in the number of deposits.

As in previous reports from this survey (for example, Stewart and Kneale, 1970) the data support the theory that a proportion of the cases were caused by obstetric radiography. We plan to present data relating to this aspect of the study in a subsequent paper. A preliminary analysis suggests, however, that there was no difference in prognosis for the *x*-rayed and non-*x*-rayed cases.

The results of analysing the relationship of various other individual factors to survival are shown in table I. The survival rate varied as might be expected with site, histological type, stage, and number of tumour deposits. It also varied with age at diagnosis, and there was a striking difference between the sexes. The results of this analysis for each classification may be summarized as follows:

Site.—Tumours in the thorax, particularly those of the thoracic ganglia had good prognosis. Those in the pelvis were slightly worse, and the abdominal and adrenal tumours, which were by far the most numerous, were very much worse. The liver, as already explained, was considered as a separate site, and patients with these tumours had a high survival rate.

Histology.—As already explained, the "unspecified" group was a collection of tumours which the pathologists described as typical of neuroblastoma, and they were therefore more likely to be similar to the "early differentiated" group than to the completely "undifferentiated" group. As might be expected, the primitive undifferentiated group had the worst prognosis with a survival rate of only 11%. The best prognosis was for the more differentiated tumours—the ganglioneuroblastomas (61%) and the benign ganglioneuromas (69%). The comparatively low rate for ganglioneuroma was probably due to the fact that many were massive tumours with a high operative death risk.

Stage.—The survival rates analysed according to stage followed a predictable pattern for stages I, II, III, and IV, with stage IV-S cases having a survival rate between that for stages I and II; a similar finding was reported by Breslow and McCann (1971).

Number of Deposits.—There was a decrease in survival rate with increasing number of sites affected. In particular, out of 115 children with tumour deposits in three or more sites only five survived for more than three years.

Age.—Younger children had a better prognosis than older children, a finding which has been reported in many previous papers. The figures in table I suggest that for children more than 2 years old survival did not worsen further with age; this was supported by a more detailed analysis.

Sex.—Girls had a much better survival rate (30·1%) than boys (17·9%). This difference was statistically highly significant ($\chi^2 = 9{\cdot}38$, $P < 0{\cdot}01$). This difference between the sexes seems to have been reported in only two of the earlier large series (Fortner *et al.*, 1968; Stella *et al.*, 1970), and in neither of these was the difference significant. de Lorimier *et al.* (1969) found that boys had a higher survival rate though again the difference was not statistically significant.

In studying the effect of combinations of the above factors we shall be concerned mainly with the question of whether the relationships of sex and age to prognosis were in some sense effects of sex and age per se, or whether they arose from the relationship of these factors to other factors of prognostic importance. For instance, it may be that, as in the case of Wilms's tumour, the effect of age was largely or entirely due to the fact that younger children had tumours at an earlier stage. Again it may be that the sex difference arose from an association between sex and the site at which the tumour occurred.

EFFECTS OF OTHER FACTORS ON OBSERVED SEX DIFFERENCE IN SURVIVAL RATES

The numbers and percentages of cases and the survival rates are given for the prognostic factors already listed, separately for each sex, in table IV. It is clear that the girls had a greater proportion of cases with favourable sites, stages, and histological grades and a much greater proportion of younger cases. The table shows, however, that even when comparisons are made *within* the various categories the girls still did better than the boys—for instance, in the youngest age group the survival rate for girls was 56·5% against 40·7% for boys.

If the prognosis was better for girls than for boys it is interesting to consider possible explanations for this. The data in table IV show that there was a progression in the male to female ratio from 1·46:1 for cases histologically classified as "undifferentiated" to 1:1 for the ganglioneuroblastomas, and 0·30:1 for the ganglioneuromas though this last figure was based on only three boys and 10 girls. Again, for cases in which histological classification was available on two separate occasions there were nine girls and only three boys for whom evidence was reported of tumour maturation. The probability that some neuroblastomas mature to the more highly differentiated form has been noted previously by Cushing (1927) and Fox (1959), and it seems possible that there is a greater likelihood of maturation in girls (Willis, 1962), which would help to explain their better prognosis.

EFFECTS OF OTHER FACTORS ON OBSERVED AGE DIFFERENCE IN SURVIVAL RATES

It can be seen from table V that one of the main differences between the age groups was the far greater proportion of favourably staged cases among the younger children. Taking Stages I, II, and IV-S together the proportions in the five age

TABLE IV—*Numbers of Cases and Survival Rates in Various Categories for Each Sex*

	Male			Female		
	No. of Cases	%	Survival Rate (%)	No. of Cases	%	Survival Rate (%)
Total	268	(100)	18	219	(100)	30
Site:						
Adrenals	66	24·6	12	46	21·0	9
Abdomen	92	34·3	17	63	28·8	18
Pelvis	15	5·6	27	17	7·8	47
Thorax	34	12·7	24	24	11·0	46
Thoracic ganglia	7	2·6	(71)	15	6·8	60
Liver	7	2·6	(29)	12	5·5	75
Other	47	17·5	11	42	19·2	33
Histology:						
Undifferentiated	83	31·0	8	57	26·0	14
Early differentiated	58	21·6	14	45	20·5	29
Unspecified	106	39·6	18	89	40·6	32
Ganglioneuroblatsoma	18	6·7	61	18	8·2	61
Ganglioneuroma	3	1·1	(100)	10	4·6	60
Stage:						
I	45	16·8	56	38	17·4	63
II	20	7·5	25	27	12·3	63
III	16	6·0	19	15	6·8	20
IV	97	36·2	4	63	28·8	6
IV-S	13	4·9	31	26	11·9	58
Unknown and multiple	77	28·7	9	50	22·8	6
No. of deposits:						
1	111	41·4	35	88	40·2	50
2	67	25·0	13	67	30·6	24
⩾3	66	24·6	0	49	22·4	10
Unknown	24	9·0	0	15	6·9	7
Age in years:						
<1	59	22·0	41	62	28·3	57
1	37	13·8	19	42	19·2	29
2-4	89	33·2	7	60	27·4	15
5-9	54	20·1	17	38	17·4	16
⩾10	29	10·8	7	17	7·8	24

Figures in brackets represent rates based on fewer than 10 cases

groups were respectively 57·0%, 36·8%, 18·1%, 27·2% and 41·1%. It is also apparent that even within a particular stage the younger children had a better prognosis than the older children. The slightly improved survival rate of children over 5 years above that of those between 2 and 4 years might be related to the higher incidence of more benign tumours in the older children. It is interesting that of 21 surviving children who were over the age of 5 years at the time of diagnosis 10 had tumours described as ganglioneuroblastoma or ganglioneuroma, suggesting that their better survival rate might be related to maturation of the tumour.

Tumour Recurrence

Metastases may be widespread in many different tissues and may also occur at varying intervals. For the purposes of this study a "recurrence" was defined as the appearance or reappearance of tumour tissue at either a different site or the same site more than one month after the initial treatment. Of the 378 deaths 208 occurred without any recurrence, while of the 109 survivors 92 had had no recurrence at the time of last follow up. The length of time between diagnosis and the recurrence and the period of subsequent follow up for the remaining 170 dead and 17 live patients is shown in table VI. All except one of these cases was followed for at least two further years or died during this time. Only three patients who survived more than two years after a recurrence subsequently died. It is particularly noteworthy that of the nine cases recurring more than two years after original diagnosis four have died but five survived for a further

TABLE V—*Numbers of Cases and Survival Rates in Various Categories for Each Age Group*

	Age in Years														
	<1			1			2-4			5-9			⩾10		
	Cases		Survival Rate (%)	Cases		Survival Rate (%)	Cases		Survival Rate (%)	Cases		Survival Rate (%)	Cases		Survival Rate (%)
	No.	%		No.	%		No.	%		No.	%		No	%	
Total	121	100	49	79	100	24	149	100	10	92	100	16	46	100	13
Site:															
Adrenals	30	24·8	17	31	39·2	13	27	18·1	0	18	19·6	11	6	13·0	(17)
Abdomen	28	23·1	50	23	29·1	17	69	46·3	9	27	29·3	11	8	17·4	(0)
Pelvis	9	7·4	(56)	2	2·5	(50)	12	8·1	42	6	6·5	(17)	3	6·5	(0)
Thorax	15	12·4	67	6	7·6	(83)	14	9·4	7	13	14·1	15	10	21·7	10
Thoracic ganglia	10	8·3	70	4	5·1	(50)	2	1·3	(100)	6	6·5	(50)	0	0	
Liver	15	12·4	73	0	0		2	1·3	(0)	2	2·2	(0)	0	0	
Other	14	11·6	50	13	16·5	23	23	15·4	4	20	21·7	20	19	41·3	21
Histology:															
Undifferentiated	25	20·7	24	25	31·6	8	49	32·9	2	28	30·4	18	13	28·3	8
Early differentiated	25	20·7	56	16	20·3	6	35	23·5	9	16	17·4	13	11	23·9	9
Unspecified	63	52·1	49	31	39·2	36	49	32·9	6	34	37·0	3	18	39·1	6
Ganglioneuroblastoma	8	6·6	(100)	6	7·6	(67)	13	8·7	46	7	7·6	(43)	2	4·3	(50)
Ganglioneuroma	0	0		1	1·3	(100)	3	2·0	(67)	7	7·6	(57)	2	4·3	(100)
Unknown															
Stage:															
I	22	18·2	77	21	26·6	38	13	8·7	77	18	19·6	56	9	19·6	(44)
II	19	15·7	79	7	8·9	(86)	7	4·7	(0)	5	5·4	(20)	9	19·6	(0)
III	3	2·5	(33)	6	7·6	(50)	17	11·4	6	5	5·4	(20)	0	0	
IV	21	17·4	14	30	38·0	7	58	38·9	0	34	37·0	3	17	37·0	12
IV-S	28	23·1	61	1	1·3	(0)	7	4·7	(29)	2	2·2	0	1	2·2	(0)
Unknown	29	23·1	21	14	17·7	0	47	31·5	4	28	30·4	7	10	21·7	0
No. of deposits:															
1	60	49·6	68	28	35·4	32	49	32·9	31	38	41·3	37	24	52·2	17
2	27	22·3	48	21	26·6	43	48	32·2	0	22	23·9	5	16	34·8	13
⩾3	17	14·0	24	27	34·2	4	43	28·9	0	22	23·9	0	6	13·0	(0)
Unknown and multiple	17	14·0	6	3	3·8	(0)	9	6·0	(0)	10	10·9	0	0	0	
Sex:															
Male	59	48·8	41	37	46·8	19	89	59·7	7	54	58·7	17	29	63·0	7
Female	62	51·2	57	42	53·2	29	60	40·3	15	38	41·3	16	17	37·0	24

Figures in brackets represent rates based on fewer than 10 cases

TABLE VI—*Length of Survival after Tumour Recurrence*

Interval from Diagnosis to Recurrence (Months)	Length of Follow up after Recurrence (Years)							
	<1		1		≥2		Total	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
0-5	0	108	0	2	7	1	7	111
6-11	0	33	0	6	3	2	3	41
12-17	0	9	1	1	1	0	2	10
18-23	0	3	0	1	0	0	0	4
≥24	0	3	0	1	5	0	5	4
No recurrence							92	208
Total	0	156	1	11	16	3	109	378

two years after their recurrence, and it seems that, even allowing for the shorter follow up of such late recurrences, they have a higher chance of survival. The 17 patients who survived after a recurrence are shown in table VII.

A more detailed examination of these data showed that the probability of recurrence increased and that the probability of surviving after the recurrence decreased with increasing age at diagnosis. These findings must be treated with caution since a large number of patients died without a recurrence, and deaths among the younger children tended to occur more quickly (see fig. 2), thus making it less likely that there would have been time for recurrence. A probable explanation, however, is that in older children the tumour is more likely to be disseminated at the time of diagnosis (see table V); some distant metastases will be detected at the time of diagnosis, but others will only be found later and will be regarded as recurrences. The age difference would in fact be expected if all or most of these tumours were initiated in utero and difference in age at diagnosis largely reflected difference in growth rate.

Differences also existed between the sexes in respect of recurrences. Firstly, girls were more likely than boys to survive without a recurrence at all. Secondly, where there was a recurrence the girls were more likely to survive after the recurrence.

It should be pointed out that though we worked in terms of a three-year survival rate, and most previous authors have used a two-year survival rate, it is actually the case that in our series nearly all deaths occurred in the first year after diagnosis or among cases in which a recurrence was observed during the first year. There were 319 deaths in the first year and 33 later deaths among 43 patients who were alive but who had had a recurrence within the year. Of 125 patients alive and not having had a recurrence one year after diagnosis only 26 subsequently died.

Discussion

Neuroblastoma is the third commonest neoplasm among children exceeded only by leukaemia and cerebral tumours. It has been of great interest for many years because of its development, arising not only in the adrenal medulla but also from the sympathetic ganglia, sympathetic chains, and small peripheral ganglia. Another noteworthy feature is the phenomenon of maturation in this tumour, which can occur from malignant undifferentiated neuroblastoma to the benign ganglioneuroma.

The present survey represents a completely unselected sample of all cases notified and histologically confirmed from the whole country, from every type of hospital, and whether treated or not. This was an epidemiological study, and we are not able to comment on treatment; but the large numbers available to us and the length of follow up made it worthwhile to establish the basic natural history and prognosis so that the effects of different methods of treatment might be more easily studied in the future.

Many of the findings in this paper have also been reported by other workers, but none of the earlier studies included so many cases. The present paper seems to be the first in which detailed data on the exact nature of the survival curves for extended periods after treatment have been presented.

The excess of boys over girls has been noted in many series of cases of neuroblastoma, while the reversal of the sex ratio among ganglioneuromas has been mentioned by McFarland and Sappington (1935) and by Willis (1962). Willis suggested that the process of maturation may occur in a higher proportion of girls than boys. In our series, where evidence of maturation was available in 12 cases, nine were girls and only three were boys. Moreover, we believe that some of the results already discussed in the present paper may provide indirect support for this theory. The girls had a better survival rate than boys; it seems reasonable to postulate that this might have been due to their tumours being more likely to mature into a benign form.

Relatively few authors have reported survival rates separately for the two sexes, and no previous authors seem to have investigated the simultaneous effects of sex and other factors on prognosis. Survival rates for the two sexes have been compared in three previous papers; two of these found that the prognosis was better in girls and the other that it was better in boys; none of these differences was statistically significant. Our findings suggest that in addition they have a better chance of survival after a recurrence.

Finally, we have confirmed the finding that death is unlikely to occur among children who survive more than two years after diagnosis; this has been reported in many previous papers (de Lorimier *et al.*, 1969; Gross *et al.*, 1959). It is of particular interest that we have found that even when a recurrence occurs after this time it is relatively less likely that death will ensue. In this context it is noteworthy that though survival *rates* were lower among the older children the *length* of survival tended to be greater. This point has been made by Fortner *et al.* (1968)

TABLE VII—*Survivors after Recurrence*

Case No.	Sex	First Tumour		Interval from diagnosis to Recurrence (Months)	Recurrence		Interval from Recurrence to Latest Follow up (Months)
		Site	Age (Months)		Site	Age (Months)	
1	F.	L. Adrenal + skin nodules	11	17	Skull	28	91
2	F.	Pelvis	19	68	Pelvis	87	28
3	F.	Abdomen + skin nodules	5	2	Skin nodules	7	89
4	M.	Abdomen + skin nodules	3	4	Abdomen	7	72
5	F.	Nasal sinuses	158	2	Nasal sinuses	160	81
6	F.	Thoracic dumbbell	9	4	Skin nodules	13	75
7	F.	Thorax	6	5	Thorax	11	69
8	F.	R. Adrenal	12	30	Skull	42	26
9	F.	Primary not found L. Ilium	56	9	Thorax	65	46
10	F.	Cervical	9	2	Cervical	11	55
11	M.	Thorax + skull	10	26	Thorax	36	31
12	F.	Thorax	120	12	Thorax	132	19
13	F.	Thorax	7	27	Thorax	34	36
14	F.	Thorax	35	25	Thorax	60	40
15	F.	Abdomen	10	4	Abdomen	14	48
16	M.	Thorax	10	3	Thorax + skull	6	41
17	M.	R. Adrenal	0	6	Abdomen + orbit	6	43

and is consistent with the suggestion that tumours in older children have slower growth rates.

We thank Dr. Alice Stewart and the staffs of the department of social medicine, Oxford University and the Marie Curie Memorial Foundation epidemiology unit, particularly Dr. Elizabeth Lennox and Mr. Peter Gorbach for their help and advice and Mrs. Audrey Cartwright for her secretarial help. The Marie Curie/Oxford survey of childhood cancers is supported by grants from the U.S. Public Health Service (Grant No. CA-12208 and Contract No. FDA 72-126) and the Medical Research Council (Grant No. G 964/230/C). The data were collected by staff of the county and county borough health departments in England, Scotland, and Wales.

References

Beckwith, J. B., and Perrin, E. V. (1963). *American Journal of Pathology*, **43**, 1089.
Breslow, N., and McCann, B. (1971). *Cancer Research*, **31**, 2098.
Cushing, H., and Wolbach, S. B. (1927). *American Journal of Pathology*, **3**, 203.
D'Angio, G. J., Evans, A. E., and Koop, C. E. (1971). *Lancet*, **1**, 1046.
de Lorimier, A. A., Bragg, K. U., and Linden, G. (1969). *American Journal of Diseases in Children*, **118**, 441.
Evans, A. E., D'Angio, G. J., and Randolph, J. (1971). *Cancer*, **27**, 374.
Fortner, J., Nicastri, A., and Murphy, L. M. (1968). *Annals of Surgery*, **167**, 132.
Fox, F., Davidson, J., and Thomas, L. B., (1959). *Cancer*, **12**, 108.
Gross, R. E., Farber, M. D., and Martin, L. W. (1959). *Pediatrics*, **23**, 1179.
Koop, C. E. (1972). In *Progress in Pediatric Surgery*, vol. 4, ed. A. H. Bill, *et al.*, p. 1. Munich, Urban and Schwarzenberg.
Ledlie, E. M., *et al.* (1970). *British Medical Journal*, **4**, 195.
McFarland, J., and Sappington, S. W. (1935). *American Journal of Pathology*, **11**, 429.
Stella, J. G., Schweisguth, O., and Schlienger, M. (1970). *The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine*, **108**, 324.
Stewart, A., and Kneale, G. W. (1970). *Lancet*, **1**, 1185.
Sutow, W. W., *et al.* (1970). *Pediatrics*, **45**, 800.
Willis, R. A. (1962). In *The Pathology of the Tumours of Children*, ed. R. Cameron and G. Payling Wright, p. 9. Edinburgh and London, Oliver and Boyd.
Willis, R. A., and Willis, A. T. (1972). In *Principles of Pathology and Bacteriology* 3rd edn. p. 573. London, Butterworths.

Appearance of Specific Colostrum Antibodies after Clinical Infection with Salmonella typhimurium

R. A. ALLARDYCE, D. J. C. SHEARMAN, D. B. L. McCLELLAND, K. MARWICK, A. J. SIMPSON, R. B. LAIDLAW

British Medical Journal, 1974, **3**, 307-309

Summary

Colostrum and serum antibodies to *Salmonella typhimurium* have been found in three patients after clinical gastrointestinal infection during pregnancy. High levels of colostrum IgA agglutinins were directed specifically against both the flagellar and somatic antigens of the infective organism. The levels of colostrum agglutinating activity exceeded those found in the patients sera, while control colostrum gave negative results.

Introduction

The mechanisms by which resistance to infection may be passed from mother to infant are not fully understood. It is established that breast-fed infants have a lower incidence of enteric *Escherichia coli* infection (Hinton and MacGregor, 1958; Mata and Urrutia, 1971) and septicaemic illness (Winberg and Wessner, 1971) than bottle-fed infants. Human milk is rich in defence factors, including a growth enhancer of lactobacilli, an anti-staphylococcal agent, immunoglobulins, certain complement components, lysozyme, lactoperoxidase, lactoferrin, and macrophages and lymphocytes (Goldman and Smith, 1973); however, relatively little is known about their effects on the infant. Nevertheless, attention has been drawn to the possible protective role of passively transferred maternal antibodies present in the colostrum and milk.

Specific and non-specific antibodies to a wide range of micro-organisms have been found in these secretions (Shearman *et al.*, 1972; Goldman and Smith, 1973), and in the few studies involving determinations of immunoglobulin classes these antibodies have been shown to be principally of the IgA type (Adinolfi *et al.*, 1966 a; Mouton *et al.*, 1970; Bennich and Johansson, 1971; Parkin *et al.*, 1973 Zipursky *et al.*, 1973).

Colostrum antibodies are not thought to be absorbed from the intestinal lumen of the newborn infant, and thus their protective influence is likely to be a local one in the alimentary tract (Nordbring, 1957; Amman and Stiehm, 1966). The known survival of maternal agglutinating antibodies to salmonella H antigens in the neonatal gut (Schubert and Grünberg, 1949) has recently been attributed to the intrinsic resistance of colostrum IgA to digestion by trypsin (Brown *et al.*, 1970; Parkin *et al.*, 1973). In addition to the early clinical studies of Schubert and Grünberg (1949) indicating the transfer of specific agglutinating colostrum antibody from mother to offspring after intradermal vaccination with formalin-killed salmonellae, Eddie *et al.* (1971) showed that rabbits fed living, but not killed, *Salmonella typhimurium* developed milk antibodies to the infective organism. The question remained: Could infection with a pathogenic salmonella by the oral route result in similar colostrum antibody production in man? We have studied the immunological reactions of three pregnant women infected with *S. typhimurium*.

Patients and Methods

Three women were selected for further investigation after clinical infection during pregnancy with *S. typhimurium* (phage type 465) as shown by stool cultures. None of them had received an inoculation of TAB vaccine before their illness. Negative stool cultures were obtained from cases 1, 2, and 3, 8, 10, and 36 days respectively after diagnosis. Widal tests were not performed because at the time there was a

Gastrointestinal Service, University Department of Therapeutics, Royal Infirmary, Edinburgh EH3 9YW
R. A. ALLARDYCE, PH.D., Research Fellow
D. J. C. SHEARMAN, PH.D., F.R.C.P.Ed., Senior Lecturer in Therapeutics
D. B. L. McCLELLAND, M.B., M.R.C.P., Lecturer in Therapeutics
K. MARWICK, F.I.M.L.T., Senior Technician

Penicuik Medical Practice, Midlothian
A. J. SIMPSON, M.B., CH.B., General Practitioner
R. B. LAIDLAW, M.B., D.OBST.R.C.O.G., General Practitioner