Late deaths after treatment for childhood cancer

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Abstract

An investigation of 749 deaths occurring among 4082 patients surviving at least five years after the diagnosis of childhood cancer in Britain before 1971 has been undertaken. Of the 738 with sufficient information the numbers of deaths attributable to the following causes were: recurrent tumour, 550 (74%), a second primary tumour, 61 (8%), a medical condition related to treatment of the tumour, 49 (7%), an traumatic death unrelated to the tumour or its treatment, 34 (5%), finally, any other cause unrelated to the tumour or its treatment, 44 (6%).

Less than 10% of five year survivors of non-Hodgkin lymphomas, neuroblastoma, retinoblastoma, Wilms' tumour, or a soft tissue sarcoma died of recurrent tumour during the next 15 years, while more than 25% of five year survivors of Hodgkin's disease, ependymoma, medulloblastoma, and Ewing's tumour died of recurrent tumour during the corresponding period. Almost 50% of five year survivors of acute lymphoblastic leukaemia died of recurrent disease during the corresponding 15 years, a large proportion of deaths being due to central nervous system relapse in an era before central nervous system prophylaxis was routinely given.

Comparison of the mortality observed with that expected from mortality rates in the general population indicated three times the expected number of deaths from non-neoplastic causes. Five times the expected number of deaths from cardiovascular causes were observed, these were predominantly myocardial infarction and cerebrovascular accidents. There was no evidence of an excess in the number of suicides observed, but there were three times the expected number of deaths from accidents observed after central nervous system tumours.

Two groups of patients were identified whose deaths were potentially avoidable. Seven patients with craniopharyngioma and panhypopituitarism presented with Addisonian crises during periods of stress not adequately covered by exogenous corticosteroids. In the other group were children who received radiotherapy and later developed problems related to radiation fibrosis.

We emphasise that our investigation relates to patients diagnosed with childhood cancer before 1971. The pattern of mortality that will emerge after recent treatment regimens, in which chemotherapy is being used more extensively, is likely to be different from that observed in our study.

Examination of the course of events leading to death among patients who survive at least five years after childhood cancer is important as it may provide further understanding of late relapse and the late effects of treatment. With the benefit of hindsight it may be possible to identify deaths that might have been preventable. If the study population is large it is likely that deaths from rare adverse consequences of the neoplastic disease or its treatment will be identified. Such an investigation requires clinical information relating to the circumstances of death and therefore access to sources other than the death certificates, including hospital records and reports from postmortem examination.

A comparison of the mortality observed with that expected from mortality in the general population, for specific causes of death—both neoplastic and non-neoplastic—may also provide further insight into the curability of childhood neoplastic disease and identify any departure from the expected pattern of mortality. For this type of comparison it is necessary to rely on death certification because the expected numbers are derived from general population rates which are themselves based on death certificates alone.

This paper is complementary to our previous report on long term survival and cure after childhood cancer.¹

Methods

The national register for childhood tumours, maintained by the Childhood Cancer Research Group in Oxford, has been routinely notified of tumours occurring in children under 15 years of age since 1962 through the national cancer registration scheme operating in Great Britain. This provides, within the limits of completeness of registration, a population based series of childhood cancer cases. From among these we have selected 2537 cases diagnosed before 1971 who survived for at least five years. A further 1545 cases, diagnosed between 1940 and 1961 inclusive, surviving at least five years, and treated at centres where complete lists of patients were available, have also been included.

A consequence of restricting the study to this period of diagnosis is that we are primarily concerned with malignant disease that was amenable to treatment with radiation and surgery, as apart from the treatment of leukaemia, cytotoxics were not in widespread use before 1971. An advantage of studying this period, however, is that sufficient time has elapsed to examine late mortality.

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For deaths occurring five or more years from diagnosis, an effort was made to obtain medical details of the circumstances leading to death. A complete copy of all relevant hospital notes extant was obtained together with a copy of the report when a postmortem examination had been undertaken.

The underlying cause of death, based on all the information available, was coded according to the following broad categories: (1) recurrent tumour; (2) a medical condition related to treatment of the tumour; (3) a second primary tumour; (4) a traumatic death apparently unrelated to the tumour or its treatment; (5) any other cause apparently unrelated to the tumour or its treatment; and (6) insufficient information.

A few conventions were used in coding deaths into these broad categories. In patients with tumours of the central nervous system, the cause of death given on the death certificate was frequently bronchopneumonia. Examination of the case records of a number of these patients showed that their general health had gradually declined, the patients had become obtunded due to recurrent tumour and had eventually died from bronchopneumonia. These deaths were all coded as recurrent tumour rather than infection. When death occurred from infections such as herpes zoster, meningitis, or pneumonia in patients on chemotherapy then they were coded as a death from a medical condition related to treatment of the tumour. One patient with Hodgkin's disease who had undergone a splenectomy and had subsequently died from a pneumococcal septicaemia, while in remission, was also coded to a medical condition related to treatment. When death occurred from infection or other cause and where there was insufficient evidence to determine whether the patient had active disease at the time, then the death was coded to insufficient information.

For the purposes of comparing the mortality observed with that expected we also recorded the International Classification of Diseases (ICD) code appearing on the death certificate. We restricted the study to revisions 6, 7, 8, and 9 of ICD,²⁻⁵ and therefore only deaths occurring after 1949 are included in this comparison. This excluded one death.

Survival was examined using standard techniques.⁶ Mortality from specific causes of

death among survivors was compared with that expected from the general population of England and Wales (Office of Population Censuses and Surveys, unpublished report). Observed and expected numbers of deaths were compared using exact Poisson methods.

Results

Of the 4082 five year survivors eligible for analysis, there were 749 deaths. A death certificate was obtained for 739 of these deaths, hospital notes for 359, and a postmortem examination report for 76.

Table 1 gives the causes of late death occurring among patients surviving for at least five years after diagnosis of various childhood neoplasms. There was insufficient information available to code the cause of death in 11 patients. Approximately 74% of the deaths were attributed to recurrent tumour, and 8% to the occurrence of a second primary tumour. There was substantial variability in the relative proportions of deaths from different causes depending on the primary diagnosis: over 75% of deaths after acute lymphoblastic leukaemia, lymphoma, and tumours of the central nervous system or bone were due to recurrent tumour. In contrast, only 26% of deaths among patients surviving at least five years after genetic retinoblastoma were due to recurrent tumour, with 65% resulting from second primary tumours. Similarly, among patients surviving at least five years after Wilms' tumour only 36% of deaths were due to recurrent tumour with 32% resulting from second primary tumours.

Table 2 gives the variation in causes of death with follow up. Among deaths occurring five to nine years from diagnosis recurrent tumour was the most common cause of death after each childhood neoplasm. The most common cause of death among 10 year survivors varied considerably depending on the neoplasm: in patients with acute lymphoblastic leukaemia, Hodgkin's disease, and central nervous system tumours, recurrent tumour was still the most common cause, whereas in patients with retinoblastoma and Wilms' tumour, death from second primary tumours predominated.

There were 188 deaths from causes other than recurrent tumour (table 1). Of these, we obtained hospital notes and/or a postmortem

Table 1 Frequency (%) of different causes of death observed among those surviving five or more years from diagnosis

	Acute lymphoblastic leukaemia	Lymphomas	Tumour of central nervous system	Neuroblastoma	Genetic retinoblastoma	Non-genetic retinoblastoma	Wilms' tumour	Malignant bone	Soft tissue	Other neoplasms	All neoplasms
Recurrent tumour	78 (95)*	97 (79)	260 (79)	15 (63)	8 (26)		8 (36)	23 (79)	24 (67)	37 (65)	550 (74)
Medical condition (related to treatment)	2 (2)	10 (8)	28 (8)	4 (16)			2 (9)	1 (3)	1 (3)	1 (2)	49 (7)
Second primary tumour		2 (2)	12 (4)	2 (8)	20 (65)	3 (60)	7 (32)	3 (10)	4 (11)	8 (14)	61 (8)
Accident, suicide, or homicide		6 (5)	17 (5)	1 (4)	1 (3)	1 (20)	2 (9)	1 (3)	1 (3)	4 (7)	34 (5)
Other cause (unrelated to tumour or its treatment)	2 (2)	8 (6)	12 (4)	2 (8)	2 (6)	1 (20)	3 (14)	1 (3)	6 (17)	7 (12)	44 (6)
Insufficient information	2	1	5					1	2		11
Total deaths	84	124	334	24	31	5	22	30	38	57	749
Total No of 5 year survivors	171	538	1257	230	267	287	365	151	352	464	4082

*% Of deaths is based on the number of deaths with sufficient information to code the cause.

Table 2 Frequency of different causes of death observed at varying times from diagnosis

	No of 5 year survivors	Causes of death 5-9 years from diagnosis					No of 10 year survivors	Causes of death 10-14 years from diagnosis				
		Recurrent tumour	Related medical condition*	Second primary tumour	Accident†	Other cause‡		Recurrent tumour	Related medical condition*	Second primary tumour	Accident†	Other cause‡
Acute lymphoblastic leukaemia	171	70	2			2	95	6				
Hodgkin's disease	328	70	4	1	3		247	9	4			1
Non-Hodgkin lymphoma	203	12	1		2	2	181					1
Tumours of central nervous system	1257	163	12	2	5	1	1066	56	4	2	7	4
Neuroblastoma	230	11					219	2	1			2
Genetic retinoblastoma	267	6		3	1	1	256	1				
Non-genetic retinoblastoma	287						283			8		
Wilms' tumour	365	7	1				354			1		
Osteosarcoma	73	6	1	1			65					
Ewing's sarcoma	40	10					30	1				
Soft tissue sarcomas	352	18	1	1		1	326	5		2		1
Other neoplasms	509	35		3		2	467	4	1	2	1	1
All neoplasms	4082	408	22	11	11	9	3589	84	10	16	8	10

The number of patients who survive to a specified time does not equal the number surviving in the previous time interval plus deaths in the interim

*Medical condition related to treatment of the tumour.

†Traumatic death unrelated to tumour or its treatment—that is, accident, suicide, or homicide.

‡Any other cause unrelated to tumour or its treatment.

Table 3 Deaths not directly related to tumour or its treatment (n=44)

Original diagnosis	Cause of death	Associated condition	Interval from diagnosis to death (years)
Hodgkin's disease	Coronary atherosclerosis		21
Hodgkin's disease	Coronary atherosclerosis		20
Non-Hodgkin lymphoma	Coronary atherosclerosis	Diabetes mellitus	11
Osteosarcoma	Coronary atherosclerosis	Addison's disease, diabetes mellitus	18
Fibrosarcoma	Coronary atherosclerosis		30
Fibrosarcoma	Coronary atherosclerosis		23
Melanoma of eye	Coronary atherosclerosis		23
Thymoma	Coronary atherosclerosis	Aortic valve incompetence	13
Ependymoma	Congenital heart disease		5
Astrocytoma	Congestive cardiac failure	Severe kyphoscoliosis	13
Non-Hodgkin lymphoma	Cerebrovascular accident	Chronic renal failure	35
Astrocytoma	Cerebrovascular accident	Disseminated lupus erythematosus	12
Astrocytoma	Cerebrovascular accident		20
Cancer of thyroid	Cerebrovascular accident	Malignant hypertension	16
Epithelioma	Cerebrovascular accident		28
Neuroblastoma	Cerebrovascular accident		12
Dysgerminoma	Cerebrovascular accident	Malignant hypertension	16
Astrocytoma	Pulmonary embolus/deep venous thrombosis	Postpartum	15
Astrocytoma	Pulmonary embolus/deep venous thrombosis	Tegretol hepatitis	23
Medulloblastoma	Cor pulmonale/bronchiectasis	Hypogammaglobulinaemia	22
Retinoblastoma	Pneumonia	Mental retardation	7
Astrocytoma	Pneumonia		13
Acute lymphoblastic leukaemia	Chicken pox pneumonia		5
Tumour of central nervous system	Aspiration pneumonia	After oesophageal dilatation	28
Rhabdomyosarcoma	Aspiration pneumonia	After fit	21
Optic nerve glioma	Meningitis		12
Wilms' tumour	Encephalitis		19
Dysgerminoma	Streptococcal septicaemia	Diabetes mellitus	7
Retinoblastoma	Acute renal failure		55
Fibrosarcoma	Acute renal failure		6
Non-Hodgkin lymphoma	Chronic renal failure		7
Wilms' tumour	Chronic renal failure		23
Neuroblastoma	Chronic renal failure	Spina bifida	11
Retinoblastoma	Diabetic ketoacidosis		15
Optic nerve glioma	Hypoglycaemic coma	Diabetes mellitus	16
Hodgkin's disease	Cirrhosis	Collagenosis	16
Non-Hodgkin lymphoma	Acute hepatitis		6
Astrocytoma	After cholecystectomy		38
Wilms' tumour	After mitral valve replacement		30
Langerhans cell histiocytosis	After aortic valve replacement		7
Hodgkin's disease	Gastric ulcer		13
Fibrosarcoma	Intestinal obstruction		14
Fibrosarcoma	Motor neurone disease		44
Acute lymphoblastic leukaemia	Cerebral degeneration		9

examination report for 150 (80%). A postmortem examination report was obtained for 40 (21%) of these deaths.

Of the deaths occurring from causes other than recurrent disease, 44 (6%) were due to causes not directly related to the tumour or its treatment (table 3). However, 49 (7%) of the deaths in five year survivors occurred from medical conditions related to treatment (table

4). The major causes of death in this group included infection (n=16), problems related to radiotherapy (n=13), and adrenal failure (n=7).

Traumatic deaths due to accidents, suicide, or homicide accounted for 5% of the deaths in five year survivors.

Table 5 gives the proportion of five year survivors subsequently dying of recurrent tumour within the next 15 years. Deaths from causes

No of 15 year survivors	Causes of death 15-19 years from diagnosis					No of 20 year survivors	Causes of death 20+ years from diagnosis				
	Recurrent tumour	Related medical condition*	Second primary tumour	Accident†	Other cause‡		Recurrent tumour	Related medical condition*	Second primary tumour	Accident†	Other cause‡
87	1					22	1				
231	3	1			1	133	2		1	1	2
180	1					121					1
986	26	4	4	3	2	658	15	8	4	2	5
214	2	2				151		1	2	1	
247	1		5			189			4		1
282				1	1	191			2		
352		1	3	1	1	220	1		3	1	2
65	1				1	46			2		
29	1					19					
314	1					240			1	1	4
456	1		1	2	2	316	1		2	2	2
3443	38	8	13	7	8	2306	20	9	21	8	17

because of losses to follow up.

other than recurrent tumour were regarded as losses to follow up. Less than 10% of five year survivors of non-Hodgkin lymphomas, neuroblastoma, retinoblastoma, Wilms' tumour, or a soft tissue sarcoma died of recurrent tumour during the next 15 years. In contrast, almost half of the five year survivors of acute lympho-

blastic leukaemia died from recurrent disease during a similar period. Late relapse and death were also common in Hodgkin's disease, ependymoma, medulloblastoma, and Ewing's tumour with more than a quarter of the five year survivors dying of recurrent tumour within the subsequent 15 years.

Table 6, derived from death certificate coding, gives a comparison of the observed and expected number of deaths from particular neoplasms for which it is possible to define a range of ICD codes, which is almost certain to include any death from recurrent tumour. A measure of the excess number of deaths observed compared with that expected is also given in table 6 and may be interpreted as the extra number of deaths observed in the study population, from the neoplasms specified, per 100 patients per year. Inspection of table 6 indicates that the excess number of neoplastic deaths among five year survivors of retinoblastoma, non-Hodgkin lymphoma, and Wilms' tumour was consistently less than one extra death per 100 patients per year. The excess among survivors of Hodgkin's disease, tumours of the central nervous system and bone tumours did not exceed five extra deaths per 100 patients per year. The largest excess observed was after acute lym-

Table 4 Deaths from medical conditions related to treatment of the tumour (n=49)

Original diagnosis	Cause of death	Related treatment factor	Interval from diagnosis to death (years)
Ependymoma	Meningitis	After surgery for recurrence	10
Medulloblastoma	Meningitis	After surgery for recurrence	5
Astrocytoma	Ventriculitis	Ventriculoatrial shunt infection	20
Glioma	Ventriculitis	Ventriculoatrial shunt infection	16
Astrocytoma	Syringomyelia	Radiotherapy necrosis of spinal cord	18
Astrocytoma	Syringomyelia	Radiotherapy necrosis of spinal cord	18
Glioma fourth ventricle	Acute brain stem syndrome	Obliteration of cerebral vasculature after radiotherapy	25
Astrocytoma	Cerebral degeneration	Obliteration of cerebral vasculature after radiotherapy	26
Astrocytoma	Hydrocephalus	Gliosis at base of brain after radiotherapy	25
Astrocytoma	Hydrocephalus	Shunt dysfunction	10
Astrocytoma	Hydrocephalus	After craniotomy	6
Ependymoma	Hydrocephalus	Tentorial herniation	5
Craniopharyngioma	Aspiration pneumonia	Ischaemic necrosis of frontal lobe after surgery	8
Glioma fourth ventricle	Aspiration pneumonia	After fit due to recurrence	9
Medulloblastoma	Status epilepticus	Mental retardation	18
Craniopharyngioma	Cerebroathrosisclerosis	After radiotherapy	26
Craniopharyngioma	Intracranial venous thrombosis	After surgery for recurrence	6
Craniopharyngioma	Addisonian crisis		9
Craniopharyngioma	Addisonian crisis	Pneumonia	9
Craniopharyngioma	Addisonian crisis	Gastroenteritis	7
Craniopharyngioma	Addisonian crisis		7
Craniopharyngioma	Addisonian crisis	Tonsillitis	9
Craniopharyngioma	Addisonian crisis	Respiratory tract infection	12
Craniopharyngioma	Addisonian crisis		22
Craniopharyngioma	Bronchopneumonia		28
Medulloblastoma	Bronchopneumonia	After surgery	24
Acute lymphoblastic leukaemia	Pneumococcal meningitis	On chemotherapy	6
Hodgkin's disease	Cryptococcal meningitis	On chemotherapy	6
Hodgkin's disease	Cryptococcal meningitis	On chemotherapy	13
Hodgkin's disease	Pelvic abscess	On chemotherapy	8
Hodgkin's disease	Pneumococcal meningitis	After splenectomy	18
Hodgkin's disease	Subphrenic abscess	After splenectomy	12
Hodgkin's disease	Disseminated zoster	On chemotherapy	6
Hodgkin's disease	Disseminated zoster	On chemotherapy	12
Hodgkin's disease	Cor pulmonale	Pulmonary fibrosis after radiotherapy	7
Neuroblastoma	Cor pulmonale	Pulmonary fibrosis after radiotherapy	16
Wilms' tumour	Cor pulmonale	Pulmonary fibrosis after radiotherapy	17
Wilms' tumour	Peritonitis	Perforated bowel ?due to radiotherapy	6
Neuroblastoma	Peritonitis	Chronic renal failure	20
Neuroblastoma	Cholangitis	Periportal fibrosis after radiotherapy	13
Non-Hodgkin lymphoma	Acute liver failure	After radiotherapy for recurrence	5
Hodgkin's disease	Hypertensive encephalopathy/ chronic renal failure	Radiation nephritis	12
Glioma spinal cord	Chronic renal failure	Neurogenic bladder	5
Neurofibrosarcoma	Chronic renal failure	Neurogenic bladder	7
Histiocytosis X	Hyperosmolar coma	Diabetes insipidus	14
Ganglioneuroblastoma	Haemorrhage	Intraoperative	15
Osteosarcoma	Haemorrhage	After pneumonectomy	8
Astrocytoma	Anaesthetic death	Unsuspected pheochromocytomas	19
Acute lymphoblastic leukaemia	Severe anaemia	Parents Jehovah's witnesses	6

Table 5 Actuarial percentage of five year survivors subsequently dying of recurrent tumour

Diagnosis	No of 5 year survivors	% (SE) of 5 year survivors dying of recurrent tumour by 20 years from diagnosis
Acute lymphoblastic leukaemia	171	47 (4)
Lymphomas:	538	18 (2)
Hodgkin's disease	328	26 (3)
Non-Hodgkin lymphoma	203	6 (2)
Tumours of central nervous system:	1257	20 (1)
Ependymoma	123	26 (4)
Astrocytoma	670	15 (1)
Medulloblastoma	165	34 (4)
Neuroblastoma	230	6 (2)
Retinoblastoma:		
Genetic	267	3 (1)
Non-genetic	287	0
Wilms' tumour	365	2 (1)
Malignant bone tumours:	151	15 (3)
Osteosarcoma	73	10 (4)
Ewing's tumour	40	30 (7)
Soft tissue sarcoma:	352	7 (1)
Rhabdomyosarcoma	87	7 (3)
Fibrosarcoma	175	5 (2)

phoblastic leukaemia and exceeded 10 extra deaths per 100 patients per year.

Table 7, again using information from death certificates only, gives the results of comparing the observed and expected number of deaths from all causes other than neoplasm. Threefold the expected number of non-neoplastic deaths were observed. We observed 13-fold the number of deaths expected from infections other than pneumonia and influenza. The excess of deaths assigned to pneumonia and influenza, particularly after central nervous system tumours, needs careful interpretation because of the tendency of many clinicians to record bronchopneumonia as the cause of death in patients with recurrent tumours of the central nervous system, but may also reflect the problem of prolonged impairment of immunity in patients with a history of cancer. Of the eight

Table 6 Comparison of observed and expected deaths from neoplastic causes

	Interval from diagnosis in years					
	5-9			10+		
	Observed (O)	Expected (E)	Excess*	Observed (O)	Expected (E)	Excess*
Acute lymphoblastic leukaemia	71	0.009	12.5	7	0.007	0.9
Hodgkin's disease	70	0.011	5.1	17	0.035	0.6
Non-Hodgkin lymphoma	8	0.006	0.9	1	0.022	0.0
Tumour of central nervous system	141	0.085	2.5	89	0.210	0.7
Genetic retinoblastoma	5	0.000	0.4	2	0.000	0.1
Non-genetic retinoblastoma	0	0.000	0.0	0	0.000	0.0
Wilms' tumour	8	0.004	0.4	2	0.005	0.0
Malignant bone tumour	14	0.005	2.1	2	0.007	0.1

$$*Excess = \left\{ \frac{(O-E) 100}{\text{person years}} \right\}$$

Table 7 Comparison of observed and expected deaths from non-neoplastic causes five or more years from diagnosis

	Infectious/parasitic diseases	Endocrine, nutritional, and metabolic diseases	Diseases of the nervous system and sense organs	Diseases of the circulatory system	Pneumonia and/or influenza	Diseases of the digestive system	Diseases of the genitourinary system	Congenital diseases	Medical misadventure	Other accidents	Suicide	Uncertain whether accident, suicide, or homicide	Other non-neoplastic causes	All non-neoplastic causes of death
Acute lymphoblastic leukaemia:														
Observed	2	0	0	0	0	0	0	0	0	0	0	0	0	2
*O/E	178													4
p Value	0.000													0.102
Lymphomas:														
Observed	4	1	0	6	1	1	0	0	0	5	1	0	0	19
*O/E	50	10		9	6	7				2	2			4
p Value	0.000	0.096		0.000	0.148	0.137				0.067	0.428			0.000
Tumours of central nervous system:														
Observed	0	4	2	4	10	2	1	1	1	11	1	2	3	42
*O/E		17	3	3	28	7	6	3	81	3	1	5	3	4
p Value		0.000	0.119	0.040	0.000	0.038	0.159	0.304	0.012	0.004	0.635	0.057	0.054	0.000
Embryonal tumours:														
Observed	1	1	0	1	2	0	1	2	2	4	1	0	0	15
*O/E	5	4		1	6		8	4	225	1	1			2
p Value	0.178	0.222		0.502	0.045		0.123	0.080	0.000	0.558	0.485			0.028
Malignant bone tumours:														
Observed	0	0	0	2	0	0	0	0	0	0	1	0	0	3
*O/E				9							7			2
p Value				0.023							0.139			0.155
Soft tissue sarcoma:														
Observed	0	0	1	2	1	1	0	2	0	0	0	0	2	9
*O/E			5	5	9	10		16					7	3
p Value			0.176	0.065	0.108	0.093		0.007					0.030	0.006
Other neoplasms:														
Observed	1	2	0	5	0	0	0	1	0	2	1	1	0	13
*O/E	13	21		11				7		1	3	6		3
p Value	0.073	0.004		0.000				0.140		0.474	0.318	0.142		0.000
All neoplasms:														
Observed	8	8	3	20	14	4	2	6	3	22	5	3	5	103
*O/E	13	10	1	5	12	4	4	5	79	2	2	2	2	3
p Value	0.000	0.000	0.314	0.000	0.000	0.016	0.101	0.002	0.000	0.031	0.207	0.129	0.141	0.000

*Observed/expected.

deaths coded to endocrine or metabolic causes, two deaths were due to the metabolic complications of diabetes mellitus, one death was from hyperosmolar coma secondary to diabetes insipidus in a patient with Langerhans cell histiocytosis, and one death was due to cor pulmonale secondary to severe bronchiectasis resulting from recurrent infections in a patient with hypogammaglobulinaemia. In the remaining four cases, the cause of death on the death certificate was inaccurate as inspection of the notes indicated that death was due to recurrent tumour. However, excluding the latter four deaths still leaves an excess (one tailed $p=0.01$).

The fivefold excess of cardiovascular deaths were predominantly myocardial infarction or cerebrovascular accidents, which occurred at a younger age than expected for these conditions. There were eight deaths due to myocardial infarction; two patients had diabetes mellitus which may have contributed to the early onset of coronary atheroma. It is of interest that three patients had received radiotherapy to the mediastinum and one to the left infraclavicular region. Seven patients, aged 26–42 years, died from cerebrovascular accidents, three patients had previously received direct irradiation to some part of the brain. Three of the cerebrovascular accidents occurred in patients who had documented severe hypertension, one resulted from a subarachnoid haemorrhage secondary to a berry aneurysm, two were unexplained and the remaining patient, treated for a craniopharyngioma, was found to have extensive cerebroatherosclerosis at necropsy. Of the remaining cardiovascular deaths, one was due to left ventricular failure in a patient with severe hypertension and chronic renal failure, and one to congestive cardiac failure in a patient with severe kyphoscoliosis. In three cases the certified cause of death from circulatory causes was inaccurate as examination of the patient's records indicated that they had actually died from the effects of recurrent disease and the death certificates in these cases were, therefore, misleading. However, even after excluding these three deaths there was still an excess of cardiovascular deaths (one tailed $p<0.001$).

There was fivefold excess of deaths from congenital causes as coded from the death certificate. Of the six deaths thus coded, three were in patients with von Recklinghausen's disease, one of the patients dying from renal failure which was tumour related and two from recurrent tumour. There were two further deaths from renal failure, one in a patient with Wilms' tumour and polycystic kidneys and one in a patient with neuroblastoma and spina bifida who had a neurogenic bladder and hydro-nephrosis. The final death in this category was due to mechanical failure of an aortic valve prosthesis in a patient with congenital heart disease.

Considering all neoplasms as a single group there was no evidence of an excess of deaths from suicides. The excess of deaths from accidents other than medical misadventure was predominantly due to observing threefold the expected number of accidents after tumours of the central nervous system. A total of 11 patients who had been treated for these tumours

died from accidents. Six of these patients (aged 10 to 35) died in road traffic accidents, two teenagers died from burns caused by accidental fires and hot water scalds at home, and two patients from complications after falls. The final death was due to manual strangulation, but in what circumstances this occurred is uncertain. Apart from one child with an optic nerve glioma who was visually handicapped we can only speculate that the effect of the tumour or treatment had resulted in some sensory or intellectual impairment that increased the risk of these patients becoming involved in accidents.

Discussion

Ascertaining the cause of death in a population of children who were diagnosed before 1971 was not easy as some hospitals destroy medical records at a specified number of years after death, and even when records were available, it was sometimes difficult to be completely sure of the actual cause of death. Fortunately, in the present study, we obtained hospital notes or a postmortem examination report for 80% of the deaths from causes other than recurrent tumour. We were most confident of our assessment where a postmortem examination report was available.

The good long term prospects for five year survivors of childhood non-Hodgkin lymphomas, neuroblastoma, retinoblastoma, Wilm's tumour, and soft tissue sarcoma, treated before 1971, are confirmed in our study with less than 10% dying of recurrent tumour during the subsequent 15 years.

For all types of childhood neoplasm the results of our study are similar to those of Li *et al* who reported on 2232 five year survivors of a variety of childhood cancers diagnosed before 1970.⁷ Our findings are also similar to those of Taylor and Potish who reported on 37 deaths occurring among 189 five year survivors of childhood cancer treated with megavoltage radiotherapy between 1953 and 1975.⁸

Our study indicates that in children with central nervous system tumours, deaths from recurrent tumour were still occurring more than 20 years from diagnosis. Many central nervous system tumours, particularly low grade astrocytomas and craniopharyngiomas, are relatively slow growing and so deaths may occur many years after the initial diagnosis. It is also recognised that both Hodgkin's disease and Ewing's tumour are indolent tumours and multiple relapses responding to further treatment can occur over a period of several years before eventual death from disease occurs.

The high frequency of deaths from recurrent disease after acute lymphoblastic leukaemia is partly explained by a large number of central nervous system relapses occurring during an era when children were not routinely given central nervous system irradiation and intrathecal methotrexate to reduce the risk of meningeal leukaemia. Central nervous system leukaemia may take a very indolent course, being partially controlled for long periods, and it may be several years before either a subsequent bone marrow relapse occurs or the child develops

resistant central nervous system disease. In addition, some children with meningeal leukaemia may develop an encephalopathy from the combination of repeated cranial irradiation and intrathecal methotrexate and this may not become manifest until several years after treatment.

In our study second primary tumours as a cause of death were relatively more commonly seen in patients with genetic retinoblastoma and Wilms' tumour. We have reported on the pattern and incidence of second primary tumours among survivors of childhood cancer elsewhere.^{9 10}

Of the 49 deaths from causes related to treatment, at least 21 occurred in children undergoing treatment for recurrent disease and these deaths were probably unavoidable due to the intensity of treatment required in the presence of resistant disease. However, it is possible that a number of the remaining 28 deaths might have been preventable. The main cause of potentially avoidable death was from endocrine failure (n=7) in children with craniopharyngioma and panhypopituitarism who presented with Addisonian crises in periods of stress related to infection. It is possible that the need for high doses of intravenous corticosteroids, which might have been life saving, was not recognised in these cases.

The other major cause of death related to primary treatment was from problems secondary to post radiation fibrosis. Five children with astrocytoma developed radiation related central nervous system degeneration, three children developed pulmonary fibrosis after whole lung irradiation and three children developed fibrosis of abdominal organs after abdominal irradiation. It is very difficult to know whether these problems could have been avoided by a more judicious approach to radiotherapy. However, in some cases radiation was given for recurrent disease and therefore the effect of radiation was probably unavoidable.

The only previous study of potentially avoidable deaths after diagnosis of childhood cancer was a Finnish study of mortality among 100 children diagnosed with acute lymphoblastic leukaemia, between 1975 and 1981.¹¹ This study identified five deaths from infections occurring during induction or primary remission that might have been avoided.

Of the 44 late deaths in our study classified as being unrelated to the primary cancer or its treatment the most frequently occurring cause of death was due to cardiovascular disease (n=20), including eight deaths due to coronary atherosclerosis and seven due to cerebrovascular accidents. Four of the eight deaths occurred in patients who had received mediastinal or chest irradiation and it is possible that the irradiation may have contributed to the early development of coronary atheroma. All the patients dying from coronary artery disease were relatively young at the time of death (age range 23-45 years). There were eight deaths from infection in patients who were off treatment and in remission from their cancer. This highlights the point that children may remain relatively immunocompromised for many years after treatment.

A previous report of an excess of cerebrovascular accidents in children diagnosed with cancer identified 26 such cases among 700 children.¹² The average follow up interval was short, however, and all of the deaths occurred a median time of five months after diagnosis. Results from this study taken together with those from our study indicate that survivors of childhood cancer are at an increased risk of cardiovascular death immediately after diagnosis and remain so beyond five years from diagnosis, although the aetiology of these early and late deaths are almost certainly different.

In conclusion we observed a five times expected excess of deaths due to cardiovascular causes, with deaths from myocardial infarction and cerebrovascular accidents being most frequent. The long term effects of radiation on the coronary vasculature of children have not been established but there is obvious concern that radiotherapy may predispose to the early development of coronary atheroma. The excess number of cerebrovascular accidents did not appear to be due to a direct effect of radiotherapy on the cerebral vasculature.

Among the deaths classified as being related to treatment we identified two groups of potentially avoidable deaths. One group consisted of children with craniopharyngioma and secondary hypothalamic-pituitary dysfunction, after surgery and radiotherapy, who died from adrenal failure during periods of stress. The other group consisted of children who received inappropriate doses of radiation and died from problems related to radiotherapy fibrosis.

We emphasise that our investigation relates to patients treated for childhood cancer before 1971 and who were treated predominantly by surgery and radiotherapy. The pattern of mortality after more recent treatment regimens, in which chemotherapy has been used extensively and radiotherapeutic techniques have been refined, are likely to be different. With the knowledge of the potential long term effects of treatment, it is hoped that future protocols can be planned to reduce the risk of late treatment related deaths. The information gained from the study of late deaths should also be of value in helping give appropriate advice and monitor the health of potentially 'at risk' groups of patients.

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Forty years ago

The 1950 volume of the *Archives of Disease in Childhood* contained papers by two paediatric pathologists. At the time of publication Ian Cathie was haematologist to the Hospital for Sick Children, Great Ormond Street, and Albert Claireaux was to become its morbid anatomist some years later.

Congenital hypoplastic anaemia

Congenital hypoplastic anaemia is characterised by the onset in the first few weeks of life of a severe normocytic, normochromic anaemia. The peripheral blood shows normal white cells and platelets but no reticulocyte response to the anaemia. The marrow contains normal myeloid precursors and megakaryocytes but grossly reduced normoblasts.

Cathie described five patients with these findings and noted a characteristic facies common to all five—tow coloured hair, snub nose, thick upper lip, wide set eyes, and an intelligent expression.¹ The only treatment available was repeated blood transfusion and Cathie commented on the need to resort to transfusing packed cells into the external jugular veins when all the peripheral limb veins had been tied off after several years of transfusions by the 'cut down' technique. (Elderly readers of this journal who were house physicians at Great Ormond Street in the late 1940s will remember these five patients only too well.)

An interesting feature of this paper was Cathie's discussion of the nomenclature of the disease. He considered 'congenital hypoplastic anaemia', the term which had been used by Blackfan and Diamond in the United States, to be inaccurate and suggested 'erythrocytogenesis imperfecta' which better described what he felt was a failure of red cell maturation. This term was used in the UK for some time but others, such as 'Blackfan-Diamond syndrome' and 'pure red cell aplasia' became more popular.

Haemolytic disease of the newborn

Claireaux reported a study of 157 cases of

haemolytic disease of the newborn collected between 1938 and 1947 in Edinburgh.²

There were 36 cases of hydrops fetalis, of whom 31 were stillborn and five died within hours of birth. In a further 110 babies there was an early onset of severe jaundice (icterus gravis neonatorum). The overall mortality in the jaundiced group was 70%, with the highest mortality in those whose jaundice developed at birth or within 24 hours. Eleven babies had haemolytic anaemia without severe jaundice and of these three died.

Late in 1947 the direct Coombs test became available and was carried out on all babies from then on. Serum bilirubin concentrations were measured in most cases of severe jaundice and ranged from 2 to 20 mg/100 ml (34 to 340 µmol/l). Babies with concentrations over 7 mg/100 ml (119 µmol/l) at birth seldom recovered.

Treatment was simple transfusion of Rh negative blood in quantities of 15 ml/pound body weight, repeated as necessary. At first the anterior fontanelle was used, then the saphenous vein at the ankle, and only in the later cases was transfusion given by the umbilical vein. Of 35 babies treated by simple transfusion 17 died. The author reported that a new transfusion technique (exchange transfusion) was being tried at the time of writing but that the early results were less satisfactory than had been anticipated.

Kernicterus did not develop in any baby before the age of 18 hours but was present in 37 (34%) of the cases of severe jaundice. The serum bilirubin concentrations in babies with kernicterus ranged from 10 to 20 mg/100 ml (170 to 340 µmol/l). All but two of the babies with kernicterus died: 33 within two weeks of birth. Four babies survived beyond the age of 2 weeks: two died in infancy and two survived to develop cerebral palsy.

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