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Population based survival rates for childhood cancer in Britain, 1980-91

C A Stiller

Abstract

***Objectives*—To investigate the survival of children with cancer diagnosed during 1980-91 in order to assess the impact of developments in medical care on a population basis.**

***Design*—Retrospective cohort study.**

***Setting*—Great Britain.**

***Subjects*—14 973 children with cancer diagnosed during 1980-91 and included in the population based National Registry of Childhood Tumours.**

***Main outcome measures*—Actuarial survival rates.**

***Results*—For all cancers combined, two year survival increased from 66% to 76% between 1980-2 and 1989-91, and five year survival increased from 57% to 65% between 1980-2 and 1986-8. Significant increases in survival rates occurred among children with acute lymphoblastic leukaemia, acute non-lymphocytic leukaemia, retinoblastoma, osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, and malignant gonadal germ cell tumours. No trend in survival was seen for children with Hodgkin's disease, central nervous system tumours, neuroblastoma, or Wilms's tumour.**

***Conclusions*—Nearly two thirds of children who have cancer diagnosed can now expect to survive at least 10 years.**

Introduction

In Britain survival rates for a wide range of childhood cancers improved substantially between 1971 and 1985 as a result of advances in treatment together with increased centralisation of care.[1] The objectives of this study were, firstly, to examine the survival of children with cancer diagnosed during 1980-91 in order to assess the impact of recent developments in medical care on survival for children with cancer diagnosed since 1985 and, secondly, to document the longer term survival of those whose cancer was diagnosed during 1980-5 and for whom follow up in the previous report was relatively short.

Patients and methods

The National Registry of Childhood Tumours includes children who lived in England, Scotland, or Wales and were aged under 15 at the time of diagnosis of a malignant neoplasm or a non-malignant intracranial or intraspinal tumour. Children are ascertained from the national cancer registration schemes, which cover the whole of Britain through a network of regional registries; from local population based childhood cancer registries in several regions; from entries to the Medical Research Council leukaemia trials; and from the register of patients treated by members of the United Kingdom Children's Cancer Study Group. The registry also receives death certificates for all deaths occurring in Britain in people under the age of 20 in whom neoplasm was coded as the underlying cause.

This study includes all children in the registry who were diagnosed during 1980-91, except for those notified by death certificate alone. These children were excluded to avoid bias since unregistered survivors could not have been ascertained. Not all cancer registrations for 1989-91 have yet been received, but if the incidence is assumed to have remained constant, less than 5% of cases from those years remain to be registered.

For children included in national and international trials and for those in the register of the United Kingdom Children's Cancer Study Group changes of diagnosis are notified to the registry routinely. Diagnoses of children who have died are checked about two years after death. Medical records of the remaining children are reviewed after about five years to confirm the diagnosis and obtain a brief outline of follow up information. Some diagnoses from 1988-91 have not yet been checked, but it is unlikely that there will be many changes. Survivors are flagged in the NHS central registers so that the registry will be notified of any further deaths and of emigrations resulting in loss to follow up. Follow up of survivors through flagging was complete to the end of 1993.

Childhood tumours comprise a wide variety of histological types, several of which are seen only rarely in adults. A classification based mainly on primary site such as the International Classification of Diseases is therefore inappropriate for childhood cancer. Diagnoses in the registry are coded according to the International Classification of Diseases for oncology; for this study they have been classified according to the standard scheme for childhood cancer,[2] which defines groups largely by histology, but with a few modifi-

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cations to take account of recent clinical and pathological practice.[1]

Survival rates were calculated by standard actuarial methods. Differences between the survival curves were tested by log rank tests and the χ^2 test for linear trend. Three tests were performed: (*a*) for overall survival from the date of diagnosis; (*b*) for survival in the first year after diagnosis in order to detect improvements in early control of disease; and (*c*) for survival after the first year in order to detect improvements in the maintenance of long term remission, though length of follow up may be insufficient to show improvements in longer term survival for children with cancer diagnosed most recently.

Results

For all cancers combined the actuarial two year survival rate increased from 66% among children diagnosed during 1980-2 to 76% among those diagnosed during 1989-91. Between 1980-2 and 1986-88, five year survival increased from 57% to 65%.

Table I shows the total numbers of cases analysed for each diagnostic group containing at least 200 cases, together with the actuarial two and five year survival rates for children diagnosed in successive three year periods from 1980-2 to 1989-91. The figure shows the actuarial survival curves for children in selected diagnostic groups.

Leukaemia—There was a significant increase in the survival rates for acute lymphoblastic leukaemia (figure (*a*)). Boys had a lower survival rate than girls, but the difference was less among those who had had leukaemia diagnosed since 1983. Children aged 2-9 years at diagnosis had a consistently better prognosis than those aged 0-1 or 10-14; the trend towards increased survival was observed for all three age groups, though it was not significant for the youngest children. The improvement in survival in the first year was significant for both boys and girls and for children aged 2-9. Increases in survival after the first year were significant for boys but not girls and for children aged 2-9 and 10-14 but not those aged 0-1. Survival rates for children with acute non-lymphocytic leukaemia were low in the early 1980s but improved significantly between then and 1989-91, with two year survival increasing from 30% to over 50% (figure (*b*)). There were significant trends in survival both during the first year after diagnosis and subsequently.

Lymphomas—Children with Hodgkin's disease had a high survival rate by 1980 and no further improvement occurred during the study period. For non-Hodgkin's lymphoma there was a significant improvement in survival, mainly occurring between 1980-2 and 1986-8 (figure (*c*)). The trend was greatest for survival beyond the first year after diagnosis.

Central nervous system tumours—The only significant trend in overall survival for any subgroup was for medulloblastoma and other primitive neuroectodermal tumours ($P < 0.05$). The significant increase in one year survival for astrocytoma was entirely due to improvement between 1980-2 and 1983-5.

Sympathetic nervous system tumours—The improvement in survival of children with neuroblastoma was not significant. Infants aged under 1 year, who have a better prognosis, accounted for a slightly higher proportion of cases in the earlier years. When age at diagnosis was allowed for, classified as 0, 1, 2, and 3-14 years, the trend was significant overall ($\chi^2 = 7.55$, df = 1), though not for any individual age group. Substantial numbers of deaths have occurred more than three years after diagnosis among children diagnosed before 1989, and it remains to be seen whether there will be any increase in the long term survival of children diagnosed since then.

Retinoblastoma—Five year survival already exceeded 85% among children diagnosed during 1980-2. Nevertheless, there was a significant improvement in survival over the study period, being strongest for survival more than one year after diagnosis. Survival rates were improved equally among children with unilateral and bilateral tumours.

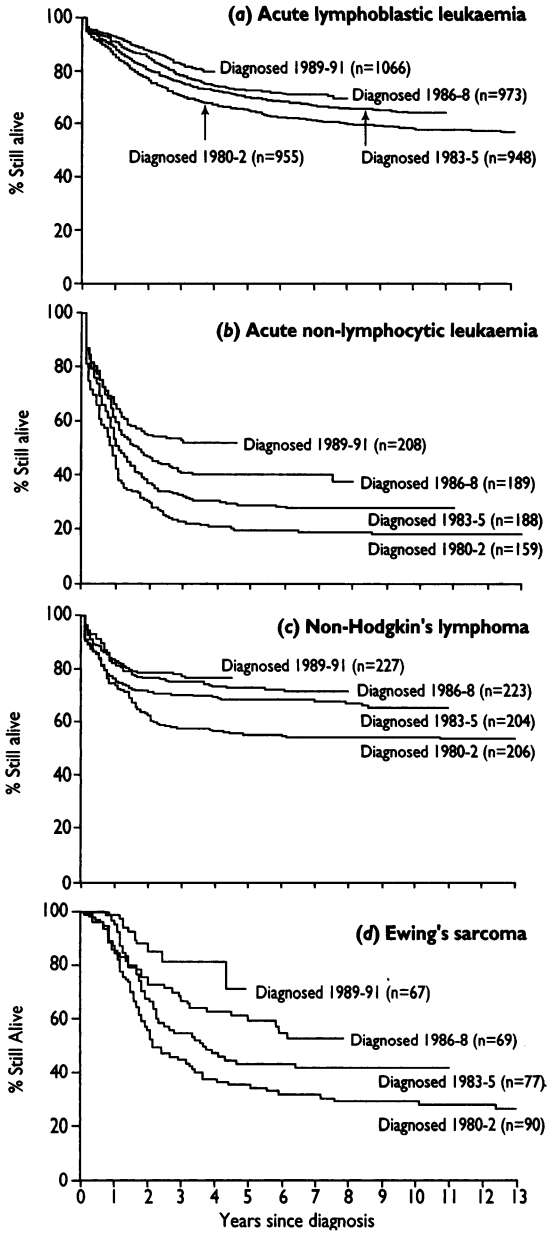
Renal tumours—An apparent modest improvement in survival occurred for Wilms's tumour during 1980-8, but survival rates for children diagnosed in 1989-91 were similar to those for 1983-5 and the trend over the whole study period was not significant.

Malignant bone tumours—Survival rates for osteo-

TABLE I—*Two and five year actuarial percentage survival rates for children according to year of diagnosis of cancer*

Diagnostic group	Total registrations	Two year survival (SE)				Five year survival (SE)			χ^2 For trend*		
		1980-2	1983-5	1986-8	1989-91	1980-2	1983-5	1986-8	Overall	First year	After first year
Leukaemia:											
Acute lymphoblastic	3942	76 (1·4)	80 (1·3)	84 (1·2)	87 (1·0)	65 (1·5)	70 (1·5)	73 (1·4)	45·8	32·4	16·5
Acute non-lymphocytic	744	30 (3·6)	37 (3·5)	46 (3·6)	55 (3·5)	19 (3·1)	29 (3·3)	40 (3·6)	38·2	19·6	20·8
Lymphomas:											
Hodgkin's disease	644	96 (1·5)	97 (1·3)	96 (1·5)	95 (2·1)	90 (2·1)	91 (2·3)	93 (2·0)	0·27	0·06	0·43
Non-Hodgkin's, Burkitt's and unspecified	860	62 (3·4)	71 (3·2)	76 (2·9)	78 (2·7)	55 (3·5)	68 (3·3)	73 (3·0)	18·0	5·83	16·3
Central nervous system plus intracranial and intraspinal:											
Ependymoma	353	57 (5·2)	61 (5·0)	74 (5·2)	63 (5·0)	39 (5·1)	53 (5·1)	50 (5·9)	0·79	2·26	0·07
Astrocytoma	1291	69 (2·6)	75 (2·4)	75 (2·3)	75 (2·5)	65 (2·7)	73 (2·5)	71 (2·5)	3·46	5·78	0·08
Medulloblastoma or primitive neuroectodermal	745	50 (3·7)	53 (3·6)	59 (3·7)	58 (3·6)	37 (3·6)	43 (3·5)	42 (3·7)	3·88	2·15	1·73
Other or unspecified	995	53 (3·2)	51 (3·2)	58 (2·9)	54 (3·3)	47 (3·2)	45 (3·2)	54 (3·0)	2·10	0·02	7·18
Sympathetic nervous system:											
Neuroblastoma	997	47 (3·4)	51 (3·4)	47 (3·0)	58 (2·9)	38 (3·3)	43 (3·4)	37 (2·9)	2·96	13·8	1·86
Retinoblastoma	415	91 (3·2)	94 (2·3)	97 (1·7)	97 (1·5)	87 (3·8)	89 (3·0)	94 (2·2)	6·57	0·28	6·91
Renal tumours:											
Wilms's tumour	860	80 (2·8)	85 (2·5)	89 (2·1)	85 (2·4)	76 (3·0)	80 (2·8)	84 (2·4)	2·36	2·29	0·42
Malignant bone tumours:											
Osteosarcoma	353	45 (4·8)	67 (5·2)	66 (5·0)	68 (5·5)	35 (4·6)	53 (5·5)	51 (5·3)	7·27	6·03	2·51
Ewing's sarcoma	303	55 (5·2)	68 (5·3)	72 (5·4)	85 (4·4)	35 (5·1)	43 (5·6)	59 (6·0)	25·9	4·88	21·0
Soft tissue sarcomas:											
Rhabdomyosarcoma	645	59 (4·0)	69 (3·6)	64 (3·7)	74 (3·4)	49 (4·1)	60 (3·9)	56 (3·9)	5·97	5·49	1·31
Gonadal and germ cell:											
Non-gonadal germ cell:											
Intracranial	98	77 (8·9)	58 (8·9)	78 (9·8)	65 (9·6)	73 (9·5)	52 (9·0)	63 (13)	1·85	3·61	0·03
Other	111	58 (9·7)	73 (11)	87 (6·2)	80 (6·3)	50 (9·8)	67 (12)	77 (7·7)			
Gonadal germ cell:											
Testicular	130	93 (4·9)	94 (4·0)	100	97 (3·0)	82 (7·2)	94 (4·0)	97 (2·8)	6·90	4·13	2·90
Ovarian	100	83 (6·8)	79 (8·3)	85 (6·8)	100	83 (6·8)	79 (8·3)	85 (6·8)			
All cancers	14 973	66 (0·8)	70 (0·8)	73 (0·7)	76 (0·7)	57 (0·8)	63 (0·8)	65 (0·8)			

*One degree of freedom. Note two sided critical values for χ^2 are P = 0·05, 3·84; P = 0·01, 6·63; P = 0·001, 10·83.



Actuarial survival curves for children with cancer diagnosed in 1980-91

sarcoma significantly increased between 1980-2 and 1983-5 but no subsequent improvement was seen. The trend was significant for the first year after diagnosis but not after the first year. Survival for Ewing's sarcoma increased significantly throughout the study period (figure (*d*)). This was largely accounted for by a big improvement in the survival of patients who had already survived one year, though there was also a significant improvement in one year survival.

Soft tissue sarcomas—Survival rates significantly increased for rhabdomyosarcoma, with greatest improvements at the start and finish of the study period. Most of the improvement related to the first year after diagnosis.

Germ cell, trophoblastic, and other gonadal neoplasms—Survival of children with malignant germ cell tumours of all non-gonadal sites combined showed little change. There was a significant improvement in survival for gonadal germ cell tumours, which was largely accounted for by the trend for boys with testicular tumours. Only one death has so far been recorded among children with gonadal germ cell tumours diagnosed during 1989-91; this was in a 14 year old boy with malignant testicular teratoma.

Children who had cancer diagnosed later in the study had only a short follow up. To predict the outcome for children who had cancer diagnosed in 1989-91 from previous results, projected 10 year survival rates were calculated as the three year actuarial survival rates for 1989-91 multiplied successively by six year survival conditional on three year survival for 1986-8, nine year survival conditional on six year survival for 1983-5, and 10 year survival conditional on nine year survival for 1980-2 (table II). The projected improvement in survival for childhood cancer from 53% for those identified in 1980-2 to 63% for those identified in 1989-91 represents a 19% increase over less than 10 years.

Discussion

Only 26% of children with cancer diagnosed during 1962-70 survived five years from diagnosis.[3] Of the major diagnostic groups, only Hodgkin's disease, astrocytoma, and retinoblastoma had a five year survival rate above 50%, and five year survival for acute lymphoblastic leukaemia was under 10%. By 1980 survival had improved greatly for most types of cancer,[1] the main exceptions being retinoblastoma, which already had an excellent prognosis with five year survival over 85%, and Ewing's sarcoma, for which survival remained below 50%. Since then further substantial and significant increases in survival rates have occurred, at least in the short term, for most of the main types of childhood cancer. The greatest improvement in survival recently was seen in diagnostic groups that previously had a poor prognosis such as acute non-lymphocytic leukaemia and Ewing's sarcoma. In cancers whose survival rates were already high by 1980 there was little room for further improvement, but there was nevertheless a significant trend for retinoblastoma, with five year survival increasing from 87% in 1980-2 to 94% in 1986-8.

Population based data on survival of children with cancer in the 1980s are available from few other countries. The only series with comparable numbers of cases are those of the surveillance, epidemiology, and end results programme in the United States[4] and the national childhood cancer registry in Germany[5] (table III). In the United States recorded survival rates were higher than in Britain for several diagnostic groups during 1980-2 but only for neuroblastoma throughout 1980-8. In Germany survival rates were also higher for several of the main types of childhood cancer during the early 1980s, and the gap between British and German survival rates for several diagnostic groups persisted until 1989-91.

TABLE II—*Ten year survival rates (%) for children with cancer diagnosed in 1980-2 and projected 10 year survival for children with cancer diagnosed in 1989-91*

	1980-2	1989-91
Leukaemia:		
Acute lymphoblastic	58	70
Acute non-lymphocytic	18	50
Lymphoma:		
Hodgkin's disease	87	86
Non-Hodgkin's	54	70
Central nervous system:		
Ependymoma	36	39
Astrocytoma	60	67
Medulloblastoma or primitive neuroectodermal	30	38
Other and unspecified	41	47
Sympathetic nervous system:		
Neuroblastoma	36	39
Retinoblastoma	83	95
Renal tumours:		
Wilms's tumour	76	78
Malignant bone tumours:		
Osteosarcoma	33	48
Ewing's sarcoma	29	64
Soft tissue sarcomas:		
Rhabdomyosarcoma	49	59
Gonadal and germ cell:		
Non-gonadal germ cell	58	64
Gonadal germ cell	83	96
All cancers	53	63

TABLE III—*Survival rates (%) for childhood cancer in Britain, United States,[4] and western Germany[5]*

	Five year survival, 1980-2			Five year survival, 1983-8		Two year survival, 1989-91	
	Britain	United States	Germany	Britain	United States	Britain	Germany
Acute lymphoblastic leukaemia	65	70	76	72	72	87	89
Acute non-lymphocytic leukaemia	19	23	38	34	30	55	59
Hodgkin's disease	90	91	93	91	88	95	98
Non-Hodgkin's lymphoma	55	62	73	71	69	78	89
Central nervous system tumours	51	55	49	57	59	64	68
Neuroblastoma	38	52	48	40	55	58	71
Retinoblastoma	87	—	93	—	—	97	98
Wilms's tumour	76	86	84	81	87	85	96
All malignant bone	35	54	—	51	56	—	—
Osteosarcoma	35	—	65	—	—	68	87
Ewing's sarcoma	35	—	44	—	—	85	79
Rhabdomyosarcoma	49	—	50	—	—	74	83
Malignant germ cell	73	—	71	—	—	85	86

FACTORS AFFECTING SURVIVAL

During the study period many children with acute lymphoblastic leukaemia, acute non-lymphocytic leukaemia, non-Hodgkin's lymphoma, osteosarcoma, rhabdomyosarcoma, and germ cell tumours were included in national or international trials for these diseases, and the improved survival in the more recent trials[6-13] is reflected in the population based survival rates presented here.

The improved survival rate for acute non-lymphocytic leukaemia up to 1988 has already been reported.[14] The results here show that in the subsequent three years, when most children were entered in the tenth Medical Research Council trial on acute myeloblastic leukaemia,[7] this trend has continued. Twenty years ago acute non-lymphocytic leukaemia in childhood was almost always fatal, but now around half of all children with this disease are probably cured.

There was little sign of any increase in survival rates for most types of central nervous system tumours. Several clinical trials have begun recently, and these will hopefully lead to improved treatment.

Survival rates for neuroblastoma in Britain were consistently lower than those in the United States and Germany. In Finland five year survival for neuroblastoma during 1980-6 was 57%,[15] again substantially higher than the figure for Britain. A survival rate of 67% during 1981-9 was reported from Japan,[16] but this was raised artificially by the inclusion of many infants with good prognosis tumours who were detected by Japan's mass screening programme for neuroblastoma. The fall in neuroblastoma mortality in the Japanese population[17] is consistent with improved treatment results similar to those in other countries.

Improved survival for children with advanced neuroblastoma treated during the 1980s has been reported from clinical trials in Germany and the United States.[18 19] During the mid-1980s many children with neuroblastoma in Britain were entered in the European Neuroblastoma Study Group's third series of studies.[20-22] Medium term survival rates from these studies have yet to be published.

The significant improvement in the already high survival rate for retinoblastoma coincided with an increase in the proportion of children who were initially referred to the national treatment centre for this tumour. In the immediately preceding period, children who were treated at that centre had a higher survival rate than elsewhere.[23]

Survival for Wilms's tumour did not improve during the study period. Most children present with localised disease and have a good prognosis, and those who were entered in national studies received less treatment, particularly radiotherapy, than previously, with the aim of decreasing the risk of late effects without compromising the high survival rate.[24]

Survival in children with Ewing's sarcoma has substantially improved, five year survival for 1986-8 being nearly 60%. Many children have been entered in the joint Medical Research Council and United Kingdom Children's Cancer Study Group trial. This trial included ifosfamide in the chemotherapy protocol, and this is likely to have contributed to the improved survival, though its effect may be most valuable in patients with primary tumours that are bulky or in sites with poor prognosis.[25]

FUTURE TRENDS

For many of the principal types of childhood cancer, survival rates during the first half of the study period were higher among patients who were treated at specialist centres, at hospitals treating large numbers of children, or in multicentre clinical trials.[14 23 26 27] During 1986-91 an estimated 72% of children received their initial treatment for cancer from members of the United Kingdom Children's Cancer Study Group, and for leukaemia, non-Hodgkin's lymphoma, rhabdomyosarcoma, and the common embryonal tumours of childhood the proportion exceeded 80%. Consequently, comparative analyses of survival between specialist centres and other hospitals for this period would be able to detect only large differences.

The projections of 10 year survival for children who had cancer diagnosed in 1989-91 suggested an overall increase in survival of 19% since 1980-2. The projections will be underestimates of the eventual true survival rate if improvements in shorter term survival are matched in the longer term, as is the hope for several diagnostic groups, but overestimates if current treatment merely postpones some deaths, perhaps a particular concern for neuroblastoma. Substantial increases are predicted for most diagnostic groups, with the exception of Hodgkin's disease, central nervous system tumours, neuroblastoma, and Wilms's tumour. Long term follow up suggests that most children who survive for 10 years can be regarded as cured.[3]

Key messages

- Two year survival for all childhood cancers improved from 66% to 76% between 1980-2 and 1989-91
- Ten year survival has increased from 53% to a projected 63%
- Survival has increased among children with acute leukaemia, non-Hodgkin's lymphoma, retinoblastoma, bone sarcomas, and rhabdomyosarcoma, though not for those with brain tumours or neuroblastoma
- There are now over 10 000 adult survivors of childhood cancer in Britain and this number is increasing by more than 500 a year
- Many survivors have received potentially highly toxic treatment and continuing follow up is essential

The trend towards higher survival rates for childhood cancer over the past 30 years has resulted in a growing number of long term survivors, many of whom have reached adulthood. The registry shows that by the end of 1993 there were over 10 000 survivors of childhood cancer in Britain who were aged 18 and over, and this number is increasing by more than 500 per year. In general, survivors of childhood cancer are fit, employable, and in most respects indistinguishable from their peers. Late effects do occur, however, mostly as a result of treatment.[28] Long term survivors have been the subject of systematic studies of the occurrence of second primary neoplasms,[29] mortality from other causes,[3] and reproductive history both in Britain and elsewhere.[30-32] As the number of survivors increases, many of whom have received potentially highly toxic treatment, it is essential that such studies are continued.

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A PATIENT WHO CHANGED MY CAREER

Corneal lens donation puts ophthalmic career in sharp focus

As an enthusiastic medical student I was inspired by the concept of the eyes being the window to the body. Ophthalmology seemed to represent all the mystery and skill of the traditional physician's craft, complemented by the glamour of surgery. I sensed that I had found a niche as others dabbled with different subjects hoping to uncover their vocation. During my fourth year of medical school I planned the foundation for my ophthalmology career. This took the form of electives in ophthalmic centres of excellence and a research study into unnecessary enucleation in children incorrectly diagnosed as suffering from retinoblastoma.

Ophthalmology clinics were hectic, the Snell chart and slit lamp proved manageable; the retina, however, continued to present images like a kaleidoscope, which I struggled to interpret. I also observed ophthalmic microsurgery and marvelled at the surgeons' patience and delicate skill.

My first surgical experience occurred when I was called to a corneal donor during my final year elective. I met the ophthalmic registrar and we headed for a local nursing home. I met my first and recently deceased patient lying in the stillness and damp chill of the nursing home mortuary. In the traditional style it was suggested by the supportive registrar that I should see one then do one. I proceeded to enucleate an eye socket before placing the eye in a small tin box. As I completed the cosmetic gesture of filling the empty orbit with cotton wool I felt a chilling rush as I saw my future. This patient had had the courage to gift sight to a visually impaired person after her death but she also allowed me to see that ophthalmology was not for me. I now enjoy orthopaedic surgery and only occasionally glance inquisitively through the body's window.—GORDON MATHESON MACKAY *is an orthopaedic registrar in Greenock*