PAPERS AND ORIGINALS

Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs*

L J KINLEN, A G R SHEIL, J PETO, RICHARD DOLL

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Summary and conclusions

A collaborative study including centres in the United Kingdom, Australia, and New Zealand was instituted in 1970 to determine the incidence of cancer in patients treated for at least three months with azathioprine, cyclophosphamide, or chlorambucil. Follow-up of 3823 renal transplant recipients showed an almost 60-fold increase of non-Hodgkin's lymphoma together with an excess of squamous-cell skin cancer and mesenchymal tumours. A series of 1349 patients without transplants showed an excess of the same tumours, though to a less extent.

These preliminary findings provide no clear evidence that immunosuppressive drugs produce the increased risk of most of the common cancers that might be expected from the simplest interpretation of impaired "immunosurveillance."

Introduction

In 1970 a study was instituted with the support of the Cancer Research Campaign to investigate the incidence of cancer in patients treated with immunosuppressive drugs. This was prompted by the great interest in "immunosurveillance," a concept that had been formulated by Thomas[1] and developed by Burnet[2]—namely, that cancer had its earliest beginnings in aberrant cells that were normally eliminated by the immune system. Support for this was adduced from work on animals, but human data were scanty until immunosuppressive drugs began to be used on a large scale in renal transplantation and for various medical disorders. It then became possible to see whether drugs that impaired immunological function favoured the development of cancer in man.

By 1970 the number of cases of reticulum-cell sarcoma reported in renal transplant recipients suggested that these patients experienced a substantially increased risk of this type of malignancy.[3,4] It was not known, however, whether the incidences of other types of cancer were also increased and whether any excess risk was associated with immunosuppressive treatment in the absence of foreign antigens in organ transplants. Since such questions could be answered only by assembling a large number of suitable cases for follow-up, a collaborative group was organised consisting of the directors of most of the larger renal transplant units in the United Kingdom and many nephrologists, rheumatologists, gastroenterologists, and other physicians who were known to use immunosuppressive drugs in their clinical practice. Shortly after the study began it was extended through Professor Sheil and the Australasian Transplant Subcommittee to cover all transplant centres in Australia and New Zealand. We present here the preliminary results of this collaboration.

*A list of past and present participants in the study is given in miniprint in this paper.

Imperial Cancer Research Fund Cancer Epidemiology and Clinical Trials Unit, Department of Social and Community Medicine, University of Oxford, Oxford OX1 3QG

L J KINLEN, DPHIL, MRCP, Gibb fellow of the Cancer Research Campaign
J PETO, MA, MSC, statistician
SIR RICHARD DOLL, D SC, FRCP, FRS, honorary director

Department of Surgery, University of Sydney, New South Wales, Australia

A G R SHEIL, FRACS, professor of surgery

Methods

NOTIFICATION

Participants agreed to notify patients in whom azathioprine, cyclophosphamide, or chlorambucil had been used for at least 12 weeks for a non-malignant disorder. Information on each patient included date of birth, underlying disorder, name of the drug, date of starting treatment, and, in the case of transplant recipients, source of the graft (cadaver, mother, etc). Patients with transplants were included from other years, since records in transplant centres permitted complete ascertainment of eligible patients. In most medical centres, however, notification was restricted to cases in

which immunosuppressive treatment was instituted after the study began. Patients known to have had cancer at the time they were eligible for entry to the study were excluded.

FOLLOW-UP

All UK patients were followed up yearly from the date of starting treatment to see whether they were alive, still receiving immunosuppressive drugs, and free from cancer. Patients no longer under the care of the notifying consultant were followed up through their general practitioners or through the consultants to whose care they had been transferred. If death had occurred or the drug had been stopped the relevant dates were recorded as well as those of any subsequent courses of the drugs in question. When cancer had been diagnosed further details were requested. A copy of the death certificate was obtained for all patients who died in the UK and for all who died after a diagnosis of cancer in Australia and New Zealand. Follow-up information on Australian and New Zealand patients was provided from the records of the Australasian Transplant Subcommittee, which were updated every six months.

PATIENTS WITH CANCER AND CONTROLS

The hospital records of all patients who developed cancer, including all tumours of the central nervous system, were examined and details of present and past medical history and doses of immunosuppressive drugs used extracted. For patients who had undergone transplantation, data were also extracted relating to the HLA and ABO blood groups of recipient and donor together with possible and definite rejection crises. For comparison similar information was obtained on patients who had not developed malignant disease, but as there were so many more of these this was sought for only one-eighth of the patients, who were chosen at random. Information was not available for all of the recent cases of cancer, and the total number of patients with cancer in these analyses is therefore lower than those used in analyses of mortality and incidence rates.

ANALYSIS

In the mortality analysis the observed numbers of deaths from cancer were compared with "expected" figures obtained by multiplying the person-years at risk for each sex and five-year age group in each quinquennium by the corresponding age-specific and sex-specific national mortality rates. The data were made as comparable as possible with those from which the mortality rates were derived by recording observed deaths as due to cancer only when death had been so attributed in the death certificate.

The observed numbers of *cases* of cancer in UK patients were compared with the numbers expected from the cancer incidence rates in the general population. The rates recorded by the Birmingham Cancer Registry[5] were taken as representative, and the Birmingham rate for each sex in each five-year age group applied to the corresponding number of person-years at risk.

Cancer registration had been introduced recently in one Australian state (New South Wales) but it was not clear how representative the data were for the whole country, and we preferred to calculate expected figures for Australasia by applying Australian age-specific mortality rates inflated by the corresponding ratios of incidence to mortality rates in New Zealand, which is the most comparable country with longstanding cancer registration. (Pilot analysis showed that the use of separate New Zealand figures for the New Zealand patients made only a trivial difference to the results. Analyses using the most recent incidence data from New South Wales will be made in future.) Expected numbers for skin cancer in Australasia could not, however, be calculated in this way, as the New Zealand data exclude skin cancer; nor would they, in any case, have been of any help, as the incidence of skin cancer varies greatly with latitude.

Because the methods differed by which the study received follow-up information on UK and Australasian patients the period covered by this report differs between the two groups. All Australasian patients were followed up to 30 April 1977, whereas the UK analysis incorporates events up to the beginning of the quarter in which the latest anniversary of starting immunosuppressive treatment occurred before 30 September 1978.

Results

The study population falls conveniently into four groups—namely, UK and Australasian transplant series, and UK and Australasian non-transplant series. Follow-up of the Australasian non-transplant series, however, was incomplete and no observations on these patients are included here. Tables Im and IIm (miniprint) give the age and sex distribution of patients with at least one yearly follow-up in each of the other three groups. As expected, the proportions of patients aged under 15 and over 54 were larger in the non-transplant series (12·6% and 25·2% respectively) than in the transplant series (3·8% and 4·3% respectively).

Tables IIIm and IVm list the underlying disorders, which were provided by the participants and varied greatly in diagnostic detail. Only when terms such as uraemia and chronic renal failure were used was the participant routinely asked for further information. The large proportion of transplant recipients with "other, multiple, and unspecified renal disorders" (table IIIm) reflects the difficulty of making a precise single diagnosis in patients who present with end-stage renal failure. The larger proportion of transplant recipients with analgesic nephropathy in Australasia than in the UK may be related to the greater prevalence of analgesic abuse in Australia, particularly in women. In the Australasian series analgesic nephropathy was responsible for 19·0% of all renal failure in women and girls treated by transplantation; in the UK series the figure was 2·1%. The paucity of such cases in the UK, however, was largely compensated for by an excess of cases of chronic pyelonephritis (the two diagnoses account for 19% and 18% of all transplant operations in Australasia and the UK respectively), and possibly the diagnostic criteria in the two countries differ.

In patients without transplants the most common underlying disorders were rheumatoid arthritis and related conditions (36%), but renal and gastrointestinal disorders were also well represented.

TRANSPLANT SERIES

Mortality

Table Vm gives the observed and expected numbers of deaths attributed to cancer in the UK and Australasian transplant series combined. Non-Hodgkin's lymphomas (including microgliomas) and skin cancers were considered separately because of evidence that their incidence was likely to be increased. A 26-fold excess of deaths from non-Hodgkin's lymphoma was evident, with eight deaths observed compared with 0·30 expected. The true excess was even greater, as three deaths certified as due to a cerebral tumour and two attributed to gastric cancer were, in fact, found histologically to be due to lymphomas. The actual number of deaths from non-Hodgkin's lymphoma was therefore 13. In contrast there was no death from Hodgkin's disease in either the UK or Australasian series (0·18 expected).

The only non-lymphoid cancer for which a material excess was observed in mortality was skin cancer; three deaths were observed, all of squamous-cell type and all in Australia, as against 0·33 expected, suggesting a 10-fold increase in mortality. In Australia four other deaths attributed to carcinomatosis or lung cancer in the death certificate were considered clinically to be due to squamous carcinomas of the skin with metastases in the lung and other sites. Such cases are very uncommon in the general population. According to J Ford (personal communication) only 0·3% of deaths certified as due to carcinomatosis in New South Wales were, in fact, due to skin cancer

MINIPRINT LIST OF PAST AND PRESENT PARTICIPANTS

UNITED KINGDOM—*Ascot*: Dr S P Liyanage, Heatherwood Hospital. *Bath*: Dr P A Bacon, Dr A K Clarke, Dr J A Cosh, Dr A St J Dixon, and Dr M Jayson, Royal National Hospital for Rheumatic Diseases. *Belfast*: Dr M G McGown, City Hospital. *Birmingham*: Mr A D Barnes and Professor J D Blainey, Queen Elizabeth Hospital; Dr R H R White, Children's Hospital, Ladywood. *Bristol*: Mr H J O White, Southmead Hospital. *Cambridge*: Professor R Calne and Dr D B Evans, Addenbrooke's Hospital. *Cardiff*: Mr J R Salaman and Mr D Crosby, Royal Infirmary. *Edinburgh*: Dr J L Anderton and Sir Michael Woodruff, Western General Hospital; Professor J S Robson, Royal Infirmary. *Glasgow*: Mr D N H Hamilton and Mr P R F Bell, Western Infirmary. *Leeds*: Dr S R Meadow, St James's University Hospital. *Liverpool*: Dr H J Goldsmith and Mr R A Sells, Sefton General Hospital. *London*: Sir Francis Avery Jones and Dr J J Mitchell, Central Middlesex Hospital; Mr G B Williams, Charing Cross Hospital (Fulham); Mr M Bewick, Professor J S Cameron, Mr F Ellis, and Professor M H Lessof, Guy's Hospital; Mr J E Castro, Professor R Shackman, Mr G Williams, and Dr S Woolledge, Hammersmith Hospital; Dr J F Scott, Kennedy Institute of Rheumatology; Dr R Williams and Dr V Pereira, King's College Hospital; Dr B E W Mace and Dr J S Stafforth, Lewisham Hospital; Dr J M Grumpel, Mount Vernon Hospital; Dr B M Ansell, and Dr M Denman, Northwick Park Hospital; Mr O N Fernando and Dr J F Moorhead, Royal Free Hospital; Professor R N Brooke, St George's Hospital; Dr J L Lennard-Jones and Dr J K Ritchie, St Mark's Hospital; Dr B Hulme and Professor W S Peart, St Mary's Hospital; Dr E N Gaffney, St Stephen's Hospital, Chelsea; Dr N F Jones, St Thomas's Hospital; Dr C Barnes, Professor H L F Curry, Dr F J Goodwin, Professor J Ledingham, Dr F Marsh, Dr M Mason, (deceased), and Professor D W Vere, The London Hospital. *Manchester*: Mr W McN Orr, Royal Infirmary. *Newcastle*: Dr W Elliott, Dr R H Jackson, Professor D N S Kerr, and Dr R Uldall, Royal Victoria Infirmary. *Oxford*: Dr S Truelove and Professor P Morris, Radcliffe Infirmary. *Sheffield*: Mr M Fox and Dr I B Snowden, Hallamshire Hospital. *Stevenage*: Dr J M T Willoughby, Lister Hospital. *Stoke-on-Trent*: Dr G M Aber, North Staffordshire Royal Infirmary. *Taplow*: Dr B M Ansell and Dr E G L Bywaters, Canadian Red Cross Memorial Hospital. *Teesside*: Dr D H Kenward, North Ormesby Hospital.

AUSTRALIA—*Adelaide*: Dr J Lawrence, Dr T Mathew, and Dr D Pugsley, Queen Elizabeth Hospital, Woodville. *Brisbane*: Professor G J A Clunie, Professor B T Emmerson, and Dr J Hardie, Princess Alexandra Hospital. *Concord*: Dr C R P George, Repatriation General Hospital. *Hobart*: Dr J Freeman, Royal Hobart Hospital. *Melbourne*: Dr G W Gurr, The Alfred Hospital; Dr D M Scott, Prince Henry Hospital; Dr V Marshall, Dr T Mathew, and Professor P Kincaid-Smith, Royal Melbourne Hospital; Dr J F Nall, St Vincent's Hospital; Dr J Dawborn, The Austin Hospital. *Perth*: Dr P E Hurst, Royal Perth Hospital. *Sydney*: Dr M Robertson, Prince Henry Hospital; Professor A G R Sheil and Dr D Tiller, Royal Prince Alfred Hospital; Professor A G R Sheil, Dr J Mahony, and Dr J Stewart, Sydney Hospital; Dr J M Hayes, St Vincent's Hospital.

NEW ZEALAND—*Auckland*: Dr P B Doak and Professor J D J North, Auckland Hospital. *Christchurch*: Dr R R Bailey and Dr P J L Little, Christchurch Hospital. *Hamilton*: Mr A D Mee, Waikato Hospital. *Wellington*: Dr R B I Morrison, Wellington Hospital.

with metastases, so the excess mortality from skin cancer was probably much greater than that implied in table Vm.

If we exclude the nine deaths from "other" cancers that were actually due to lymphoma or skin cancer the slight excess of deaths attributed to cancers other than skin and non-Hodgkin's lymphoma (16 observed, 9·72 expected) is changed to a deficit. A deficit was, in fact, to be expected if the incidence of these cancers was not influenced by treatment, as patients had to be initially free from cancer to be admitted to the study, whereas this restriction did not apply to the national population, whose mortality rates were used for comparison.

Incidence of cancer

Table VI shows the numbers of cases of cancer that were observed and expected. Skin cancer in Australasia and cervical carcinoma-in-situ in both series are omitted because of the difficulty of obtaining appropriate figures for estimating the numbers expected. The pronounced contrast between the number of deaths from cancer (27) and the number of cases of cancer (69) was due partly to the fact that some patients with cancer survived to the end of the study period and partly to the fact that some patients with cancer had another cause certified as the underlying cause of death. Table VI shows that there was a grossly increased incidence of non-Hodgkin's lymphoma (34 cases observed as against 0·58 expected) and, in the UK, an excess incidence of squamous-cell cancer of the skin (three cases observed as against 0·13 expected). Fifteen of the 34 non-Hodgkin's lymphomas affected the brain and presented typically as space-occupying lesions that prompted standard investigation. The extent of the specific increase in the risk of cerebral non-Hodgkin's lymphoma could not, however, be measured separately, as neither incidence nor mortality data are available for this condition in any population. It is, however, normally so rare that the occurrence of two cases was commented on in 1968,[6] and the increased risk must be enormous.

The excess of lymphomas could not be explained by the close medical supervision of transplant recipients that led to a high necropsy rate, as only six cases (18%) were first detected post mortem.

A striking feature in table VI is the short interval between transplantation and the appearance of an excess of non-Hodgkin's lymphomas: this was over 70-fold within two years of entry to the study (within two years and 12 weeks of transplantation) and remained fairly constant thereafter. Indeed, seven cases were diagnosed in the first six months after entry, six in the second six months, and six in the second year.

Numerically the most important tumour other than non-Hodgkin's lymphoma was skin cancer. The implication that there is an increased incidence of squamous-cell carcinoma in UK transplant recipients

TABLE VI—*Observed (O) and expected (E) numbers of cases of cancer (excluding cervical carcinoma-in-situ) in transplant recipients at various times after entry to study*

Type of cancer	Years after entry to study: <2 O	<2 E	2-3 O	2-3 E	≥4 O	≥4 E	Total O	Total E
Non-Hodgkin's lymphoma	19	0·26	6	0·16	9	0·16	34	0·58
Skin (UK only):								
Basal-cell carcinoma ..	0	0·38	1	0·24	0	0·23	1	0·85
Squamous-cell carcinoma	0	0·06	1	0·04	2	0·03	3	0·13
Melanoma	0	0·05	0	0·03	1	0·03	1	0·12
Other (excluding skin cancer in Australia) ..	13*	7·85	6†	5·06	11‡	4·88	30	17·79
Total	32	8·61	14	5·53	23	5·33	69	19·46

*Rhabdomyosarcoma (1); hypernephroma (2); ovary (1); lung (1); vulva (1); colon (1); oesophagus (1); urethra (1); thyroid (1); carcinomatosis (1); acute leukaemia (1); Kaposi sarcoma (1).
†Renal pelvis (1); stomach (1); colon (1); lung (1); mesothelioma (1); hepatoma (1).
‡Colon (1); rectum (1); lung (1); prostate (1); bladder (1); vulva (1); cervix (1); acute leukaemia (1); myeloid leukaemia (1); metastasising carcinoid (1); renal pelvis (1).

is supported by the findings in Australasia (table VIIm). Basal-cell carcinoma is common in Australia, and the incidence of this type of skin cancer may not be abnormal. For squamous carcinoma, however, the rates were so high that they cannot be typical of the general population. If they were, over 50% of men and 35% of women would develop the disease by 55 years of age. Support for the conclusion that a real increase in incidence had been produced comes from the fact that most skin cancers in transplant recipients were squamous-cell carcinomas (62%), whereas tumours of this type constitute a minority of skin cancers in the general population. Virtually all affected areas of the skin were regularly exposed to sunlight.

Other non-lymphoid cancers apart from skin cancer showed a roughly two-fold excess (combined series, 30 cases observed as against 17·8 expected). It has already been implied that cancer may be detected more promptly and more completely in transplant recipients, who are under close medical supervision, than in the general population. Because of this and the fact that an appreciable excess was not observed in the mortality data the excess of these other cancers should be interpreted with caution. Types of cancer that were detected in these patients and might have been missed in the general population included two hypernephromas in recipients' own kidneys that were removed after transplantation and an asymptomatic thyroid cancer found at necropsy. Two other cases that would have been less likely to occur in the general population were the two renal pelvis cancers in patients with analgesic nephropathy, since a relation between these disorders is established in the absence of either immunosuppression or transplantation.[7] Among the remaining 26 cases (compared with slightly fewer than 17 expected) some rare types of malignancy were represented by more than one case—for example, squamous carcinoma of the vulva (two) and mesenchymal tumours (a rhabdomyosarcoma, a Kaposi sarcoma in a black patient from West Africa, and a mesothelioma).

Clinical features

Most transplant recipients (including those who developed cancer) received azathioprine continuously. The average dose given to the UK patients who developed lymphoma was higher than that given to the control patients, particularly during the first six months; this difference, however, was not statistically significant (table VIIIm), and no such difference was shown in Australasian patients (table VIIIm). The average azathioprine dose given to the Australasian patients was higher than that given to the UK patients. Doses, however, are normally given/kg body weight, and the Australasians may have been heavier.

Australasian patients who developed skin cancer received on average a significantly higher dose during the first six months than the controls ($P<0·01$). A similar but not statistically significant difference was observed in the UK.

Information on whether antilymphocyte globulin (ALG) was given after transplantation was not provided routinely on all Australasian patients. Most who received it were treated at one centre, where it was notified as having been given to 47% of the 347 who received a transplant. Six patients developed a lymphoma, of whom three were notified as having had ALG. (A fourth patient with lymphoma, who

MINIPRINT TABLES I-VII

Im

TABLE I—*Age and sex distribution of transplant recipients*

	Age at entry to study (years): 14	24	34	44	54	64	65	Total
United Kingdom								
Male	45	257	386	370	274	44	1	1377
Female	42	188	233	226	173	30	0	902
Australasia								
Male	28	135	206	234	213	56	1	875
Female	20	95	137	202	184	30	1	669
Total	145	675	964	1032	844	160	3	3823

IIm

TABLE II—*Age and sex distribution of patients in non-transplant series*

	Age at entry to study (years): 14	24	34	44	54	64	65	Total
Male	93	77	86	78	125	105	40	604
Female	77	97	118	127	131	124	71	745
Total	170	174	204	205	256	229	111	1349

IIIm

TABLE III—*Underlying disorders in transplant recipients*

	United Kingdom	Australasia	Total
Chronic glomerulonephritis	919	694	1613
Chronic pyelonephritis ..	382	124	506
Polycystic disease ..	189	98	287
Hypertension	190	85	275
Analgesic nephropathy ..	31	167	198
Other, multiple, and unspecified renal disorders ..	568	376	944
Total	2279	1544	3823

IVm

TABLE IV—*Underlying disorders in patients without transplants (UK only)*

	Male	Female	Total
Chronic glomerulonephritis	160	81	241
Lupus nephritis and polyarteritis ..	14	19	33
Other and multiple renal disorders ..	88	55	143
Rheumatoid arthritis and ankylosing spondylitis	171	321	492
Crohn's disease and ulcerative colitis	136	144	280
Other collagen disorders	22	102	124
Skin and other disorders	13	23	36
Total	604	745	1349

Vm

TABLE V—*Observed (O) and expected (E) numbers of deaths from cancer in transplant recipients at various times after entry to study*

Type of cancer	Years after entry to study: 2 O	2 E	2-3 O	2-3 E	4 O	4 E	Total O	Total E
Non-Hodgkin's lymphoma	3	0·13	2	0·09	3	0·08	8	0·30
Skin (including melanoma)	1	0·14	0	0·09	2	0·08	3	0·31
Other	5*	4·31	3†	2·76	8‡	2·65	16	9·72
Total	9	4·58	5	2·94	13	2·82	27	10·33

*Oesophagus (1); ovary (1); lung (1); cerebral tumour (2).
†Stomach (2); renal pelvis (1).
‡Lung (3); "carcinomatosis" (3); acute leukaemia (1); cerebral tumour (1).

VIIm

TABLE VII—*Incidence of skin cancer in Australian and New Zealand transplant recipients*

Age (years)	Male: Person-years	Squamous-cell carcinoma: No	Squamous-cell carcinoma: Rate*	Basal-cell carcinoma: No	Basal-cell carcinoma: Rate*	Melanoma: No	Melanoma: Rate*	Female: Person-years	Squamous-cell carcinoma: No	Squamous-cell carcinoma: Rate*	Basal-cell carcinoma: No	Basal-cell carcinoma: Rate*	Melanoma: No	Melanoma: Rate*
14	61·0	0	0	0	0	0	0	32·1	0	0	0	0	0	0
-24	357·4	1	3	1	3	0	0	275·7	0	0	0	0	0	0
-34	847·6	11	13	6	7	0	0	681·7	3	4	2	3	0	0
-44	812·7	13	16	7	9	1	1	743·3	11	15	7	9	0	0
-54	725·7	29	40	14	19	1	1	679·9	13	19	4	6	1	1
-64	206·4	5	24	6	29	1	5	158·1	3	19	4	25	0	0
65	1·4	0		0		0		0·9	0		0		0	0

*All rates expressed per 1000 yearly.

was the only one at the centre for whom no information about ALG was notified, was found to have been given ALG when the hospital records were searched specifically for this.) Lymphomas occurred in two of the 130 UK patients who received ALG (relative risk 222) and in 13 of the remaining patients who did not (relative risk 61). The difference between these risks was not, however, significant.

Table IXm shows the number of rejection crises experienced by control patients and those who developed non-Hodgkin's lymphoma or skin cancer together with the numbers that would have been expected if the patients with cancer had experienced the same incidence of crises as the controls. A rejection crisis was defined as an occasion on which at least 150 mg prednisone, or an equivalent dose of other steroid, was given after at least five consecutive days at a daily dose below this. Table IXm shows the numbers of crises recorded by one, two, and four years after the index operation, including the experience of each patient up to the time of diagnosis of cancer or, in the case of controls, the time of follow-up or death. There was no evidence that patients with lymphoma suffered more or fewer rejection crises than those who did not develop the disease, nor was any difference suggested when different time periods were examined or when 100 mg was used to define the occurrence of a crisis. A higher proportion of patients with skin cancer than controls suffered no rejection crises, and this difference was significant at one year ($P < 0.05$).

One difference between patients who developed lymphoma and the controls was that the former tended to have had a longer period of dialysis before transplantation, but the difference was not significant. The biggest difference recorded was in the proportions who had received dialysis for three years or more. Among the patients with lymphoma and the controls these proportions were 27% (3/11) and 13% (28/214) respectively in the UK series, and 6% (1/16) and 1% (1/93) respectively in the Australasian series.

Patients with cancer and the controls were also compared for the numbers of transplants they had received. The results showed no tendency for patients who developed lymphoma or skin cancer to have received any greater number than the controls (table Xm). These tumours occurred in patients treated for chronic glomerulonephritis, polycystic disease, analgesic nephropathy, malignant hypertension, and chronic pyelonephritis, and there was no apparent predilection for them to occur in any particular disorder.

The proportion of patients with lymphoma or skin cancer with ABO blood group other than O who received kidneys from donors of blood group O was not significantly different from that of control patients. No other cases of discrepant ABO blood groups between donor and recipient were noted among patients with cancer. Data on HLA groups were incomplete, but no significant differences between cases and controls were noted when these details were available.

Table XIm shows the incidences and observed and expected numbers of cases of non-Hodgkin's lymphoma in various age groups in the transplant and non-transplant series. The relative risk fell somewhat with increasing age, while the absolute risk appeared to increase; the trend of increasing incidence with age, however, was not quite significant ($P < 0.10$).

NON-TRANSPLANT SERIES

Mortality—Table XIIm shows the mortality rates from non-Hodgkin's lymphoma and all other tumours in patients in the non-transplant series. No statistically significant excesses were observed.

TABLE XIII—*Observed (O) and expected (E) numbers of cases of cancer (excluding cervical carcinoma-in-situ) in UK patients without transplants at various intervals after entry to study*

Type of cancer	Years after entry to study: <2 O	<2 E	2-3 O	2-3 E	≥4 O	≥4 E	Total O	Total E
Non-Hodgkin's lymphoma	2	0·12	1	0·10	1	0·12	4	0·34
Skin:								
Basal-cell carcinoma ..	0	0·58	0	0·48	1	0·60	1	1·66
Squamous-cell carcinoma	0	0·13	0	0·11	2	0·14	2	0·38
Melanoma	0	0·05	0	0·04	0	0·05	0	0·14
Other	9*	7·62	12†	6·23	12‡	7·89	33	21·74
Total	11	8·50	13	6·96	16	8·80	40	24·26

*Lung (3); larynx (1); vulva (1); colon (1); rhabdomyosarcoma (1); meningioma (1); salivary gland (1).
†Lung (5); bladder (2); leiomyosarcoma (1); melanoma of eye (1); pancreas (1); intrahepatic bile ducts (1); "upper digestive tract" (1).
‡Lung (2); bladder (2); breast (2); stomach (2); ileum (1); myeloma (1); Hodgkin's disease (1); cerebral tumour (1).

Incidence of cancer—Patients in the non-transplant series showed an increased incidence of non-Hodgkin's lymphoma (four cases as against 0·34 expected; $P < 0.001$), squamous carcinoma of the skin (two as against 0·38 expected; $P = 0.06$), and all other tumours other than skin cancer (34 as against 21·74 expected; $P < 0.01$) (table XIII). The last group included three mesenchymal tumours (a rhabdomyosarcoma, a leiomyosarcoma, and a meningioma) and one cancer of the vulva. Interestingly, although the mortality data showed little evidence of an excess of these types of cancer, most of the sites showing an excessive incidence of cancer were similar to those noted in the transplant series—that is, non-Hodgkin's lymphoma and skin, vulval, and mesenchymal tumours. As in transplant recipients, an excess of non-Hodgkin's lymphoma was evident soon after starting treatment with immunosuppressive drugs and the excess of skin cancer was confined to squamous-cell carcinoma.

Clinical characteristics—There were no gross differences in the doses of immunosuppressive drugs given to the patients who developed cancer and the controls. Of the four patients who developed non-Hodgkin's lymphoma, two had rheumatoid arthritis, one had chronic glomerulonephritis, and one had dermatomyositis.

Discussion

Our results provide evidence of an excess of non-Hodgkin's lymphoma, squamous-cell skin cancer, and possibly some mesenchymal tumours both in patients with transplants and,

MINIPRINT TABLES VIII-XII

VIIIm

TABLE VIII—*Azathioprine treatment after transplantation in controls (C) and patients with lymphoma (L) and skin cancer (other than melanoma) (S)**

		Months after transplantation: 0	6	12	24	48	72
United Kingdom							
(a) No of patients surviving without cancer	C	214	197	174	131	62	27
	L	11	9	7	5	3	0
	S	4	4	4	3	1	0
(b) No (%) given azathioprine for at least five of the preceding six months	C		179 (91)	165 (95)	124 (95)	56 (90)	25 (93)
	L		9 (100)	7 (100)	5 (100)	3 (100)	
	S		4 (100)	4 (100)	3 (100)	1 (100)	
(c) Mean (± SE) daily dose of azathioprine (mg) in preceding six months taken by patients listed under (b)	C		125 2·8	140 3·3	142 4·1	145 6·0	146 9·0
	L		154 17·3	159 22·1	153 37·0	150 28·9	
	S		131 23·4	159 26·5	147 31·9		
Australasian							
(a) No of patients surviving without cancer	C	93	90	84	70	31	10
	L	16	16	11	6	2	0
	S	45	40	34	23	8	0
(b) No (%) given azathioprine for at least five of the preceding six months	C		87 (97)	82 (98)	67 (96)	31 (100)	9 (90)
	L		15 (94)	11 (100)	4 (100)	2 (100)	
	S		39 (98)	34 (100)	23 (100)	8 (100)	
(c) Mean (± SE) daily dose of azathioprine (mg) in preceding six months taken by patients listed under (b)	C		142 4·7	156 6·2	156 7·2	169 11·7	151 17·7
	L		147 13·2	153 12·8	132 19·4	91 19·1	
	S		165 5·3	167 6·5	172 6·2	149 7·2	

*Each patient contributes to every column before diagnosis of cancer or (in controls) follow-up or death.

IXm

TABLE IX—*Numbers of controls and patients with lymphoma and skin cancer who had no, one or two, or three or more rejection crises at various times after index transplantation**

Time after index transplantation (years)	No of rejection crises: Controls 0	Controls 1-2	Controls 3	Lymphoma 0	Lymphoma 1-2	Lymphoma 3	Skin cancer (other than melanoma) 0	Skin cancer (other than melanoma) 1-2	Skin cancer (other than melanoma) 3
0	307	0	0	27	0	0	49	0	0
1	58	126	74	5 (4·0)	7 (8·8)	6 (5·2)	15 (16·5)	18 (18·6)	5 (10·9)
2	46	94	61	4 (2·1)	2 (4·2)	3 (2·7)	10 (6·0)	12 (12·2)	4 (7·9)
4	26	44	29	1 (1·4)	2 (2·4)	2 (1·2)	6 (2·5)	2 (4·3)	1 (2·2)

*Figures in parentheses are numbers of cases expected from experience of control patients.

Xm

TABLE X—*Numbers of controls and patients with lymphoma and skin cancer who had been given one, two, or three or more transplants**

Time after index transplantation (years)	No of transplants: Controls 1	Controls 2	Controls 3	Lymphoma 1	Lymphoma 2	Lymphoma 3	Skin cancer (other than melanoma) 1	Skin cancer (other than melanoma) 2	Skin cancer (other than melanoma) 3
0	283	21	3	24 (24·9)	2 (1·8)	1 (0·3)	46 (45·2)	3 (3·4)	0 (0·5)
1	231	25	2	16 (16·1)	2 (1·7)	0 (0·1)	35 (34·0)	3 (3·7)	0 (0·5)
2	179	20	2	9 (8·0)	0 (0·9)	0 (0·1)	24 (23·2)	2 (2·6)	0 (0·3)
4	82	10	1	4 (4·4)	1 (0·5)	0 (0·6)	8 (7·9)	1 (1·0)	0 (0·1)

*Figures in parentheses are numbers of transplants expected from experience of control patients. Previous transplants rejected within 12 weeks and thus not qualifying for admission to the study are included.

XIm

TABLE XI—*Relative risks and incidences of non-Hodgkin's lymphoma at various ages in transplant and non-transplant series (O Observed, E Expected)*

Age group (years)	Transplant series: No of cases O	No of cases E	Ratio of cases O to E	Incidence 100 000 year	Non-transplant series: No of cases O	No of cases E	Ratio of cases O to E	Incidence 100 000 year
25	3	0·030	100	140	0	0·023	0	0
25-	17	0·264	64	233	1	0·045	22	51
45-	14	0·288	49	405	1	0·174	6	52
65	—	—	—	—	2	0·095	21	290
All ages	34	0·583	58	264	4	0·337	12	79

XIIm

TABLE XII—*Observed (O) and expected (E) numbers of deaths from cancers in UK patients without transplants at various intervals after first immunosuppression*

Type of cancer	Years after entry to study: 2 O	2 E	2-3 O	2-3 E	4 O	4 E	Total O	Total E
Non-Hodgkin's lymphoma	0	0·09	0	0·07	1	0·09	1	0·25
Other	2*	5·43	8†	4·52	9‡	5·87	19	15·83
Total	2	5·52	8	4·59	10	5·96	20	16·08

*Larynx (1); lung (1).
†Lung (5); rhabdomyosarcoma (1); carcinomatosis (1); intrahepatic bile ducts (1).
‡Lung (2); stomach (2); bladder (1); colon (1); ileum (1); cerebral tumour (1), hepatic adenoma (1).
§All neoplasms in ICD (8th revision) codes 140-239.

to a less extent, in patients without transplants treated with immunosuppressive drugs.

LYMPHOID TUMOURS

The most striking excess occurred in non-Hodgkin's lymphomas (mainly described as reticulum-cell sarcomas and microgliomas) in the transplant series, which confirms what has been reported before.[8] So pronounced was the excess that its existence was deduced from cases that had been reported by 1970[4] before any prospective study had been started. This excess of lymphoid tumours was extraordinary in its magnitude, its predilection for the brain, and the very short induction period. Possible explanations include hypotheses concerning immunosurveillance, graft-versus-host reaction, chronic antigenic stimulation, and oncogenic viruses. For each of these there is laboratory support. The short induction period, sometimes within a few months after transplantation, suggests a viral origin, since transformation could take place immediately if the virus was already present.

That patients without transplants also showed an excess of lymphoid tumours suggests that immunosuppression is important, though the presence of a graft may contribute, since in transplant recipients the excess was much greater. Other observations support the primary importance of immunosuppression. Firstly, there was no tendency for lymphoid tumours to be more common in recipients who experienced repeated rejection crises (table IXm) or in those who had multiple grafts (table Xm). Secondly, a study of patients receiving dialysis, who have severely depressed immune function, showed that they also had an increased incidence of non-Hodgkin's lymphoma and that in one of them, who had never been given immunosuppressive drugs, the lymphoma affected the brain.[9] Thirdly, certain rare hereditary disorders characterised by major immunological impairment, such as the Wiskott-Aldrich syndrome, are associated with an increased risk of lymphomas. It may also be relevant that a reticulum-cell sarcoma has been reported in the brain of a woman who apparently had no IgA in her serum.[10]

A direct mutagenic effect of the chemical agents appears to be unlikely because of the abrupt increase in incidence, the subsequent constancy of the risk from the time of first exposure, and the lack of any noticeable dose effect—all of which are in pronounced contrast to the usual findings with known chemical carcinogens.

Only four patients without transplants developed non-Hodgkin's lymphoma (three treated with azathioprine and one with cyclophosphamide) and the excess must be interpreted with caution. An explanation could be that it was due to the underlying condition for which the patients were treated. A threefold excess of lymphomas was observed in a very large series of patients with rheumatoid arthritis in Finland,[11] but it is not clear whether this was associated with any particular form of treatment. In our series two cases occurred in patients with rheumatoid arthritis (0·18 expected) and two in patients with other conditions (0·16 expected). Of these second two cases, one occurred in a woman being treated for dermatomyositis, which is associated with an increased risk of malignancy but not characteristically with a risk of lymphoma. In none of these cases was the brain affected, but three such cases in patients without transplants being treated with similar drugs have been reported.[12–14]

From our findings the risk of non-Hodgkin's lymphoma is probably smaller in patients without transplants than in transplant recipients ($P < 0{\cdot}001$). Differences in the type, amount, and duration of drug treatment were, however, substantial. Azathioprine was given initially to only 64% of patients in the non-transplant series and was continued for over two years in less than 30%, whereas azathioprine was continued in over 90% of the transplant recipients throughout the period of observation. Similar differences were observed in the case of prednisone. When azathioprine was used the doses were comparable, but the average doses of prednisone given to patients without transplants were roughly half those given to patients with transplants and even less (about a quarter) during the first six months. Another difference between the two series was that the transplant recipients had experienced the immunosuppressive effects of severe renal failure before transplantation, whereas only a minority of patients in the non-transplant group had a renal disease, let alone one of comparable severity. Part of the difference, therefore, may have been due to the longer and more intense immunosuppression experienced by the transplant group. Support for this also comes from our observation that transplant recipients with lymphoma tended to have had a longer period of dialysis before transplantation than other patients.

SKIN CANCER

The predominance of skin cancer among cases of malignancy in transplant recipients collected by Penn *et al* from around the world was striking even in their first reports[3]; but in the absence of any means of calculating "expected" numbers, their findings might simply have reflected the fact that many transplant recipients lived in areas with high ultraviolet irradiation. Evidence that the excess was real was obtained by Walder *et al*,[15] who found an inversion of the usual ratio of basal-cell to squamous-cell carcinomas; Hoover and Fraumeni,[8] who compared the incidence in a heterogeneous population of transplant recipients from different countries with that expected from incidence rates for skin cancer in the USA; and Hardie *et al*[16] in Queensland, where a special effort had been made to obtain a baseline figure for the general population. In the experience of Hardie *et al* the incidence of skin cancer in patients given cadaveric renal transplants was increased some 20-fold.

In our study an excess of skin cancer was observed in both the transplant and non-transplant series. An observed 10-fold increase in mortality from skin cancer in transplant recipients (based on three deaths) may be an appreciable underestimate, because four further deaths from this cause were attributed in death certificates to carcinomatosis or lung cancer. All were due to squamous-cell carcinoma, which was also predominant among the non-fatal cases. Indeed, there was little reason to suppose that the incidence of basal-cell carcinoma was abnormal at all.

There were too few cases of melanoma to provide any firm evidence of a specific risk. One case occurred in the UK transplant series (0·12 expected) and none in the non-transplant series (0·14 expected). Four occurred in Australia, where the disease is relatively common. If the rates for both sexes recorded in table VIIm are compared with those obtained by McCarthy *et al*[17] in New South Wales it appears that the incidence might have been increased about fivefold.

OTHER TUMOURS

There were three cases of acute leukaemia, all in transplant recipients, compared with an expected figure of less than one, and six mesenchymal tumours when effectively none were expected. The mesenchymal tumours consisted of two rhabdomyosarcomas (one in the transplant series, one in the non-transplant series), one leiomyosarcoma (non-transplant series), one Kaposi sarcoma (transplant series), one mesothelioma (transplant series), and one meningioma (non-transplant series). Both rhabdomyosarcomas were diagnosed within two years of starting immunosuppressive treatment, which raises questions similar to those in relation to lymphoid tumours.

There were four cases of bladder cancer in patients without transplants when less than one was expected, and a single

case in a transplant recipient. Cyclophosphamide was used more often in patients without transplants than in the others (46% as against 5% in the first three years), and the excess was more pronounced in those who had received the drug (three cases observed as against 0·29 expected; $P < 0.01$). Two further cases occurred in patients without transplants treated with cyclophosphamide after the latest follow-up date used for this analysis, and several other cases of bladder cancer after cyclophosphamide treatment have been reported elsewhere.[18] Hence the risk of this disease is apparently related specifically to the use of cyclophosphamide.

Of other rare tumours, three were squamous carcinomas of the vulva (one in the non-transplant series), one was a metastasising carcinoid tumour (transplant series), and one was an intrahepatic biliary carcinoma (non-transplant series). The three cancers of the vulva were similar in character to squamous carcinoma of other parts of the skin and are perhaps more appropriately classed with skin cancers than with "other" cancers. The intrahepatic biliary carcinoma in a patient in the non-transplant series is interesting in view of Hoover and Fraumeni's[8] report of similar cases in transplant recipients.

Our findings provide no clear evidence that immunosuppressive drugs produce an increased risk of most of the common cancers. Few of the patients, however, had been under observation for over five years, and an increase may appear later.

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Requests for reprints should be addressed to Dr L J Kinlen.

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Effects of indomethacin on postural hypotension in Parkinsonism

G ABATE, R M POLIMENI, F CUCCURULLO, P PUDDU, S LENZI

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Indomethacin significantly reduced the fall in blood pressure on standing ($P < 0.001$) and lessened or reversed orthostatic symptoms. Furthermore, there was an enhanced response to the cold pressor test and a reduction in forearm blood flow.

These findings suggest that indomethacin has a positive effect on systemic vascular resistance.

Summary and conclusions

A study was conducted to evaluate the effect of indomethacin on orthostatic hypotension in Parkinsonism. Twelve elderly patients participated and the drug was given in two ways—as an intravenous infusion of 50 mg over 30 minutes and by mouth 50 mg thrice daily for six days. Results were assessed by measuring the degree of hypotension on standing, response to the cold pressor test, and forearm blood flow (by strain-gauge plethysmography).

Geriatric Clinic, University of Chieti, Italy
G ABATE, MD, director and professor

Medical Clinic II, University of Bologna, Italy
R M POLIMENI, MD
F CUCCURULLO, MD
S LENZI, MD, director and professor

Department of Therapeutics, University of Bologna, Italy
P PUDDU, MD, director and professor

Introduction

Orthostatic hypotension is a common, disabling problem in Parkinsonism. The lesion responsible may be localised within the efferent sympathetic fibres of the baroreceptor system,[1] though other lesions cannot be excluded.[1 2] We do not know whether Parkinsonism and orthostatic hypotension constitute an incomplete or variant form of the Shy-Drager syndrome. Most workers believe that such a diagnosis requires evidence of autonomic failure (orthostatic hypotension, sexual impotence, urinary incontinence, rectal incontinence, loss of sweating, etc) in addition to the features of Parkinsonism and pyramidal or cerebellar signs.[3–5]

Since indomethacin proved to be effective in the Shy-Drager syndrome[6] we decided to evaluate its efficacy against postural hypotension in idiopathic Parkinsonism.