Methylation of exon 1 can be detected by the failure of the restriction enzyme Sac II to cleave a 4.3 kb EcoRI fragment. The methylation state of *p16* in the thyroid cell lines was examined on Southern blots of 5 μg genomic DNA digested with 15 IU Sac II and EcoRI and probed with exon 1 (conditions as previously reported [2]). In five of six samples, signals at 3.3 kb were detected indicating unmethylated exon 1 (see Figure 1). However, in the papillary cancer cell line BCPAP, a signal at 4.3 kb resistant to cutting by Sac II was seen, indicating methylation of exon 1 on both alleles which, from previous studies [3], would be predicted to downregulate *p16* expression.

We are now examining DNA from primary thyroid tumour samples using these methods in order to determine the importance of *p16* abnormalities *in vivo*. The data reported here confirm the necessity of studying multiple aspects of *p16* structure and function when assessing its role in tumorigenesis.

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Table 1. Patient and treatment characteristics

	HD	NHL	Total number of patients
Number of patients	15	17	32
Median age (range) in years	31(16–50)	62(38–79)	43(16–79)
Number who received previous treatment			
1	3	9	12
2	3	4	7
3	2	3	5
4	2	1	3
>4	5	—	5
Disease status			
Refractory	8	4	12
Relapsed	7	13	20
Disease extension			
≤3 sites	8	8	16
>3	7	9	16
CY dose calculated by			
BSA			15
GFR			17
Number of courses of CY			
1	4	8	12
2	3	6	9
3	4	1	5
4	2	1	4
>4	2	1	2
Median (range)			2(1–8)
Delayed CY	7	8	10
Median delay time (days)			7
Range			4–15
Dose reduction	4	1	2

HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; BSA, carboplatin dose based on body surface area; GFR, carboplatin dose based on glomerular filtration rate; CY, carboplatin.

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Lack of Carboplatin Activity in Malignant Lymphomas

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THE ACTIVITY of cisplatin as a single agent in haematological neoplasms [1] has led to the development of association regimens such as DHAP (dexamethosone, high dose cytarabine and cisplatin) [2] and ESHAP [3] (etoposide, methylprednisolone, high dose cytarabine and cisplatin) for salvage treatment in both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). These regimens produce an overall response rate of 50–60%, and long-term survival rates slightly in excess of 10%. Thus, these are often used as conditioning regimens before high-dose chemotherapy programmes [4]. In spite of the fact that carboplatin activity at conventional doses has only been tested in a single study with overall negative results [5], it has sometimes been included at higher doses in the induction phase of autologous bone marrow transplantation (ABMT) programmes [6, 7].

In an attempt to verify carboplatin activity at conventional doses in lymphomatous malignancies, a phase II trial was started in patients with relapsed or refractory HD or intermediate/high grade NHL. Eligible patients were required to have a good performance status (Karnofsky > 60), adequate bone marrow reserve (unless impaired due to bone marrow infiltration), normal organ function (heart, liver and kidney), and measurable and/or evaluable disease. Written informed consent was required, and the trial was conducted according to good clinical practice recommendations.

When feasible, the carboplatin dose was calculated according to glomerular filtration rate in order to provide an

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average area-under-the-curve of 5 mg/ml [8]. In all other patients, a dose of 300 mg/m^2 was administered every 3 weeks. Unless there was disease progression or stable disease after the first two cycles, patients were treated up to maximum response followed by two consolidation cycles. 12 patients who received carboplatin at first relapse also received consolidation treatment with conventional polychemotherapy salvage regimens such as MINE (mitoxantrone, ifosfamide + MESNA, etoposide) or CEP (CCNU, etoposide, prednimustine). From April 1992 to December 1994, 32 patients (15 HD and 17 NHL) were enrolled in the study. Patient and treatment characteristics are shown in Table 1.

Overall, two complete remissions (CR), 1 patient with HD and 1 with NHL, and 1 partial remission (PR) were observed, for an overall response rate of 9%. Currently, the patient who achieved CR with HD is alive and without evidence of disease after 36 months following six doses of carboplatin and consolidation radiotherapy on the only site of nodal relapse. The other 2 responding patients experienced sensitive relapse after 5 and 7 months; both are alive and disease-free after salvage chemotherapy. 21 of 29 patients who did not respond to carboplatin received further chemotherapy with a response rate of 57%. The administration of carboplatin was globally well tolerated. Grade IV neutropenia occurred in four cycles (5%), with no hospitalisation due to infection. Grade three and four thrombocytopenia were rare (5%) and related to heavily pretreated patients (at least three previous regimen and/or extended fields radiotherapy) and for carboplatin doses based upon BSA (six cases) rather than on GFR (two cases). 2 patients were admitted to the hospital because of severe thrombocytopenia requiring platelet transfusion and careful observation. Nausea, vomiting, neuro- or nephrotoxicity were sporadic and mild.

In conclusion, clinical activity of carboplatin in pretreated malignant lymphomas seems very limited at standard doses, as only 3 of 32 patients attained objective response, for an overall response rate of 9%. Our data confirm previous negative results obtained with standard dose single-agent carboplatin in lymphomas [5]. However, the low non-haematological toxicity of carboplatin has permitted dose-escalation studies in both solid and haematological tumours [6, 7], and its activity in lymphomatous malignancies when used at higher doses should be further evaluated.

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Radon Exposure and Incidence of Paediatric Malignancies

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WE READ with interest the editorial by Parker and Craft [1] which commented on our paper *Radon in Devon and Cornwall and Paediatric Malignancies* [2] and provided a detailed critique of the background factors which had necessarily been only summarised in our report. A study like ours, limited to a decade, and regional rather than national, clearly may not have sufficient power to detect small excesses in incidence that might be due to radon. However, our analysis was provoked by a paper [3] which suggested that excess from radon could be high and, therefore, our study might be of sufficient power. This does not appear to be the case as we detected no excess risk for all childhood cancers in our study.

The data showed a significantly raised incidence of neuroblastoma and a non-significantly raised incidence of acute myeloid leukaemia (AML) in high radon postcode sectors in the decade 1976–1985. The editorial discussed whether our finding for neuroblastoma was likely to have been due to chance. We have now looked at the incidence of the two malignancies in the subsequent decade. Table 1 shows the incidence rates in Devon and Cornwall for AML and neuroblastoma as given in our original paper, incidences for the decade 1986–1995 and incidences for the two periods combined.

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