Significant increase in trisomy 21 in Berlin nine months after the Chernobyl reactor accident: temporal correlation or causal relation?

Karl Sperling, Jörg Pelz, Rolf-Dieter Wegner, Andrea Dörries, Annette Grüters, Margareta Mikkelsen

Abstract

***Objective*—To assess whether the increased prevalence of trisomy 21 in West Berlin in January 1987 might have been causally related to exposure to ionising radiation as a result of the Chernobyl reactor accident or was merely a chance event.**

***Design*—Analysis of monthly prevalence of trisomy 21 in West Berlin from January 1980 to December 1989.**

***Setting*—Confines of West Berlin.**

***Results*—Owing to the former "island" situation of West Berlin and its well organised health services, ascertainment of trisomy 21 was thought to be almost complete. A cluster of 12 cases occurred in January 1987 as compared with two or three expected. After exclusion of factors that might have explained the increase, including maternal age distribution, only exposure to radiation as a result of the Chernobyl reactor accident remained. In six of seven cases that could be studied cytogenetically the extra chromosome was of maternal origin, confirming that nondisjunction had occurred at about the time of conception.**

***Conclusion*—On the basis of two assumptions —(*a*) that maternal meiosis is an error prone process susceptible to exogenous factors at the time of conception; (*b*) that owing to the high prevalence of iodine deficiency in Berlin a large amount of iodine-131 would have been accumulated over a short period—it is concluded that the increased prevalence of trisomy 21 in West Berlin in January 1987 was causally related to a short period of exposure to ionising radiation as a result of the Chernobyl reactor accident.**

See editorial by Boice and Linet also papers by Auvinen and Hjalmas

A global risk study on the health implications of the Chernobyl reactor accident in 1986 concluded that *"probably no adverse health effect will be manifest by epidemiological analysis."*[1]

Introduction

Trisomy 21 is a main cause of human prenatal and postnatal morbidity and mortality. It can be diagnosed unequivocally and simply and thus offers important prerequisites for epidemiological study. Most cases result from meiotic nondisjunction, particularly during oogenesis.[2] Maternal age distribution and selective abortion after prenatal diagnosis have the strongest influence on its frequency. If these variables remain constant, then any sudden increase in frequency must be due either to chance or to an environmental factor. Despite decades of research, however, no single exogenous factor responsible for trisomy 21 has been unambiguously identified.[3] The possible effect of low dose radiation remains controversial.[4]

Trisomy 21 in West Berlin, 1980-9

Up till late 1989 the "island" of West Berlin provided a favourable setting for the epidemiological study of trisomy 21. Cytogenetic services were provided solely by the university institute of human genetics and one associated laboratory, so that all prenatal and postnatal diagnoses should have been recorded there.

This analysis is restricted to cases with standard trisomy 21 diagnosed from 1980 to 1989. All probands with translocations and mosaicism were excluded, because these conditions may have a different aetiology. Misclassification is highly unlikely in prenatally detected cases, and ascertainment therefore depended only on the numbers of women having prenatal diagnosis. Ascertainment of liveborn cases with trisomy 21, however, depends on awareness by paediatricians who examine newborn infants. In such cases the median age at tentative clinical diagnosis was 4 days, 94% of affected infants being diagnosed cytogenetically within 14 days. Cytogenetic tests were provided free during the study period, which might have aided ascertainment.

Analysis and results

Data are reported from 1980 because from that date the criteria for ascertainment remained unchanged. Moreover, during the 10 years the average age of all pregnant women remained fairly constant (around 27·4 years; table I). The same was true for the

TABLE I—*Annual numbers of births and prenatal chromosome analyses on amniocytes and chorionic villi (figures in parentheses) from 1980 to 1989 in West Berlin in relation to numbers of prenatally and postnatally diagnosed cases of trisomy 21*

Year	No of live births	Average maternal age (years)	Percentage of mothers aged ≥35	No of prenatal diagnoses	Annual maternal age (years) in cases with trisomy 21			No of trisomy 21 cases		Prevalence of trisomy 21 per 1000 live births*
					Postnatal	Prenatal	All	Postnatal	Prenatal	
1980	18 536	27·4	10·7	785	29·5	40·5	31·1	24	4	1·44
1981	18 955	27·4	10·4	824	30·9	40·0	33·1	22	7	1·42
1982	18 662	27·4	10·6	817	29·3	39·4	31·9	23	8	1·53
1983	17 819	27·5	11·2	953	32·2	39·6	34·4	22	9	1·59
1984	17 799	27·6	11·8	1 195	28·6	38·4	31·5	19	8	1·38
1985	17 921	27·6	12·1	1 393 (46)	32·5	37·0	33·9	21	10	1·56
1986	18 688	27·2	11·0	1 457 (90)	31·6	39·2	34·2	19	10	1·35
1987	19 554	27·2	11·5	1 723 (140)	30·5	38·6	33·3	30	16	2·11
1988	20 980	27·2	10·8	1 786 (222)	29·1	38·5	32·1	28	13	1·77
1989	21 159	27·7	11·9	1 989 (319)	30·6	37·8	34·0	18	16	1·38
All	190 073	27·4	11·2	12 922	30·4	38·7	33·0	226	101	1·56

Data on maternal age distribution provided by Statistische Landesamt Berlin.
*Calculated as number of postnatally diagnosed cases plus 70% of prenatally diagnosed cases in relation to number of births.

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BMJ 1994;309:158-62

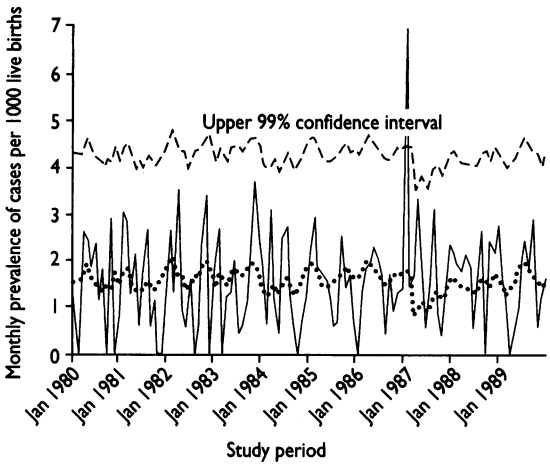
percentage of childbearing mothers aged 35 or more. This was invariably above 10%, with an average of 11·2% over the 10 years (table I).

Of the 190 073 live births registered during the study period, 226 (0·1%) were cases of trisomy 21. A further 101 cases were diagnosed prenatally (table I). There was an increasing number of prenatal diagnoses during the 10 years, from 785 in 1980 to almost 2000 in 1989. Cases diagnosed prenatally were weighted by 0·7, because only this proportion is expected to survive until birth.[5] Thus an estimated total of 297 cases of trisomy 21 were diagnosed prenatally and postnatally among the live births. This high proportion (0·16% or one in 640 live births) supports the assumption of almost complete ascertainment. As a further check on ascertainment we compared the maternal age specific risk figures for trisomy 21 in Berlin with those of a Swedish study[6] in which ascertainment was very high in a comparative analysis of 19 populations.[7] From that study the expected number of trisomy 21 cases in our population was 290. The estimated total exceeded this and thus underlines the completeness of ascertainment.

The highest number of trisomy 21 cases occurred in 1987 (table I). This was due almost exclusively to a peak of 12 cases in January (10 among newborn infants, two among fetuses diagnosed by chorionic villus sampling). The monthly prevalence of cases for the whole observation period did not show a consistent tendency to increase or decrease over time (figure).

Spectral analysis, which estimates the amount of variance in a series accounted for by cycles of different periods, excluded any kind of gross periodic changes. Several simple autoregressive moving average models were applied to the time series.[8] These help to detect random fluctuations that exceed usual levels and determine the point at which variation is too great to attribute to chance. One model that fitted the data reasonably well (and which did not have a seasonal component)[12] is shown in the figure. The autocorrelations and partial autocorrelations of the residuals were randomly distributed and the Box-Ljung statistic was not significant in any lag. The model also gives the upper confidence interval (99%) for the original series. Plainly the prevalence in January 1987 greatly exceeded that value. The same was found for all other autoregressive moving average models calculated. All statistical calculations were carried out with SPSS/PC+ V.3.01.

Trisomy 21 is among those classes of genetic defects that are easily identified and show almost no seasonal variation. Thus, in addition, we tested the goodness of fit for the monthly frequency of trisomy 21 with the expected Poisson distribution. As a Poisson distribution is defined only for integers, we did not apply the correction factor (0·7) to prenatal cases but counted every case diagnosed prenatally and postnatally as an observed case. This gave a mean of 2·7 cases per month over the 10 years. With this mean taken as λ the observed cases of trisomy 21 per month fitted a Poisson distribution (P=0·99; Kolmogorov-Smirnov test). We did not take into account the variation in total monthly births, because the number of trisomy 21 cases per month did not show any correlation with these figures in our dataset. The upper 99% confidence interval for the Poisson distribution estimated according to Clopper-Pearson[9] was 10·5 cases. The number of observed cases in January 1987 exceeded this, so making it unlikely that the temporal increase in trisomy 21 occurred by chance.[10,11]



Time series analysis of monthly prevalence of all prenatally and postnatally diagnosed cases with trisomy 21 in West Berlin from January 1980 to December 1989 (solid line). Autoregressive moving average model that fitted data reasonably well is superimposed (broken line)

TABLE II—*Histories in 10 cases of Down's syndrome born January 1987 in West Berlin and in two cases of prenatally diagnosed fetuses with trisomy 21 (aborted after chorionic villi sampling) (and estimated dates of birth in these two cases)*

Case No	Parental age (years)		Date of first day of last menstrual period (1986)	Date of delivery (1987)	Sex of proband	Thyroid stimulating hormone (mU/l)	Stage of nondisjunction
	Mother	Father					
1	40	40	30 March	15 Jan	M	<10	ND†
2	26	26	10 April	11 Jan	M	ND	ND†
3	45	46	10 April	3 Jan	M	<10	Maternal I
4	38	41	15 April	20 Jan*	F	ND	Maternal I
5	23	29	16 April	8 Jan	M	<10	ND
6	25	30	18 April	7 Jan	M	16	Maternal I
7	34	35	21 April	10 Jan	F	<10	Maternal I
8	41	50	22 April	27 Jan*	M	ND	ND†
9	33	38	30 April	22 Jan	M	19	ND‡
10	22	23	3 May	13 Jan	M	<10	Maternal I
11	35	38	3 May	22 Jan	M	<10	Paternal I
12	39	37	19 May	31 Jan	F	<10	Maternal I

ND=Not tested.
*Estimated date of birth (pregnancy aborted after chorionic villi sampling).
†Not interviewed.
‡Not in Berlin on day of conception.

POSSIBLE CAUSATIVE FACTORS

Maternal age

Maternal age is the most important risk factor for trisomy 21. Of the 12 mothers in the January 1987 cluster of cases, six were aged 35 or over (table II). This agrees with the age distribution of all 327 mothers of trisomy 21 cases in the series, 148 (45%) of whom were in this age group. The mean (median) age of the 12 mothers (33·7 (34·5) years) differed only slightly from that of all mothers of cases (33·0 (34·2) years). To assess this difference 100 random samples of 12 women were taken from the whole cohort with the procedure SAMPLE of SPSS. The mean (median) age in 33% (42%) of the sample was higher than that of mothers in the January 1987 cluster, confirming that the age distribution was not in an extreme range.

Radiation exposure

Nine of the 12 parents in the January 1987 cluster were interviewed by a physician about their obstetric, medical, and radiation histories in the year before conception (table II). Two couples refused interviews and one had emigrated. No serious illness or drug misuse was reported. The mother in case 3 had had a routine chest *x* ray examination in May 1985, and the mothers in cases 10 and 12 had had radiography of pelvis and the teeth, respectively, in March 1986.

The only common exogenous factor was exposure to radioactive clouds from the nuclear explosion at Chernobyl which had passed over Berlin nine months previously. Only one couple was not in Berlin at the time. None of the interviewees expressed exaggerated anxiety over the exposure to radiation. Two couples, however, had begun excluding meat and milk products from their diet.

The first cloud reached Berlin on 29 April 1986 at 6 pm, leading to a large increase in airborne

radioactivity, mainly due to nuclides with short half lives such as iodine-131 (eight days) and tellurium-132 and iodine-132 (78 hours). The second cloud passed over Berlin on 4 May. During the whole period the weather was sunny and dry. A heavy shower during the night of 7-8 May removed practically all artificial radionuclides from the atmosphere and subsequently any inhalation of these was negligible. Irradiation from the ground was increased by a maximum of only 60% above normal.[12]

The main exposure to the Berlin population was from 29 April to 8 May and was due primarily to inhalation of ^{131}I and ^{132}I,[13] which accumulate preferentially in the thyroid. No representative direct measurements of the thyroid dose have been performed in Berlin. However, for this period the time integrated airborne radioactivity of particulate bound iodine and caesium in Berlin was estimated as 100-200 and 50-100 Bq/h/m^3, respectively.[13] This calculation excluded contributions from gaseous elemental and organically bound radioiodine, so that the total activity was likely to have been three times higher.[13] With respect to the overall dose received during the period a severalfold increase above normal seems to be realistic.

Based on the date of the first day of the last menstrual period, cases 4-8 were conceived during the time of highest exposure (table II). Given the variability in the length of the preovulatory cycle and the uncertainties in determining the first day of last menstruation, cases 2, 3, and 9-11 may also have been conceived during this period or shortly thereafter. The parents in case 9, however, were not in Berlin at the time (table II).

In seven of these 10 families the origin of the extra chromosome was studied by examining chromosomal heteromorphisms. In six cases failure had occurred during oogenesis and thus at around the time of conception. In case 11 paternal nondisjunction was observed, which must have occurred about two months before conception[14] and consequently before the Chernobyl reactor accident. Thus in eight cases (2-8 and 10) a temporal correlation between meiotic failure and the increase in radioactivity in Berlin cannot be excluded. The question is whether this also points to a causal relation.

Discussion

In a global risk study on the health implications of the Chernobyl reactor accident it was stated that outside the Chernobyl region "probably no adverse health effect will be manifest by epidemiological analysis."[1] This assumption was based mainly on the 50 year radiation dose commitment and a linear-quadratic dose-risk relation for genetic defects. Though the assumption may be plausible for biological anomalies due to gene mutation, it may not be so for numerical chromosome anomalies. These arise through a completely different mechanism. If we accept that the risk of nondisjunction is highest at the time of conception when maternal first and second meiotic divisions take place,[4] then we may assume that exposure to any dose of radiation at this time will be more critical than exposure to the same dose some time before or even spread over one year.

The "negative" findings in children of the atomic bomb survivors of Hiroshima and Nagasaki are of little relevance to our series, as those children were conceived long after detonation of the bombs. Verification of our findings should therefore come from an independent investigation of the effect of the Chernobyl reactor accident on the incidence of chromosomal anomalies.

Such a study was performed in West Germany in 1986 based on 28 773 prenatal cytogenetic diagnoses after amniocentesis. Altogether 237 cases with standard trisomy 21 were detected, in which the predominant factor was high maternal age.[15] The highest incidence of trisomy 21 occurred among fetuses that were conceived in the same critical period as in Berlin (first day of last menstrual period 7-20 April) and in the most heavily contaminated, southern part of Germany. There 11 cases were observed, which was more than twice the number expected.

The number of cases expected in southern Germany (four) was estimated from the relative frequency of trisomy 21 (0·85 per 100 amniocenteses) and the calculated number of diagnoses performed by laboratories in that area (479). In the northern part the ratio between observed and expected cases was six to five. Thus in this completely independent investigation (no cases with trisomy 21 were observed in Berlin after amniocentesis) the correlation between the increase in radioactivity and the incidence of trisomy 21 was confirmed. When five other aneuploidies observed in the supraregional study were included the temporal and regional clustering was even more pronounced: four cases (two 47,XXX, one 47,XY,+9; one 47,XY,+13) were found in southern Germany and only one (47,XXY) in the northern part.

In some other studies no clustering of trisomy 21 was evident. In a large perinatal study based on questionnaires returned by clinicians in Lower Saxony and Bavaria in 1986 and 1987 no temporal or spatial effect on the rate of chromosome anomalies could be inferred.[16] But that study was limited on several counts. Only a proportion of all births were registered, details of prenatal diagnoses were not recorded, and diagnoses were based on phenotype alone.

In a collaborative study of 19 birth defect registries in Europe 621 cases of trisomy 21 were recorded from January 1986 to March 1987 that did not show any appreciable clustering. The authors admitted to several limitations of their study, of which possible underregistration of cases in the critical period and lack of information on karyotypes in 30% of cases seem to be the most important.[17] Additional shortcomings in several of the participating centres included, for example, no information about termination of pregnancy after prenatal diagnosis and no record of cases diagnosed after the early neonatal period.[18]

Three regional studies, however, compared prevalences of trisomy 21 before and after the Chernobyl reactor accident. In Finland no differences between control and study groups were observed.[19] This was also true for fetuses conceived during the short term exposure to ^{131}I in May 1986. Absolute numbers were small, however, and the authors stated that "the negative finding is inconclusive as such." In contrast, a significantly greater number of cases with trisomy 21 in the first year after Chernobyl was recorded in the Lothian region of Scotland[20] and in Sweden (B Källén, personal communication). This temporal association, however, was not as distinct as in Berlin and no biologically plausible explanation could be given.

A complementary study in the former East Germany based on 1155 prenatal analyses and 10 cases with trisomy 21 in 1986 did not show any clustering.[21] This is easily explained by the small numbers.

In contrast, a non-significant increase in the prevalence of trisomy 21 was found by the Hungarian Congenital Malformation Registry during January to March 1987.[22] The time of conception was not given in these cases and only 15% of cases diagnosed clinically among liveborn infants were confirmed cytogenetically.[23] Nevertheless, the Hungarian observations do not contradict our own.

IODINE UPTAKE

Indirect evidence suggests that the uptake of radioactive iodine after the Chernobyl accident may have

been somewhat higher in West Germany than in Hungary and most other European countries. Iodine prophylaxis is not mandatory in West Germany, and the prevalence of iodine deficiency is among the highest in Europe.[24,25] For example, median urinary concentrations of iodine in full term newborn infants were 883 and 867 nmol/l in Helsinki and Stockholm but only 221 nmol/l in Berlin.[26]

We measured thyroid stimulating hormone concentrations in newborn infants as an index of maternal iodine uptake during pregnancy. In two cases with trisomy 21 a transient increase was recorded (table II). Values were, however, in the normal range for newborn infants with Down's syndrome.

As the inhalation of radioactive iodine occurred at around the time of conception a direct effect of low dose irradiation on the gonads must be taken into account. This does not, however, rule out completely an indirect mechanism acting via altered thyroid function. There are several, if controversial reports that mothers of children with Down's syndrome have a higher prevalence of thyroid antibodies and thyroid disease.[27,28] Either case would imply that low dose irradiation at the time of oogonial meiotic divisions could induce nondisjunction.

So far as we know there are only two epidemiological studies in which parents were exposed to a high dose of irradiation at the time of conception. These concerned the inhabitants of Kerala, India, and Yangjiang County, China, who received high background radiation from monazite soil containing thorium. The dosage was perhaps comparable to that in Berlin during the critical two weeks. Though some ascertainment bias could not be excluded,[4] both studies found a significant increase in trisomy 21.[29,30] In conjunction with our findings, this implies that chromosomal segregation during human oogenesis can easily be disturbed.

Direct evidence that maternal meiosis may be disturbed by exogenous factors at the time of conception remains a matter of controversy, as does the postulated effect of preconceptional *x* irradiation or viral infections.[3,31] Recently a convincing correlation between the accidental ingestion of metriphonate (employed against fish parasites) at around the time of conception and trisomy 21 has been reported.[32] Indirect evidence, however, is provided by the occasionally observed seasonality in the frequency of aneuploidies, which has been explained by seasonal variation in endocrine factors[33,34] or reproductive activity,[35] and especially by the high spontaneous rate, possibly affecting 20-30% of all zygotes.[36] This incidence is more than an order of magnitude higher than in mice, which is why with respect to the induction of nondisjunction (but in contrast with gene mutations) extrapolation from mice to humans poses problems in principle.

Taking all the evidence together, we conclude that the significant increase in trisomy 21 in Berlin nine months after the Chernobyl reactor accident was not simply a chance event. Assuming (*a*) that maternal meiosis is an error prone process that is most sensitive to endogenous or exogenous factors at around the time of chromosomal segregation, and (*b*) that inhalation of large amounts of radionuclides with short half lives, (especially ^{131}I) was limited to a period of less than two weeks in Berlin, we believe that a causal relation was the most likely explanation. The extent of the increase in trisomy 21 remains difficult to explain, however, despite the low amount of radioactive fall out that people in Berlin were exposed to.

Our interpretation of the findings contradicts current textbook opinion. Accepting it as valid has immediate practical consequences for genetic counselling and also considerable theoretical implications concerning the process of chromosomal segregation in humans.

Clinical implications

- Nine months after the Chernobyl reactor accident a cluster of 12 trisomy 21 cases occurred in West Berlin instead of the expected two or three
- Most of these cases originated from maternal nondisjunction that coincided with the time of highest radioactive exposure, particularly inhalation of iodine-131
- It is concluded that in women the time around conception is most sensitive for the induction of numerical chromosome anomalies by low dose irradiation
- Any exposure to ionising radiation (or other harmful exogenous factors), especially around conception, should be avoided
- A history of exposure to ionising radiation at around conception is an indication for genetic counselling and possibly prenatal diagnosis

This work was supported by a grant from the Umweltbundesamt. Data on maternal age distribution were kindly provided by O Burkhardt from the Statistisches Landesamt Berlin. We are grateful to Professor Dr H Lindenberger and Professor Dr F Vogel for their most valuable comments and to Dr M Digweed for help in preparing the manuscript.

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(Accepted 6 April 1994)

Late deaths and survival after childhood cancer: implications for cure

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Abstract

***Objectives*—To investigate causes of death and survival in subjects who had survived at least five years after diagnosis of childhood cancer; to compare observed mortality with that expected in the general population; and to compare results with a corresponding cohort diagnosed earlier.**

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

***Setting*—Population based National Register of Childhood Tumours.**

***Subjects*—9080 five year survivors of childhood cancer diagnosed in Britain during 1971-85, of whom 793 had died. Comparison with corresponding cohort diagnosed during 1940-70.**

***Main outcome measures*—Cause of death established from all available sources of information (including hospital and general practitioner records and postmortem reports) and underlying cause of death coded on death certificate.**

***Results*—Of the 781 deaths for which sufficient information was available, death was attributed to recurrent tumour in 578 (74%) cases, treatment related effect in 121 (15%), second primary tumour in 52 (7%), and other causes in 30 (4%). Comparison of observed mortality with that expected in the general population indicated a fourfold excess of deaths from non-neoplasic causes. The risk of dying of recurrent tumour in the next 10 years after surviving five years from diagnosis during 1940-70 and 1971-85 fell from 12% to 8%. The risk of dying from a treatment related effect increased slightly from 1% to 2%.**

***Conclusion*—Improvements in five year survival after childhood cancer have been accompanied by a reduction in risk of dying from recurrent tumour during the subsequent 10 years and by a slight increase in risk of dying from treatment related effects. The results provide information relevant to decisions concerning balance between effective treatments and their potentially harmful effects.**

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BMJ 1994;309:162-6

Introduction

Survival after childhood cancer has dramatically improved over recent decades, with many diagnostic groups now showing a five year survival rate of at least 60%.[1] This has resulted from increasing use of intensive chemotherapy combined with other modalities of treatment, improved generalised supportive management, and increased centralisation of care. With increasing numbers of long term survivors, the long term effects of treatment for childhood malignancy must be carefully monitored because these will become increasingly important in determining future treatment protocols.

Patients who survive at least five years after childhood cancer experience an excess of deaths compared with the general population.[2] The Childhood Cancer Research Group examined cause of death after five year survival in a cohort of children treated for cancer before 1971 and found excess mortality from certain causes and preventable deaths.[3] Children treated more recently would probably show different patterns of mortality because of the improvements in survival and modern treatment regimens, in which chemotherapy is used more extensively. A recent study of causes of death in all patients (not just five year survivors) who had been treated for non-Hodgkin's lymphoma showed that there was considerable mortality related to treatment, of which a substantial proportion was related to chemotherapy.[4]

The objectives of this study were, firstly, to determine the causes of deaths of children treated for cancer during 1971-85 who had survived at least five years and to relate the causes of death to type of tumour and treatment; secondly, to compare the observed mortality from specific causes with that expected in the general population to identify any departure from the expected pattern of mortality; and thirdly, to compare these results with those from our previous study of late deaths[3] to detect any differences in the pattern of late mortality after treatment in 1940-70 and 1971-85. By investigating the proportion of patients dying of recurrent tumour at specified times after five year survival, we hoped to clarify the extent to which different childhood neoplasms have proved curable in the two periods of diagnosis.

Methods

The National Register of Childhood Tumours, maintained by the Childhood Cancer Research Group in Oxford, has been routinely notified of tumours occurring in children aged under 15 years since 1962 through the national cancer registration scheme operating in Britain. This provides, within the limits of completeness of registration, a population based series of childhood cancer cases. From this series we selected patients who had cancer diagnosed between 1971 and 1985 and who had survived at least five years after diagnosis. All diagnoses from the Birch and Marsden classification[5] apart from Langerhan cell histiocytosis