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Viruses, Clusters and Clustering of Childhood Leukaemia: a New Perspective?

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Clusters of childhood leukaemia have, during a lengthy and controversial history, focussed attention on two alternative putative aetiological agents: infections and localised environmental pollution. In the United Kingdom emphasis is currently placed on the latter because of reports of localised clusters in the vicinity of two nuclear reprocessing plants. Now the most recent studies of spatial clustering in the United Kingdom also support the hypothesis that a substantial population of cases of childhood acute lymphoblastic leukaemia (ALL) arise as a rare host response to certain patterns of exposure to common infectious agents—the aberrant response model. Relevant aspects of the epidemiology of ALL are reviewed from this perspective and the hypothesis shown to be capable of unifying reported associations with different types of risk factor. It is probable that specific agent(s) are involved though none have been identified and these may share many epidemiological characteristics of herpes viruses. The possible relevance of these results to associations with prenatal parental occupational exposures to dusts and ionising radiation is explored.
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INTRODUCTION

WHEN THE first clusters of leukaemia in 1897–1922 were reported [1, 2] they were interpreted as evidence for the current belief that "acute leukaemia is an infectious illness" [2]. Since then numerous reports of leukaemia clusters, especially amongst children, have been published (see below) and for these the emphases have, until relatively recently, been focused on an infectious origin. The identification of viruses as causes of leukaemia in chickens [3] and many other animal species [4] and of several human malignancies [5] provided strong support for this. At least two haematopoietic diseases can be caused by viruses: Burkitt's lymphoma [6] by the Epstein–Barr virus (EBV—a herpes virus) and adult T-cell leukaemia [7] by a retrovirus (ATLV1). A childhood leukaemia virus has, however, proved elusive, the epidemiological evidence for its existence doubted [8] and the statistical evaluation and scientific status of leukaemia clusters questioned [9]. The involvement of an infectious agent of low power was first suggested in 1937 [10] and Greaves has proposed a detailed biological model [11, 12] under which acute lymphoblastic leukaemia (ALL) at the childhood peak ages might arise following unusual patterns of exposure to common infectious agents.

Testing hypotheses relating viruses and other infectious agents to malignant disease is difficult, especially for human disease [13] and when no candidate agent has been identified modern methods of molecular biology are not helpful. One important epidemiological tool is the study of clustering. The first formal methods of statisical analysis used space–time interaction tests which apply primarily to "ordinary" infectious diseases where latent periods are measured in days. Results (see below) for leukaemia have been equivocal. Since the latent period could be both lengthy and variable, lack of clustering does not negate viral hypotheses [14]. Nevertheless, it removes one strand from the potential circumstantial evidence and Doll has argued, ". . . the question whether childhood leukaemias generally have a tendency to occur in clusters more often than would be expected by chance remains unanswered. . . . If there were any such factors (environmental factors such as ionizing radiation or possibly viral infection) one means of discovering them would be the demonstration that clusters of cases occurred in excess of those that might be produced by chance [15]."

Conversely, the existence of clusters can point to other aetiological factors and the identification of small intense clusters in the neighbourhood of putative point sources [16–21] has shifted the focus of attention towards nuclear facilities, contaminated water and other fixed environmental hazards. Nevertheless, any causal association between these sources and the clusters remains controversial [22] and epidemiological evidence suggesting an infectious aetiology has continued [23].

It will be argued below that there is now a strong case for a further shift of emphasis following a series of analyses of epidemiological data from the United Kingdom [24–34] which demonstrates weak, but quite widespread clustering of childhood ALL and thus changes the perspective described by Doll. A specific epidemiological model is proposed, the aberrant response model which, while not attempting to define biological mechanisms, is consistent with Greaves' hypothesis for the childhood peak but extends to all childhood ALL.

Established causal factors for childhood leukaemia include exposure to moderate and high doses of ionising radiation, chemotherapeutic agents, *in utero* X-ray and certain inherited or congenital conditions [15]. These can explain only a minority of cases and the evidence to date has been interpreted as suggesting a multiplicity of aetiological pathways [35] even for ALL which represents 75% of cases in developed countries.

Some recent studies have reported statistical associations between prenatal parental occupational exposures to ionising radiation and dusts and childhood ALL [36–39]. Radiation damage to germ cell DNA was suggested as a biological mechanism [36] but several authors have deemed this to be implausible on quantitative genetic and radiobiological grounds, e.g. [40–44]. At the same time new reports have emerged of associ-

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ations of childhood ALL or leukaemia with familial immune dysfunction and related illness [39, 45] and with relatively non-specific neonatal factors including, in two independent studies, physiological jaundice [39, 46]. These new results could be further pointers to multifactorial aetiologies. Alternatively, it will be proposed that the aberrant response model may provide a unifying hypothesis. Many other reported risk factors serve as proxies for the relevant exposures or can be interpreted as (in part) contributing to the same aetiological pathway.

Although this review focuses on ALL many of the contributing papers use larger groups: leukaemias, leukaemias and lymphomas or even childhod cancers. Where results are quoted they always refer to the diagnostic grouping closest to ALL.

CLUSTERS AND CLUSTERING OF CHILDHOOD ALL

Large numbers of clusters of (childhood) leukaemia have been reported yet the definitions, usually implicit, are varied and often obscure. The general idea is of a group of cases bounded in some way whose number is not compatible with the size of the corresponding population at risk (and reference rates of disease). Cases are normally located just once but this may be at birth, onset of symptoms, diagnosis or death. For the majority the boundaries include both space and time (space–time clusters) but some authors describe small areas with ongoing excess incidence as clusters (spatial clusters); a small number of reports refer to individual houses (e.g. [47]) or families (e.g. [48]). Age and sex boundaries for cases and population at risk and diagnosis for cases need to be laid down. The problems inherent in evaluating these reports are well known; they include estimation of the population at risk, choice of reference rates, and adjustment for multiple testing involved in the selection of the particular boundaries (from all of those which *might* have been applied) [49–51]. *Post hoc* reports are anecdotal and incapable of formal statistical analysis but may still provide aetiological clues, although they can also raise inappropriate anxiety if locations are identified.

A selection of these reports is included in Table 1. The most striking is the one at Niles, Illinois [52] which was associated with one primary school, rapid population growth [29], synchronous "rheumaticky" illness and congenital abnormalities in the population [53] and unusual immune response in case families [54]. Similar features were noted in other cluster reports: population reproductive abnormalities [55, 20], other family illness [56], population increase or mixing and its possible effect on herd immunity [57, 58], association with one school/workplace [18, 59, 60]. Because of the difficulty of evaluating them, reports of individual clusters are now infrequently published. Exceptions include one restricted to T-cell ALL, of interest because of the viral origin of adult T-cell leukaemia [61], and one involving 49 cases [60]. In addition, assiduous investigations by regional television companies, alert clinicians and local pressure groups have led to the identification of a small number of intense clusters of childhood leukaemia which have been associated with putative point sources, often, but not exclusively, nuclear facilities [16–21]. One common feature of these reports is that environmental exposure to known leukaemogens *is* involved but that doses are so small as to be incompatible with the recorded elevations of risk according to reasonable models [62, 20].

Reports of leukaemia clusters are, however, ongoing. In a review of 22 years work by the US Centre for Disease Control, Caldwell [63] reported 108 investigations of which 41 were of clusters of leukaemia and a further 44 included leukaemia. As noted above, the perspective has changed from one where clusters were actively sought with the aim of identifying tumour viruses to one where the primary interest is environmental contamination.

Formal statistical analyses normally focus on clustering in which the distribution of cases amongst the population at risk is examined for evidence of a tendency to aggregate. The first valid tests were of space–time clustering. Analyses using Knox's [64] and similar methods have been reviewed by Linet [65] for whom 14/23 studies showed some evidence of clustering. She noted that these normally involved children often aged under 6 years at onset of symptoms or diagnosis, and used incidence data rather than mortality registers. Studies of this type involving childhood leukaemia are summarised in Table 1; since arbitrary definitions of close are required, multiple testing is a recurrent feature of these analyses and the overall evidence is equivocal. Few analyses of this type have been conducted since their low power for chronic disease was formally established [66].

A modification due to Pike and Smith [67] addresses this problem by collecting residential histories and investigating pairs of cases who were close enough to have effective contact during times of their presumed infectivity and susceptibility. The use of these concepts is more realistic than restricting attention to location at diagnosis (or birth) but unless a clear aetiological hypothesis suggests when these times may be arbitrary definitions still lead to multiple testing. In the only application of this method significant results were obtained for susceptibility during gestation and infectivity stretching from birth to diagnosis [68]. These authors were envisaging the possibility of case-to-case transmission of a specific virus; it is appropriate now to take quite general definitions:

—a child is *susceptible* to exposure to an agent Z, if infection established at that time may eventually contribute to a diagnosis of ALL.

—a child is *infective* is she/he is a marker for a source of infection by Z which is localised both in time and space and capable of contributing to leukaemia in exposed children.

Note that this definition of infectivity includes the identification in time and space of local micro-epidemics where high-dose exposure might occur and need not imply any particular ability to transmit the agent. No analysis to date has been able to distinguish the latter at all reliably.

More recently, good statistical methodologies have become available for the analysis of spatial clustering of events in human populations. This is more appropriate than space–time analyses for investigations of fixed environmental sources and, also, infectious agents associated with lengthy and variable latent periods. Residential mobility over long latent periods remains a problem for either of these which will lead to reduced statistical power. One of the first analyses of spatial clustering [69] reanalysed data which had displayed space–time clustering and found highly significant spatial clustering in the same areas. Examination of ages and dates of diagnosis of nearest-neighbour pairs showed that susceptibility and, possibly, also infectivity must occur prenatally; this was at the time taken as evidence against an infectious origin.

It is in the U.K. that the most intense methodological activity has occurred. At the same time good and reliable national [70] and semi-national [71] data sets have become available for small area analyses. Several of the new methods have been applied to national incidence data collected by the Childhood Cancer Research Group (CCRG) from 1966 to 1983 (6500 cases) and results include demonstration of spatial clustering of ALL

Table 1. Reports of clusters and clustering of childhood leukaemia

Reference	Diagnosis	Ages	Cases: Place/time*	Cases: Source	Numbers: O	Numbers: T	Numbers: E	Description: Cluster(a)/ clustering(b)	Description: Localised in time?	Description: Definition	Description: Results	Description: Comments
Anecdotal and *post hoc* clusters†												
57	L/L	All	Kingston, U.K. 1958–1964	Diagnostic lab	14	462	?	a→b	Ongoing 6 years	"Residential Foci" within "micro-epidemic"	Controls studied and different residential patterns observed but no formal analysis. Emphasis on extremes of closeness in space or time	Authors found no evidence for occupational, residential or other exposure to radiation/chemicals; reported features characteristic of infectious diseases and speculated on herd immunity/changes in hygiene. Adults mainly affected
52, 53	AL	Children	Niles, Illinois 1950–1960	Special search	8	21	?	Cluster	Localised—two district periods	Observed excess	O/E in range 15–20 and statistically significant (no adjustment for choice of boundaries)	Synchronous population excess of congenital heart disease and all cases linked to one RC school where "rheumatic-like" disease reported. Rapid population growth [29]
53	L	Children	Orange, Texas 1960	?	3	?	0.4	Cluster	Localised—9 months	Observed excess, Observed time–space concentration	O/E not statistically significant; these were the only cases in the town 1956–1960	Synchronous cluster of congenital malformations. Cases arose in newly developed residential area, lived $<\frac{1}{2}$ mile apart
173	AL	Children	Louisville, Illinois 1961	?	2	?	0.1	Cluster	Localised	Observed excess and temporal concentration	No formal analyses	Children lived on adjoining farms in rural community and attended the same school
55	L	All	Almond, New York 1978	?	4	?	0.46	Cluster	Localised (10 month period)	Observed excess and temporal concentration	Formal analyses revealed excess in larger area	Area within Canisteo river basin and rates elevated following major flood; accompanied by increase in spontaneous abortion rates
59	ALL	All	Small village in Eire 1969–1973	?	6	?	0.005	Cluster	4 year	Observed excess	No formal analyses	History of direct contact reported, speculations of infectious process
174	L	All	Single house, U.S.A. 1950–1967	Special search	4	15	?	Cluster	Ongoing	Observed concentration in one house	No formal analysis but 3 cases from 53 persons in 15 families occupying house, 1 a frequent visitor	Water and household radiation found to be normal
175	L/L	All	Single house, Pennsylvania 1940–1960	Special search	6	7	?	Cluster	Ongoing 20 years	Observed excess in single house	From four families but no formal analysis	No unusual radiation etc. in house; no other cases in town over this period; IM also reported by household members

16	L/L	ages 0–24 years	Seascale, Cumbria, U.K. 1968–1978	(Initially) special search; (later) regional/national registries	6	?	1.4	Cluster	Ongoing	Observed excess	Extensive evaluation: e.g. ranked 1st/4th out of >400 similar small areas (see [176]) O/E >10 for Seascale village 1956–1983 and children <10 years	Associated with nuclear reprocessing plant at Sellafield but no causal relationship established (see also [36]—occupational exposure of parents?) Continuing phenomenon [205]
17	L/L	ages 0–24 years	Thurso, Scotland 1968–1984	National registry	6	?	2.3	Cluster	Ongoing but concentrated in one 5-year period 1979–1984	Excess of O over E in circles centred on nuclear facility at Dounreay, radii 12.5 and 25 km	Circles drawn and other boundaries fixed *before* cases examined and excess statistically significant, O/E = 9.15 for radius 12.5 km and time 1979–1984	Associated with nuclear reprocessing plant at Dounreay but no causal relationship established; a case–control study [177] did not attribute excess to occupational exposure of parents; see also [22]‡
19	L/L	ages 0–14 years	Reading, England 1972–1985	(Initially) paediatric oncology clinic; (later) national registry	31	?	20.9	Cluster	Ongoing	Observed excess noted first by clinicians centred on *two* "nuclear" sites at Aldermaston and Burghfield; radii 10 km	Extensive evaluation confirmed excess as statistically significant. Excess restricted to ages 0–4 years (O/E = 1.9)	No causal association established; case–control study in progress, see also [178, 22]. Area experienced substantial increase in commuting during this period [30]
20	L	Children (age 19 and under)	Woburn, Massachusetts 1964–1983	Special ascertainment	20	?	9.1	Cluster	Ongoing	Chance discovery of toxic wastes and contaminated water led to health surveys	Formal comparison of O, E gives $P = 0.001$. Statistical modelling found significant association with proximity to contaminated wells. No allowance for *post hoc* nature the analysis but extensive published discussion [20]	No causal relationship established; synchronous excess of certain congenital anomalies including Downs Syndrome. Later immune abnormalities in leukaemia families [55]
60	L	Children	West Central Phoenix, U.S.A. 1965–1986	(Initially) report from one school; (later) CDC survey	49	?	29	Cluster	Ongoing	Observed excess in one school then excess of O over E in larger area	$P = 0.0004$ based on Poisson distribution	The initial report related to just 8 cases from one school so this is not truly a *post hoc* analysis; attention focussed on drinking water and air pollution and pesticides but rapid population expansion was also noted. No cause found.
Systemic searches of data-base for clusters§												
179	L	0–9 years	New York State, U.S.A. 1948–1960	Death certificates	12	54	?	Cluster	2-year period	High county rates within state for 1950–1951	Rates for Oneida County were $19.9/10^5$ but for New York State $4.3/10^5$	Mother of 1 case died of AL 1 year later
180	L	Children	South East Scotland 1970–1984	Special ascertainment	11	?	3.6	Cluster	Ongoing	Excess of O over E for Largo Bay area	$P = 0.0013$ but no allowance made for the assiduous search	

Cont.

Table 1. Continued

Reference	Diagnosis	Ages	Cases: Place/time*	Cases: Source	Numbers: O	Numbers: T	Numbers: E	Description: Cluster(a)/ clustering(b)	Description: Localised in time?	Description: Definition	Description: Results	Description: Comments
181	L	0–15 years	Indiana, U.S.A. 1951–1960	Death certificates	21	591	?	5 individual clusters	Very localised in time	Space–time concentrations	No formal analyses	One 'cluster' involved cases attending the same school in a rural area, and a class-mates mother died of AL 2 years later. Overall the death rates were uniform geographically and over time
182	L	0–14 years	New Zealand 1953–1963	Special collection of National Incidence Data	11	?	?	3 individual clusters	Very localised in time	Both space–time concentrations and excesses of O over E	Incidence rates compared to national rates–ratios of 10 200 reported	Reported clusters are in suburban and rural areas but there were also apparently urban clusters
183, 27	L/L	0–14 years	North of England, 1968–1982 and 1966–1983	Specialist tumour registry	18	113	2.5	5 individual clusters	Ongoing	Excesses of O over E for electoral wards	Poisson probabilities all <0.01–5 smallest in area	Includes Seascale—these results are for [183]
61	T-cell ALL	0–19 years	Naples, Italy 1980–1983	Special ascertainment	11	16	?	Cluster	30-month period	Observed geographic heterogeneity of distribution	11 of the 16 cases in Campara, were in a small area of Naples province. O/E >3, no formal analyses	5 of the 11 cases had a history of social contact and/or very close residence and dates of onset. Authors suggest association with (retro-) virus. Uniform distribution for 42 other cases of childhood ALL. Volcanic area of high natural radioactivity
Space–time interaction tests‖												
184	L	Children	Buffalo, New York, U.S.A. 1943–1956	Cancer registries	—	137	—	Clustering	Localised	Space–time interactions at onset	$P < 0.05$ for one definition of "close" but no adjustment for multiple testing	Family and friendship associations between close cases also noted. see also [69]
185	L	0–14 years	North East England 1951–1960	Regional registry	—	185	—	Clustering	Localised	Space–time interactions at diagnosis	Significant clustering for children aged <6 years but not older children	
186	L	Children	Liverpool, England 1955–1964	Hospital series	—	74	—	Clustering	Localised	Space–time interactions at diagnosis	Excess for pairs 4 km, 300 days apart, no adjustment for multiple testing	
187	L	Children	Oregon, U.S.A. 1950–1961	Special ascertainment	—	258	—	Clustering	Localised	Space–time interactions at diagnosis	$P < 0.05$ for pairs 4 km, 350 days apart, but authors concerned at choice of "closeness" by data inspection	
188	AL	0–14 years	New Zealand 1953–1964	Death lists	—	280	—	Clustering	Localised	Space–time interactions at diagnosis	$P < 0.05$ for children under 6 years; no adjustment for multiple testing	Authors suggested excess attributable to non-uniform population growth. Least evidence of clustering for ages 2–9 years

189	AL	0–14 years	Georgia, U.S.A. 1956–1968	Special registry	—	100	—	Clustering	Localised	Space–time interactions at diagnosis	Single definition of closeness: space = same census tract, time = same 2.3 years. $P < 0.05$	Adults analysed in the same way showed no evidence of clustering
190	L	0–14 years	Connecticut, U.S.A. 1945–1959	?	—	333	—	Clustering	Localised	Space–time interactions at diagnosis	No evidence of clustering. Single definition of closeness: space = same town, time = same calendar year	
191	L	0–9 years	Greater London, England 1952–1961	Death records	—	483	—	Clustering	Localised	Space–time interactions at (a) onset (b) birth	Weak clustering for ALL at onset (all and those dead by age 6) and at birth (those dead by age 6)	13 subsets analysed
192	L	Children	Los Angeles, U.S.A. 1960–1964	Death records	—	298	—	Clustering	Localised	Space–time interations at death	No evidence of clustering	
193	L	0–14 years	New York, U.S.A. 1943–1962	Cancer registry	—	1640	—	Clustering	Localised	Space–time interactions by location at birth and report	No evidence of clustering at birth, weak clustering at report especially for those aged under 5 years. One definition of closeness: space = same town, time = same calendar year	Clustering at birth not investigated for children over 5 years at diagnosis
194	L	0–4 years	Michigan, U.S.A. 1950–1959	Death records	—	375	—	Clustering	Localised	Space–time interactions by location at birth	No evidence of clustering spacial proximity = same county	Note coarse spatial units
195	L	0–14 years 2–14 years	San Francisco, U.S.A. 1946–1965	Special ascertainment	—	149	—	Clustering	Localised	Space–time interactions at diagnosis	No evidence of clustering	
196	L	0–9 years	Midlands, England 1953–1960	Special ascertainment	—	228	—	Clustering	Localised	Space–time interactions at (a) onset (b) birth	(a) $P < 0.04$ for 5 km, 15 months apart. (b) $P < 0.02$ for 2 km and 148 days; number of tests done not stated	Interview data from Oxford Survey of Childhood Cancer for cases and controls used to evaluate experience of children involved in close pairs. Inconclusive results but authors see some evidence of association with epidemics of common childhood infectious diseases
197	L, ALL	0–14 years	West Netherlands 1973–1980	National registry	—	293	—	Clustering	Localised	Space–time interactions at diagnosis	No evidence of clustering	
26	LL	0–14 years	England, Wales, Scotland 1966–1983	National register	—	5710	—	Clustering	Localised	Space–time interactions at diagnosis	$P < 0.05$ for 1 km, 0 months apart after adjustment for multiple testing (24 close pairs)	Similar results for ages 0–4 years, and for 0–4 years × 5–14 years (for all leukaemias, LL not reported)

Cont.

Table 1. Continued

Reference	Diagnosis	Cases: Ages	Cases: Place/time*	Cases: Source	Numbers: O	Numbers: T	Numbers: E	Description: Cluster(a)/ clustering(b)	Description: Localised in time?	Description: Definition	Description: Results	Description: Comments
Space–time interactions with allowance for latency¶												
68	L	0–6 years	Greater London, U.K. 1952–1965	Special ascertainment	—	253	—	Clustering	Localised	Space interactions with overlap of susceptible/infective periods	$P < 0.05$ for pairs <4 km distance with susceptibility during gestation, infectivity birth–diagnosis	No adjustment for multiple testing. Data set includes that of [191]
34	LL	0–14 years	Wards in England, Wales, Scotland showing spatial concentrations 1966–1983	National register	—	487	—	Clustering	Localised	Space interactions with overlap of susceptible/infective periods	$P < 0.01$, $P < 0.05$ for two analyses	Choice of susceptible and infective periods given by prior hypothesis. Investigator does not define the boundaries
Spacial clustering¶												
69	L	Children	Buffalo and San Francisco, U.S.A.	Data from [179, 195]	—	137 149	—	Clustering	Ongoing	Nearest neighbour analysis	$P < 0.001$, $P < 0.05$	See also [184, 195]
17	L	Children	Scotland 1979–1984	National registry	—	301	—	Clustering	Ongoing	Examination of counts in small areas of equal size	No evidence of clustering	Method lacks statistical power [188]
18	L	0–14 years	North Humberside 1976–1986	Specialist registry	—	53	—	Clustering	Ongoing	Nearest neighbour analysis	Significant clustering ($P < 0.05$)	Possible associations with two schools but not restricted to age-ranges of pupils; no confirmation of suspected association with aluminium smelter
25	LL	0–14 years	England, Wales and Scotland 1966–1983	National registry	—	5710	—	Clustering	Ongoing	Global test of heterogeneity of ward counts	$P < 0.05$	Effect concentrated in sparsley populated areas; similar results for 0–4 years
24	LL	0–14 years	England, Wales and Scotland 1966–1983	National registry	—	5710	—	Clustering	Ongoing	Test of heterogeneity of counts in equal size small areas	$P < 0.05$	Similar for ages 0–4 years
Other forms of clustering?												
33	L/L	0–14 years	Three areas of England 1973–1986	Specialist registries	—	107	—	Proximity of cases throughout their residential histories	—	Modified nearest neighbour method	$P < 0.006$ (using controls for comparison)	Requires no prior definition of times of susceptibility and infectivity

L, leukaemia; L/L, leukaemia and lymphoma; AL, acute leukaemia; LL, lymphocytic leukaemia; O, observed in cluster; E, expected within cluster boundaries; T, total for analysis; ?, information not supplied.

*For some clusters several analyses have included different time periods.

†A selection of the most striking and well documented reports.

‡Area associated with major population mixing through employment at oil terminal construction (Kinlen *et al.*, *Br Med J* 1993, in press).

§This list is believed to be complete for reports published since 1980. Note that [27/28] are new methodologies for searching data bases for evidence of spatial clusters (or data-base anomalies) but publication of sites was not included in the OPCS Monograph [69] for reasons described in the introduction.

‖The majority of published reports are included.

¶These lists are believed to be complete.

Note that temporal and seasonal clustering are not considered here.

(especially amongst young children) [24, 25] and space–time clustering of ALL [26]. Two of the collaborating U.K. research groups are of the opinion that a systematic search of the data base for clusters is more appropriate than global tests of clustering [21, 72]. These authors in their analyses of the CCRG data provided evidence suggesting that individual intense clusters of childhood leukaemia are more widespread than had hitherto been documented [27, 28]. At present, all these are statistical results and may be attributable to data anomalies (e.g. inappropriate use of census counts) as well as to aetiological processes.

During this time two separate U.K. groups have followed lines of research aimed at testing patterns of infection as causes of localised excess incidence of childhood leukaemia. In a series of studies, Kinlen and colleagues have identified extreme instances of population mixing. Since this would lead to disregulated herd immunity and community micro-epidemics of common infectious agents, clusters of leukaemia would be predicted by a hypothesis relating high viral dose to childhood leukaemia. Three groups of clusters have been found: in new towns [29], areas with marked increase in commuting [30] and areas with encampments of army personnel [31]. The ages at diagnosis of the children differ with population mixing of children associated with leukaemia clusters at the childhood peak and of adults with leukaemia of older and younger ages of onset.

Alexander and colleagues in testing Greaves' hypothesis have found doubling of incidence in the childhood peak in the most rural areas [32] in two independent data sets; her analysis of the CCRG data [25] showed that clustering was confined to these types of area and could not be explained by uniformly high rates within them. A pattern of relatively stable rates in urban areas and isolated incidence peaks in rural ones is typical of many infectious diseases. A case–control study conducted by this group [33] has investigated residential proximity as proxy for shared social contacts in the vicinity of three of the documented U.K. clusters and reported significant clustering according to this criterion which, when examined further, suggested susceptibility around the time of birth and infectivity from conception to diagnosis—as found by Smith *et al.* [68]. Preliminary confirmation of this has come from an extended analysis of CCRG data [34]. This uses an adaptation of the Knox test to cope with latency which is similar in spirit to the method of Pike and Smith but with the crucial difference that an aetiological hypothesis leads to times of infectivity and susceptibility so that multiple testing is not a problem. It is relevant that for another chronic disease whose aetiology may involve delayed effects of viral infection (multiple sclerosis), a recent analysis has applied space–time interaction tests with emphasis on specific times of susceptibility/infectivity and demonstrated striking age-at-exposure effects [74].

There is an urgent need to use these methods (i) to test for spatial clustering of ALL in the other suitable large data sets where statistical power is adequate, and (ii) to seek confirmation of the spatial temporal patterns which have been described. Meanwhile, the available evidence indicates that weak clustering may be quite common in the distribution of childhood ALL. The data are consistent with their interpretation as an imperfect reflection of some underlying population infective process; background noise may be attributed to a variety of factors including (i) low risk of ALL in those exposed, (ii) risk influenced by dose but individual viral burden not correlating very strongly with population epidemicity, (iii) variable times of susceptibility and latency so that location (and time) of birth and diagnosis are inadequate proxies for those of critical exposures, (iv) population movement—migration and day-to-day social contact—so that locations of exposure are inaccurately known, (v) significant risk of ALL in the unexposed (due to other aetiological factors and/or persistent maternal infection).

INFECTIOUS AETIOLOGIES FOR CHILDHOOD ALL

One of the most striking features of the descriptive epidemiology of childhood ALL has been the development of the childhood peak with maximum incidence at ages 3–4 years. This was first noted in the United Kingdom [75] and has since been observed in all developed societies. This is attributable to just one immunophenotype [76]—common ALL (cALL)—which represents over 60% of cases in these societies, but which has a 10-fold deficit in black Africans [77]. The peak has emerged amongst diverse ethnic groups as "modernisation" has occurred and is usually attributed to some aspect of community lifestyle associated with its development, of which changes in the pattern and timing of exposure to infections (reviewed in more detail in [12]) are the most plausible candidates.

The study of clusters and clustering outlined above also suggests an aetiological role for one or more infectious agent(s). If so, the agent must be common or even ubiquitous because, for example, it is present in each instance of population mixing studied by Kinlen and colleagues [29–31]. Since ALL is itself a rare disease, unusual host factors or exposure circumstances must be essential aetiological components. Symptoms associated with initial infection must be unremarkable since, otherwise, an association would presumably have been noted already.

Under Greaves' hypothesis [11] immunological isolation in infancy increases the risk of cALL arising in the childhood peak. Eventual conversion to leukaemia may be modulated by generally high levels of antigenic challenge or by exposure to an (unknown) specific agent [12]; for the latter, delayed exposure and/or high dose may be relevant. The demonstration of spatial clustering and residential proximity for cases of ALL at this age suggest the influence of a specific agent. That high viral dose may contribute is supported by the results of Kinlen and colleagues [29]; in addition, better socio-economic circumstances [70] and community isolation [32] could lead to early immunological isolation while the reported concentration of clustering in rural areas [25] had been predicted if delayed exposure to a specific infectious agent increased leukaemia risk [78]. A considerable body of biological and epidemiological data provide indirect support for this broad hypothesis (reviewed in [12]).

Fleming [79] has noted that international variations in age incidence of ALL are consistent with its being a consequence of *in utero* exposure following primary infection of non-immune mothers in developed societies. Within the U.K., an association of low socio-economic status with maternal seropositivity has been established for at least one common virus (another herpes virus, cytomegalovirus—CMV [80]). However, one large study [81] has shown that mothers of children with leukaemia have had more possibility for social contact as children and are, therefore, less likely to be immune than control mothers. These results have not been confirmed but, even if correct, leave open the possibility of persistent infection in the case mothers. It is known that reinfection or reactivated infection of a persistently infected mother can lead to fetal exposure and damage [82].

Persistent infection is a feature of most animal and human models of viral oncogenesis. Persistence is usually established following *in utero*, neonatal (often while protected by maternal

antibodies) or late primary exposure and/or high viral dose [83]. For other viruses (e.g. herpes viruses—see below) persistence always follows primary infection but the ability of the host to contain the virus in a latent state is believed to be reduced when exposure occurs unusually early or late. The spatial–temporal patterns of clustering reported by Alexander [33, 34] provide evidence that persistent infection established *in utero* or early infancy may be associated with childhood ALL (especially when diagnosed *outside* the childhood peak). Further support for this comes from results of Smith *et al.* [68] and Lewis [69] and from two recent studies by Kinlen and colleagues [30, 31].

The aim of the remainder of this review is to consider other aspects of the epidemiology of childhood ALL from the perspective of a provisional hypothesis that the aetiology of most cases involves a common virus or viruses. In order to do this the components of reasonable models are separated in Table 2.

The epidemiological data reviewed below are all consistent with the hypothesis that ALL commonly arises as a rare sequelae to exposure to a common virus or viruses and *either* gestational or neonatal exposure leading to persistent infection (and failure of containment) *or* primary infection at an older age in children whose immune system has been protected from early challenge, with in both cases, host susceptibility, high viral dose and heterologous exposures being modulating factors. The clustering reported earlier [33, 34] supports the possibility that exposure to the same agent(s) is involved at the different stages of fetal and child development but does not prohibit specificity of certain related viruses to ages-at-exposure and/or ALL diagnostic subtype. This is the aberrant response model (Fig. 1).

In the review, results for a number of key case–control data sets will be cited frequently; these are summarised in Table 3, which includes all case–control studies of childhood leukaemia or ALL which are of adequate size and methodology and include exposures relevant to the factors listed in Table 2. The details provided in the table enable the reader to judge the quality of each of these studies. Few provided details of disaggregation by age and for all (though to varying degrees) epoch of birth and age at diagnosis are associated so that age-specific and birth-cohort effects cannot reliably be separated. In addition, the age at diagnosis structure (and even the age ranges) of the studies differ very substantially which could lead to inconsistent results for overall odds ratio (OR) for factors whose effects were specific to certain ages at diagnosis. Most of these studies have matched for age and used some multivariate analyses to adjust for a limited range of other confounders. The factors we are currently considering are often highly correlated and their role as potential confounders for one another is critically dependent on which biological pathway is under investigation.

FAMILIAL, MATERNAL AND GENETIC FACTORS

Several large case–control studies have reported associations between family history of autoimmune, immune dysfunction and related disease and childhood leukaemia/ALL. These include significantly elevated OR (mostly in the range of 2–4) for familial rheumatoid arthritis and maternal multiple sclerosis from the CCSG studies [39, 45], general auto-immune disease in families (North London and Minnesota studies [84, 85]), and skin disease in parents (IRESCC, 86). The overall impression from these studies is an emphasis on maternal and maternal family disease. A number of small case–control studies have applied laboratory tests to parental blood. The results have not been entirely consistent with small numbers of abnormal results reported from a variety of tests. A common factor has, however, been evidence of non-specific indicators of chronic infection in the mothers [84, 85, 87–89]. Whilst these initially suggest viral transfer across the placenta and fetal infection as the putative biological pathway to childhood leukaemia we note that the well-being of the fetus and postnatal morbidity can be influenced by maternal exposure even if it does not result in overt maternal infection [90] or fetal exposure [82].

Interaction between human leukocyte antigen (HLA) and specific viruses is becoming increasingly evident in cancer aetiology [5] and, where no specific agent has been identified, HLA linkage is suggestive evidence of some viral component of the aetiology; preliminary results of such linkage have been reported for ALL families [91, 92]. The genetic effect could

Table 2. Infectious aetiology of childhood ALL: putative component factors

		Person directly involved	General (non-specific) infections or specific agent	Relevant time period	Other possible contributing circumstances
1a	Genetic factors	Mother	—	—	—
b	(e.g. HLA)	Child			
2a	Immune dysfunction	Mother	General	Prenatal (especially gestation)	—
b		Mother	Specific	Prenatal (especially gestation)	—
c		Child	Specific	Gestation and postnatal	
3a	Primary infection	Mother	Specific	Gestation	High viral dose
b		Child	Specific	Neonatally	High viral dose
c		Child	Specific	Prediagnosis	High viral dose Late age at first diagnosis
d		Child	General	Prediagnosis	High total antigenic challenge
4a	Reinfection/	Mother	Specific	Gestation	High viral dose Heterologous strain
b	Reactivated Infection	Child	Specific	Prediagnosis	High viral dose Heterologous strain
5	Immunological isolation	Child	General	Infancy	—

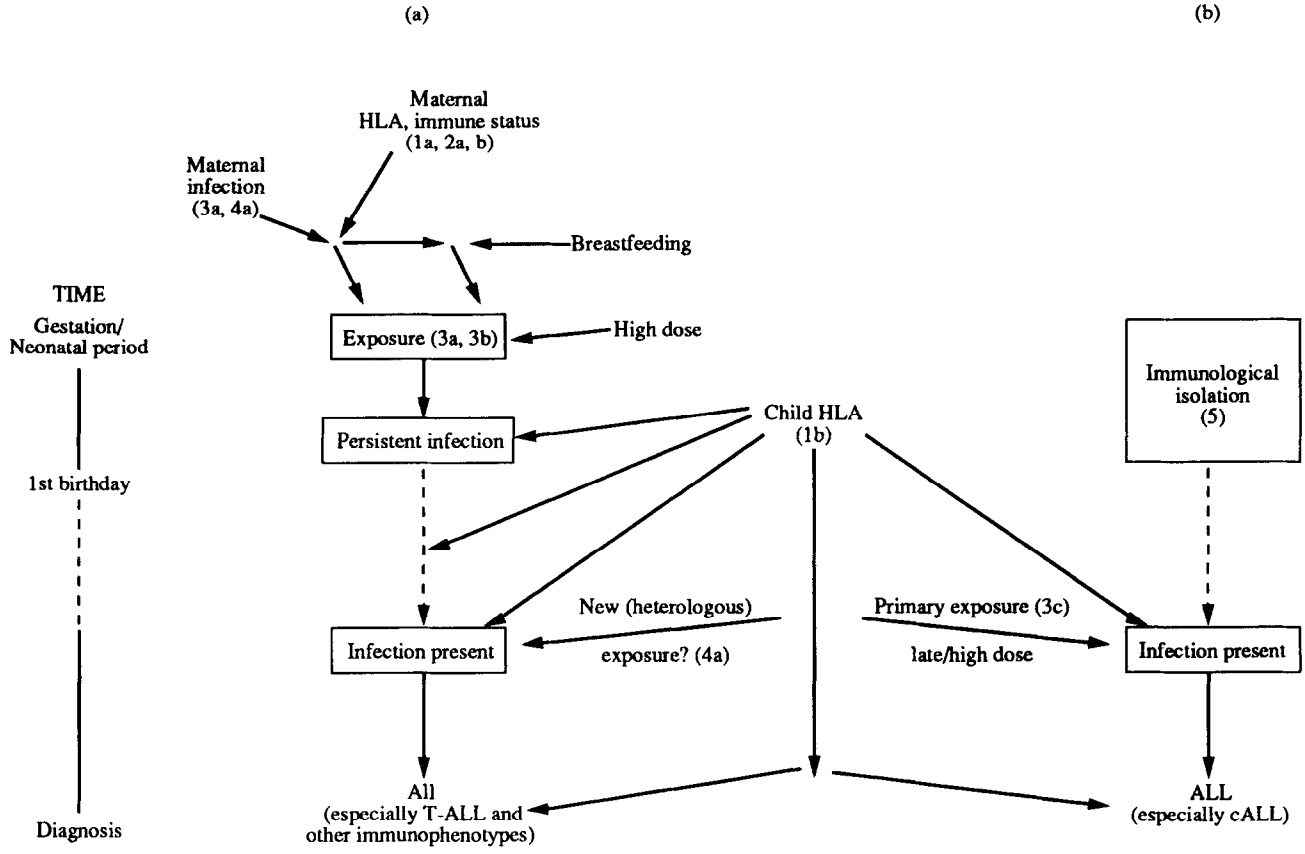

Fig. 1. The aberrant response models for ALL.

apply directly to the mother and/or her child but the emphasis on maternal factors suggests that maternal infection and/or immune function are directly involved in the aetiology of at least some childhood ALL. Further evidence of antigenic stimulation in the intra-uterine life of leukaemia cases comes from a study of cord blood of their siblings; elevated levels of IgM were found for all six children studied [89]. Animal models predict that host HLA of both mother and foetus may be relevant to fetal consequences of maternal infection [93].

Several case–control studies have found significant associations of childhood leukaemia/ALL with maternal infertility or fetal loss(es); these include the CCSG study [39], the Netherlands registry-based study [94] and the tristate survey [95]. Negative results all derive from studies utilising data from birth records (Minnesota study [96], Swedish registry-based study [46] and an early study of mortality data [97]) and may be attributable to incomplete ascertainment [46]. Although these associations are capable of a variety of interpretations and confounding by, for example, maternal age, two recent reports from the Minnesota studies [96, 99] of excess loss of the *preceding* pregnancy provide support for an interpretation involving the intra-uterine environment.

This literature provides evidence for several of the risk factors listed in Table 2: for genetic factors (1a, b), general maternal immune dysfunction (2a), maternal infection (4a) and possibly also ineffectual maternal immune response to specific infections (2b). It thus offers persuasive support for a of Fig. 1 and weaker, more indirect, support for b.

IN UTERO EXPOSURE TO INFECTIONS

The Oxford Survey of Childhood Cancer has reported significant risks of leukaemia/lymphoma for children whose mothers had acute respiratory infections (OR = 1.81) or were vaccinated (OR = 1.80) while pregnant [99] and two smaller case–control studies (North London study [84] and Finnish registry-based study [100]) have provided reports consistent with this, although non-significant. Ecological analyses have, however, failed to demonstrate any repeatable association between influenza and childhood leukaemia, suggesting [101] that the infections reported in case–control studies may be proxies for maternal immune status.

For one specific agent—varicella zoster virus (VZV)—there is some consistent evidence that primary (chicken-pox) or secondary (herpes zoster) infection in the pregnant mother confers a substantial risk of leukaemia to her child (Table 4). Case–control and cohort studies have reported substantial increases in risk, and detailed case reports are suggestive of chronic susceptibility to infection in these children. However, the number of cases involved is extremely small and the possibility of publication bias favouring positive reports must be considered. Moreover, the percentage of pregnancies complicated by overt VZV infection is very small and the risk of primary infection during pregnancy is higher in underdeveloped countries [102]. Thus, it appears likely that VZV can be involved only in rare instances and may perhaps serve as a marker for synchronous infection by other (herpes) viruses (see below).

Two recent ecological studies [30, 31] showing an association

Table 3. Details of case–control studies included in this review

Study name/key reference: OSCC (Oxford Survey of Childhood Cancer), Stewart *et al.* [200].
Case selection: All deaths from cancer in England and Wales from 1953 before 10th birthday (initially) and of older children (later).
Control selection: 1/case matched by age, sex, time of birth and "locality"—it appears that controls were born and resident at the time of the death of the case in the same locality as the case residence at death.
Data: Questionnaire.
Potential sources of bias/error: Controls selected from families who are less mobile—this was explanation offered for deficit of 1st born children amongst controls (relative to U.K. childhood population). Inclusion of dead cases only leads to selection bias in later years of the study.
Other comments: Other studies using this data-base: [99, 116, 147, 202].

Study name/key reference: Tri-state study, Graham *et al.* [201].
Case selection: Cases of leukaemia diagnosed in study area of U.S.A. 1959–1962 (319 childhood leukaemias).
Control selection: 884 controls from two stage sampling (households selected from census then children from households).
Data: Interviews and medical records.
Potential sources of bias/error: Lack of matching may have led to small numbers in certain cells but not otherwise invalid; control selection process may have favoured children in small families.
Other comments: Part of a larger study which included adults. Other studies using this data-base: [95, 153, 158].

Study name/key reference: IRESCC (Inter-regional Survey of Childhood Cancer), Birch *et al.* [199].
Case selection: Population based; all newly diagnosed cases in specified regions of the United Kingdom, 1980–1983. Ages 0–14 years. 171 leukaemias (includes 78 cALL and 70 other ALL).
Control selection: Matched by age, sex, time period of birth.
1 control/case from same GP practice as case (population based).
1 control/case from selected hospital admissions (hospital based).
Data: Face-to-face interviews, medical records.
Potential sources of bias/error: Hospital and population controls amalgamated for all formal analyses, but marked differences between them were evident in some published data (e.g. % admissions to special care baby unit, numbers of viral infections in first 6 months of life); use of hospital controls may have introduced social class bias. Analysis does not appear to have been matched.
Other comments: Part of a larger study of childhood cancer and not all analyses were disaggregated by diagnosis. OR were not published if $P > 0.05$ and $0.5 < OR < 2.0$. Studies using this data-base: [86, 106, 148].

Study name/key reference: Netherlands Registry-based Study, van Steensel-Moll *et al.* [94].
Case selection: Cases of childhood leukaemia registered by Netherlands cancer registry 1973–1980. Ages 0–15. 519 ALL cases.
Control selection: From population register matched by year of birth, sex, place of residence at diagnosis.
Data:
Potential sources of bias/error:
Other comments: Other studies using this data base: [107, 114, 160].

Study name/key reference: CCSG (Childhood Cancer Study Group). Buckley *et al.* [45].
Case selection: Newly diagnosed cases of leukaemia aged 0–18 years attending a CCSG institution 1982- onwards (1027 ALL cases).
Control selection: (i) 1250 similar children with cancer other than leukaemia, lymphoma, (ii) 838 healthy control children identified using random digit dialling.
Data: Self-administered questionnaire.
Potential source of bias/error: (i) Case selection: hospital series and only 50% of eligible cases were included. (ii) Control selection biases may follow from use of other cancers as controls and from random digit dialling; no age or sex matching was used, and hence in particular secular patterns by time-of-birth could confound the results.
Other comments: Other studies using this data base: [39].

Study name/key reference: Minnesota studies, Kaye *et al.* [96].
Case selection: Incidence cases of leukaemia 1969–1988 ascertained by retrospective review. Eligible if (i) born in Minnesota (U.S.A.) and (ii) treated by specified institutions in and around Minnesota, (iii) resident in Minnesota at diagnosis; believed to represent population coverage subject to residential criteria. 337 ALL cases 0–18 years.
Control selection: 4/case randomly selected from Minnesota live births of same year.
Data: Birth certificates (+ supplement in use in Minnesota).
Potential sources of bias/error: Controls not checked for vital status, cancer diagnosis nor residence in Minnesota. Information unbiased but some aspects (e.g. previous fetal loss) may be incomplete, hence possible conservative bias.
Comments: Several of the other studies using these data have been based on earlier (restricted) subsets: [85, 98].

Study name/key reference: Swedish Registry-based Study. Zack *et al.* [46].
Case selection: Diagnosis of leukaemia at ages 0–11 years to 1984 in births 1973–1984 ascertained by linkage of Swedish birth and cancer registry computer files; 337 ALL cases.
Control selection: 5/case matched by sex, month and year of birth selected from birth register and checked for cancer-free survival to date of case diagnosis using record linkage.
Data: Swedish medical birth register.
Potential source of bias/error: Some non-differential misclassification (e.g. for previous fetal loss) will have led to conservative biases of unknown magnitude. No information on socio-economic status.

Study name/key reference: North London Study. Till *et al.* [84].
Case selection: Newly diagnosed cases resident in North London 1973–1975 treated in specified hospitals but representing population coverage. 82 leukaemia cases, 0–14 years (including 54 ALL).
Control selection: Friends and neighbours selected by case parents—1/case matched for child's age.
Data: Questionnaire, laboratory analyses of blood samples.
Potential sources of bias/error: Unusual method of control selection could have led to selection bias.

Table 3. Continued

Study name/key reference: Finnish Registry-based study. Salonen and Saxon [99].
Case selection: Cases registered with Finnish cancer registry 1959–1968 (aged 0–14 years), and found in maternity records. From 1409 malignancies 1008 were available for analysis (including 373 leukaemias).
Control selection: Preceding birth record on list from maternity welfare district containing the case.
Data: Maternity records and questionnaires sent to maternity hospitals.
Potential sources of bias/error: Controls not checked for vital status at time of case diagnosis.
Other comments: Case–control twin pairs arose but were excluded. Previous fetal loss not recorded unlike other studies using maternity records.

Study name/key reference: North of England Study. McKinney *et al.* [38].
Case selection: Cases of childhood leukaemia and non-Hodgkin lymphoma resident in one of three areas in the North of England at birth and diagnosis. Diagnoses 1976–1988, interviewed 1988; 109 cases.
Control selection: 1/2 controls/case matched by sex, month and year of birth and area of residence (at birth and diagnosis).
Data: Face-to-face interviews.
Potential sources of bias/error: Long recall periods (hence especially errors in recall of exact dates—believed to be non-differential).
Other comments: Other studies using same data: [33, 103].

Study name/key reference: Shanghai Case–control Study. Shu *et al.* [130].
Case selection: Cases of leukaemia aged 0–14 years from Shanghai Cancer Registry 1974–1986; resident in Shanghai at diagnosis. 172 ALL.
Control selection: 2/case matched by sex and calendar year of birth selected from current (1986) Shanghai population register.
Data: Interview and hospital records.
Potential sources of bias/error: Control selection: (i) controls were healthy, resident in Shanghai in 1985–1986, (ii) three stage sampling selected families/groups of families at first two stages and individual children only at third stage—could have favoured certain family structures. No adjustment for social class.

Study name/key reference: Hokkaido study. Nishi and Miyaka [117].
Case selection: All cases on non-T-cell acute lymphoblastic leukaemia attending relevant hospitals in Hokkaido prefecture, Japan, 1981–1987, ages 0–14 years.
Control selection: 2/case matched by age, sex, district of residence at 1986–1987. Selected at routine visits to health centres.
Data: Face-to-face interviews conducted by single experienced interviewer.
Potential sources of bias/error: Control selection favours attenders at routine health centres (but 80–90% of Japanese children attend), and excluded migrants and early deaths.
Other comments: Although the numbers are small the study is important because of its concentration on specific cell types.

The studies are arranged approximately chronologically within continent.

between population mixing of adults and childhood leukaemia have been discussed above and a recent analysis of the North of England case–control study [103] has reported excess change of residence during the pregnancies of case mothers compared with controls. All three studies show risk concentrated in ages at diagnosis outside the childhood peak and describe maternal circumstances which could predispose to exposure to infectious agents involving both high dose and variety of viral strains.

These data provide little direct support for a hypothesis involving *primary* exposure of pregnant women although they are not inconsistent with this if the infection were clinically silent or accompanied by non-specific symptoms. They offer more persuasive, albeit indirect, evidence for an association of childhood leukaemia with reactivated/reinfection of the mother (Table 2:4a). Contributing factors would include high viral dose and reduced immune response in pregnancy [104, 105]. The limited data which are available focus on ALL diagnoses without the childhod peak and/or persistently infected children and support A of Fig. 1.

POSTNATAL MEDICAL HISTORY

The neonatal period

One analysis of Inter-regional Study of Childhood Cancer (IRESCC) data reported significant risks for infections specific to the neonatal period—ICD9 771 (5 ALL cases, 1 general practitioner (GP) control, 0 hospital control, OR = 10.3, $P = 0.03$) [106] and the Swedish registry-based study has found significant but moderate risks of lymphoid leukaemia from a variety of non-specific neonatal conditions [46] which included phsiological jaundice (OR = 1.4). The latter, which has recently been confirmed using data from the large CCSG data base [39] and the Dutch registry-based study [107], led to a hypothesis involving lighting and phosphorygene [108], but only one of these studies used bilirubin measures and, where the data are available, there is no association of ALL with phototherapy [39, 106], so that the link to intensity of illumination is very tenuous.

The epidemiology of physiological jaundice is largely unknown [109] but other studies have shown slightly elevated risks of leukaemia for admission to special care baby units (SCBU) [OR = 1.43, (IRESCC—106) calculated using data from obstetric notes using neighbourhood controls published in [106]—see Table 3] and hospital rather than home delivery (OR = 1.3, 95% confidence interval 1.0–1.8 Netherlands registry-based study [107]). It seems possible that all these factors may be pointers to nosocomial infection in newborn nurseries; such infections tend to follow community epidemics [110], are common (involving 4.1% of infants born in a large paediatric hospital over 2 years and 22% of discharges from the SCBU [111]), and apply primarily to infections transmitted by the airborne route—especially respiratory infections although VZV has also been reported [112]. Some direct support comes from a second analysis of IRESCC data [86] which restricted attention to viral infections (ICD9 0450-0799 and 4800-4809) and reported separately those occurring at ages <6 months. There was a statistically significant excess based on small numbers (OR = 4.1, $P < 0.01$ for leukaemias and lymphomas and for ALL alone: 5 cases, 1 GP control). The ages of occurrence of the viral diseases for the ALL cases were between 6 weeks and 5 months so they are "early" diagnoses (with probable protection by maternal antibodies), though not strictly neonatal.

Table 4. Maternal VZV and childhood leukaemia

Study [reference]	Design	Exposure	Cases *n*	Controls *n*	Exposed *n*	Magnitude of excess	Comments
Vianna and Polan [203]	Cohort	Maternal chickenpox during pregnancy	3	—	63	Rate of leukaemia to 3 years = 5% of relevant live births	Exposed cohort ascertained prospectively; cases found by record linkage—ages 1 year, 2 years. Short-term follow up. Study motivated by ecological analysis in same reference
Adelstein *et al.* [194]	Cohort	Maternal chickenpox during pregnancy	2	—	270	E = 0.15 (all cancers) O/E = 6.6 (all cancers)	Exposed cohort ascertained prospectively. Study of all deaths ages 2–19 years but only two were leukaemia diagnosed at ages 4–5 and 3 years. One of these mothers had chickenpox for the second time
Till *et al.* (North London study) [84]	Case–control	(a) Maternal VZV while pregnant	2	0	—	—	2/54 ALL cases exposed, 0/388 other case/control pregnancies reported. Questionnaire reports
		(b) Maternal zoster or repeat chickenpox before conception	4	0	—	—	4/54 ALL cases exposed, 1/28 AML cases exposed, 0/82 controls exposed. Questionnaire reports
Oxford survey of childhood cancer (OSCC)*							
Stewart *et al.* [200]	Case–control	Maternal zoster while pregnant	2	0	—	—	Restricted to children; <10 at death; ages of exposed cases 7/8 years
Bithell *et al.* [202]		Maternal chickenpox while pregnant	3	0	—	OR estimated at 3.7	Ages at leukaemia diagnosis 3, 4, 11 years. Analysis conducted for all cancers and $P < 0.01$
		Maternal zoster while pregnant	(5)‡	(5)	—	—	All cancers—diagnosis not stated. 9000 cases and controls
Blot *et al.* [203]†		Maternal chickenpox while pregnant	(7)	(8)	—	—	All cancers—diagnosis not stated
		Maternal zoster while pregnant	(3)	(1)	—	—	All cancers—diagnosis not stated. 1700 cases and controls

*These analyses are for distinct non-overlapping subsets of the OSCC data; total number of cases and controls are equal.
†This is the latest of the series and covers the latest period; 1971–1976. Two differences should be noted. (i) the questionnaire had been changed so that chickenpox (though not zoster) became a directed question; (ii) the use of mortality data at this period is less reliable than hitherto.
‡Number given in brackets when leukaemia diagnoses not reported separately.
Note that a number of other studies (e.g. IRESCC) have collected relevant data but no results are published; bias in favour of positive reports is likely.

On the other hand, physiological jaundice and other neonatal conditions have been associated with interruption and cessation of breast feeding and with execessive maternal protection, the "vulnerable child syndrome" [113], which could lead to immunological isolation during infancy.

The first year of life

Only one case–control study has analysed infections during the first year of life; the Netherlands registry-based study reported fewer infections overall, fewer requiring hospitalisation during this period [114] and also lower values of a score designed to quantify likely exposure; all but the first of these were statistically significant in a multivariate analysis. The IRESCC analysis showing *more* viral infections at ages under 6 months discussed above is sometimes quoted as contrary evidence but this does not necessarily follow since different ages are involved. Note that the IRESCC study used hospital as well as population controls and these differed for this factor (Table 3). Data on non-specific and minor infections at this time period are extraordinarily difficult to collect retrospectively and proxies are likely to be more reliable. Some early studies suggested BCG vaccination in infancy was protective against leukaemia but the methodology has been criticised [115]. Evidence that routine immunisation is itself protective [OR = 0.2, $P = 0.03$ (IRESCC-86)] is perhaps more convincing and confirms results from the Oxford Survey of Childhood Cancer (OSCC) [116] and the Japanese study of non-T-cell ALL [117]. All of these are consistent with a protective effect of antigenic challenge at this stage of development.

Later and close to diagnosis

Clinical case histories suggest episodes of infection may lead to leukaemia but this may merely reflect the early stages of disease. Formal analyses are few and complicated by the difficulty of identifying onset of leukaemia but two studies (the IRESCC [86, 106] and the North London Study [84]) show some evidence of increased numbers of later infections in leukaemia cases compared with controls. So as to avoid early symptoms of leukaemia the IRESCC analysis [86] specifically excluded infections which occurred in the 6-month period preceding diagnosis. This could also have had the effect of excluding recent exposures relevant to the aberrant response model; infections in 6 ALL cases and 1 control were excluded for this reason (PA McKinney: personal communication)—the cases had a variety of viral infections during the period but it may be relevant that 4 of the ALL cases suffered from VZV infections (three chickenpox and one herpes zoster in a child who had had chickenpox at 12 weeks). Lower titres of antibody to common herpes viruses in leukaemia cases have been reported in one study [119]. This could, if confirmed, have several interpretations including either absence of infection or persistent infection [83].

These data present a somewhat equivocal spectrum of results which are capable of numerous interpretations but are all consistent with the basic hypothesis outlined above, and provide indirect support for components involving primary/secondary infection of the child as well as immunological isolation (3b,c,d, 4b and 5 of Table 2) and both a and b of Fig. 1.

DAY CARE, SOCIO-ECONOMIC STATUS AND FAMILY STRUCTURE

Longitudinal and international comparisons of ALL incidence rates point to associations with higher levels of socio-economic status (SES) [15, 119]. Within developed countries similar trends are apparent in both ecological and case–control studies [120–124]. In general, higher SES and its correlates (e.g. less household crowding) are associated with reduced and older age at exposure to infectious agents [125–127].

Family size and birth order have been analysed in several studies with, in general, higher risk of leukaemia for only and first-born children (e.g. the Netherlands registry-based study [114], the OSCC and one cohort [97]) but this is not always found (the Swedish registry-based study [46]). Selection bias with controls potentially more mobile (and hence favouring single and first-child families) may have influenced the negative results of several studies (see Table 3) and the opposite bias the OSCC. Similar selection bias is possible for the only study [130] to report a significant case excess of children of later birth. Increased risk for children at least 5 years younger than the nearest sibling has also been reported from the Minnesota study [96] which may indicate immunological isolation of the infant but could also point to increased opportunity for gestational or neonatal infection because of the presence within the family of a child of primary school age [128]. Day care of self and siblings is probably the best available proxy for exposure to infections [128, 129] but has only been reported from one case–control study ([114], the Netherlands registry-based study) where day care in infancy *reduced* the risk of leukaemia.

These data focus primarily on immunological isolation in infancy (5 of Table 1) and provide strong, though indirect, support for the ideas in Greaves' hypotheses, including b of Fig. 1. The importance of using index and sibling day care patterns as proxies in analyses of timing and dose of exposure to infections has not been appreciated to date.

HERPES VIRUSES

One member (EBV) of this family of ubiquitous viruses is known to be oncogenic in humans [4, 7] whilst others (e.g. herpes simplex virus-2, VZV [102] have shown epidemiological associations with human malignancy or oncogenic potential in animal experiments. Following primary infection, these viruses usually persist in latent form during a period of containment under the control of the host immune system. For VZV, primary infection is almost invariably accompanied by symptoms of chickenpox and secondary infection can be indicated by herpes zoster. For this reason the epidemiology of its containment has been studied most closely. It is likely, however, that similar features apply to the other herpes viruses and that asymptomatic reactivation and reinfection occur commonly during the containment phase for VZV [102].

Population-based studies have shown that early zoster (i.e. failure of containment) is elevated following fetal, neonatal (and *older*, i.e. >20 years) primary exposure to VZV [131–134]. Reinfection by a heterologous strain can cause both overt and silent disease; this is influenced by dose and one study has reported subclinical reinfection in 64% of household-exposed adults [135]. Gross fetal damage can follow overt VZV infection of the pregnant mother and this has been shown in one case report to represent an almost immediate zoster stage following mild primary disease and failure to establish latency [136].

Transient, but generalised, cell-mediated depression of immunity is associated with human infections by herpes viruses [137–139]. Zoster patients have been shown to have poor immune response to herpes simplex virus and cytomegalovirus (CMV) [140]. Subjects with a recent history of zoster have significantly higher geometric mean titres of human herpes

virus-6 (HHV6) antibodies (Alexander, unpublished analysis of control data from [141]). These results show that reports linking VZV to ALL may be interpreted as associations with the family of viruses. Some (e.g. HHV6, EBV, CMV), though not VZV, have the appropriate international variations in intensity and age at exposure, and socio-demographic correlates. Pregnancy has been associated with reactivation of EBV [105] and of complications following chickenpox [104]; it is possible that immune response to a range of herpes viruses is impaired during pregnancy with consequent risk of fetal infection—that this can occur following reactivation in the mother is known for VZV and CMV [82, 102]. It has been estimated that primary CMV infection occurs in approximately 1% of pregnancies in the U.K. [80] and reactivation, identified by viral secretion, in around 10% [125, 142].

These data indicate that the epidemiological characteristics of herpes viruses are consistent with one (or more) members of this family being the specific agent(s) postulated in the aberrant response model. More generally, they provide examples of suitable viral models, and there is, at present, no firm evidence implicating herpes viruses; other known and unknown agents with mild clinical symptoms occur as epidemics amongst young children, commonly infect the fetus and are associated with haemopoeisis (e.g. parovirus B19 with estimated maternal susceptibility of 50% and fetal infection rate of 33% following maternal infection [143]).

The remainder of the review is more tentative and explores the relevance of the basic hypothesis of the aberrant response model to other groups of risk factors and, finally, other ages at diagnosis.

PRENATAL EXPOSURE TO IONISING RADIATION

Pelvic X-ray of pregnant women is a well-established epidemiological risk factor for childhood cancer and leukaemia (reviewed in [144, 145]). OR in the range 1.4–2.0 have been reported from a number of case–control and cohort studies and the association is usually interpreted as casual. No excess mortality from leukaemia was found among 1263 children exposed *in utero* to radiation from the bombs in Hiroshima and Nagasaki [146]. The numbers exposed were, however, small and follow-up confined to those who survived the first 4 years postexposure; depletion of the numbers due to excess deaths of preleukaemias during postbomb epidemics must, therefore, be considered [147]. Detailed consideration of this topic is not appropriate here but would require attention to the energy and quality of the radiation (X-rays, gamma rays, alpha particles, specific radio-nucleides, etc.) with distinct dose–response relationships and other biological effects.

A number of features in this literature are pertinent. Firstly, although the timing of the childhood peak suggests prenatal malignant events no study has reported any concentration of risk for ALL diagnoses in the childhood peak; the majority report excess risk continuing well beyond the fifth birthday while the IRESCC study [148] found risk restricted to diagnoses before the second birthday. Secondly, risk is not specific to any one group of childhood cancers and even extends to Hodgkin's disease (Alice Stewart, personal communication) which has never been associated with (postnatal) exposure to ionising radiation.

There is overwhelming evidence that exposure to ionising radiation can cause mutations and other genetic events which may lead to leukaemia. Nevertheless, the Japanese data and factors discussed above and the analyses of reported clusters around U.K. nuclear facilities [16, 17, 19, 36, 40–42, 62] all suggest that other, possible complementary, mechanisms may operate in the fetus.

The aberrant response model provides one new possibility for such a mechanism since exposure to ionising radiation (including ultraviolet light and radiotherapy) can lead to reactivation of herpes simplex [149], VZV [150, 151], possibly CMV [152] and presumably other herpes viruses in suitable human hosts. That some mothers may be susceptible to reactivation of viral infection is supported by reports of interactions between the mothers prior fetal loss and X-ray during the index pregnancy from the tristate study [153, 154] and elsewhere [155]—though this is not always seen [156]—and of increased all-cause and infectious disease mortality of children X-rayed *in utero* [157].

Risk from paternal (and maternal) preconception X-ray exposure has been suggested in two studies [130, 158] but the studies have potential for bias and a possible causal pathway, if any, is unclear (see below). The site of X-ray appears unimportant [130]. Any factor which promotes reactivation of common latent viruses in the father should, indirectly, have the capacity to (re-)infect his spouse; thus the aberrant response models could conceivably provide some part of the explanation for these observations.

PARENTAL OCCUPATIONAL EXPOSURE

This literature is extensive (reviewed in [159]), and only two exposures will be considered here: radiation and dusts. Two recent case–control studies have reported significantly elevated risks for fathers occupationally exposed to ionising and possibly also non-ionising radiation before/around the child's conception [36, 38]. The numbers are very small and the cases included in these two studies not entirely independent. Scientific controversy has led investigators to seek evidence for unusual fetal sensitivity and/or novel mechanisms (see above).

Four studies have shown significant associations of leukaemia of ALL with parental prenatal occupational exposure to dusts including wood and cotton, wool or synthetic fibre [37–39, 160]. Wood dust was the only occupational factor which was statistically significant for both mothers and fathers in the North of England Study [38]. This study involved the same subjects as the analysis of clustering by residential proximity [33] reported earlier; in that analysis 4 cases were identified as being potentially "infective" (near-neighbours to several other cases) and it is intriguing that all their fathers were occupationally exposed in the prenatal period (to ionising radiation: $n = 1$, to non-ionising radiation: $n = 1$, to wood-dust: $n = 2$).

The ability of ionising radiation to reactivate herpes viruses has already been noted. Wood-dust exposure can cause chronic antigenic stimulation and consequent immune dysfunction [161]. One analysis (Alexander: unpublished analysis of control data from [162]) has confirmed an association between herpes zoster in youth/middle age and employment in the wood industry (OR = 3.03, 95% confidence interval: 0.97–9.49). It is, therefore, possible to interpret these controversial associations (in the same way as diagnostic X-rays) as, in part at least, contributing to the basic pathway of the aberrant response model (a).

Meanwhile, we note that many other investigators have been pursuing alternative lines of research and one [163] has reported evidence for novel mechanisms for heritable damage from, especially, alpha particles.

ADULT ALL

The age-incidence curve for ALL in developed societies reaches its minimum at age around 24 and climbs very gradually

thereafter [15]. ALL in adults is rare and there are no established risk factors. Prognosis and cytogentic abnormalities differ from childhood cases and risk factors may also be distinct but results from two large registries, one longitudinal and one cross-sectional, suggest overlaps in the aetiologies [164, 165].

It is conceivable that adult ALL is associated with secondary infection (involving the same agent(s) as childhood ALL) following the ending of the containment period for persons infected, at a normal or perhaps unusual older age. There are, however, no data to support this except reports from case–control studies of risk of ALL following herpes zoster (e.g. [162]). Such studies can be interpreted as evidence, instead, of zoster marking the early leukaemic state but this is unlikely since risk persists when zoster attacks occurring less than one year before the diagnosis of ALL are excluded (OR = 9.5, 95% confidence interval: 0.96–93.8). A significant association between Bell's palsy and lymphoid leukaemia has been noted [165] but for ALL this relied on just 4 cases. Bell's palsy has been deemed a recognised complication of VZV infection [167] and may be confused with the Ramsey–Hunt syndrome, which is zoster-related [168].

CONCLUSION

Until recently the lack of consistent evidence of clustering of childhood leukaemia/ALL was evidence against a viral component to its aetiology [15], despite the biological plausibility of Greaves' hypothesis and the persuasiveness of Kinlen's arguments. A review of new evidence of clustering (including the work of Kinlen and colleagues) permits a change of attitude and has now led to an extension and refinement of Greaves' hypothesis.

Under Greaves' original hypothesis either non-specific antigenic challenge or infection by a specific agent modulated the late-stage malignant events leading to cALL in the childhood peak. The data now suggest (a) that a specific agent is likely to be involved here and (b) the same (or a related) agent is aetiologically associated with (childhood) ALL at other ages. Together these have led to a general hypothesis: the aberrant response model. A review of the current epidemiological literature from the perspective of this model finds considerable support and shows its capacity to unify many existing lines of research: primarily those relating to familial and maternal health, family structure and circumstances, *in utero* exposures to infection and past medical history. The model relies very heavily on earlier hypotheses of Greaves and Kinlen but is more general than either of these (and in certain respects more specific). In consequence it has greater ability to explain known risk factor associations.

A useful hypothetical model must also be *testable* [169]. Two distinct epidemiological approaches are appropriate here—one "breaking-down" and the other "building-up". For the first, data should be examined for evidence of support for, or inconsistency with, each of the individual components outlined in Table 2. On the other hand, the building-up approach should use simple scores (e.g. counts of the number of components positive) to summarise for each individual the strength of the evidence for pathways a and b so that overall association of disease with either pathway can be evaluated using statistical tests with single degrees of freedom and avoid complex statistical models involving risk factor interactions. Either approach will require detailed and careful analysis of the proxy exposures including socio-economic status, fecundity, fertility, family structure, family day care, index and familial illness, individual and community migration patterns. Since many of these are highly correlated multivariate analysis will be essential but very careful consideration must be given to the identification of confounding factors and this must reflect each biological pathway (both of the components of Table 2 and a, b overall) as it is investigated. Disaggregation of all results by age at diagnosis (<2, 2–4, >5 years) and possibly immunophenotype is recommended. These analyses will be possible for existing data sets and also for data from the new case–control studies which are currently in progress in the U.K., the U.S.A. and elsewhere [169].

Under the model, a specific (though currently unknown) transmissible agent is causally associated with childhood ALL. For children diagnosed in the childhood peak, primary infection may occur shortly before diagnosis while for other ages at diagnosis attention has focused on gestational/neonatal exposure leading to persistent infection. In this situation too, exposure close to diagnosis may be involved and some reports of temporal clustering would support this [170]. The effects of secondary heterologous exposures to VZV [102] and pest-viruses [171] may provide suitable viral models. There is no evidence of *direct* case-to-case transmission of the (unknown) agent and most studies are consistent with an effect of high-dose exposure occurring in community micro-epidemics. Only one study [33] has suggested that preleukaemic children might possibly shed the agent more readily; if this occurs at all it could be similar to hepatitis-B for which children with Down's syndrome have been shown to be both more likely to be persistently infected and, if so, more likely to have a capacity to infect others [172]. Such a subtle effect is far removed from any suggestion that the preleukaemic child is a threat to his/her fellows; from the public health perspective it is critical that this be recognised.

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Thyroid Cancer in the Age Group 0–19: Time Trends and Temporal Changes in Radioactive Fallout

Evis Sala and Jørgen H. Olsen

ALTHOUGH MORTALITY rates from thyroid cancer appears to be decreasing, the time trends for incidence (all ages combined) are increasing in many countries [1–6]. There is a marked female preponderance for this type of cancer; this is most remarkable in the sub-group of papillary carcinomas, which comprise approximately 40–60% of cases [4–7]. In adults, who dominate the picture, the increase has been attributed to widespred use of radiation therapy for benign conditions of the head and neck [8, 9]. Another possible cause of thyroid cancer, also in young patients, is environmental radiation pollution, as the thyroid is highly susceptible to radiogenic induction of cancer [10, 11]. In a cancer registry-based study of childhood cancers (ages 0–14 years) in the Province of Torino, Italy, a downward trend in incidence rates of thyroid tumours was found for the period 1967–1988 [12]. Although statistically not significant and based on only 13 cases, this decrease was reported to parallel dilution of radioactive pollution from nuclear tests carried out in the early 1960s.

The population of Denmark has been covered by complete cancer registration for almost 50 years. As radiation therapy for