OCCASIONAL COMMUNICATIONS

THE CHANGING FACE OF CHILDHOOD LEUKAEMIA

GJ Piller, Honorary Fellow, Institute of Child Health, University of London and Honorary Research Fellow, University of Leeds and RA Cartwright, Professor of Cancer Epidemiology, University of Leeds

In 1931 the major causes of death in children for England and Wales (and also similarly for other developed countries) were according to Campbell:

1. Diphtheria
2. Pneumonia
3. Road accidents
4. Tuberculous meningitis
5. Rheumatic heart disease

By 1966, as infections became much more manageable by a range of antibiotics and the introduction of inoculations, the league table was altered to:

1. Road accidents
2. Leukaemia
3. Other cancers
4. Congenital heart disease
5. Pneumonia

The death rates from leukaemia per annum in England and Wales from 1930–60 had increased nearly threefold. For the period 1950–60 they had risen by 47%. For children younger than 14 years the increase in deaths rose from 285 in 1955 to 407 in 1960, an increase of 43%. This somewhat alarming trend has caused a number of questions to be asked – was leukaemia on the increase? In reality, this was not so. The death rate from the four leading infectious diseases in the period 1931–61 – measles, diphtheria, whooping cough and tuberculous meningitis – dropped dramatically from 1945 onwards. The infectious diseases had hitherto masked the incidence of the rarer diseases including leukaemia which now had a greater chance of recognition and diagnosis. The setting up of the National Health Service provided free access to healthcare, better medical diagnostic facilities, an accelerating increase in the number of haematologists and improved disease classification.

SCOTTISH CASE SERIES 1974–96
We report on the Scottish national statistics relating to childhood leukaemia (patients aged under 15 at diagnosis). These data are from the national cancer registration scheme and comprise all registrations and incidence rates of predominantly acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) from resident populations between 1974 and 1996. The data include age and date of birth, sex, month and year of diagnosis, and data linking the case to a geographical area. This is achieved by linking postcodes to census output areas, and in turn, these can be aggregated into larger areas.

These data were used to analyse age and sex-specific attributes of the condition together with investigations of changes with time and seasonality and space-time clustering.

Results
The presentation of acute leukaemia in children (0–14 years) from 1974–96 provided 905 cases throughout Scotland. This comprised:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>773</td>
</tr>
<tr>
<td>AML</td>
<td>115</td>
</tr>
<tr>
<td>Other types</td>
<td>17</td>
</tr>
<tr>
<td><strong>Total cases</strong></td>
<td><strong>905</strong></td>
</tr>
</tbody>
</table>

This breakdown conforms with the expected pattern of incidence of childhood acute leukaemia.

Figure 1 gives the incidence rates for ALL for males and females and shows that the cases of ALL peak at the age of two years. There is a predominance of males until the age of seven years, thereafter to the age of 14 there is an equal division between males and females.

The presentation of AML is significantly different as shown in Figure 2. Over the age period considered, there are three peaks: below two years, at six years and again at 14 years. The total case numbers are fewer than in ALL. Figure 2 shows a predominance of males prior to the age of four years but thereafter, apart from at age six years, there is no clear male predominance.

Our findings show an earlier peak in childhood acute leukaemias than hitherto documented.

The seasonal distribution of cases, month by month, from 1974–96 of ALL and AML respectively was collated and analysed. Two formal tests for seasonality showed no significant case excess in any month (data available).

Case clustering was investigated using the Knox method’ and found no suggestion of clustering for AML. However, for ALL there was some indication of clusters occurring in the 448 cases from 1974–96 aged 0–4 only (under 2 km and diagnosed in two months or less). Three significant clusters were found at <2 km, one or
FIGURE 1
Childhood acute lymphoblastic leukaemia, Scotland 1977–96: age-specific incidence cases per 100,000 per year.

FIGURE 2
Childhood acute myeloid leukaemia, Scotland 1974–96: age-specific incidence rates per 100,000 per year.
two months apart, <3 km at one, two or three months apart and <4 km one, two or three months apart. These results remained significant after stratification by period of diagnosis (1974–8 etc. through to 1991–6) and the calculation of a summary statistic to adjust for the long time-period over which cases have been aggregated.

Careful examination of the ALL data for time trends has shown that overall rates have varied little (data available). When the time period was divided into cases diagnosed before and then during/after 1985, a shift in case distribution became apparent (Figure 3). Figure 3 also shows that although two years is the age of the childhood peak throughout the period, in the later half there is an increase in cases in the 4–5 age range. When age groups are examined the trend is confined to the 0–4 age group (Figure 4).

In the AML data there is borderline statistical evidence of a decline in incidence in all age groups (Figure 5). This decrease takes place in both sexes but is not statistically significant (due to small numbers) in either sex, but is nearly so in males.

No sib pairs were identified. Of the 905 cases, there were three diagnosed with acute leukaemia at birth or soon after, but with no evidence of related hereditary diseases. Contrary to published hypotheses, the occupation of parents of cases showed no predominance of the higher social classes.

**Conclusion**

This study reports data from Scotland for childhood leukaemia. This was chosen for study partly because of the stability of the Scottish population in the last 50 years and partly due to the completeness of cancer registrations. In June 1998 the total population was 5·12 million compared with 5·24 million in 1971, with the 0–14 age group remaining relatively constant at around approximately 960,000. As an analysis of the leukaemias in the age group 0–14 years, this study is based on confirmed diagnoses entered through cancer registration and hospital case records examining past medical events in the cases.

The data from 1974–96 show that there are significant differences between the presentation of childhood ALL and AML. Acute lymphoblastic leukaemia has a clear early peak based on a male excess at the age of two whilst AML has an early male excess and three peaks at later ages.

However, some signs of case clustering are noted in ALL suggesting the possibility of some infectious element in the pathogenesis of ALL. This is coupled with new evidence of subtle changes taking place in the age at

![Figure 3](image)

**FIGURE 3**

Acute lymphoblastic leukaemia, Scotland 1974–96; age-specific incidence rates per year by period of diagnosis, sexes pooled.
FIGURE 4
Acute lymphoblastic leukaemia, Scotland 1974–96;
age-specific incidence rates per 100,000 per year by age group, sexes pooled.

FIGURE 5
Acute myeloid leukaemia, Scotland 1974–96;
age-group incidence specific rates per 100,000 per year by age, sexes pooled.
presentation of ALL and slight evidence of a decline in incidence of AML, albeit based on small case numbers. The increase in ALL in the 4–5 age group has never been reported before and would need confirmation from other data sources but is a sign of the complex and unexplained changes in the epidemiology of the condition. This clustering method accounts for population density and highlights the transient nature of these phenomena with no area with a prolonged case excess.

In the study of the 905 cases of childhood leukaemia in Scotland, reported from 1974–96, we noted from the patients’ medical histories a high frequency of infections. Notwithstanding the fact that a suppressed immune system is a feature of acute leukaemia, this merits closer examination. From early in the last century the literature has suggested that acute leukaemia may have an infectious aetiology.10–12

To pursue this we examined more closely those cases of acute leukaemia diagnosed in 1990–5 within the study of 1974–96 in the age group 0–5 years (i.e. when childhood ALL peaks). Of the 139 cases examined which had a recorded health history, 84 (60.4%) had a previous history of infectious disease, 53 of which were prior to a diagnosis of acute leukaemia, and 31 were after the diagnosis of leukaemia was made. The breakdown of the 53 cases revealed that chickenpox claimed 33 (62%), with measles at ten cases (19%) and various other infections at ten cases (19%). Rolleston13 stated that chickenpox was a worldwide disease and that there were examples of repeated attacks. Sheldon14 wrote first of a relationship between chickenpox and herpes zoster. In our current study there were some patients who had chickenpox twice.

CASE SERIES 1990–9
In view of these observations, an additional and separate case series was set up comprising all cases of acute leukaemia treated at one large tertiary referral centre in Scotland (Edinburgh) between 1990 and 1999, in the age group 0–14 years (n = 101). The appraisals were made from a comprehensive study of the case notes on admission and later on hospital wards, and also from letters of referral from general practitioners and consultants together with subsequent correspondence. Particular attention was given to evidence of involvement by infective agents and the length of time from clinical good health to the diagnosis of leukaemia (the prodromal period).

Medical history leading to case diagnoses (prodromal period)
The previous medical histories of children diagnosed with acute leukaemia, both ALL and AML, were abstracted. The period of time leading directly to the diagnosis of leukaemia was assessed from information provided as detailed above.

Table 1 shows the length of the prodromal period before a confirmed diagnosis of ALL or AML. The interval between good health and a diagnosis of acute leukaemia was generally short for all age groups, and is shown in Table 2. It varied between an average of 2.2 weeks to 3.8 weeks with an overall average of 3.1 weeks, the interval being longest in the age group 10–14 years and shortest in the 0–2 age group.

The brevity of the prodromal period adds some further weight to the claim that acute leukaemia has an infectious aetiology, more particularly because the current prodromal period in acute leukaemia is close to the incubation period of most infectious diseases.

The study by Till et al.15 of cases of childhood leukaemia in Greater London produced an interval of between two to six weeks and Saha et al.16 indicated that acute

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td><strong>Weeks</strong></td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td><strong>Ages 0–5 years</strong></td>
</tr>
<tr>
<td>ALL</td>
</tr>
<tr>
<td>AML</td>
</tr>
<tr>
<td><strong>Ages 6–14 years</strong></td>
</tr>
<tr>
<td>ALL</td>
</tr>
<tr>
<td>AML</td>
</tr>
<tr>
<td><strong>All ages</strong></td>
</tr>
<tr>
<td>ALL</td>
</tr>
<tr>
<td>AML</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

J R Coll Physicians Edinb 2003; 33:202–208
leukaemia had a lag time (prodromal period) of 5–4 weeks. This suggests that in recent years, diagnoses are made more rapidly. An important observation was that 11% of the cases of acute leukaemia were diagnosed in less than one week from the patient being well. Judged from the prodromal evidence, one possible hypothesis is that cases of acute childhood leukaemia originate initially from the cell transformation initiated by a virus. The prodromal period of acute leukaemia appears to vary little throughout the period of investigation. However, we were led to further consider the possibility that earlier signs of infection might be significant in a pathogenic process.

Infections and childhood leukaemia
That there may be an infectious element to the aetiology of ALL in childhood is suggested by other groups, (Greaves and Alexander and Greaves). We, like other investigators, have found weak evidence of case clustering for childhood ALL and have formed the view that diseases which are now contained by preventive measures are unlikely to be linked to leukaemia. However, chickenpox, which was made a compulsorily notifiable disease from 1989 in Scotland (although not elsewhere in UK) is not associated with the immunisation programme.

By far the most prevalent virus involved in the case series was apparently varicella-zoster. Data were collected from the 1990–9 study in the age group 0–14 years on diagnoses of cases with chickenpox and other infections before the prodromal period and also post diagnosis. The total number of cases entered was 101 (87 cases of ALL and 14 of AML). One case of congenital leukaemia and four cases with incomplete medical histories were omitted. We found:

- Previous history of chickenpox prior to diagnosis of leukaemia 31·25%
- Chickenpox or direct contact with chickenpox post diagnosis of leukaemia 31·25%
- Previous history of mixed infections other than chickenpox 20·8%
- No previous infectious illnesses 16·7%

Possible viral background to ALL and the involvement of varicella in leukaemia
Bernard considered a viral aetiology of leukaemia to be a possibility and he modified the concepts of Furth to suggest that it seemed probable that a virus together with other aetiological factors could cause leukaemia.

Chickenpox is a highly infectious virus infecting many thousands of children each year but leukaemia remains a rare disease as shown by incidence statistics. It is easily argued that there would be a very much larger number of cases of childhood leukaemia if the disease was caused by the varicella virus alone. A clue to what effect the virus has in acute leukaemia is the prodromal factor. The particular family of viruses we have recognised is human herpes viruses comprising alpha herpes virus H5V1/2, varicella-zoster virus and the beta herpes virus cytomegalovirus, HHV6 and 8 and the gamma herpes virus EBV. We concentrated on the varicella-zoster virus because this virus produces different diseases – varicella (chickenpox) as the primary disease, and zoster, also called herpes zoster (shingles), which is a re-activation of latent virus usually occurring many years after childhood varicella. In relation to leukaemia, the choice of this virus might have some parallel with the acute and chronic forms of leukaemia, varicella with acute childhood leukaemia and zoster with chronic, particularly lymphoblastic leukaemia which is predominantly a disease of the elderly.

The herpes viruses are double-stranded DNA and are large viruses which have a high molecular weight nucleic acid and therefore code for proteins and for many enzymes involved in their replication.

The aetiology of acute leukaemia – a hypothesis
Leukaemia is not infectious, neither is it endemic. It is not a disease affecting only humans; many species of animals are known to suffer it. It can strike anyone, anywhere and at any time and it presents as a disease that does not obey any logical patterns of behaviour. It could be accused of setting false clues to its aetiology, especially within the environment, by its inscrutable nature. What kind of disease it is and what its nature is, are questions which have been discussed since leukaemia was first identified in 1845. The setting aside of dogma and the clues remaining suggest that although the acute disease presents as if it were a virus with a prodromal timetable, this is not sufficient on its own to create the disease. However, viral proteins with the capacity to change themselves, and thereby, avoid being destroyed by the immune defence cells, may cause dysfunction in normal cells which goes beyond the responsibility of the virus, and which in turn may interact with other foreign proteins to infiltrate the blood.

Viral aetiologies dependent on gamma-herpes viruses and retroviruses have been established for certain
human and animal leukaemias and lymphomas. In these instances, the clonal or oligoclonal presence of viral genomes in the leukaemic cells can be demonstrated. In the case of childhood ALL there has been no evidence of such clonal viral involvement. However, we hypothesise that a common childhood infection, possibly VZV, may influence the clonal development of leukaemia. A number of indirect mechanisms may be possible:

1. Hit and run infections with integration of small fragments of the viral genome might produce the form of genetic instability observed by McDougall in CMV infections in vitro.

2. A florid immune response to VZV infection may initiate feedback expansion of lymphoid precursor cells, resulting in selection of a cell already containing a critical mutation, a mechanism proposed by Greaves.

3. VZV infection may result in the induction of a local cytokine profile that favours expansion of ALL precursor cells. Indirect mechanisms of leukaemogenesis are obviously more difficult to investigate than direct transforming virus infections.

Nevertheless, with the recent advances in molecular biology these possible modes of action should be amenable to experimental evaluation.

We propose therefore that ALL is dependent on an interplay between viral infection and pre-existing or induced genetic changes within the precursor leukaemia cell. The role of virus infection may be multifaceted with feedback effects on the immune response and direct mutagenic events playing a role. The integration of proteomics with genomics will be one of the technical biological revolutions of the early years of the twenty-first century. Leukaemia should be added, therefore, to the list of serious diseases for which a cure is not fully obtainable at present and for which there will be realistic hopes for new therapy and preventive measures resulting from advances in cytological chemistry.

ACKNOWLEDGEMENTS
We would like to thank Dr A. Thomas and the staff of the Department of Paediatric Haematology and Oncology at the Royal Hospital for Sick Children, Edinburgh; Dr B. Gibson and the staff of the Department of Haematology, Royal Hospital for Sick Children, Glasgow; Dr C. King, Aberdeen; Professor DE Onions; the Information and Statistics Division, National Health Service in Scotland; Dr J Kohler; Dr E. Gilman for help with analyses; Ann Pickles for secretarial help; and particularly the John Woodward Foundation for financial support of this five-year study.

REFERENCES
21. Montaigner L. Personal communication.