LEUKAEMIA
towards control

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Office of Health Economics

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Introduction

Until the end of the 1960s leukaemia killed about 400 children annually in the United Kingdom. Excluding infant deaths (that is, those occurring in the first year of life) leukaemia alone was responsible for approaching 10 per cent of total child mortality at that time and between 40 and 50 per cent of all child cancer deaths. Amongst adults around 3,000 individuals were, and still are, lost each year as a result of one or another of the various forms of the illness.

But by the late 1970s medical advances against leukaemia had cut the toll imposed on the very young by over a third. The Registrar General's latest figures indicate that in the order of 150 children are being saved in Britain each year. And recent American data suggests that perhaps one in two of all those who contract a leukaemic disease in their first fifteen years will with appropriate treatment live on to adulthood. For girls diagnosed as having the most common type of childhood leukaemia there is now a roughly 80 per cent chance of long-term survival (five years plus) and probable cure following the use of anticancer medicines. This stands against the prospect only thirty or so years ago of almost certain death in a few months from the first symptoms.

In the case of adults progress has not been so rapid. Leukaemia mortality has actually tended to rise, largely because of population ageing. Almost two-thirds of all leukaemia deaths are now recorded in the 60-plus age group. For individuals unfortunate enough to contract an acute form in middle life the prognosis is still poor and even those with the relatively benign chronic leukaemias of later years will in most cases ultimately die as a direct or indirect result of such diseases. However, modern medicine can normally provide several years of virtually symptom-free life for such sufferers. This is a considerably better outlook than that which existed before the 1950s.

Against this encouraging background this paper examines the nature of the leukaemias and their treatment, where possible relating the available information to possible advances in curative techniques and the organisation of caring services. It also raises a number of economic issues relevant to the provision of cancer chemotherapy and the extension of facilities for bone marrow transplantation in Britain, an operation which if made more widely available and/or applicable might reduce further the number of leukaemia deaths during the 1980s.

One objective is to help generate a realistic view of the impact that this group of neoplastic diseases has on the community. Another is to highlight the overlapping relationship between research and basic service provision in this and other areas of

cancer care. The analysis provided indicates an obvious need for improved treatments, likely to be met only by a process of prolonged, careful therapeutic experimentation and evaluation. This carries with it important implications regarding the distribution of the limited resources available to the NHS, even though charitable organisations such as the Leukaemia Research Fund contribute significantly to innovative activity in this context.

The nature of the leukaemias

In 1845 Bennett in Scotland and Virchow in Germany published independently, and yet within a month of each other, observations of a hitherto unreported disease. The outstanding characteristics at post-mortem were splenic enlargement and the appearance of the blood as a 'yellowish-white almost greenish mass'. Virchow at first coined the term *Weisses Blut* (white blood) to describe this phenomenon. In 1947 he translated it into Greek, so creating the word leukaemia (*leuc-haemia*).

In the period which followed leukaemia came to be widely regarded as an inevitably fatal affliction involving a proliferation of the white cells of the blood – the leucocytes. However, there was much uncertainty as to the precise nature of the illnesses involved and their relationship with other morbid states. Nineteenth-century authorities like Gowers and Neumann contributed significantly to knowledge about the role of organs like the bone marrow, the spleen and the lymph nodes in the processes of forming blood and maintaining its function but the techniques then available gave observers little opportunity to form a comprehensive view. Even after Ehrlich's early twentieth-century discovery of staining techniques capable of revealing the various different types of leucocyte, progress towards describing the detailed pathology of the leukaemias was very slow.

The fuller but still incomplete understanding of this group of neoplastic disorders affecting cell populations found in the blood and blood-forming tissues which has emerged in the last two or three decades has come hand in hand with advances in other areas including the development of biochemical, cytogenetic and immunological techniques of cytological analysis.

Blood
In the normal, healthy adult blood accounts for a little under one-tenth of total body weight. Its key functions are to transport oxygen, substances absorbed from food, hormonal messengers and other bodily products to the tissues and to take from the

Table 1 *Cells normally found in the blood*

	Cell type	Normal count	Comments
	Erythrocytes	Men: 4·5–6·5 million per mm³ Women: 4–5·5 million per mm³	The red corpuscles obtain their colour from haemoglobin which carries oxygen. They are relatively rigid bi-concave discs, so shaped for maximum surface area and optimal transfer of oxygen.
Leucocytes	Neutrophils Eosinophils Basophils	4,000–10,000 per mm³ 50–400 per mm³ 20–200 per mm³	These cells are collectively referred to as granulocytes or myelocytes. They are larger than erythrocytes yet because of their fluid structure are able to pass through vessel walls, in which instance the neutrophils have a key role to play in phagocytising bacteria. Eosinophils and basophils are involved in allergic responses.
	Lymphocytes	1,500–3,500 per mm³	The lymphocytes are divided into 3 populations, B cells T cells and null cells. The former are involved in humoural antibody production whilst T cells control cell mediated immunity and the activity of the B cells.
	Monocytes	200–800 per mm³	Monocytes are immature cells which when they leave the blood develop into macrophages in the tissues. These phagocytise foreign bodies.
	Platelets	150,000–500,000 per mm³	Platelets play a vital role in the process of coagulation and repairing damage to vascular tissues. When depleted excessive haemorrhaging occurs.

Note Normal counts of blood cells may be subject to substantial variation. In leukaemia it would be incorrect to consider abnormal counts alone as a cause for alarm.

Figure 1   *The development of blood cells*
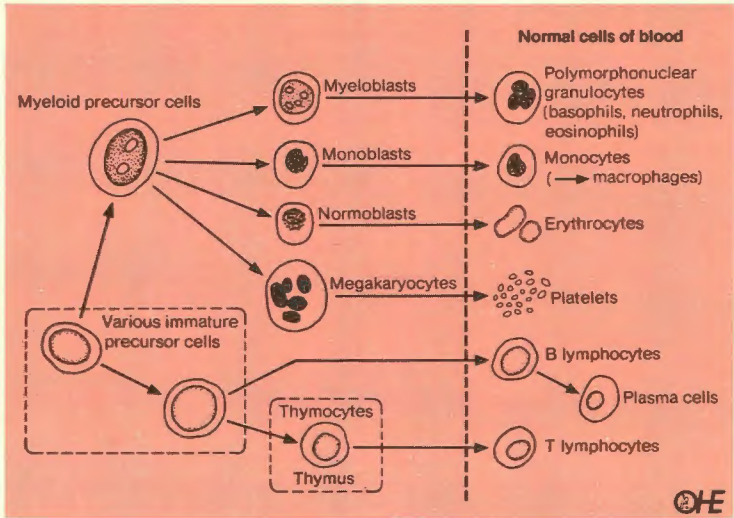
Source   After Janossy 1979.

latter wastes which may subsequently be broken down and/or excreted. Also it contains cells and substances vital for immunological defence and for repairing damage to the vascular system.

The bulk of the general transporting task is done by the plasma, the fluid portion of blood. The cellular populations found have more specific roles. Red corpuscles (erythrocytes) carry oxygen. Blood platelets play an important role in the process of clotting. And the white corpuscles (leucocytes) are involved in the capture and destruction of bacterial and other foreign bodies and the repair of wounds; functions which in many instances are performed after the cell concerned has passed through a capillary wall and entered the body tissues.

Table 1 shows that the leucocytes may themselves be split into three distinct groups; granulocytes, lymphocytes and monocytes. These may in turn be divided into several distinct sub-populations of mature cells, the function and relative numbers of which are briefly described in the Table. And Figure 1 indicates that the development of these discrete groups of mature blood cells involves in each case a chain of immature precursors usually found only in the bone marrow.

At the head of these chains are thought to be primitive 'pluripotential' stem cells from which all blood cells are ultimately derived. This elaborate process of blood formation (haemopoesis),

which in the case of lymphocytes involves immunological 'education' of active cells in the thymus (T cells), spleen and lymph nodes (B cells) as well as an earlier formative stage in the bone marrow, is not as yet fully described. But enough is known for it to be realised that the genesis of some forms of leukaemia must initially involve cells far back towards the primitive, 'uncommitted' end of the spectrum. For the leucocytes found to excess in the blood of patients with leukaemia are often not normal mature cells but have the characteristics of those found only in the bone marrow. In some cases they even lack the 'markers' which differentiate the lymphocytic series from the granulocytes and monocytes.

The main phenomenon underlying these neoplastic conditions is not necessarily excessive multiplication; rather a failure of immature cells to develop into those capable of conducting vital functions, coupled with abnormalities in their 'life expectancies'[1] and the mechanisms for the storage and destruction of older cells. The principal organs involved here are the lymph glands, the liver and the spleen, all of which may be affected by symptoms like swelling during a leukaemic episode.

The progressive accumulation of leukaemia cells in the bone marrow may also occasionally be associated with some discomfort. The gradual replacement of the normal blood forming cells ultimately means that supply of the required numbers of erythrocytes, leucocytes and platelets to the circulating blood is prevented. The reduction in the number of the former leads to lassitude whilst lack of white cells increases the subject's vulnerability to bacterial or viral illness. Loss of platelets results in a tendency to bleed or bruise easily. In the untreated disease death may thus result from overwhelming infection or cerebral haemorrhage.

The types of leukaemia

The leukaemias may be divided into four broad groups on the basis of two simple criteria. First, whether the disease is when untreated acute, and hence rapidly fatal, or likely to follow a chronic, prolonged course. Second, whether it involves cells in the lymphocytic or in the myeloid (marrow related) lines. The chronic and acute myeloid and lymphoid leukaemias may be further subdivided on the basis of the precise type of cell involved. Table 2 illustrates this although it is itself simplified and

1 On average leucocytes such as neutrophils (also known as polymorphs) exist in the blood stream for only about 7 hours. By contrast some lymphocytes may have a span of a year or more. Erythrocytes remain viable for around 100–120 days. But in leukaemia the more primitive 'blasts', which become unable to mature, may have indefinite life expectancies. When they divide the 'daughter' cells retain primitive characteristics and are also unable to develop further.

Table 2 *The main types of leukaemia*

Type	Relative incidence/mortality	Comments
Acute Lymphoblastic Leukaemias Null cell B Cell T Cell	Acute leukaemias in this group accounted for around 12 per cent of all leukaemia mortality in the mid-1970s and over 15 per cent of the estimated total incidence. This discrepancy is due largely to succesful medical intervention.	In normal blood over two-thirds of the lymphocytes are T cells and around a fifth are B cells. But in the commonest form of lymphoblastic leukaemia (some 80 per cent of cases) cells without the markers characteristic of either of these groups of mature cells predominate. T cell acute lymphoblastic leukaemia, which has a relatively poor prognosis, accounts for 15–20 per cent of cases whilst the B cell form is normally estimated at 2–3 per cent of total incidence. Other factors relevant to likely outcome include the presence or otherwise of lymph nodes or liver swelling, the make up of the bone marrow cell population and the white blood cell count (WBC) at diagnosis. Although no hard and fast rules apply with respect to any of these indicators it may be roughly assumed that an initial WBC of 10,000–20,000 per mm^3 provides grounds for optimism whilst one of over 100,000 per mm^3 is less desirable.
Acute Myeloid Leukaemias – broad examples Acute granulocytic Acute progranulocytic Acute myelomonocytic Acute monocytic Acute erythraemic myelosis	These account for between 40 and 45 per cent of all leukaemia deaths and a rather lower incidence proportion, in part because in the early stages cases in this group can be difficult to classify.	There are considerable overlaps between the types of leukaemia classified here, an observation which reflects the common early development pathways of cells in the granulocytic, monocytic and erythrocytic series. Prognosis in this group is often relatively poor. Yet there are exceptions. For example, acute progranulocytic leukaemia is, if untreated, characterised by fatal haemorrhagic symptoms. But these can now be controlled, in which case long term survival chances are relatively good.

| **Chronic Myeloid Leukaemias**
Philadelphia positive
Philadelphia negative
Juvenile CML | Collectively these cause between 15 and 20 per cent of all leukaemia deaths. | Ninety-five per cent of cases are Philadelphia positive. That is cells in the granulocytic, erythroid and megakarocytic lines all carry the Philadelphia chromosome. This is acquired in life, pointing again to a monoclonal origin for leukaemic illness. In the untreated chronic stages WBC may rise to 300,000 per mm³ or over although drug control normally keeps it well below this figure. The terminal 'blast crisis' is marked by a rapid rise in the number of precursor cells, normally found only in the bone marrow, observable in the circulating blood. It may be seen as the loss of ability of the neoplastic cells to mature into the normal form found in the blood.
Juvenile CML may be regarded as a discrete condition. It is frequently Philadelphia negative. |
| **Chronic Lymphocytic Leukaemias**
B Cell
T Cell
Other | This group causes approximately 25 per cent of leukaemia deaths. | In over 90 per cent of cases the neoplastic cells present are believed to be of monoclonal B cell origin, although in some instances there seems instead to be mature T cell involvement. Conditions related to, or sometimes confused with, chronic lymphocytic leukaemia include the lymphocytic lymphomas and prolymphocytic leukaemia, both of which normally involve cells with B cell markers. 'Hairy cell' leukaemia, accounting for less than 2 per cent of all leukaemia incidence, is now also believed to stem from abnormalities in the staged development of a group of B cells. The Sezary syndrome, which is distinguished by characteristic skin lesions, involves a proliferation of a type of T cell but is distinct from other T cell chronic lymphocytic leukaemia(s). |

there is still a need for further clarification of some types of leukaemia at a fundamental research level.

There are also some problems related to the fact that the leukaemias are closely associated with some other malignant conditions[2] for which they might be mistaken. Also acute myeloid leukaemia sometimes develops from (a) chronic condition(s), known as smouldering leukaemia or preleukaemia, in which the bone marrow is functionally defective. The exact relationship between these states is as yet not fully understood. And finally some non-malignant illnesses, mostly infections, can cause high leucocyte counts. Today it is unusual for such phenomena to be confused with leukaemia, even when the clinical picture is similar, although in the past diagnostic errors were probably relatively more frequent.

Occurrence

Many problems face epidemiologists studying trends in leukaemia incidence and its possible causes. For example, analyses over time are complicated by the fact that the leukaemias were under-diagnosed in the past. Even today recording standards may vary between regions and between countries. And for those wishing to derive aetiological hypotheses there are major barriers to obtaining reliable figures on the various cytological sub-groups coupled with difficulties regarding the uncertain period between possible exposure to a leukaemogenic factor and the appearance of diagnosable illness.

A clear illustration of the first of these points is provided by the debate about the dramatic rise in recorded leukaemia death rates over the course of the twentieth century. In the case of males in their seventies, for instance, the Registrar General's figures for England and Wales show a roughly thirty-fold increase in the period between 1911 and the start of the 1970s. In just the time span covered in Figure 2, 1960 to 1978, the rate for those aged between 80 and 85 has almost doubled. Similar, but less marked trends, exist in the figures for both sexes and all age groups up until the start of the 1960s (Alderson 1980) but since that time death rates amongst those under 60 have stabilised or fallen, as shown.

The explanation for increased leukaemia death rates appears

2 These include the lymphomas, multiple myeloma, chloroma, aplastic anaemia and polycythaemia vera. Some of these conditions, most notably Hodgkin's lymphoma, have like childhood acute lymphoblastic leukaemia become successfully treatable by antineoplastic medicines in the last ten to twenty years.

Figure 2 *Leukaemia death rates per million, selected age groups, England and Wales* 1960–78
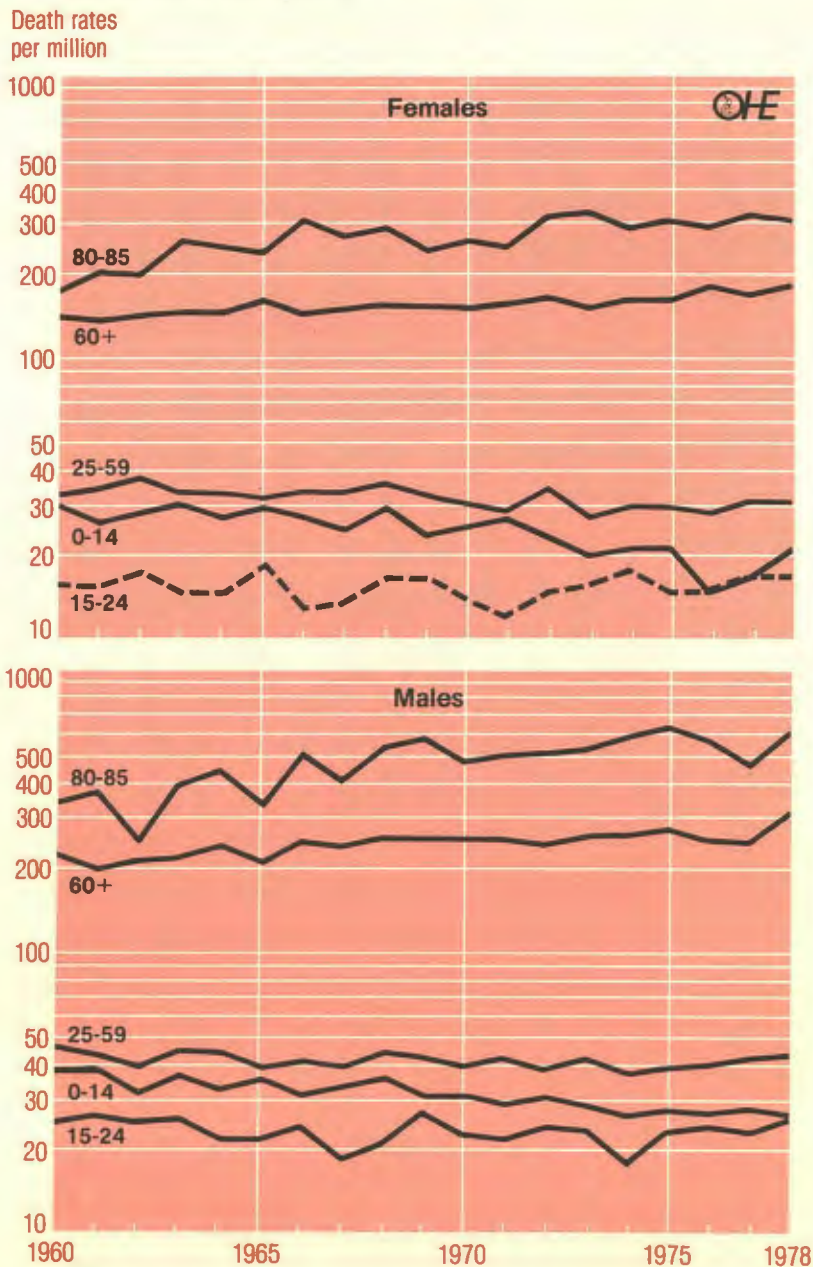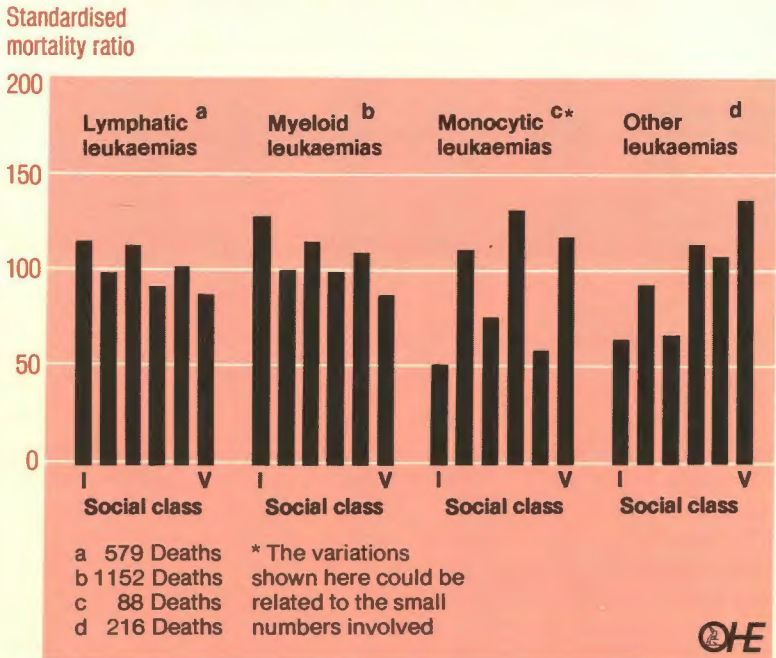

Source Registrar General.

Table 3   *Social class gradient in mortality from leukaemia adjusted for age*

Period	Sex	Social class SMR				
		I	*II*	*III*	*IV*	*V*
1930–32	Males	153	125	96	94	85
1949–53	Males	123	98	104	93	89
1959–63	Males	106	100	103	97	108
1970–72	Males	113	100	102	104	95

Source   Registrar General's Decennial Supplements on Occupational Mortality for 1931, 1951, 1961 and 1971.

Figure 3   *Leukaemia mortality and social class in the working population, England and Wales 1970–72*

Standardised mortality ratio

a   579 Deaths   * The variations
b 1152 Deaths   shown here could be
c   88 Deaths   related to the small
d   216 Deaths   numbers involved

Source   Registrar General.

mainly to be improved identification. For example, amongst the elderly declines in the numbers of swift deaths due to infections intervening in the early stages, coupled with greater access to medical services, must have strongly influenced the overall trends. Technical advances, such as the automation of many pathological investigations allowing the extension of their routine

use, have promoted diagnosis by chance during the investigation of other complaints. In the past deaths due to unnoticed leukaemia might have been attributed to, say, other malignancies or to cerebrovascular events.

This view is supported by the balancing out of variations in social class linked leukaemia mortality recorded during the period 1930–70, shown in Table 3. Factors like a more equal exposure to medical-source radiation must be considered in this context (Susser and Watson 1971). But the main element is almost certain to have been improving standards of care for the less advantaged sections of the population, despite the fact that the reverse shift with regard to 'other leukaemia' deaths and class in Figure 3 could be due to remaining class related variations in diagnostic accuracy. The disappearance in the last few decades of previously marked north/south and urban/rural leukaemia death rate variations also adds credence to the 'improved diagnosis' hypothesis (Hewitt 1960, Doll 1972).

However, amongst the authorities who have studied the available data closely several (see, for example, Lea and Abbatt 1958, Doll 1972, Adelstein and White 1976, Alderson 1980) have shared two conclusions. First, amongst children, better diagnosis and the use of medicines to prevent early deaths from infections like pneumonia can explain the upward trend in the first half of the century. Second, the increase amongst adults is in part real.

Recent reports relevant to this debate include an apparent trend towards an increased incidence of myeloid leukaemias in Lancashire (Geary *et al* 1979) and a suggestion of a raised child acute lymphoblastic leukaemia rate in the Manchester region (Birch *et al* 1979). But these observations are not as yet supported by the published experiences of other British regions and may be due to chance or even some sort of recording distortion. The long delays involved in collecting data on cancer incidence in some localities make monitoring of this field difficult, although the Cancer Research Campaign and the Leukaemia Research Fund have recently provided resources for new prospective epidemiological studies.[3]

Thorough surveillance of leukaemia occurrence in the community is clearly desirable. Nevertheless, concern in this context should not be allowed to grow out of proportion. The data pre-

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3 One theory which might be worth investigating further in this context is the suggestion of Swedish researchers (Brandt *et al* 1979) that unrecognised leukaemogens in the industrial environment, conceivably hydrocarbons such as petroleum, could be responsible for some changes in the rate of acute leukaemia deaths amongst older adults, particularly males. Another is the albeit unlikely possibility that past radioactive emmissions from nuclear power stations into the sea could have presented some level of hazard in areas like Lancashire.

sented above on mortality may be used to calculate that, because of improved control amongst children, the total number of years of potential life annually lost in Britain has fallen by some 20 per cent in the last decade. This is despite the marked upward shift in diagnosed disease in the elderly.

The challenge for the future is to build upon this initial success in dealing with the existing problem. Leukaemias still kill approaching 1,500 people of working age or below each year. Thus even though their prevalence at any one time is relatively low (around 15,000 sufferers some two-thirds of whom are aged over 60) because of the short average survival time[4] in middle life their impact on society is still great. If years of life lost are put against years of disablement suffered then it may be seen that leukaemia is still a burden to the community comparable to, say, multiple sclerosis in young adults.

Sex and cytological type variations

Figure 4 compares the age specific overall male and female leukaemia death rates in England and Wales in 1960–62 with those of 1975–77. Figure 5 relates the pattern of leukaemia mortality to that of cancer generally. They emphasise two further aspects of the disease.

First, both series show a consistent surplus of male leukaemia deaths. This is widest at the extremes of the age spectrum, where there is approaching twice the male as opposed to female leukaemia mortality. In the young this is partly accounted for by differences in treatment outcome but in the elderly the discrepancy shown accurately reflects an incidence differential.

Second, although raised cancer rates of all types are normally associated with age leukaemia stands out as being deviant with regard to children and adults in their twenties and thirties. This suggests unusual causal factor(s) or a more rapid response to common oncogenic agents than that displayed in most other neoplastic diseases.

Figure 6 illustrates the different distributions of mortality associated with the main types of leukaemia. Here again the variations shown imply either distinct causal mechanisms and/or different processes of leukaemic development associated with alternative groups of 'target' cells.

The general pattern reveals a number of basic points. First, acute lymphoblastic leukaemias are the most prevalent form in childhood and the least so in later life. Second, acute myeloid leukaemias are the predominant cause of life wastage amongst young adults. (In this context there is an unusual peak in inci-

4 On early 1970s figures only 20 per cent of sufferers survive for more than five years after registration.

Figure 4 *Age specific leukaemia death rates per million,*
England and Wales 1960–62 and 1975–77

Death rates per million

Males (1975-1977)
Males (1960-1962)
Females (1975-1977)
Females (1960-1962)

Age Group
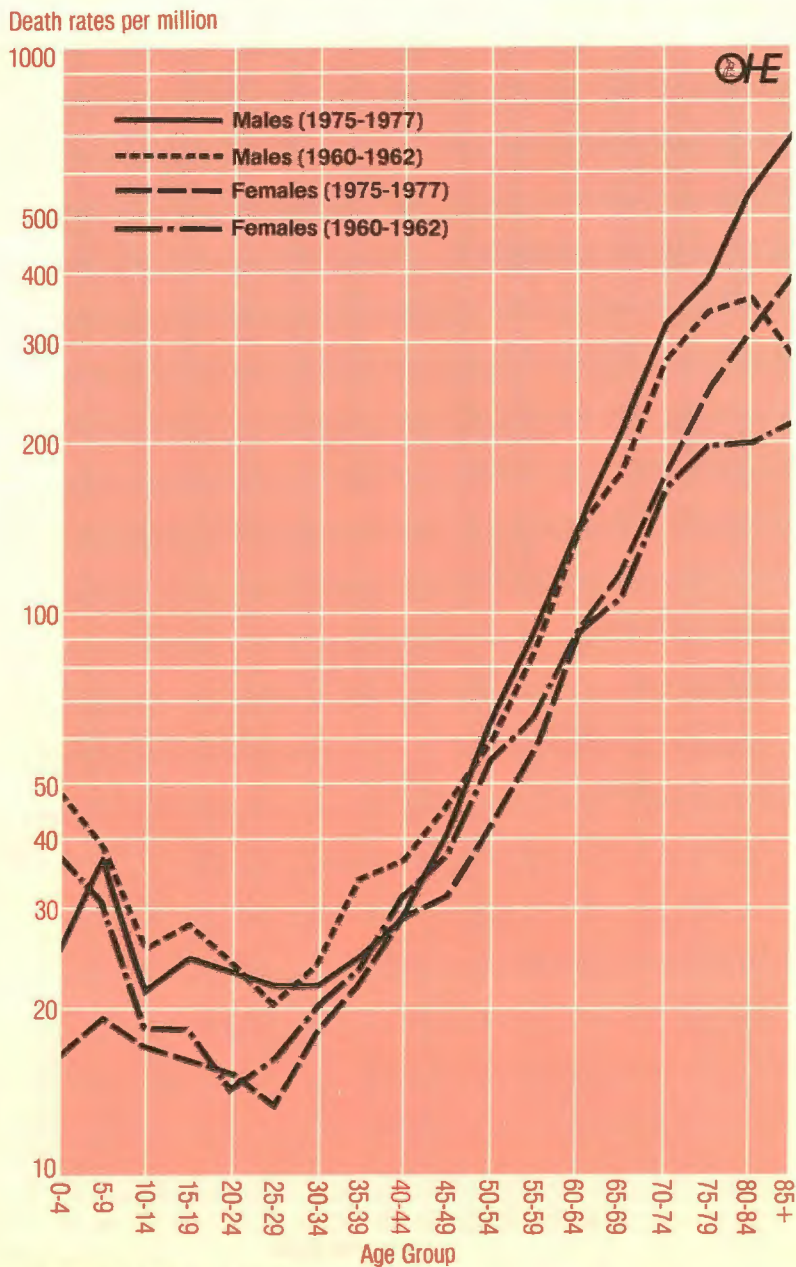
Source Registrar General.

Figure 5 *Leukaemia and all cancer deaths rate per million population, England and Wales 1977*

Death rates per million

Age group
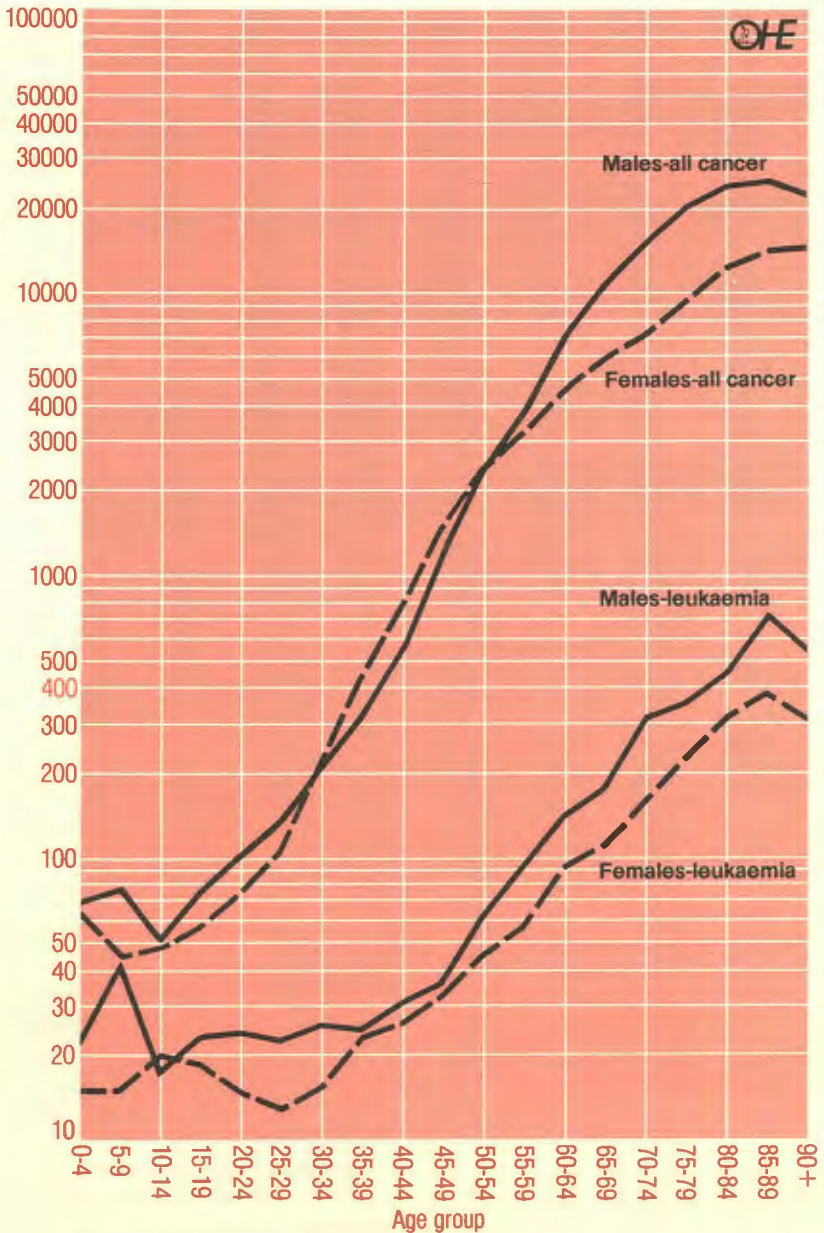
Source Registrar General.

Figure 6   *Leukaemia deaths by broad cytological type*
England and Wales 1975–77

Death rate per million

Females

Acute lymphoblastic leukaemia
Acute myeloid leukaemia
Chronic lymphocytic leukaemia
Chronic myeloid leukaemia

Males

0– 5– 10–15–20–25–30–35–40–45–50–55–60–65–70–75–80–85 +
Age
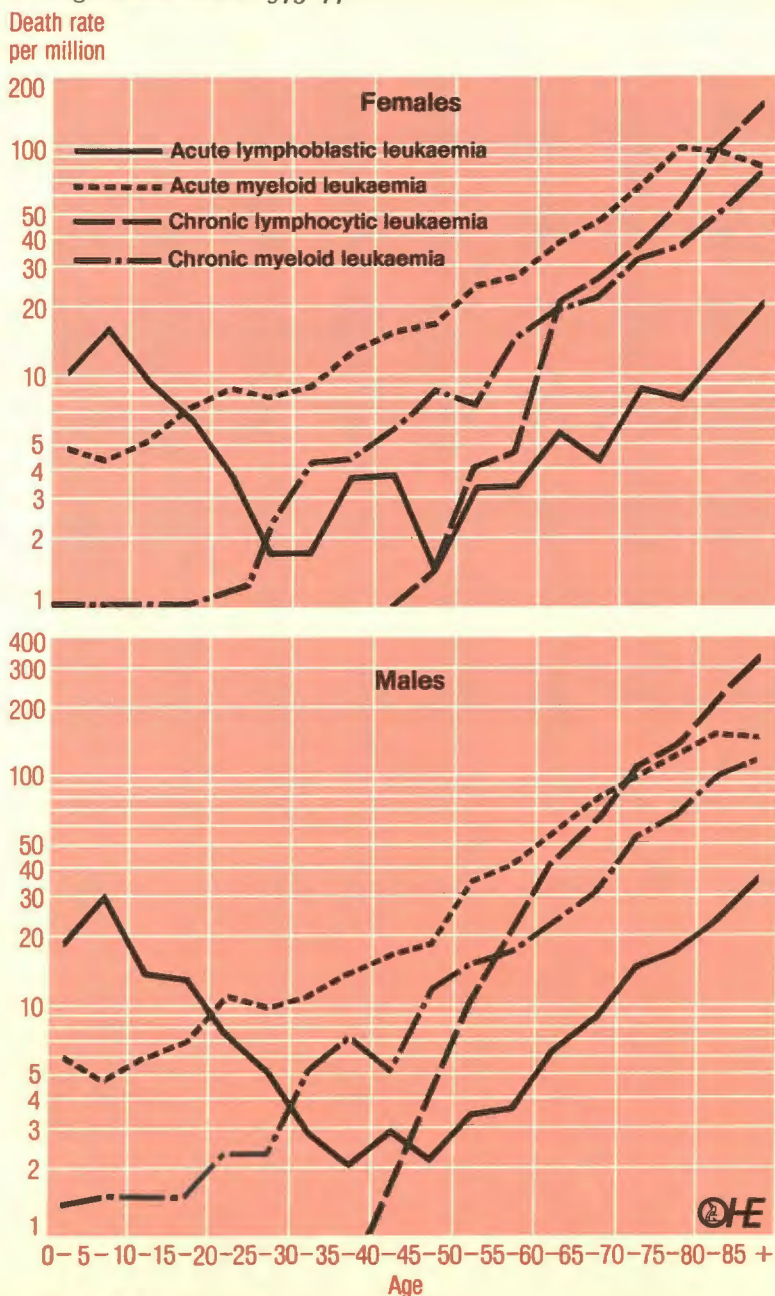
Source   Registrar General.

dence in late adolescence and death shortly after, first noted by Lee 1961). Third, chronic lymphocytic leukaemia is clearly confined to the 35-plus age group and shows a markedly steeper rate of incidence increase in later life than do other leukaemias, a fact which Doll (1972) has argued is indicative of the impact of long-term, cumulative exposure of the population to leukaemogen(s). Chronic myeloid leukaemias show a broader distribution although in children the one form found differs significantly from that in adults.
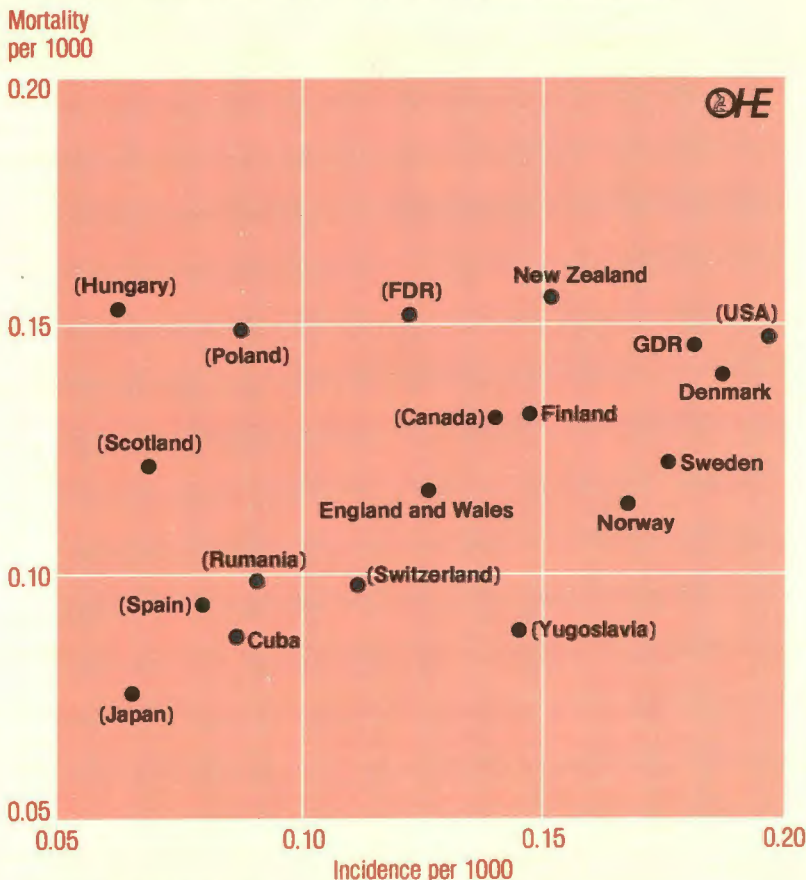
International comparisons

All the cautions which apply to intranational investigations of leukaemia stand with regard to international epidemiological studies. Confounding factors range from data distortions caused by relatively easily identifiable factors like the effect of differing age structures on crude population rates to more elusive ones like variations in diagnostic practice. Even so a number of interesting observations may be drawn from the available figures which, when contrasted with international studies in other areas of oncology, show a reasonably good degree of coherence.

For example, in Japan leukaemia rates amongst the older population groups are below those found in Western Europe and North America, a point clearly illustrated in Figure 7. The reason relates to the rarity of chronic lymphoblastic leukaemias.

In the United States, by contrast, overall rates appear rather higher than those recorded in the United Kingdom for adults, including those younger than the 55–64 year old population described in the Figure. There seems little reason to believe that case identification is more complete than in this country, a conclusion which points to real variation between the two populations. It has also been reported that incidence rates are much below national average in us blacks and unusually high in whites in states like California (Doll 1972).

Theoretical explanations for the latter range from higher identification rates amongst the richer whites through to postulated genetic influences on incidence and the possible role of variations in exposure to leukaemogens like radiation from medical and other sources. One clue may be that studies in the 1950s and 1960s indicated a raised leukaemia incidence rate amongst Jews both in Israel and America, the highest being amongst European Jews in Israel. One correlate of a social groups' access to medical care (hence to diagnostic services and perhaps to radiation from medical sources) is the number of doctors per head in the group concerned. The number of physicians *per capita* in Israel is high as is the proportion of Jewish origin doctors relative to the Jewish population in America.

Figure 7 *Leukaemia: Male mortality rates 1974–75 and incidence rates around 1970 at age 55–64 in nineteen countries*

Mortality
per 1000

0.20

OHE

0.15

(Hungary)

(FDR)

New Zealand

(USA)

(Poland)

GDR

Denmark

(Canada) Finland

(Scotland)

Sweden

England and Wales

Norway

0.10

(Rumania)

(Switzerland)

(Spain)

Cuba

(Yugoslavia)

(Japan)

0.05

0.05   0.10   0.15   0.20

Incidence per 1000

Source Alderson 1980.

Note Brackets indicate partial data.

Causes

At present one of the more clearly established facts about leukaemias is that they often are associated with chromosome abnormalities, and that the nature of these abnormalities is to a considerable degree non-random. In addition, diseases in which the chromosomes are known to be particularly liable to fracture are generally linked with a raised incidence of leukaemias of all types. Over half those with the so-called 'pre-leukaemic' state show chromosome abnormalities, and amongst those who eventually display acute myeloid leukaemia the proportion is higher.

In a rare variant of the latter, acute hypergranular promyelocytic leukaemia, about half show a particular translocation involving a chromosome each of the pairs numbers 15 and 17. Another abnormality involves chromosomes 8 and 21. This appears to be associated with a good prognosis (*Lancet* 1978).

In childhood acute lymphoblastic leukaemias Down's syndrome (once referred to as 'mongolism', characterised by an extra chromosome number 21) is associated with 10 to 20 times the normal risk level (Stewart *et al* 1958, Miller 1970). And most clearly of all adult chronic myeloid leukaemia is in over 90 per cent of cases associated with the 'Philadelphia chromosome'. Janet Rowley showed this to involve a translocation between chromosomes 22 and 9. Also it has recently been reported that abnormalities in chromosome 12 may be found in cases of chronic lymphoblastic leukaemia (Gahrton *et al* 1980).

The specifity of some of these associations suggests that in some instances precise leukaemogenic mechanisms may one day be found. However, on a broader level it is theoretically possible that the high levels of chromosomal abnormality found in leukaemic patients are indicative of some general failure of mechanisms involved in the repair of genetic material. People with such constitutional deficiencies could be at special risk of developing leukaemia (or other neoplastic illnesses) when exposed to environmental factors which damage the latter. These include radiation, cytotoxic drugs, certain viruses and the solvent benzene.

However, regarding chronic lymphoblastic leukaemia there is no evidence linking its incidence with exposure to radiation. Also many cases of the acute leukaemias do not involve observable chromosomal abnormality. Leukaemogenesis thus for the present remains an imperfectly understood, complex process involving a variety of factors which may interact either sequentially or synergistically and which probably differ between types of the disease.

In the light of this analysis the remainder of this section examines two extensively researched areas in further detail. These are the effects of radiation and the possible role of infections and immune responses in causing neoplastic blood disorders. Both are of topical interest although it should not be assumed that they are the only leukaemogenic agents in man. Other areas such as the possibility that hydrocarbons other than or containing benzene, like petroleum spirit, may be involved are beginning to attract attention.

Radiation and leukaemogenesis

A raised incidence of leukaemia in people exposed to ionizing radiations was first reported in 1911 (Jagie *et al* 1911). In the

Figure 8 *Leukaemia deaths in atomic bomb survivors, 1950–74*

Deaths per 100,000 persons per year
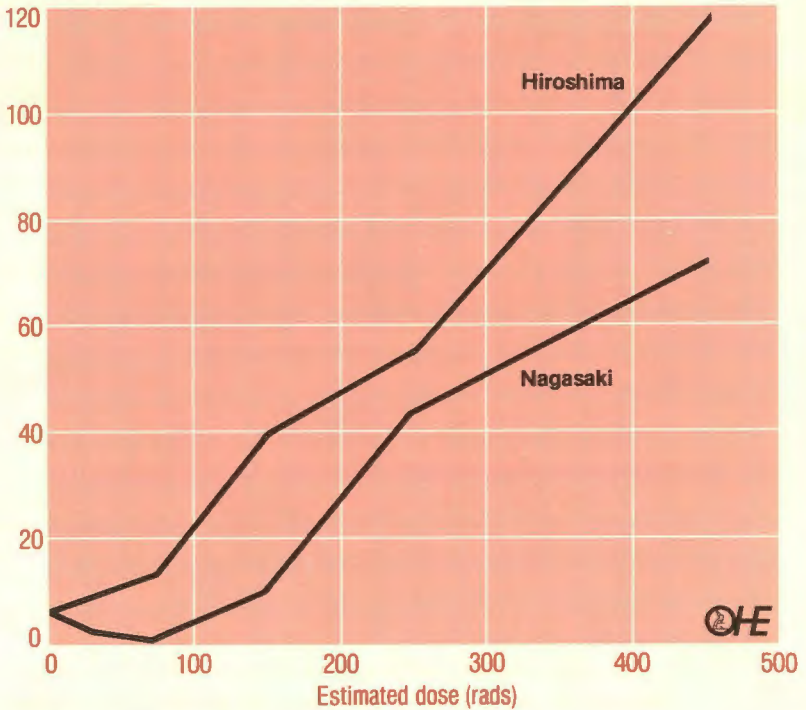
Source Beebe *et al* 1977.

interwar period several studies revealed excessive mortality in groups like radiologists, although by the late 1930s this began to fall as increasing regard for safety began to modify professional practice. However, it was not until the end of the Second World War that, in the aftermath of the nuclear attacks on Hiroshima and Nagasaki, public attention really focused on the dangers of high level radiation. Figure 8 shows the startling increase in leukaemia incidence recorded in the former city (where the weapon used emitted large doses of high energy neutron radiation).[5]

Many of the radiation safety regulations drawn up in the last two or three decades or so were based on data derived from the Japanese wartime experiences. However, subsequent research

5 Mole (1975) pointed out that increased numbers of chronic myeloid leukaemia cases were found in Hiroshima but not Nagasaki. This has significant implications regarding the genesis of the Philadelphia chromosome.

regarding medical and occupational exposures has cast doubts on some of the information derived, particularly with regard to the effects of low dose radiation.

For example there is a substantial body of data which links maternal exposure to X-rays late in pregnancy (even in very low doses) to a raised risk of leukaemia. This was first demonstrated in the UK in the 1950s (Stewart *et al* 1958) and has since been replicated by a number of studies. At a theoretical level one explanation of why foetuses and younger children may be particularly affected by radiation is that they are growing rapidly and that cells undergoing division are vulnerable to disruption from this source.

It has also been suggested that certain groups of children, such as those who suffer from allergies, may be at special risk (Bross and Natarajan 1972, Morgan 1979). But there is little evidence in support of this hypothesis which may well be related to the fact that early stage instabilities in the blood of those developing leukaemias promote abnormal immune responses.

Thus overall the available data indicates that only a very small proportion of childhood cases in the UK, probably no more than one or two per cent, are associated with medical radiation delivered during pregnancy. Consciousness of the latter's possible complications coupled with the development of more sophisticated, safer, X-ray techniques and alternatives like ultra-sound imaging mean that today exposure has been reduced to very low levels.

Regarding adults, conventional estimates indicate that in the order of 10 per cent of all cases may be attributable to some form of man-made radiation. Smith (1979) has suggested that up to 25 cases of leukaemia might ultimately be caused by exposing one million people to one rad.[6] Other authorities have estimated the figure to be as high as 40 per million per rad.

Figure 9 illustrates some of the findings of one of the best known studies in this field, which involved patients with ankylosing spondylitis (a back condition) treated by irradiation (Court Brown *et al* 1967). The peak incidence was four to five years after exposure and it showed a direct association with the age of the subject. Several studies of radiation used for other medical purposes have produced evidence supportive of the relationship shown, whilst spondylitics not so treated do not display raised leukaemia rates.

However, the dosage received by these patients was high. In the area where there is currently most popular concern, that of the

6 For low energy radiation 1 rad (radiation absorbed dose) is approximate equivalent to 1 rem (roentgen equivalent man). The average X-ray delivers around 0·025 rem. Mole (1980) has stressed that the role of radiation in leukaemogenises is complex, perhaps involves two or more discrete processes.

Figure 9 *Leukaemia in patients irradiated for ankylosing spondylitis*

Excess incidence
per 1000 persons
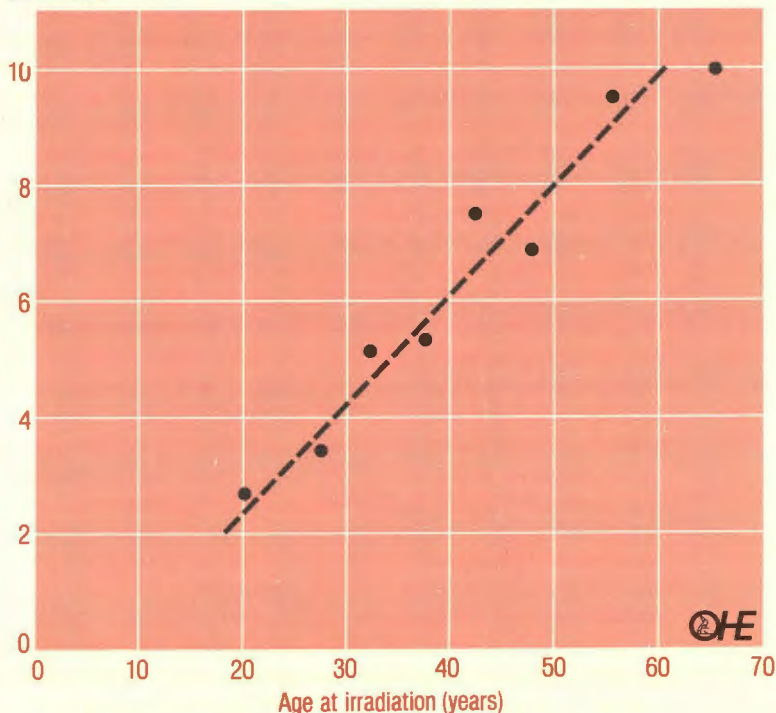
Source Doll 1972.

low level exposure, the radiation received even by workers in 'high risk' industries reaches a maximum of 5 rads per year. For comparison, this is probably in the same order as the peak dose received in just one day by the populations of some small communities in Utah following the testing by the United States government of nuclear weapons on the Yucca flats. People in Harrisburg, the scene of the recent American nuclear power station radiation emergency, received according to official US data less than 0.1 rad over and above background level.

The extent to which exposure to these degrees is leukaemogenic or otherwise carcinogenic is not precisely known. The epidemiological studies so far available are not reliable guides (Doll 1979). For instance, in a recent *Lancet* article (Najarian and Colton 1978) it was claimed that a statistically significant rise in leukaemia deaths in workers on American nuclear submarines had been observed. Problems about this data include the fact that

only a limited proportion of the population at risk was surveyed (due not least to a lack of official co-operation) and the dose to which those who suffered subsequent neoplastic disease were exposed was not practically measurable.

In conclusion, therefore, whilst it is obviously desirable to keep radiation hazards to as low a level as is reasonable given the range of choices available (which may, of course, in some instances involve exposing a few individuals to relatively large risks rather than very many people to small ones) it is also prudent to remember that between a half and two-thirds of the radiation most people are exposed to is from natural sources. In areas like Aberdeen in Scotland or Denver in the United States this proportion is significantly raised. If low level exposure did involve risks above those suspected from higher dose relationships, leukaemia incidence shifts between greater and lesser level natural backgrounds should be more than those which to date have been observed. (See, for instance, Court Brown *et al* 1960.)

Also approximately 90 per cent of all man-made radiation is from medical sources. The principal factors involved in the release of radiation in industrial contexts are radiological inspection techniques. In the immediate future further reductions in unnecessarily high X-ray dosages, as may occur in some techniques of dental examination (*Lancet* 1975), would seem to be the most pressing objective.

Infection and immunity

It has been hypothesised that cancers may sometimes develop as a failure of the body's immune defences to detect and eliminate them in a normal manner. In leukaemia there are reported associations between conditions causing immunological abnormalities and incidence of the disease and it has also been suggested that stimulation of the immune system may have some curative or protective effect. Yet claims that BCG vaccination dramatically cuts child leukaemia rates (Davignon *et al* 1970) have not been confirmed and the value of immuno-therapy in acute myeloid leukaemia appears limited.

However, mechanisms of immunity may be relevant to leukaemia in other contexts, in as much as some infectious agents could play a part in human leukaemogenesis. This is known to be so in leukaemias of domestic cats and cattle as well as in many laboratory animals. Although in man no such agent has as yet certainly been identified there have been several observations of virus-like or associated objects in human leukaemia cells. (See, for example, Karpas *et al* 1978). And recently Gallo (1980) has reported a unique virus associated specifically with a sub-class of human T cell disease. If such agents are eventually proven causal, medicines or vaccincies could be developed.

One possible reason why the search for the postulated infectious agent(s) involved in leukaemia in man has proved difficult is that natural communities tend to be very diverse, both in terms of inherited constitution and life style. Most of the animal models of virus-induced leukaemia used in research, by contrast, employ highly inbred strains. Leukaemogenesis even amongst them tends to occur only in particular, special circumstances. Given this and the problems relating to the pinpointing of space-time relationships in epidemiological studies of rarer conditions and/or those with slow onset, the weakness of existing observations in support of infectious factors in the generation of some types of leukaemia might be expected even if such phenomena do in fact exist.

For example, one study in the early 1970s seemed to show a link between maternal influenza during pregnancy and subsequent leukaemia incidence in their children (Fedrick and Alberman 1972). These results have not been repeated and could well have been a statistical freak. But alternatively the virus strain involved at that particular time could have had some special property which investigators had no direct way of identifying.

A second illustration of this point relates to the space-time clustering of acute lymphoblastic leukaemia in children. No firm epidemiological evidence exists which in this context indicates an infectious aetiology. But the same can be said of some conditions definitely known to be of bacterial or viral origin. Thus despite the plethora of conflicting results it would be unwise at this stage to dismiss the fact that several studies have reported a weak association of such cases in children under six (Knox 1964, Till *et al* 1967, Gunz and Spears 1968).

Other findings which may be consistent with the hypothesis that infections play a role in causing at least some forms of leukaemia include reports of correlation between birth rank and the disease's incidence in childhood and the fact that in a few cases healthy bone marrow cells grafted into leukaemic subjects have themselves become leukaemic.

Regarding the former, first-born children are seemingly up to 50 per cent more at hazard than fifth-born ones (Stewart *et al* 1958, MacMahon and Newill 1962). This is particularly unexpected in the light of the known increased chance of chromosomal abnormality with maternal age. One explanation could be that mothers are more likely to have become resistant to causal infection(s) by the time their later children are born. Thus whilst there is overall a greater risk of leukaemia in children of older mothers in part related to conditions like Down's syndrome the existence of, say, an oncogenic virus might create the opposite trend with birth rank, as in rubella associated impairments.

Treatment

Spiers (1972) described the historical development of treatment for the leukaemias as taking place in four stages. The first is palliative. The second involves the emergence of techniques for inducing remissions of the illness, that is a temporary return to normality of blood and bone marrow composition coupled with a disappearance of leukaemic signs and symptoms such as swelling of the spleen and liver. The third is concerned with prolonging remissions with maintenance therapies. And the final stage represents the most desired goal that patients are seeking when they turn to the medical services for help, that of cure.

Only in the field of childhood acute lymphoblastic leukaemia can the latter as yet be expected with any degree of confidence. In other areas, particularly the chronic conditions, life for sufferers can certainly be made far more comfortable than it was in the past but cure has not, at least until very recently, been a realistic therapeutic objective. And even with regard to young 'good prospect' cases of lymphoblastic leukaemia treatments may still be regarded as somewhat heroic in character. The administration of highly toxic medicines like those described in Table 4 and the use of radiation to kill abnormal cells that the drugs cannot is in various ways not satisfactory from the viewpoint of either the clinicians or their patients.

Even the manner in which today's still relatively crude techniques work is not fully understood. For example, in the case of the pharmaceutical agents used it is known that rapidly multiplying cells may be particularly vulnerable to their effects, essentially because they interrupt cellular metabolism at some or all of the stages of division. But this may not be their key mode of therapeutic action in clinical practice, as in many instances the rate of multiplication of leukaemic cells is not unduly raised. Other more specific mechanisms could be involved.

For example, in the case of steroids leukaemic cells appear in certain instances to show a raised number of appropriate receptors which may make them vulnerable to high concentrations of such hormones (Kay 1980). This raises the possibility that throughout the cancer field improved drugs will eventually be developed. One theory currently being investigated suggests that the cellular organelles known as mitochondria are unusually sensitive in some forms of neoplastic illness. If so, future medicines might be tailored to exploit this in such a way as to do little harm to normal cell populations (Wilkie 1979).

Innovations of this nature should help to reduce the hazards and side effects of current leukaemia therapy. Sickness and hair loss are examples of the latter often associated with intensive programmes. And despite the provision of facilities like barrier

nursing, antibiotics and granulocyte and thrombocyte transfusions about one in five adults with acute leukaemia die during attempts to bring them into remission.

But against cautionary observations like these it must also be stressed that progress is being made and that the achievements of clinicians treating the leukaemias already rank as one of the outstanding stories of modern medical history; achievements which may well by the turn of the century be seen as the introductory chapter to a successful battle to understand and control many other forms of neoplastic illness.

At present leukaemia research is proceeding along many lines. One aims at further differentiation of the various cytological types of disease. Another, designed to provide a guide to determining appropriate clinical responses, involves 'staging' conditions in such a way as to relate the precise characteristics on diagnosis to eventual outcome. A third seeks the long term follow-up of leukaemia survivors, so as to assess the full impact and sequelae of treatment regimes.

The work of Draper and his colleagues in Oxford is of particular importance in this last context. In a collaborative study of surviving children they will investigate their general health and analyse in detail the occurrence of any second primary tumours; the outcome of any pregnancies; and the occurrence of any congenital defects and/or malignant disease in the children of those who have received successful treatment for leukaemia in their early lives.

The brief review below touches on several strands of current clinical innovation although it does not seek to examine the important steps possible regarding the psychological and social support of leukaemia sufferers and their families.[7] Rather its objective is to highlight the positive biomedical advances of the recent past and those which might be realistically expected in the near future, provided that adequate resources are made available for research and service developments.

7 Aspects of this area have been reviewed by a number of commentators (see, for example, Knapp and Hansen 1973, Lascari 1973, McCarthy 1975a 1975b, Peck 1979, Maguire 1980). Most concentrated on the problems confronting leukaemic children and their parents. Issues explored include the young child's fear of separation rather than death *per se* and parental experience of anticipatory grief and mourning which, where successful treatment is not possible, may precede the child's actual death and if not recognised can in some unfortunate cases lead to isolation of the patient in the manner he or she most fears. Class related factors related to coping need more examination, as do the problems of adolescents with the disease and the social and psychological needs of younger parents who themselves have leukaemia. Little work has been done on how such individuals attempt to discharge their responsibilities to their families. Similarly mourning in children has only recently started to be studied seriously (see Bowlby 1980). The Leukaemia Research Fund has published papers relevant to this general field.

Table 4   *Antineoplastic medicines used in the treatment of leukaemia*

Group	Specific Examples	Comments
Alkylating agents	Busulphan Chlorambucil Cyclophosphamide Melphalan Carmustine	These alkylate and cross link guanine bases in DNA, so arresting cell division. All actively dividing cells are affected. Main hazards in use relate to leucopaenia and bone marrow depression although there are also specific difficulties with particular medicines in this group such as the Addison's disease like syndrome sometimes associated with busulphan use.
Antimetabolites	Cytarabine Mercaptopurine Methotrexate Thioguanine	These prevent or distort the normal synthesis of nucleic acid by combining with the enzymes which react with natural cell metabolites. For example, methotrexate inhibits the process by which folic acid is used in the synthesis of purines and nucleic acid whilst mercaptopurine is an analogue of adenine. Its incorporation into cell DNA distorts the genetic message and so blocks multiplication. Side effects may include nausea and other gastro-intestinal symptoms.
Antineoplastic antibiotics	Actinomycins Daunorubicin Doxorubicin	Most antibiotics have potent toxic effects on bacterial cells but do little harm to those of mammals. A few, however, have cytotoxic or cytostatic effects which act on metabolic pathways common to both. For instance, daunorubicin and the related medicine doxorubicin inhibit DNA synthesis by complexing with preformed DNA. The actinomycins interfere with RNA readout from DNA. Their general toxicity generates symptoms like, in the case of daunorubicin, abdominal pain and gastric discomfort, alopecia, skin rashes and, in excess, cardiac damage.

Plant alkaloids	Vinblastine Vincristine	Alkaloids from the colchicine group have been used in leukaemia therapy but the most commonly employed substances in this class are the vinca alkaloids (derived from the Madagascar periwinkle which does not, in fact, belong to the genus vinca) in particular vincristine. Its action is to disrupt mitosis. Side effects are similar to those of the other antineoplastic medicines, although vincristine can also cause severe constipation.
Corticosteroids and other hormones	Prednisolone	The use of these substances in leukaemia therapy stems from early work on the effects of ACTH on lymphoid tissue during the 1940s. Today the latter is not commonly used but steroids like prednisolone are frequently employed, in part because of their relative lack of myelotoxicity. However, they carry other hazards. Therapeutic effect may be related to interference with subcellular organelles such as lysosomes.
L Asparaginase (colospase)		This is an enzyme which breaks down the amino acid L-asparagine. Since some malignant cells cannot synthesise the latter this interrupts their metabolism.

Note Various additional medicines, including radio-pharmaceuticals, antilymphocytic antiserum, immunoglobulins, metal based cytotoxins, methyl-GAG and others have been or may be employed in this context. The above table is not intended to be comprehensive in its coverage or its illustration of side effects or other phenomena.

Acute lymphoblastic leukaemias

Before the Second World War life expectancy for both children and adults with acute lymphoblastic leukaemia was only a few months from diagnosis. Induction of remission[8] was first achieved in the late 1940s, a century after Virchow coined the term leukaemia. In France success was claimed in 1947 with the use of transfusion techniques but in the sense in which remission is usually meant the key breakthrough came later in the same year with the employment of the drug aminopterin by Farber of the Children's Cancer Research Foundation in the United States. This technique led to immediately observable increases in the survival durations of sufferers. But death still seemed inevitable, save in the 1 per cent or so of cases in which spontaneous recovery occurred.

It was the fact that some individuals were apparently curable which encouraged a few clinicians to adopt a more aggressive approach to the disease. In 1962 Pinkel and his colleagues at the St Jude's Children's Research Hospital, Memphis, set out deliberately to challenge the generally accepted medical view that palliation was the only realistic goal. Using a combination of the then recently introduced plant alkaloid vincristine coupled with prednisolone they were able to induce remission in over 90 per cent of their patients with childhood acute lymphoblastic leukaemia. This was backed by maintenance therapy using the medicines methotrexate, cyclophosphamide and mercaptopurine. But many of the children so treated eventually relapsed because leukaemic cells had penetrated their nervous system where the blood/brain barrier protected them from the cytotoxic drugs. Since the efficacy of therapy falls as the leukaemic cells become 'resistant' over time the eventual result is overt, rapidly fatal illness.

The major contribution which Pinkel and his team then made was to develop a technique of prophylaxis which cut dramatically the rate of meningeal relapse. After some experimentation it was found that a course of radiation to the head coupled with injections of methotrexate given immediately after directly into the fluid round the spinal cord was effective (Pinkel 1971). Shortly after information about Pinkel's work became available the British Medical Research Council began a series of trials which have contributed significantly to various aspects of the international understanding of leukaemia therapy.

From the results of these it is clear that the outlook for girls with acute lymphoblastic leukaemia is better than that for boys, although in the first trial (UKALL I) survivorship amongst males

8 The term remission does not mean cure. Rather it means in relation to leukaemia a hopefully permanent, but perhaps temporary, return of the cellular composition of the circulating blood to normal.

was significantly better than in later studies. One explanation for the former point could be testicular infiltration by leukaemic cells which may then be protected much as in cases where the CNS acts as a sanctuary. This possibility is currently being investigated as are the options for the development of prophylactic techniques like testicular radiation. It is less certain why the boys in UKALL I appeared to do better than those in the investigations which have followed. Such patients in some centres in the United States also seem to survive more frequently than their UK counterparts. One possible reason relates to the use of the drug asparaginase in the early stages of therapy. The most recently initiated MRC trial, UKALL VIII, seeks to clarify this issue.

The most recent figures indicate that approaching one in every two children under 15 who contract acute lymphoblastic leukaemia may be cured, in the ratios of about one-third boys and two-thirds girls. However, within these totals it may be noted that the prospects for those with the common 'null' cell form are much better (up to 90 per cent long term survival reported) than those for individuals with leukaemic cells carrying B or T cell markers. And in more mature sufferers, those aged over 15, survival chances are also disappointingly limited.

The reasons why current treatments are less effective in some groups are again uncertain, but it is clear that new approaches to therapy will be needed. Various new medicines are in research. Yet in the next few years the methods most likely to be intensively explored are those involving rescue by bone marrow transplantation. Results from centres in Seattle, New York and London all suggest that for children with acute lymphoblastic leukaemia who have relapsed and been brought into second remission such a transplant, the details of which are discussed below, offers a genuine chance of survival despite the risk of further relapses.

Acute myeloid leukaemia – one in two also curable?

Acute leukaemias in the monocytic, granulocytic and erythrocytic series are the major killers of young adults. To date progress in their control has proved slow although some two-thirds of all subjects can now be brought into remission. This proportion is higher in young patients and remission rates of over 80 per cent have been reported following very intensive drug programmes (Gale and Cline 1977, Gale 1979). But the side effects of the agents employed (daunorubicin, for example, can be cardiotoxic) and the hazards of myelosuppression are significant. Even after treatment the development of resistance may lead to a fatal leukaemic relapse, median life expectancy after remission being under two years. Some individuals, however, live on for much longer.

Yet there are some grounds for cautious optimism even here.

For example, in the case of hypergranular promyelocytic leukaemia the realisation that a particularly high risk of early death was associated with an abnormal blood clotting phenomenon known as disseminated intravascular coagulation (DIC) has already led to therapeutic improvements. In some cases this hazard can be controlled by prophylactic large platelet transfusions and the medicine heparin. Sufferers enabled to survive and who enter remission have an exceptionally good chance of long term health as compared to the average acute myeloid leukaemia patient.

In the 1970s many trials of immunotherapy were carried out and these too have encouraged hopes of further progress. Powles *et al* (1977) demonstrated that the stimulant properties of BCG vaccine mixed with killed leukaemic cells slightly improve survival. The reasons for this are uncertain but interest in the area continues and other methods of immunotherapy are being actively investigated. The potential of interferon therapy is also under scrutiny, and a preliminary trial of its value in treating acute myeloid leukaemia is in progress at St Bartholomew's Hospital. But as in acute lymphoblastic leukaemia the area which is currently the main centre of attention is that of bone marrow transplantation.

The objective of the latter (which has a unique advantage amongst transplant operations in that the tissue transferred is taken from living donors who are subjected to very little risk and who can, if necessary, give marrow cells on more than one occasion) is to completely replace the recipient's blood and blood forming cells. The availability of a graft permits the administration of cell-destructive medicines in doses which would normally result in death; the aim of this is the elimination of every leukaemia cell in the body. After such therapy the 'new' marrow cells are injected into the patient's bloodstream. Within three to four weeks they colonise the marrow of their host and regenerate normal populations of blood cells.

Success depends on compatibility between the donor's and the recipient's tissues. This can be best achieved by confining the choice of donors to the siblings of those needing a graft who are matched as closely as present techniques allow. But unfortunately such methods are not yet perfect and in about one-half of cases the donated cells react against those of the recipient which they recognise as belonging to a foreign body.[9] The resultant illness, known as graft versus host disease (GVHD), can sometimes be fatal although it is possible that it may also have some beneficial

9 In fact recent evidence suggests that the aetiology of GVHD may be, at least in a proportion of cases, rather more complex. For example, GVHD symptoms have been reported in transplants between identical twins who in theory should have entirely compatible tissues.

aspects in as much as any residual leukaemia cells may be killed by.it.

Further research is thus needed in order to identify the most desirable therapeutic approach. At present the role of the new medicine cyclosporin A is being investigated. The drug now appears likely to be of value in this context despite initial problems relating to dosage and management (*Lancet* 1979, Powles 1980, Kay 1980). A possibility for the future is that control will be further improved by the availability of specific anti-T cell immunoglobulins produced on a large scale by new monoclonal antibody culturing techniques. In theory the elimination of these cells (which influence the activity of other lymphocytes) in the donor population might avoid GVHD and will perhaps open the way to the widespread use of unrelated donors for marrow transplantations.

However, even with today's methods results from matched sibling donor (and, to a lesser degree, autologous[10]) operations are encouraging. Although survival amongst those acute myelogenous leukaemia patients treated after their first relapse appears to be only about 20 per cent at 2 years (Gale 1979) those receiving a transplant during first remission may have a between 60 and 70 per cent chance of long term survival (Storb 1980, Kay 1980, Powles 1980). At present, of course, not all patients are brought safely into remission and there is only a limited chance that those that are will have a brother or sister who is a suitable match. But with better induction techniques and the possibility that unrelated donors may become employable it seems plausible even on these figures that eventually one in two of all acute myeloid leukaemia victims will be considered curable.

The chronic leukaemias

In the last thirty years or so the chronic leukaemias have been to an extent controllable, but not curable, by drug therapy. With regard to the myeloid state(s) Galton first introduced the alkylating agent busulphan into clinical practice in the early 1950s, since when it has become the medicine of choice for this indication. It limits symptoms during the relatively benign stage of the illness. But unfortunately no treatment is effective in the terminal 'blast crisis', when large numbers of immature cells appear in the blood and bone marrow.[11] Median survival has

10   Involving cells taken from the subjects themselves during remission.
11   In the 'blast crisis' phase there is in about one-fifth of cases an apparent transition to acute lymphoblastic leukaemia. The probable explanation for this phenomenon (first proposed by Boggs 1974) is that the cell initially involved in CML has the potential to develop into either lymphoid or myeloid cells. Only the latter show the chromosome translocation typical of CML until the blastic phase when the 'lymphoid' blast cells carry the Philadelphia chromosome.

thus remained at approximately three and a half years from diagnosis, although a proportion of patients enjoy a span of ten or even twenty years.

It has been suggested that removal of the spleen[12] early in the disease course may, in addition to stopping pain or discomfort associated with swelling of the organ, extend the benign period. This has been the subject of an MRC trial, although it now appears that the operation is unlikely to alter the long term prognosis unless perhaps combined with more active efforts to eliminate the leukaemic cell population before it reverts into 'blast crisis'. One possible strategy is to employ intensive radiation and cytotoxic medication regimes in an attempt to eliminate all abnormal (Philadelphia chromosome bearing) cells. 'Rescue' by marrow transplant of either donor or autologous origin could follow. The viability of the latter would be much enhanced if some form of sorting to eliminate leukaemic cells could be developed.

Trials are in progress and some encouraging results have already been reported (Fefer et al 1979). Of special interest is the grafting of bone marrow from identical twin donors during the chronic stage of the illness. Intensive therapy seems to be more effective in destroying the leukaemic cells in this period than in the 'blast-cell' stage. In Seattle there are currently 15 surviving (but not necessarily cured) transplantees who have been so treated (Storb 1980).

The possible benefits of extending such an approach to a wider population by grafting from non-twin donors must be balanced against the hazards in a condition where conservative therapy can bring several years of good quality life. But if given a choice some younger people with chronic myeloid leukaemia would probably accept the opportunity of cure which aggressive treatment may offer.

Turning to chronic lymphocytic leukaemia, chlorambucil, another alkylating agent, is generally regarded as the most acceptable therapeutic option. Its use slows the build up of abnormal cells, especially in the bone marrow. It thus reverses the deterioration in the latter's function which is the major feature of the advanced disease. But it does not prevent altogether the condition's progress and conventional therapy is of limited value amongst those diagnosed late.

With a disease in which so many sufferers are elderly and where median survival from diagnosis is around 6 years (more than 10 years for those who are in an early stage at recognition)

12 Splenic involvement in leukaemia may sometimes be associated with beneficial effects. For example, Manoharan et al (1980) reported that in childhood ALL cases with splenomegaly in remission may be more likely to survive without splenectomy.

the cautious application of potentially lethal therapies is obviously desirable. However, preliminary trials have indicated that aggressive treatments employing radiation and/or intensive chemotherapy can induce complete remissions in more than half the cases (Johnson 1977, Phillips 1977, Richards *et al* 1978). Once again the MRC has organised one of the largest of the current trials relating to this field.

Future prospects

The progress made in leukaemia treatment since the start of the 1950s in many ways illustrates the changes which are occurring, or may be expected, throughout the cancer field. The gradually improving chance of survival, especially in children, has brought with it new concerns about the initiation and potential hazards of intensive therapy; about balancing the need for specialised centres of technical excellence against that for a diffusion of skills to peripheral hospitals; and about the costs of cancer care.

It is amongst older patients that the benefits of aggressive approaches to leukaemia have been most questioned. For example, Burge *et al* (1975) at University College Hospital employed a moderate, palliate regime to treat a group of people with acute myeloid leukaemia. They aimed to as far as possible reduce the dangers that immunosuppressive and marrow damaging drugs may expose patients to. And they reported a rather longer median survival time than that for patients more intensively treated in two previous MRC trials. Few in the UCH group obtained remissions but the quality of life for those who did not was claimed to be superior to that experienced by those receiving more powerful drug combinations but who nevertheless failed to remit.

Since its publication this study has been widely criticised and Galton (1980) has argued that advances in supportive therapy have in any case changed the balance of risk and benefit in the context considered. But it raises the point that occasionally it may be easier for patients, particularly older individuals, and their families to accept outright the approach of death in as calm and constructive a manner as possible, rather than live with not only the hope of success offered by intensive treatments but also their costs in terms of side effects and anxiety generating uncertainty of outcome.

Decisions about the path to be taken can also be complicated by research requirements. In certain instances there may seem to be a conflict between society's collective need to learn more about diseases like leukaemia and the interests of individual sufferers.

Some commentators might even argue against the principle of controlled trials of alternative therapies on the grounds that each patient requires personal attention directed towards meeting his or her specific needs. However, this is a potentially destructive opinion. The value of the Medical Research Council co-ordinated multi-centre research is indisputable from the viewpoint of all those wishing to see further advances in the cancer field generally and that of leukaemia in particular. Indeed, at present understanding of the effects of variations in therapeutic approach is in many areas so limited that it would be illusory to suggest that individual interests differing from trial protocols are likely to be identifiable, except maybe in the sense of treatment withdrawal.

Thus perhaps a more profitable approach to adopt is that wherever possible patients with rare and potentially fatal conditions like leukaemia should be helped to understand the close links between research and therapy and given sufficient information to be actively involved in both processes. Many people would, in such circumstances, probably choose to risk hazards like those of cancer chemotherapy in order to gain an extra chance of survival. For a proportion of those who despite such interventions unfortunately have to face premature death it may be of assistance to understand how their personal experiences will ultimately contribute to the emergence of new and effective curative procedures. Seen from this angle it might even be suggested that all patients with cancer have a 'right' to participate in properly supervised experimental trials if they so desire. Such a view carries with it far reaching implications regarding both the day to day running of services and the level of NHS provision in areas where the available treatments may be classified as experimental.

The organisation of care

There have been a number of recent reports relevant to the structuring of oncological services in Britain, all of which have some bearing on leukaemia care. They include an unpublished study by members of the Royal Colleges of Surgeons and Physicians on medical training requirements in this area; an enquiry chaired by Lady Marre into the organisation of regional and supra-regional paediatric oncology services based in Manchester; a review of alternative patterns of the provision of cancer services in Scotland, which offered an economic analysis of certain areas; and the production of a radiotherapy and oncology development plan by a sub-group of the London Health Planning Consortium.

The conclusions reached by these and other investigations appear generally to be compatible with one another. There is at the planning level at least fairly broad agreement on, for example, the need for special child centred facilities, especially now that

survival times are increasing. And it is widely accepted that there should be a close and constant liaison network between centres with specialist capacities in cancer treatment and service providers at less sophisticated district hospitals. This pattern should offer the advantages of both concentrations of highly skilled specialists and the availability of care to patients from doctors and hospitals which are relatively easily accessible and perhaps comfortingly familiar.

Nevertheless, there is despite this overall consensus both a degree of concern regarding certain current developments in cancer services generally and provisions relating to leukaemia in particular. In the context of the former, for instance, it may be suggested that initiatives in the sphere of health education and cancer have been slow to be translated into practical action. One somewhat cynical view of this is that although popular commentators tend to emphasise the individual responsibility and primary prevention aspects of health education programmes, it could be argued that in cancer there are equally pressing needs for politically led social interventions and better secondary prevention. Conflicts of economic interest and fears of 'excessive' demands on the NHS may make these difficult areas.

In the specific context of the organisation of leukaemia services there was debate in the mid-1970s following the publication of a paper by McCarthy (1975) which concluded that 'a regional policy for childhood leukaemia should be concerned to improve treatment regimes at local hospitals rather than attempt to concentrate care at a few centres.' This called into question the 1971 view of the Central Health Services Council (HMSO 1971) which led to the establishment of the four pilot Regional Cancer Organisations along guidelines recommending concentrating the treatment of certain rarer cancers, including childhood leukaemia, in special hospitals.

Many authorities in the field saw the paper as a direct attack on the continued existence of the special units,[13] based on the (still) erroneous belief that childhood leukaemia had been effectively mastered and was no longer a research problem. Their fears were increased by reports that DHSS and Welsh Office

13   This was not necessarily the case. Some of McCarthy's findings, such as his observation that in social and allied terms there was little to choose between DGHs and special centres, tended to favour the latter, given their superior treatment results. It is of note in this context that unpublished research conducted by the DHSS Operational Research Unit indicates that in cases of leukaemia, regarded as a serious illness, patients and relatives accept the extra travelling time involved going to a specialist unit. They may also draw some comfort from the reputation and acknowledged expertise of such a centre when a child is the patient. For older subjects the attractions of local treatment tend to grow, particularly where there is little chance of medical intervention changing the long term outcome.

officials accepted (or may even have promulgated) this view. In this context some tensions were generated by the new financial arrangements introduced in the 1974 reorganisation and the switch in NHS philosophy towards favouring more autonomous peripheral policy formation. Before 1974 various special centres were supported by central funds but after the reorganisation they became dependent on the finances of the localities in which they were situated.

In fact since the mid-1970s attempts have been made to involve more closely the staff of district hospitals with the work of regional or super-regional centres. Much of the follow-up of children treated for leukaemia at specialist units is now being conducted by the former. In this sense there has been a shift towards a more integrated system which to a degree may be thought a vindication of some of McCarthy's findings. But the concerns of those wishing to defend the interests of leading centres of excellence have also proved justified, at least on economic grounds. This is in part because with the introduction of new techniques their costs have tended to rise faster than have the funds available to Regional and Area Health Authorities. And in part because of the special problems of the NHS in London where, perhaps unfortunately, British medical expertise has in the past tended to concentrate.

Current pressures to cut back or rationalise inner London NHS spending and that of the London University Medical Schools are seen by some physicians involved in areas like leukaemia as threatening their work (Hobbs 1980). The most obvious example is the possible loss of the Westminster Hospital, with its bone marrow transplant unit and substantial children's facilities and expertise in radiotherapy.

Such fears should not be exaggerated. Without rationalisation extensions of care into novel areas could prove impossible. But there does seem to be reason for some concern on the ground, for example, that the officially perceived need to reduce the central London concentration of medical resources may in part be based on spurious logic.[14] Also government's decisions on economic policy and the arbitrary allocation of an overall health budget might result in an implicit evaluation of care in fields like leukaemia below that which the community would display if all the opportunities for progress in the economy could somehow be selected one against the other.

Economic aspects

The personal and social costs of premature mortality caused by neoplastic conditions like leukaemia are considerable but ex-

14 The population fall of the last few decades may have been balanced by increased mobility and greater concern for treatment standards as opposed to local access to services.

tremely difficult to measure. For example, loss of a parent during childhood may affect the mental state and work performance of subjects throughout their lifetimes (Brown *et al* 1978). Subsequent generations might also be adversely influenced. But it would be virtually impossible, at least at this stage in research on the aetiology of conditions like depression, for an observer to attribute economic costs to the social and psychological sequelae of a cancer death occurring perhaps decades previously. And attempts to value years lost to individual victims are subject to major methodological problems. It is thus possible that the burden imposed by conditions like leukaemia may be underestimated by economists. Any such tendency may be exacerbated by the fact that in service cost terms cancer is relatively inexpensive to treat as compared to many chronic conditions of later life.

DHSS estimates for the year 1976 (Wrighton 1979) indicate that just over 5 per cent of NHS current spending can be attributed to cancer care even though neoplasms cause about a fifth of all mortality in the country. Extrapolation of these data to 1980 shows a current total UK NHS cancer treatment incurred cost of approximately £500 million, ninety-five per cent of which is met in the hospital sector. Of this, roughly £15 million can be attributed to leukaemia of which it appears that up to 20 per cent (£3 million) is spent on anticancer medicines. Overall outlay on such drugs is now estimated at about 8 per cent of NHS cancer treatment costs.

Such figures only provide a rough guide to the magnitude of the sums involved and may be subject to errors through, for example, the problems involved in trying to estimate spending on antibiotics incidentally associated with cancer therapy. Yet they show that leukaemia has special costs associated with drug usage and that cancer treatment is a specifically hospital concentrated activity. In the light of cash limits on hospital spending this points to potential problems, especially in the context of further introductions to the market of sophisticated antineoplastic and immunosuppressive medicines. Some specialist centres already spend 12 to 14 per cent of their total budgets on cancer related pharmaceuticals (Wrighton 1980).

Several authorities have expressed concern about this topic (see, for example, Berry and Bryan 1978). Few, however, have attempted to analyse the economic problems of cancer chemotherapy in the context of Britain's Pharmaceutical Price Regulation Scheme, which operates in such a way as to limit pharmaceutical industry costs and profits to levels negotiated with the DHSS. It is possible, for instance, that under the scheme companies might be encouraged to 'subsidise' antineoplastic products with funds derived from other areas. This might help to relieve hospital cash pressures. Yet in the longer view it may also have counter-

productive effects, not the least of which could be artificial inflation of medicine spending in other areas, particularly family practitioner services. General practitioners may then be blamed for prescribing 'waste' because of real (and justified) cost increases actually incurred elsewhere in the NHS.

Such observations strongly suggest that the subject of NHS medicine spending needs to be approached with rather more sophistication than is normally attempted. It would, for example, be useful if the DHSS could prepare adequate figures on the hospital consumption of drugs for conditions such as leukaemia. But for their implications to be fully understood further measures, such as estimates of the marginal costs of additional consumption in each therapeutic area, are also needed.

A potentially more serious economic problem related specifically to the treatment of leukaemia lies in the possible expansion of demand for bone marrow transplantation, a technique which is currently of very limited availability in the NHS. It has been estimated that even today total 'legitimate' demand (that is, cases where a suitably matched donor is available) is in the order of 300–500 operations yearly for all leukaemia, aplastic anaemia and immunodeficiency cases (Hobbs 1980).

Yet existing centres like the Royal Marsden, the Westminster, the Hammersmith and the Royal Free can together supply only about 50 annually. Hence several hundred potentially treatable children and adults die yearly. And current results from America and Britain strongly suggest that additional acute leukaemia cases (and perhaps a proportion involving the chronic myeloid condition) may soon require either allogenic or matched sibling donor transplants. Indeed, if the problems of non-related donor tissue compatibility and graft versus host disease are overcome demand could rise much further.

Yet bone marrow transplant operations cost in this country in the order of £5,000 to £6,000 over and above the resources needed to bring a leukaemia sufferer into remission (Kay 1980). This has led administrators in some areas of the NHS to urge clinicians not to conduct this operation, even though long term economic arguments strongly support provision.

This last point may be illustrated in the case of acute myeloid leukaemia. Today costs stand at between £5,000 and £10,000 per sufferer brought successfully into remission – the actual figures being influenced by the numbers of treatment failures and being subject to considerable specific patient and centre variations. This sum purchases only between one and two years of extra life for most recipients. But if whilst in remission a bone marrow transplant can be successfully conducted indefinite survival in between 60 and 70 per cent of those treated may soon prove achievable (Storb 1980). The cost per year of life saved

would be far lower than in cases left at the initial stage of re-mission induction even if the fact that those dying of leukaemia will require expensive terminal care is ignored. In reality the latter could cost almost as much as a marrow transplant.

These data are not as yet fully verified and the final place of bone transplantation in the management of leukaemia is still far from clear. It is possible that in the decade or so that it will take to fully analyse its role it will be superseded by better chemo-therapy (Galton 1980). And in the short term some of the current difficulties related to supplying grafts to the 15 per cent or so of leukaemia patients currently thought likely to benefit (given the problems of donor matching) may be partly resolved by the recently announced Leukaemia Research Fund investment of £600,000 in bone marrow research.

Yet a significant overall shortfall in supply for all indications already exists. Hence the area raises problems for the NHS parallel to those already more widely appreciated in fields like heart surgery and renal dialysis and transplantation; current NHS policy in this last context puts the implied value of a life at between £30,000 and £40,000 in 1980 terms (OHE 1978). This is between two and three times the average cost of bringing a suit-able acute leukaemia patient into remission and then undertaking the marrow graft procedure but is well below the cost of a life implied by official policy in some fields outside health (Card and Mooney 1977, National Radiological Protection Board 1980).

Questions which arise include 'is there any way to avoid the NHS becoming increasingly reliant on privately raised "seed" money for the introduction of services close to the forefront of medical discovery?' and 'are there alternatives to current funding procedures which would relieve the economic problems of units serving as supra-regional referral centres for the delivery of such care?' But there are unlikely to be any easy answers. For example, one possibility with regard to the latter is that some form of internal NHS charging system might be introduced, with the health district where a patient is resident paying a fee to the centre supplying treatment. This has the attraction that indi-vidual units offering extremely specialised care could in effect compete for funds available throughout the NHS. Against this, however, is the question of administrative cost and the fact that delaying tactics at local level could result in prospective patients' deaths and so health authority 'savings'.

Conclusions

A commentator wishing to question the significance of the leukaemias in the community and the value of investigations into their causes and cure might put forward criticisms along the following lines: the leukaemias are rare diseases, with the number of sufferers at any one time being only a tiny fraction of that claimed by the common incapacitating conditions; even with regard to loss of life leukaemias cause only 2.5 per cent of all cancer deaths and 0.5 per cent of total mortality in the United Kingdom; they are unlike the much more common solid carcinomas, such as lung cancer, which are derived from a different type of tissue and may require different therapeutic approaches; and the treatments currently available for leukaemias are to an extent experimental and can be hazardous. Thus it could be surmised that, in a time of health resource restrictions and pressing service demands, spending on leukaemia research and care innovations should not be a priority for Britain.

However, if objectively viewed the data presented in this paper provide very powerful arguments against this line of thought. These may be conveniently divided into four main groups. Those relating to the diseases' influence on the health of the community; those relating to research and the possible therapeutic rewards of further investment; those relating to progress against cancer generally; and those relating to the economy overall.

First, the special impact of this form of neoplastic illness on the young is apparent from the official mortality statistics. As a major cause of cancer-related death in childhood, adolescence and early adulthood leukaemia is disproportionately significant as a source of human suffering. Also it is only because death still often intervenes that the number affected at any one time is low. That is, leukaemia incidence is high as compared to its prevalence.

Second, steps towards the control of leukaemia have to date been most successful in younger sections of the population, where the social and economic costs imposed by the illness are highest. The fact that a degree of progress has already been achieved in chemotherapy and, more recently, marrow transplantation is a strong indicator of the desirability of further efforts. Development phase research always tends to be more productive than attempts to make fundamental breakthroughs in completely new areas. It is of course true that there are personal as well as economic costs involved in even successful treatments at this stage due to factors like drug side effects, but it has to be recognised that improved therapies will probably not be evolved without controlled experimentation in clinical practice. The Medical Research

Council's leukaemia trials stand as a world-wide example of excellence. And it can be argued in this context that research and the provision of basic caring services should be inseparable activities.

Third, regarding cancer generally, there is good reason to hope that despite its special characteristics, advances in understanding leukaemia will generate theoretical findings of relevance regarding the origin and course of other neoplastic illnesses. Also, on the service provision side, expansion of leukaemia related facilities may be seen as a useful bridgehead for the establishment of oncology as a discipline.

Finally, regarding the British economy as a whole, it may be noted that investment in medical research and services for leukaemia sufferers could help to bring long term rewards in fields like medicine exports and the provision of sophisticated medical care for foreign purchasers. If through underfunding this country's still outstanding centres of medical expertise are broken up or their development unduly slowed innovation will increasingly take place abroad, as cancer therapy is likely to be a major world-wide growth market in the 1980s and 1990s. In 'high technology' medicine clinical strength and industrial strength are likely to be correlates of one another. This is one reason why to date the British based pharmaceutical industry has in many instances outperformed its rivals in other countries. Competition from nations like Japan in the cancer field is likely to become particularly intense in the relatively near future.

Thus, in conclusion, it appears that this country has an interest in devoting adequate resources towards leukaemia treatment and research. Although charities like the Leukaemia Research Fund have made significant efforts to raise private money for the latter (over £1.25 million in the current year) the National Health Service has clear responsibilities in these closely linked areas.

It would be misleading to suggest that at present the facilities available to leukaemia sufferers in Britain are inferior to those available in other developed countries. On the contrary, the NHS provides an in many ways notably good standard of care. But given the strong possibility that demand for treatments like bone marrow transplants and maybe some advanced forms of chemotherapy (for example, interferon's value in cancer control is still unknown – *Lancet* 1979) will rise in the not too distant future this may not continue to be the case. This country's record in transferring research procedures into routine service is not outstanding. It may be argued that in areas of high cost treatment ideally supplied by just a few national centres the DHSS ought to state its objectives more clearly than it does at present. That is, national goals in these special cases should be overtly defined. And perhaps new arrangements should be made for the resources needed

to meet them to be centrally directed. At present the only allocation route is an indirect one via RAWP, since medical special development money can only be given in limited circumstances for projects defined as being purely research rather than service activities. This paper has sought to show that this latter division is in many ways unsatisfactory, particularly when it leads to vitally linked research/care programmes being dependent on uncertain, 'soft', funding.

It may of course be asserted that local health authorities must be responsible for planning their local provisions and that direct DHSS involvement in service management is undesirable. This for most widely supplied forms of care seems reasonable. Yet one of the lessons that experience with renal dialysis and transplantation in the 1970s should have for health planners in the 1980s is that in fields involving high cost, relatively rarely required life or death medical interventions public confidence in the NHS is not likely to be maintained if apparently arbitrary and inequitable factors determine the availability of care.

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