(Astler-Coller C1) [5, 8]. It is also certain that number of positive nodes and/or apical nodal status are important and independent factors [1, 5, 7]. There is evidence that "differentiation" is not an independent variable, whereas grading based on the character of the invasive margin (expanding or infiltrating) is [1]. Diffuse infiltration and perineural invasion are closely correlated and only one is likely to be independent (this was diffuse infiltration in an unpublished multivariate analysis by the author). Venous spread is independent in some studies [5] but not others [1, 7]. Age is only relevant when the clinical endpoint is death due to any cause as opposed to death due to cancer [7].

It is clear that the Dukes classification and minor modifications thereof are inadequate for prognostic purposes and for planning adjuvant therapy [1, 5, 7]. Using more refined staging systems (Table 1), a large subset of B cases (B1) can be identified as having the same prognosis as the majority of A cases. There is no rationale for offering adjuvant therapy to patients with ACPS B1 cancers (Table 1). It is likely also that subsets of C cases within favourable prognostic groups do not require adjuvant therapy [1, 7]. Two examples of "good" C cases would be those in which direct spread is limited to the muscularis propria and those associated with a marked peritumoural lymphocyte reaction. There is the proviso that there should not be more than four positive nodes [1], apical lymph node involvement [5], evidence of venous [5], perineural [7] or diffuse infiltration [1], or free serosal surface invasion [5].

If a rectal cancer extends exclusively towards peritonealised rectal wall (a cancer of the upper anterior rectum) and does not extend into the mesorectum, the anatomical factors determining the risk of local recurrence are essentially those of colonic rather than rectal cancer. This should affect the decision to offer adjuvant radiotherapy. Penetration of the peritoneum by tumour is presumably associated with generalised intraperitoneal spread and calls for the development of novel approaches to adjuvant therapy. The importance of the peritoneum in defining the precise location and determining the management of rectal cancer has been neglected [4, 5].

A final issue relates to the range of new technologies that have highlighted potentially important variables such as oncosuppressor gene loss [9] and HLA-DR expression [10]. It is important that such studies adopt a multivariate approach that incorporates a comprehensive set of traditional pathological variables ascertained according to standardised protocols. There is no evidence that any of the new, technology-based variables add to let alone replace the traditional pathological factors.

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The Search for Causes of the Leukaemias

F.E. Alexander

THE ARTICLE by Groves and colleagues in this issue (pages 941–949) summarises the descriptive epidemiology of these conditions in terms of mortality, incidence and survival. In the last two decades, there have been enormous advances in methods of management so that the prognosis, at least for childhood leukaemia, is now good. It is encouraging to see that this now applies to acute myeloid leukaemia (AML) as well as the dominant childhood leukaemia, acute lymphoblastic leukaemia (ALL). Despite these advances, leukaemia remains a major source of morbidity and mortality in children (around 5% of all deaths in children aged 1–14 years in developed countries and urban areas of developing countries). Although in proportionate terms, the disease becomes less striking in older people, absolute rates are considerably higher in adults than children. There remains a clear challenge to the epidemiologist

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to identify causes so that (some) leukaemias can be prevented and the search for clues from descriptive epidemiology should clearly focus on incidence data.

Limitations in international coding of disease have enforced aggregation of "the leukaemias" but this is no longer necessary for incidence data and the disadvantages have been highlighted. The numbers of total leukaemias are dominated in most countries by chronic lymphocytic leukaemia (CLL) but this is misleading for two important reasons. Firstly, CLL may not be typical of leukaemia and may be closer to the non-Hodgkin's lymphomas (NHL) [2]; secondly, CLL ascertainment is unreliable since management is frequently in out-patient departments (not necessarily linked to cancer registration systems), diagnoses may be incidental consequences of other medical investigations and the disease predominantly affects the elderly.

For these and other reasons, it is more informative to concentrate on individual subtypes — principally the four main categories of ALL, AML, chronic myeloid leukaemia (CML) and CLL. Yet even within these, there is considerable heterogeneity of disease and hence, potentially at least, of aetiological factors. Indeed, one of the over-riding problems facing the leukaemia epidemiologist is the need to choose between *lumping* and *splitting* [3].

For those attracted to *splitting*, there is now an abundance of riches including age-groups, cell lineage, chronicity, morphological classification, immunophenotype and chromosome changes. There is evidence that all of these may indicate broad aetio-subgroups or even delineate disease subgroups specific to individual causal exposures. Some examples represent notable successes for epidemiology: (i) when cell surface markers were introduced to sub-classify ALL [4], one subtype (common-ALL) was seen to be responsible for the striking childhood peak which had, hitherto, appeared to be heterogeneous [5]; and (ii) for adult T-cell leukaemia/lymphoma (ATLL), the cycle of discovery, identification of the cause (the retrovirus HTLV1) and introduction of preventive strategies was completed in a few years as cases of CLL associated with HTLV1 were recognised to be clinically distinct [6].

Alternatively, *lumping* can be justified by examples of risk factors which are shared, not merely by all the leukaemias, but by the entire spectrum of haematopoietic malignancies. A parallel analysis of seven case-control studies conducted with an identical core protocol [7] made this clear. Odds ratios for a family history of leukaemia/lymphoma were consistently elevated; this was one of several factors which emerged as statistically significant in the pooled data set with no evidence of heterogeneity of the association. The geographical and ethnic variations in incidence suggest that cultural and lifestyle factors are critical in the aetiology of the leukaemias and that these may interact with inherited characteristics. Although occupational exposures have been of importance historically, the modest male excess (for all subtypes apart from CLL) and its frequent absence in younger adults suggests that other exposures may now be more important. The relevant doses are smaller than those which have previously been extensively evaluated; methods of extrapolation to low doses are uncertain, and direct evaluation of the effect of low doses is difficult because of inaccurate or absent dosimetry.

Although the aetiology of the leukaemias is obscure at present and known risk factors are unable to explain the observed patterns, broad categories of causal factors have been identified and the search for further causes should concentrate on these groups: chemical leukaemogens (occupational, environmental and iatrogenic), ionising radiation (in the same three categories), immune function defects (inherited or acquired), other inherited factors, infectious agents (including patterns of exposure) and possibly, extremely low frequency electromagnetic fields (i.e. 50–60 Hz). It is appropriate to consider these briefly in turn.

CHEMICAL LEUKAEMOGENS AND IONISING RADIATION

These include the principal known causes of leukaemia: moderate to high doses of ionising radiation and certain solvents (notably benzene), and chemotherapeutic agents (especially alkylating agents and the epidophillotoxins).

Ionising radiation of moderate–high dose causes ALL, AML and CML [reviewed in 8] but not, apparently, CLL [9]. The leukaemia subtype induced by ionising radiation appears to depend on the age at exposure and, probably also, on the quality of the radiation. X-ray exposure of the fetus is known to cause a 1.5–2.0-fold increase in the risk of childhood leukaemia (of all types) [8], but the evidence that lower doses are leukaemogenic is inconclusive [10].

Occupational exposure to ionising radiation is now legally restricted, and attention is increasingly focused on low-dose environmental exposures. The possibility that exposure to radon gas is associated with AML and possibly other leukaemias has recently emerged from ecological studies [11–13] and has limited support from at least two case-control studies [14, 15] with "exposures" taken from geological maps and housing material (tuff), respectively. Uranium miners do not, in general, show elevated leukaemia rates [16] but their exposure involves particulates.

There has been some concern, primarily in the U.K., that environmental exposure associated with nuclear facilities and weapons testing could cause cases of leukaemia. The cluster around the nuclear re-processing plant at Sellafield led to an alternative hypothesis—that preconception, paternal irradiation could cause childhood leukaemia [17]. Extensive research in recent years has failed to confirm this hypothesis [18]. The clusters of cases of childhood leukaemia around three nuclear facilities in the U.K. remain unexplained.

Benzene has been associated with leukaemia since the 1920s and several formal epidemiological studies have demonstrated an association (e.g. [19]); it was finally classified as a human leukaemogen in 1981 [20]. In contrast to ionising radiation, benzene is linked to specific subtypes, primarily AML. The evidence relies on moderate–high occupational exposures of a magnitude which has been prohibited since the mid-1960s. It has been estimated that only 1% of benzene exposures in the United States today are occupational [21] and it has been proposed that environmental low-level exposure from, in particular, motor cars may be a major cause of leukaemia [22]. The evidence that low dose benzene exposure, in general, is leukaemogenic is at present very limited but if this association were real it would have major public health implications.

Smoking is almost certainly a cause of myeloid leukaemia [reviewed in 23], although it is unclear whether the relevant pathway involves chemicals (e.g. benzene, with an estimated 55% of exposures in the U.S.A. attributed to smoking) or ionising radiation (e.g. polonium-210), or other substances, and whether the risk extends to ALL or CLL. Twelve studies included in the review by Siegel [23] examined myeloid leukaemia and all but two were consistent with an odds ratio for smokers (and ex-smokers) of around 1.5. The designs of these two studies [24, 25] used increased sampling of survivors which

may explain their results, since smoking-associated AMLs may be poor prognosis types (e.g. of FAB type M2 or with trisomy of chromosome 13, [26]) and CMLs may have accelerated acute phase [27]. From the odds ratio estimate of 1.5, Siegel calculated a population attributable risk of 22% for the U.S.A. which would make "smoking the leading known cause of leukaemia" [23]. It follows that leukaemia is one of the many public health problems which will be ameliorated as smoking is reduced [28] but is not one of the major causes of death among smokers. It also follows that safeguards against confounding by smoking must be included in new epidemiological studies.

Occupational and residential involvement in agriculture has been consistently linked with the entire spectrum of haematopoietic malignancies (reviewed in [29]). The evidence is most convincing for ALL and least for CML. Although exposure to animals (and hence possibly zoonotic viruses) has been implicated [30], most investigators interpret the results in terms of agrichemical exposure [reviewed in 31]. Neither specific chemicals nor specific types of agriculture have been associated with leukaemias, but both genotoxic and epigenetic effects have been documented for a variety of pesticides [32]. Pesticide use in agriculture in the U.S.A. tripled between 1965 and 1985; 75% of cropland and 70% of livestock are now treated with pesticides. Use in homes has also increased and 90% of U.S. households now use pesticides [31]. Some pesticides persist in the home environment and important sources of exposure for young children may include house dust and lawn residues. The reported increases in ALL incidence [1] are consistent with an interpretation involving pesticide exposure but little is known of the chronic health effects of low level home exposures. Further occupational studies with high quality dosimetry offer the best opportunity of identifying individual agents capable of causing leukaemia in exposed persons or their children [33] or other adverse reproductive outcomes.

Finally, iatrogenic exposures must be noted. Alkylating drugs, epidophillotoxins and other chemotherapeutic agents are known to cause secondary leukaemias, principally AML, with odds ratios of 10 or higher frequently reported [reviewed in 34]. Chloramphenicol and related antibiotics have also been associated with acute leukaemias, both myeloid and lymphoid [35, 36].

The recent identification of mutations of a particular gene (HRX/MLL) in at least 90% of infant leukaemias of all cell types [37] is of considerable interest. The DNA damage is similar to that in secondary epidophillotoxin-associated AML suggesting the involvement of chemically similar exposures, and these must (in some or all cases) occur *in utero* [38]. This renders study of gestational events and exposures in cases of infant leukaemia an urgent research priority.

IMMUNE FUNCTION DEFECTS

Personal and family history of immune function defects, including both immune deficiency and auto-immune disease, have frequently been associated with the leukaemias and other haematopoietic malignancy [7] although cases of NHL predominate in cohorts of subects with primary immune deficiency. Elevated risk of auto-immune and related conditions (e.g. multiple sclerosis) have been reported in families of probands with CLL [39], members of leukaemia-prone families (e.g. [40]), mothers of cases of childhood ALL [41, 42] and in relatives [43] and school contacts [44] of cases occurring as clusters of childhood leukaemia.

OTHER INHERITED FACTORS

The association of CLL with ethnic origin is striking, with a marked deficit [1] in Orientals which parallels a deficit in NHL (especially those of B-cell phenotype) and of Hodgkin's disease. Since these observations apply also to North Americans of oriental origin they are strongly indicative of inherited factors. This is supported by the noted familial aggregation of cases of CLL [8]. The particular factors remain to be identified. By contrast, the available evidence suggests that the environment and lifestyle are more important than inherited factors for ALL. In particular, the childhood peak of ALL and the relative frequency of common-ALL are related both between and within countries to geographical and temporal patterns of socio-economic development [45–47]. Where socio-economic status is similar, rates of ALL (especially childhood) in immigrants approach those of the host community [48]. The high rates now noted in "Latin" populations in Europe, North and South America confirm previous reports for total childhood leukaemia [49, 50]. It is unlikely that cultural factors will be shared in these distinct settings and inherited predisposition should be investigated. The effect of inheritance in childhood leukaemia, ALL and AML is usually considered to be small [51] but it is possible for a substantial effect to pass unnoticed [52]. This would be exacerbated if susceptibility to induction of leukaemia by specific risk factors were inherited.

INFECTIOUS AGENTS

Although most animal leukaemias are caused by viruses, the first virus to be identified as a cause of a human leukaemia was HTLV1 for ATLL (see above). It is now known that HTLV1 (and a related virus, HTLV2) can also cause a broad spectrum of chronic neuro-degenerative and lymphoid disorders [reviewed in 53]. It may have an indirect role via its immune suppressive effects in some cases of B-cell CLL [54]. Reports of clusters of cases of childhood leukaemia and excesses associated with population mixing [reviewed in 55] suggest that one or more common viruses may be associated with childhood leukaemia. Further evidence comes from the association of common-ALL and the childhood peak with community isolation and socio-economic status. There is substantial indirect support for one hypothesis [56]: children with little antigenic stimulation during infancy but substantial (delayed) exposure to a specific but unknown agent or to non-specific infections have increased risk of cALL. A recent report of an association of leukaemia with occupation in childcare which is statistically significant for AML and CML has been interpreted in terms of exposure to childhood infections [15].

ELECTROMAGNETIC FIELDS (EMF)

Occupational studies have shown increased AML in several categories of electrical workers including electricians, welders, electrical technicians, radio/television repairers and telephone linesman [reviewed in 57]. It is possible to interpret these in terms of exposure to electromagnetic fields but this is by no means certain since accurate EMF dosimetry has not been available and information on exposure to solvents and other leukaemogenic chemicals has been lacking [57]. The possibility that environmental exposure to EMF may increase the risk of leukaemias and other cancers, especially in children, is the subject of much speculation but the available evidence in inconclusive [58] although well-designed studies are in progress. The energy from electromagnetic radiation of this frequency is believed to be insufficient to cause DNA damage so that EMF,

if causally involved in leukaemogenesis, must act as a promoter [59] which could be general or specific to certain leukaemogens. One possibility which should be investigated is of an interaction between EMF and the chemicals to which the electrical workers are exposed.

The present situation offers both opportunities and challenges. It is unlikely that "more-of-the-same" will alter the present unsatisfactory absence or knowledge regarding the causes of the leukaemias. New studies require careful thought and critical judgment concerning the importance of the questions being asked and the ability of the methodology to answer them. Critical aspects of methodology include study size, precision of case diagnostic definition and quality of exposure measurements for risk factors and confounders.

In general, *splitting* may lead to loss of statistical power since the numbers of cases in the individual subgroups are often small whilst inappropriate *lumping* will lead to dilution and hence masking of real effects. The consequence of either of these is that results of epidemiological studies may be misleading in suggesting false negative conclusions. A further problem arises when splitting (especially when post-hoc) leads to a multiplicity of statistical tests which can generate false positive reports. AML cases with *RAS*-oncogene activation have been associated with solvent exposure [60] but risk for total AML was not elevated in this study. Future studies will determine whether this is an example where lumping causes dilution of a true effect or of a false positive result from multiple testing in subgroup analyses.

In general, future studies should utilise all modern classifications of the leukaemias and involve large numbers so that alternative methods of splitting can be examined in subgroups of adequate size. These will permit hypothesis generation and testing would, ideally, be available from comparable studies conducted simultaneously in other centres. Strenuous efforts must be made to include accurate dosimetry since it is almost impossible to be certain that odds ratios in the region of 1.5, even if formally statistically significant, cannot be attributed to unrecognised confounding.

Attention could usefully be focused on unifying hypotheses and on new ideas where rapid progress may be possible (e.g. the childhood peak of cALL, infant leukaemias). In these and certain other situations, studies targeted at specific case subgroups may be useful. Finally, the possibility of mixed models involving both environment and inherited susceptibility must be taken seriously, and for this, new methodological designs [61] may be appropriate.

In the meantime, efforts to restrict occupational and environmental exposure to known leukaemogens, to minimise effective doses of chemotherapeutic agents and to identify viruses capable of contributing directly or indirectly to leukeamia must be encouraged.

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Pancreatic Cancer: A Plea for More Trials

E. Van Cutsem and J. Fevery

PANCREATIC CANCER is one of the most devastating neoplasms in view of the difficulty in obtaining an early and biopsy proven diagnosis, the poor prognosis and lack of efficacy of conventional therapy. Indeed, the majority of patients with pancreatic adenocarcinoma have unresectable, incurable disease at the time of diagnosis. The survival of these patients is short, on average 3–6 months. Moreover, these patients often have severe debilitating symptoms that require palliation. Even for the minority of patients whose tumours are resected, 5-year survival is less than 20%.

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METASTATIC CANCER

Chemotherapy in metastatic pancreatic cancer has currently a purely palliative role. Although responders to chemotherapy may have survival durations that greatly exceed those of non-responders, no chemotherapeutic regimen has been demonstrated to offer a clear survival benefit for the entire group of