onto infectious agents. What would be of further interest is to learn the migratory patterns of the parents of all the case children.

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SIR,—Dr Kinlen suggests that the increased incidence of childhood leukaemia near Dounreay and Sellafield is attributable to geographical isolation and delayed exposure to viruses. The hypothesis that childhood leukaemia can arise as a rare consequence of a common infection is similar to a more specific biological explanation proposed for childhood acute lymphoblastic leukaemia (ALL).[1,2] This model seeks to explain both why leukaemia is the dominant type in childhood malignant disease and the unusual age distribution and demographic features. This hypothesis is relevant to the excess leukaemias that may be associated with low-dose radiation but it differs, subtly but significantly, from Kinlen's ideas. The hypothesis has three tenets:

(1) Lymphocyte progenitor cells (the major target in ALL) are at special risk in early development because of a unique constellation of risk factors—namely, a high proliferation rate (which can be further increased by positive feedback from immune responses), defective DNA repair capacity, and active recombinase and terminal deoxynucleotidyl transferase, enzymes with mutagenic potential.

(2) Spontaneous mutations can arise in such cells frequently enough to account for the annual incidence of childhood ALL (2–4 cases per 100 000). No inherited mutation or mutation induced directly by leukaemogenic agents is required. More than one mutation is almost certainly needed, as in most cancers.

(3) The sharp age distribution of the common form of ALL and the predominance of the B rather than T precursor phenotype,[3] the HLA linkage,[4] and the apparent increased incidence associated with higher socioeconomic status[5,6] are all explained by a crucial link with the pattern of immune response to common infections in infancy.[2]

In essence, it is the immune response itself which promotes the development of leukaemia by inducing proliferative stress in the bone marrow lymphocyte precursors, so increasing the risk of spontaneous mutations in an already vulnerable cell population. The significance of viruses and/or bacteria lies in their antigenicity, not in their leukaemogenic potential.

Infants face a major immunological assault by microorganisms, and both the immune system itself and breastfeeding habits have been programmed to deal with this challenge in a developmentally timed manner. Human societies, however, have changed the rules: increasing incomes and technical development are usually associated with immunisation programmes, less breastfeeding, smaller families, and reduced exposure to common infectious organisms—in other words, infants are becoming more and more immunologically insulated. Kinlen (and Darby and Doll[7]) suggests another factor—namely, the isolation of young communities and subsequent mini-epidemics. For many children, the first frank exposure to infection may be delayed until there is more substantial contact with others (eg, in play groups and schools). This delay could lead to exaggerated or dysregulated feedback to vulnerable lymphocyte precursor cells in the bone marrow.

This model accounts reasonably well for most of what we know about childhood ALL but it would be premature to conclude that it convincingly or completely explains the excess leukaemias reported around nuclear reprocessing plants. Radiation remains a possible explanation. Radiation-induced mutations in the germ cells of the parent(s) could mean that a child inherits one of the required mutations and, by analogy with familial retinoblastoma,[8] is at increased risk of leukaemia arising from an independent, spontaneous mutation. This explanation can be ruled out if the child was conceived before the parents moved into the area but would be credible if all cases had at least one parent working at a reprocessing plant. Alternatively, if bone marrow lymphocyte precursors are unusually susceptible to mutation and malignant transformation, especially early in development, they could be at risk from bone-seeking α-emitters even when these are present at levels well below those normally considered necessary for inducing mutations.

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COMPARING THE EFFICACY OF PERTUSSIS VACCINES

SIR,—The Division of Drugs, National Board of Health and Welfare in Sweden, has recommended rejection of a licence for the two-component acellular vaccine, JNIH-6. As clinical coordinator of the vaccine trial, I have no reason to question this recommendation. However, I would like to comment on the interpretation of efficacy in one of the reviews asked for by the Division of Drugs.

The reviewer notes the difficulties inherent in comparing different studies of efficacy.[1] He argues that typical cases of whooping cough should be used in the calculation of protective efficacy and that the estimated efficacy of JNIH-6, when calculated as in other studies,[2,3] should be 45%. This interpretation conflicts with the basic design of the controlled, double-blind, randomised clinical trial. In the study protocol it was clearly stated that a case definition based on a combination of clinical symptoms (of varying severity) and specific laboratory tests should be used. In the Swedish study children were examined and specimens for pertussis culture obtained if the child had coughed for seven days, even if pertussis was not suspected clinically. Cultures were also obtained when pertussis was confirmed or suspected in the family or day care centre, the aim being to detect atypical cases. Such cases were primarily to be expected among vaccinated children.

With the above design we would expect to pick up several episodes of cough not related to pertussis, and such episodes should be distributed at random between vaccine and placebo groups. It was clearly stated that cases documented by clinical criteria alone should not be included in the estimation of vaccine efficacy. The analysis of "clinical pertussis" which the reviewer presents confirms that clinical pertussis without laboratory confirmation or epidemiological linkage in this study consisted mainly of episodes of cough unrelated to pertussis. The children in the Swedish trial were $\frac{1}{2}$ to 1 year of age and were closely followed up to 2 years—an age when respiratory tract infections are very common and it is difficult to separate pertussis from other respiratory tract infections.

Differences in "case ascertainment" may be decisive. Case ascertainment in the earlier controlled efficacy trials cited by the reviewer[2,3] were based on clinical suspicion of whooping cough. Most atypical cases would not have been detected. Furthermore, a cough of long duration would not have been noted if there was no clinical suspicion of whooping cough. A controlled study with the Swedish protocol therefore would be expected to give a lower estimate of efficacy than the older studies. The point is well documented in the follow-up of the Swedish study cohort. By passive open follow-up for one year after the end of the blind follow-up, we have found a higher efficacy for culture-confirmed pertussis than we did during the controlled trial (*JAMA*, in press). For pertussis of more than 30 days' duration and for pertussis with more than eight coughing spasms per day, observed efficacy was 91% and 95%, respectively (*Swed Med Assoc J*, in press). The

estimated efficacy against whooping cough as reported by parents was 82% for JNIH-6. These results from the open follow-up phase suggest that two doses of acellular vaccine after two years protects to the same degree as three doses of whole-cell vaccine.

Dr Paul Fine was very cautious in stating the efficacy of whole-cell vaccines. He has suggested that these vaccines "shift the entire spectrum of response towards milder and subclinical forms".[4]

If a direct comparison with whole-cell vaccine is required before accellular vaccines can be licensed, a controlled clinical trial of a whole-cell vaccine and one or more acellular vaccines is needed. The protective efficacy should be estimated according to prior established strict case definitions and based on uniform case ascertainment. Such a study would involve a much larger cohort than ours, and it may be difficult to organise such a large study with acceptable quality. Alternatively, consensus could be sought about the degree of protective efficacy required, under well defined conditions, to permit licensure of a vaccine.

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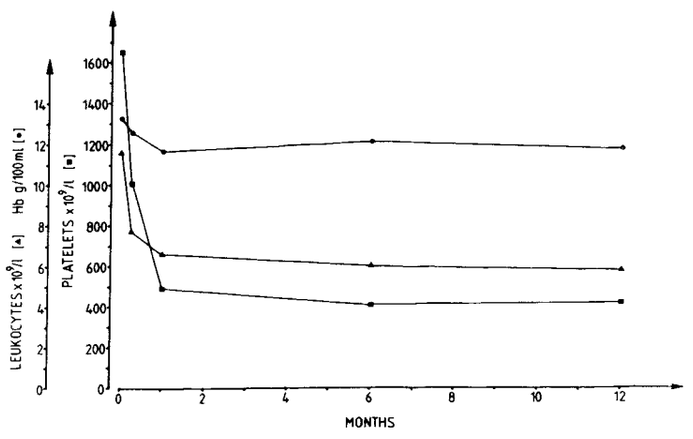
TREATMENT OF ESSENTIAL THROMBOCYTHAEMIA WITH INTERFERON ALPHA-2b

SIR,—Giles et al[1] have reported success with interferon alpha-2a or alpha-2b treatment in essential thrombocythaemia. In our hospital nine patients aged 14–72 years (median 39) with essential thrombocythaemia, diagnosed on the criteria of the Polycythaemia Vera Study Group, have been treated with interferon alpha-2b. No patient had previously been given any specific treatment but splenic vein thrombosis had necessitated splenectomy in two, one of whom had also had partial resection of the small intestine due to thrombosis of the mesenteric vein. In another patient portal vein obstruction with oesophageal varices was a complication of disease. One patient had had a stroke and another had severe Raynaud's phenomenon. Four patients had no disease-related symptoms before interferon therapy. Initial platelet counts were 900–2430 $\times 10^9$/l (median 1650).

Induction therapy consisted of subcutaneous interferon alpha-2b 4×10^6 U/m^2 daily. In all patients platelet counts fell to normal in 3–12 months (median 4) (figure). After that, patients were put on maintenance therapy at between 2 and 6×10^6 U daily (median 3·5) sufficient to keep the platelet count normal. In 1–26 months (median 15) of follow-up the control of malignant thrombocytopoiesis continues to be effective in all but one patient. After 15 months of interferon alpha treatment, this patient was put on combination therapy with interferon alpha-2b (5×10^6 U daily) and interferon gamma (50 μg daily). His platelet count subsequently returned to normal.



Platelet and leucocyte counts and haemoglobin levels during treatment with interferon alpha-2b.

The main side-effects were influenza-like symptoms, which disappeared after 1–4 weeks, and weight loss. Neither white blood cell counts nor haemoglobin levels fell significantly and disease-related thrombosis and bleeding were not observed.

Like Giles et al we conclude that interferon alpha-2b is effective in essential thrombocythaemia and has few side-effects.

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NON-INVASIVE SAMPLING METHOD FOR DETECTING CHLAMYDIA TRACHOMATIS

SIR,—We confirm the finding of Dr Caul and colleagues (Nov 26, p 1246) and agree that screening urine samples for *Chlamydia trachomatis* by an amplified ELISA ('IDEIA', Boots Celltech) may prove helpful in the diagnosis of genital tract infection. However, unlike Caul and colleagues, we compared urine ELISA cell culture with the "gold standard" of urethral cell culture.[1]

We divided 631 unselected males attending a genitourinary clinic into two groups. In the first group (n = 422) a first-catch urine was collected before the urethral swab. The swab cell culture isolation rate was 16·1% compared with 12·3% by urine ELISA. In the second group (n = 209), where swabs were taken before urine collection, the results were 21·5% and 15·8%, respectively. The number of *C trachomatis* infections that could have been detected by urine ELISA was 76·5% when the urine was taken first and 73·3% when collected after swabbing. Although our detection rate by urine ELISA was not as high as that of Caul et al, we consider that the sensitivity of the test could probably be further enhanced if first-pass urines were always collected before any swabs, and increased still further if early morning urine was collected and examined on the same day.[2]

We are now investigating the link between sterile pyuria and *C trachomatis* infections by amplified ELISA. Early results suggest that as many as 19% of 75 sterile pyuria patients have *C trachomatis* infections. The use of urine for the detection of *C trachomatis* has been criticised as being too insensitive.[3,4] What we and Caul and colleagues have demonstrated is that this method of sampling now warrants reconsideration.

We thank Dr J. Clay for permission to study her patients.

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SIR,—We share Dr Caul and colleagues' concern that asymptomatic *Chlamydia trachomatis* infection in the urethra in males is often missed. A simple, non-invasive test (eg, on urine) would be welcome. However, we do not find screening urine for leucocyte esterase activity a satisfactory alternative to the present methods of direct identification of *C trachomatis*.

We have evaluated leucocyte esterase dipsticks ('Nephur Test + Leuco' [A] and 'Cytur Test' [B]; Boehringer Mannheim) in a genitourinary clinic where facilities for testing all male patients for *C trachomatis* are not available. 159 consecutive new attenders were