The 'delayed infection' (aka 'hygiene') hypothesis for childhood leukaemia

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Abstract

The common variant of childhood acute lymphoblastic leukaemia (cALL) is the most frequent paediatric cancer subtype. Its incidence rate appears to have increased substantially in Western societies during the mid-20th century and continues to increase at ~1%/year. Worldwide cALL appears to track with affluence of societies. The 'delayed infection' hypothesis, first formulated in 1988, parallels the hygiene hypothesis and has an evolutionary foundation in the concept of a mismatch between prior genetic selection and programming (of the immune system) and contemporary social circumstances. In essence, the hypothesis predicts that ALL is triggered by an abnormal immune response to one or more common microbial infections and that the abnormality arises for two reasons: (i) infectious exposures being delayed beyond the immunologically anticipated period of infancy; (ii) some degree of inherited genetic susceptibility *via*, for example, allelic variation in genes involved in the MHC and/or immune response network. The hypothesis also has a framework in the underlying cell and molecular biology of ALL and its natural history. Epidemiological studies of social contacts in infancy (as a proxy for common infections) and risk of ALL provide indirect but strong support for the hypothesis. The idea still requires mechanistic and genetic endorsement and the appropriate studies are in progress.

Background: childhood leukaemia descriptive epidemiology

Leukaemia, in common with all cancers, develops *via* sequential mutation and clonal selection. The end product, in the absence of early and effective intervention, is a weed-like sub-species of cell that hijacks tissue ecosystems with lethal impact. This process is Darwinian natural selection in action – at the level of somatic cells [1].

Paediatric acute leukaemia comprises a group of distinctive cancers differing in cellular origins, phenotypes, genetic abnormalities and clinical response (Tab. 1). The most frequent or common (c) subtype is B cell precursor acute lymphoblastic leukaemia (cALL) which has a very distinctive age incidence peak at 2–5 years [2]. The overall annual incidence of ALL in USA, Europe, Australia/New Zealand

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Table 1 - Biological subtypes of blood cell cancer in children

A. Acute leukaemia		
1. Acute lymphoblastic leukaemia (ALL) ~80%[1]		
- B cell precursor/common	(80%)[2]	(2–5 yr peak)[3]
- T cell precursor	(15%)[2]	(2-15 yr)
- pro-B/monocyte precursor	(5%)[2]	(infants, <18 mths)
2. Acute myeloblastic leukaemia (AML) ~20%[1] (subtypes)		
B. Non-Hodgkin's lymphoma (subtypes)		

[1]as percentage of total ALL.
[2]as percentage of total acute leukaemias.
[3]This subtype (and others) are heterogeneous in terms of underlying chromosomal and mutational drivers of cancer. For cALL for example, ~25% share a chimaeric fusion gene ETV6-RUNX1 (also known as TEL-AML1), ~35% a hyperdiploid karyotype and the remainder have diverse, less common genetic lesions. Most (~85%) infant ALL (pro-B/monocyte) have chimaeric gene fusions involving the important developmental gene MLL. T-ALL have a wide diversity of genetic alterations though many are chromosome translocations involving T cell receptors (γ,β).
Other very rare subtypes exist, e.g., juvenile chronic myelomonocytic leukaemia, acute mixed (lympho/myeloid) lineage.

and Japan is in the range of 25–45 cases/10^6 equating to a risk (0–15 years) of ~1 in 2000 [3]. Epidemiological studies and cancer registry data suggest that the age peak of ALL at 2–5 years has an interesting history and geography distinct from other subtypes of childhood leukaemia. In the USA (whites) and UK, the peak first appeared during the period 1920–1940, later in Japan and in US blacks (1960s) and later still in China (1970s) [2]. On a worldwide basis, and where reliable registration data is available, the disease appears to track with affluence. In this respect, it parallels childhood Type 1 diabetes and allergies; indeed international incidence rates of ALL and Type 1 diabetes are significantly correlated, hinting at shared risk factors [4]. Currently in the UK, Scandinavia and USA, cALL is increasing at ~1% per year [5].

Clinicians treating childhood leukaemia in the first half of the 20th century favoured an infectious aetiology, primarily because of the correspondence of diagnosis in time with common childhood infections such as measles. However leukaemia was clearly not itself contagious and no evidence was available to support

the contention. Some favoured an anonymous but specific virus, others an indirect mechanism that comes close to the hypothesis discussed in this chapter.

> "*We incline on our evidence to the belief that the solution of the problem of leukaemia lies rather in some peculiar reaction to infection than in the existence of some specific infective agent.*"
>
> J Poynton, H Thursfield and D Paterson,
> Great Ormond Street Hospital for Sick Children, London, 1922 [6]

As epidemiological science became established (after the 1950s), numerous relatively small-scale studies have, over several decades, sought to implicate many different types of environmental exposure (Tab. 2). The only unambiguous observation derives from the 1945 atomic bomb exposure which was associated with a significant increase in ALL [7]. Ionising radiation is therefore a cause of childhood ALL but it is unlikely to be *the*, or a, major causal factor. The problems with prior case/control epidemiological studies were compounded: under-powering, lack of appropriate control group selection, no distinction drawn between subtypes of leukaemia that might have distinctive aetiologies and prevailing ignorance of the

Table 2 - Postulated causal exposures

- Car exhaust fumes
- Pesticides
- Ionising radiation
- Non-ionising radiation
- Electric fields
- Vitamin K injection at birth
- Hot dogs or hamburgers (depending on whether the consumer (patient) was in California or Colorado)
- Domestic animals
- Organic dust from cotton, wool or synthetic fibres
- Natural light deprivation through melatonin disruption
- Artificial, fluorescent light exposure in hospital neonatal care units
- Parental cigarette smoking
- Maternal medicinal drug taking (during pregnancy)
- Maternal alcohol consumption (during pregnancy)
- Chemical contamination in drinking water
- Infections

natural history of the disease and therefore likely timing of key exposures. The only other established risk factors for childhood leukaemia are rare: inheritance of predisposing mutations (e.g., for Fanconi's anaemia or Bloom's syndrome), Down's syndrome or genotoxic therapy – collectively amounting for no more than 5% of cases [8]. The major causal mechanisms and exposures in ALL have therefore remained unidentified.

A biological framework for the natural history of childhood ALL

We have taken the stance that unravelling the aetiological, causal mechanisms for childhood leukaemia would benefit from taking into account the biological heterogeneity of disease and a clearer understanding of its natural (preclinical) history. We therefore focussed on identifying and validating the distinctive biological subtypes of ALL [2] and, subsequently, in identifying the timing of key events in the natural history of the major subtype of childhood leukaemia – cALL. Figure 1 illustrates the current picture we have of the sequential events that drive the clinical emergence of cALL, their developmental timing and incidence or probability rates (reviewed in [9, 10]). Reassuringly, the data endorses an entirely speculative 'two hit' model for cALL that we proposed in 1988 [11]. The key observations are:

1. cALL is usually initiated *in utero via* chromosome translocation or hyperdiploidy. These events generate a clinically silent and persistent (→ 15 years) preleukaemic clone which requires additional genetic abnormalities to convert to overt, clinically diagnosable ALL. This 'two hit' principle is endorsed by modelling with murine [12] and human cells [13].
2. The initiation of ALL prenatally occurs some 100× the frequency of the disease itself [14].
3. Common or recurrent genetic abnormalities involving gene (or region) copy number variation (CNV) or sequence mutation are identifiable in ALL samples [15]. CNV are postnatal in origin and are critical or essential 'secondary' mutations [16].
4. It is suggested (but currently unproven) that the 2–4 secondary CNV/mutations in ALL occur as a bolus or suite proximal to diagnosis (~a few months prior) and may promote or trigger clonal evolution leading to rapid proliferative exposures, marrow failure and diagnosis of ALL.

This model immediately identifies some previously entirely cryptic causal complexities: (i) two distinctive, developmental stages of mutation and clonal selection and therefore two potential windows of exposure; and (ii) rare disease prevalence is associated with relatively common initiation but low penetrance. This suggests a key bottleneck in the development of ALL is the postnatal trigger of secondary mutations [17].

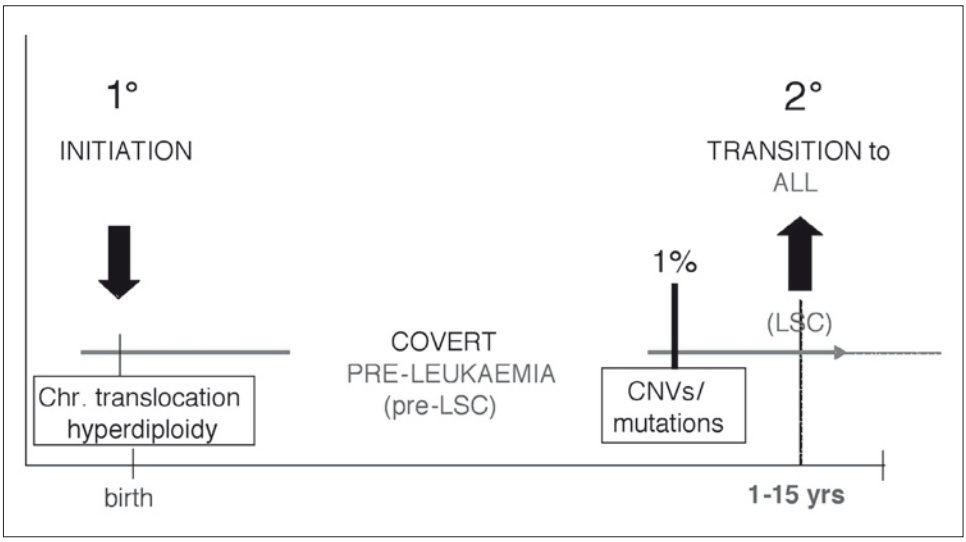

Figure 1
Natural history of paediatric acute leukaemias. Chr, chromosome; LSC, leukaemic stem cell; ALL, acute lymphoblastic leukaemia; CNVs, gene copy number variations.

The 'delayed infection' hypothesis for cALL

In the context of the two-hit, pre-/postnatal hypothesis, an entirely speculative explanation was proffered for the aetiology of ALL [11, 17]. It was suggested that the first hit, *in utero*, was largely independent of exogenous genotoxic exposure and a consequence of endogeneous, developmental stress during foetal lymphopoiesis, i.e., spontaneous mutation reflecting intrinsically accident-prone systems of DNA and cellular maintenance. Such a level of mistake could be tolerated in an evolutionary context if they only very rarely led to lethal disease outcomes. The second hit was proposed to have external origins in the form of common infections. Specifically, it was suggested that a deficit of common infections in infancy, followed by subsequent 'delayed' infection would provide, *via* immune system deregulation, the proliferative stress to the bone marrow that could trigger the critical secondary mutation. The logic of this explanation is entirely Darwinian (Box 1). George Williams' memorable phrase "*evolution has no eyes to the future*" aptly captures the problem. If environmental or, for humans, social circumstances rapidly change, then prior genetic programming which was contingent upon prevailing selective pressure, becomes mismatched with the new circumstances. There are several examples of this in medicine [18], and especially for cancer [19]. For childhood leukaemia, the evolutionary context is the organisation of the immune system. The 'delayed infec-

The 'delayed infection' hypothesis –
A genetic adaptation – lifestyle mismatch?

- **Evolutionary adaptation**
  1. The immune system has been evolutionarily *programmed* to anticipate infectious challenge after birth
  2. The neonatal immune network is not hardwired and *requires* modulation by infectious exposure
  3. Human genetic variants in immune response genes (strength of signal)
     - adaptive selection by past plagues / epidemics
- **The mismatched lifestyle/cultural factors**
  Affluent societies / families provide greatly reduced opportunities for 'natural' infectious exposure in infancy (- reduced family size, hygiene measures).
- **The consequences of mismatch:**
  1. Unprimed immune systems in infancy
  2. Later (inevitable) childhood infections precipitate highly dysregulated immune responses
  3. Proliferative / apoptotic stress to bone marrow
     - selection of pre-leukaemic stem cells?
- **Definition of those at risk:**
  1. Those with pre-existing pre-leukaemia (foetal) clone
     - developmental accident / imperfect fidelity of DNA maintenance/repair?
  2. Those with minimal infectious exposure in infancy
     - social circumstances?
  3. Those who have particular immune response gene alleles
     - historical contingency / adaptive selection?

Box 1

tion' hypothesis was proposed independently of Strachan's 'hygiene hypothesis' for childhood allergies [20] but clearly they are very similar.

Epidemiological testing

The 'delayed infection' hypothesis has not been easy to test by epidemiological methods. If one specific transforming virus, like, say, EBV or HTLV1 [21], had been

involved, this would have changed matters. Extensive screening for viral footprints by all available PCR-based methods have failed to identify such a culprit [17]. In the absence of such evidence, the hypothesis has remained that the infectious trigger is one or, more probably, several common infections (bacterial and/or viral). In this situation, the appropriate tactic has to be to resort to reliable proxies of infectious exposure. A UK nationwide case/control study of childhood leukaemia was designed (around 1990-1992) to look at this aspect – alongside several other candidate exposures including natural ionising radiation and electromagnetic fields (EMF) and electric fields [22]. The UK Childhood Cancer Study (UKCCS) found no evidence for the latter exposures contributing anything other than a very small fraction of causal exposures [23, 24]. Our principle test or prediction of the 'delayed infection' hypothesis was that social interactions at playgroups in infancy should be protective. And it was (Tab. 3) [25]. The study has been replicated in California [26] and Scandinavia [27] with essentially the same positive association with lowered risk of ALL. The UKCCS, and particularly the California study [26], provided evidence for a significant trend or dose response with greater social contact levels providing more risk reduction. Playgroup or day care attendance (and levels or number of contacts) is a well established proxy for exposure to common infections that spread by person-person contact [28] and it is difficult to draw any conclusion from these data other than early infectious exposure is protective for ALL.

Two other subsidiary predictions were also made. It was anticipated that risk might be modified by birth order/parity and by early exposure to known or specific infections. Studies of these two parameters have produced mixed or conflicting results [29]. Two recent reports indicate that GP records of infections in infancy may tell a different story than parental recall as used in most case/control questionnaires [30, 31]. While this may be true, the failure of infection history as documented in GP records in these studies to reflect any protective impact [30, 31] does not necessarily negate the hypothesis. The authors correctly concluded that the GP record stud-

Table 3 - Social contact in first year of life and risk of acute lymphoblastic leukaemia [25]

Cases **Controls**	**# 1277** **6268**	**OR (CI)**
None		1.00
Social activity but no day care		0.73 (0.62–0.87)
Informal day care		0.62 (0.51–0.75)
Formal day care		0.48 (0.37–0.62)
	p for trend = <0.001	

OR (CI): odds ratios (95% confidence intervals).

ies provided no evidence for the hypothesis. The problem with these studies is the unstated, underlying premise: that protective impact of infectious exposure in infancy is necessarily reflected in symptoms prompting a visit to GPs [32]. Clearly, many infections are asymptomatic or sub-clinical. In the context of the parallel 'hygiene hypothesis' for allergies, G Rook suggests *via* the 'old friends' variant hypothesis that the critical infectious exposure might well be innocuous, symbiont species.

Validation

Although case/control studies of ALL assessing the infectious hypothesis are ongoing, they may contribute little more. Validation may rest more on genetics and mechanistic insights. If the hypothesis is correct, then it is likely that inherited genetic variation should impact on risk and we would anticipate or predict that relevant genes should include some that encode products integral to immune network regulation, e.g., HLA or key regulators such as IL-12, IL-10, TGF-β, etc. There is some evidence for this (in the UKCCS) *via* association with particular HLA-DP alleles, particular alleles either decreasing or increasing risk [33]. Small-scale pilot genetic screening implicated IL-12 [34] but such studies are known to be generally faulty. We have therefore embarked on a genome-wide (SNP) association study (GWAS) in the UK involving some 900 cases (and similar number of controls from the Wellcome Consortium Study). Similar (though usually larger) GWAS for adult cancer have proven very productive though the picture they paint of genetic susceptibility is complex [35, 36].

Endorsement of the model also requires some mechanistic insight into how an abnormal or dysregulated immune response might help promote transition of pre-leukaemic to leukaemic stem cells (Fig. 1) *via* the acquisition of further genetic lesions. A lead here comes from screening candidate cytokine molecules that are known to be key immuno-modulatory components of the regulatory T

Table 4 - Model systems for exploring the molecular pathogenesis of childhood ALL initiated by ETV6-RUNX1 gene fusion

		Reference
1.	Hormone inducible ETV6-RUNX1 in a murine cell line (BaF3) *in vitro*	[37]
2.	Transgenic mice expressing human ETV6-RUNX1 selectivity in the B cell lineage under the control of the IGH enhancer mouse stem cells or human cord blood	[37]
3.	Mice repopulated with murine or human stem cells retrovirally infected with ETV6-RUNX1 fusion gene construct	[12, 13]

cell network. We first developed three model systems with either murine or human progenitor cells transfected to express the leukaemia initiating fusion gene ETV6-RUNX1 (Tab. 4). Screening of several candidate molecules – γ-interferon, TNF and TGF-β in each of these models revealed that the response to one of them – TGF-β, was strikingly altered by expression of the leukaemia gene [37]. B progenitor cells induced to express ETV6-RUNX1 proliferate more slowly than normal. TGF-β is a potent suppressor of proliferation in haemopoietic stem cells and progenitors. In normal B cell progenitors, this is signalled *via* SMAD3 activation and downstream transcriptional activation of the cell cycle inhibitor p27. In the presence of ETV6-RUNX1 protein, this response is blocked. ETV6-RUNX1 binds to SMAD3 and recruits transcriptional co-repressor molecules NCoR and Sin3A; SMAD complexes are then unable to activate the p27 promoter. The consequence of this is that normal progenitors cease dividing but the cells expressing ETV6-RUNX1 continues to divide. The selective effect appears to be most pronounced for modelled human (cord blood) pre-leukaemic stem cells that preferentially expand at the expense of normal B progenitors. This altered response to TGF-β therefore provides a possible route *via* which the relatively small size pre-leukaemic clone in patients (10^{-3}–10^{-4} of blood lymphoid cells) could expand both in bone marrow niches and in blood (Fig. 2). Increase in numbers of these cells by one or more orders of magnitude is a

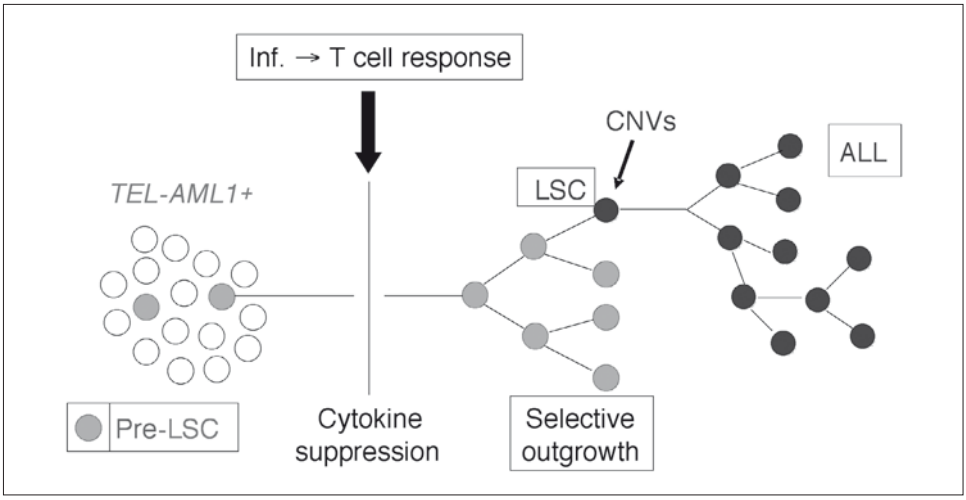

Figure 2
Infection, the immune response and 'selection' of pre-leukaemic clones
LSC, leukaemic stem cell; CNV, gene copy number variations (mostly deletions); TEL-AML1 (aka ETV6-RUNX1) gene fusion resulting from chromosome translocation; A common (pre-natal) initiating event in childhood ALL. Inf, common (but delayed) infection.

prerequisite for the acquisition of additional mutations (in the absence of facilitation by genetic instability). How the mutations might actively be induced *via* immune response-derived TGF-β is unclear. It is unlikely to be simply stochastic. Oxidative damage *via* free radicals in the context of a persistent inflammatory response is a possibility, as in the activation of intrinsic mutagenic enzymes in B cell progenitors – RAG1/2 or AID [38, 39]. Further *in vivo* mouse and human cell (in NOD/SCID) modelling may further endorse the involvement of these signalling pathways in the infection-driven pathogenesis of ALL.

'Natural' experiments

Alongside continued modelling experiments, further support for the aetiological model might come from 'experiments of nature' in which changes of social circumstances appear to be followed by changes in the incidence rates of ALL. Three socio-political changes during the latter half of the 20th century fit with this expectation. Costa Rica has a very modest GDP; it is not a wealthy country. Yet it is top of the league in childhood leukaemia rates at ~55/10^6/year, contradicting the general association between affluence and incidence [3]. Why might this be? Costa Rica is a unique Central American country. In the 1970s, the radical political decision was made to abandon the military and divert resources into education and medicine. Literacy rates are now higher than the USA and medical care is excellent. Over a 20 year period, parity dropped from around seven children per family to around 2.5 on average. One interpretation therefore is that these rapidly changing social circumstances significantly reduced the opportunities to natural infectious exposures in infancy.

East Germany statistics on the incidence of childhood ALL may be especially informative. Prior to 1989, the reliable data indicated a rate of ALL some one third below that of West Germany. In the period after reunification of Germany, 1992–1996, the incidence rate of ALL increased dramatically by 25% [40]. If we assume that case ascertainment did not change (which the authors of the report appear confidently assert), then clearly something 'environmental' had changed abruptly to alter the risk of ALL. The authors suggest the most plausible explanation was the dramatic change in child care that followed the collapse of the Berlin wall and the old East German communist regime in 1989. Prior to this date, effectively all 3 months plus infants attended large state-run crèches, in order that their mothers could return to work. This ceased almost immediately after 1989 with infants and toddlers being kept at home. In the context of the 'delayed infection' (or 'hygiene') hypothesis, this is precisely a circumstance that should change (increase) incidence rates of ALL.

The SARS incident in Hong Kong in 2003 provides another very unusual circumstance and 'natural experiment'. An emergency and province-wide gov-

ernment directive ensured that all children stayed at home rather than travelling to attend school. This embargo lasted for one year. So which prediction follows from this with respect to the 'delayed infection' model? This cohort of children with greatly reduced infectious exposure (confirmed by documenting levels of measles, chicken pox and scarlet fever) should immediately be deprived of the 'triggering' infection for ALL and rates for ALL should drop in that same year. A significant drop did indeed occur which the authors interpreted in the light of the 'delayed infection' hypothesis [41]. Another prediction however is that individuals who were infants (< 12 months) during that year should, paradoxically, have an increased risk of ALL some 3–5 years later. The data for this are not yet available.

Other infection-based hypotheses

One other infection hypothesis for childhood leukaemia has achieved significant support. This is the 'population mixing' idea of Leo Kinlen [42]. Based initially on a consideration of a cluster of cases in proximity to the nuclear reprocessing plant near Seascale village, Cumbria, United Kingdom, Kinlen's subsequent studies elsewhere in the UK consistently showed that where a sudden influx of migrant workers (engineers for the Seascale plant or, elsewhere, oil industry workers or army recruits) or rapid increases in population (rural 'new towns'), this was followed a few years later by a transient increase (av. ~two fold) in leukaemia rates (though often documented as leukaemia deaths rather from incidence rates). Some other supportive data from independent studies have been provided including our own from the Hong Kong new territories [43]. Kinlen's favoured explanation is that based on herd immunity [42]; namely that in the setting of rapid population mixing, one population infected with a 'leukaemia virus' could infect previously unexposed and non-immune individuals.

Historically, the first marked cluster of cases of ALL was in Niles, a suburb of Chicago in 1967 in which most cases attended the same school or church [44]. This transient increase in ALL coincided with an episode of streptococcal/rheumatic fever. The latest cluster, and the most marked one to date, is in the small town of Fallon, Nevada, USA, which happens to be very close to a 'top gun' naval air base. Conspiracy theories abound including that leakage of very carcinogenic jet fuel is to blame [17]. Of the 13 cases of ALL (and only one case of AML), where only ~1 was expected, most were actually born outside the area which immediately suggests that whatever environmental event has occurred, its impact on leukaemia risk was postnatal – and therefore likely in the secondary, promotional phase [17]. An abnormal response to infection is the most plausible, but unprovable, explanation. The increase of cases was during 1999–2003 and no new cases have occurred subsequently [45].

Retrospective identification of causal agents or exposures in transient clusters of leukaemia is extraordinarily difficult, if not impossible. This author's view is that the 'population mixing' and 'delayed infection' hypotheses are entirely compatible and point, jointly, to the same single explanation. Kinlen, an epidemiologist, suggests that causation involves an, as yet unidentified, transforming virus, that this applies to all forms of childhood blood cell cancer (Tab. 1), including non-Hodgkin's lymphoma, and that the critical infection may operate around the time of birth. I see no evidence to support these particular contentions despite the overall data sets providing persuasive, indirect evidence for an infectious aetiology.

Infection and other cancers

Some 15% of adult cancers worldwide involve specific infectious agents that colonise particular tissues, including DNA and RNA viruses, bacteria and parasitic worms [46]. Additionally, a large fraction of gastrointestinal cancers involve premalignant chronic inflammation, at least some of which is infection-related [47]. Infection is therefore a very significant cause of cancer, particularly in less developed countries where it accounts for some 40% of all cancer cases. Primary prophylactic trials are now in progress for some of these agents (HPV, EBV and hepatitis B/C). In the case of gastric cancer associated with *Helicobacter pylori* – and more recently other mucosal lymphomas associated with distinct bacterial species [48], antibiotic regimes have proven remarkably efficacious in resolving the tumour. More advanced or malignant gastric lymphomas are independent of bacterial/T cell drive and unresponsive to antibiotics.

In these cancers, and cancers in general, I have argued that vulnerability can be understood best from the perspective of evolutionary biology or 'Darwinian medicine' [1, 19]. Does, however, the 'delayed infection' or hygiene hypothesis apply to these cancers? I suspect not, particularly since the evidence is that risk (for Hep B/C liver cancer, EBV Burkitt's lymphoma, HTLV-1 and all T cell leukaemia/lymphoma, gastric cancer/lymphoma and *H. pylori*) is associated with early (not delayed) and chronic or persistent infection.

There is one exception, however, and that is for another blood cell cancer – Hodgkin's lymphoma (HL) in young adults (~15–40 years). Some subtypes of HL are associated with Epstein Barr virus but the majority of HL in young adults are not. The incidence trend of HD parallels childhood ALL. It is most elevated in affluent countries and there is evidence that risk may be linked to a delay or absence in exposure to common childhood infection [49]. The authors of these studies drew the analogy with polio with reference to the much earlier observation that the pathological impact of polio virus depends on social circumstances and age of exposure [50].

Prevalent diseases of children and young adults in affluent societies: the paradoxical outcome of evolutionary mismatches?

Others in this book have discussed the application of, and evidence for, the 'hygiene hypothesis' for allergies, Type 1 diabetes and multiple sclerosis. Notwithstanding that alternative explanations for the pathogenesis of these diseases and their apparent link with affluence are still tenable, there is an underlying theme in these ideas that is grounded in the evolutionary programming of the immune system.

The immune system network structure, versatility and function have been historically driven by the arms race challenge of potentially lethal infection. This has resulted in very marked allelic variation in the many genes involved in human immune systems and likely prior selection over thousands of years by endemic lethal infections and periodic plagues. Additionally, and critically as an adaptive system, much like the brain, genetic programming of the immune system at birth is not hard-wired. Rather it is set up for fine tuning by early infectious exposures, primarily *via* the agency of regulatory T cell function. It would be quite extraordinary if the otherwise very beneficial impact of depriving our infants and their naïve immune systems of this infectious educational or 'priming' experience did not come at a price.

Whether this diminished exposure in contemporary, affluent societies is *via* the respiratory, skin or gastrointestinal sites; whether it involves lessened contact with soil, domestic animals or other children; whether it involves one species of microbe (or parasitic worm) or another, the same principle may hold. It is striking that ALL, allergies and Type 1 diabetes track each other in international rates. Yet within individuals of families they do not. ALL and allergies have a reciprocal relationship in risk. There are a number of explanations for these relationships. Common risk factors (- diminished 'early' infection in affluent societies) may precipitate different pathologies dependent upon the genetic background of the individual. An allergic episode could re-set the immunological rheostat and diminish risk of ALL. Different microbes or parasites might be allied to these distinct pathologies.

If these explanations are correct and shown to be so, then the challenge is clearly for prevention. Encouraging more social contacts in the very young should be beneficial but any central or governmental edict in this direction would doubtless be seen as over-prescriptive social engineering. A more viable alternative, as actively being considered in the allergy and autoimmune fields, is prophylaxis in infancy or early life with an appropriate microbial or parasite-derived vaccine. Could a generic vaccine along these lines reduce the incidence and disease burden of all three types of disease? And if it did work out this way, would it not be the best possible endorsement of Darwinian medicine and the relevance of the evolutionary perspective on human ailments [51]?

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