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Could visible light contribute to the development of leukaemia and other cancers in children?☆

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Summary This paper suggests to rigorously test the hypothesis that there are causal links between visible light and the development of leukaemia and other cancers in children. Light can be considered as a candidate risk factor because it suppresses melatonin biosynthesis which may play a role in a series of anticancer defences. Indeed, melatonin may offer some protection against all ''hallmarks of cancer'' [i.e., self-sufficiency in growth signals; insensitivity to growth-inhibitory signals; evasion of programmed cell death (apoptosis); limitless replicative potential; sustained angiogenesis; tissue invasion and metastasis] recently suggested by Hanahan and Weinberg. Already ongoing investigations into the possible nexus of light, endocrine systems and the development of cancers will be further fueled by recent insights into photoreception and – transduction, including the discovery of ''novel'' photoreceptors in the eye. Among a variety of different photosensory tasks, these receptors constitute crucial gates for light information from the environment which is employed for the temporal organization of our physiology and it has been proposed that chronodisruption, i.e., a significant disturbance of the coordination and thus order of biological rhythms, could contribute to the development of cancers.

With regard to public health, the pervasive exposures to light – at work and in homes – imply that visible radiation could be a strong risk factor defined epidemiologically as a causal contributor to disease in a large proportion of cases. Importantly, if light were to be corroborated as a contributor to cancers in children, it would be amenable to manipulations with the perspective of reducing inherent risks significantly. In fact, it could be much easier – and much more effective – to reevaluate and modify lighting systems than to manipulate other possible determinants of the chronic processes of cancer such as genetic, nutritional or lifestyle factors.
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''[One] of the qualities of science is that it teaches the value of rational thought, as well as the freedom of thought; the positive results ... come from doubting that the lessons are all true''.

Richard Feynman, 1966 [1].

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[1] From Richard Feynman's address ''What is Science?'' to the National Science Teachers' Association in April 1966 [1].

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Cancer involves complex processes which are not understood to a large extent despite a plethora of research efforts in past decades. Clearly, we have gained insights into how cancers develop but, equally clearly, the apparent complexities suggest that we are unlikely to identify treatments for some specific cancers, let alone develop far-reaching, i.e., rather universal, means to prevent or treat cancers more generally in the near future. Most of what we know about carcinogenesis comes from studies in adults, but much of what was found there will be valid for cancer developments in children as well.

A mutation paradox

According to Darwinian rationale, when we grapple with cancer, we are looking at evolution [2]—clearly, not at its best in our short-term judgement but, equally clearly, at one of its primary keys to our — and other species' — long-term success and competitive edges: indeed, when there are no changes in genes, there will be no cancer. However, with unchanged genes, there would be no evolution and therefore, no us. Genes are the building blocks of heredity and changes of genes constitute milestones of evolution (see Fig. 1). Strictly speaking, though, from an evolutionary point of view, the correct question should not be ''why does cancer occur?'' but ''why does cancer continue to occur and stay or remain with us?''.

The problem is not just terminological. Why cancer if it impairs and kills organisms? To answer this, it is best to recall the logical scheme for which ''evolution by natural selection'' is a quick encapsulation. Evolution is clearly unintentional per se, meaning that it is not capable of anticipation and blind to its immediate consequences. Only what serves cells, organs and organisms on the long run will remain and accompany us — for at least some time. The important point to note is the following: most of us will not develop cancer. And yet, due to changes of genes this malignancy will occur in a fraction of our population as a legacy of and conditio sine qua non for evolution. If you will, we are looking at a mutation paradox here: in individuals, mutations may have adverse health effects, including extreme outcomes such as cancer, but populations as a whole do benefit on the long run from changes of genes. As a matter of fact, on an evolutionary scale, changes of genes have helped, do and will help organisms to adapt to changing environmental conditions and thus to survive and reproduce. Therefore, the clear-cut answer to a possible question, namely ''will cancer go away in a nearer future?'' is no. Tumours have been documented in dinosaurs [3] and cancers have been recorded for some thousand years in humans. Quite clearly, as long as genes change, we will witness cancer. Since these malignancies will not just go away by themselves it remains for us to better understand — at least some of — the causes which may be amenable to our manipulations in order to better intervene and possibly prevent as many cases as possible.

Causes of cancer

Cancer may be described as growth disorder or, if you will, growth chaos which involves complex processes which we still do not understand to a larger extent despite much research over many years. Statistically, cancer represents a very unlikely cascade of events which follows a mismatch of DNA alterations and DNA repair, of growth and antigrowth signals. With regard to the causes of cancer, more generally, environmental (exogenous) and genetic (endogenous) factors jointly determine the development of many cancers.

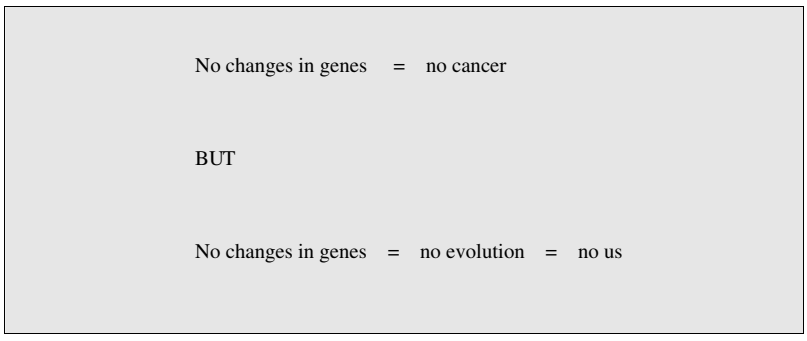

Figure 1 The ''Greaves equations''. Cancer: the evolutionary legacy [2, p. 47].

More specifically, evidence from a powerful study of some 44,000 pairs of Scandinavian twins has suggested that environmental factors contributing to newly acquired or non-inherited genetic abnormalities rather than inherited genetic factors are the dominant determinants at many anatomical cancer sites [4]. The ''environment'' therefore has a key role in the causation of the vast majority of cancers and, in principle, the identification of exogenous factors contributing to malignant diseases could promise radical prevention of cases. In addition, targeted studies of mechanistic links between particular environmental factors and cancers may yield specific means to intervene. The latter suggestions actually correspond with views held by leading scientists ranging from Doll and Peto to Greaves [2] that up to 90% of cancer cases can be attributable to ''environmental'' causes and that up to 9 of 10 cases may be preventable.

To explain the generation of childhood cancers, relatively few endogenous and exogenous factors have been identified. With regard to leukaemia, the incidence appears high in individuals with certain inherited disorders [e.g., Bloom's, Down's, Klinefelter's and Wiskott–Aldrich syndrome or Fanconi's anaemia] and with certain environmental exposures [e.g., ionizing radiation, benzene, pesticides, herbicides and chemotherapeutic agents]. For two reasons it is imperative to identify further causative factors. First, the low prevalence of suggested factors in the affected populations can not explain many cases of leukaemia and of other cancers in childhood, suggesting that these factors are not *necessary causes* [5]. Second, the relatively low incidence of leukaemia in those who have the inherited disorder, or who experience one of the suspect environmental exposures, suggests that the various endogenous and exogenous factors may be *component causes* but are not *sufficient causes*, i.e., they are not sufficient in themselves to inevitably produce the disease.

In situations like this one — we have conducted much research to understand leukaemia and other cancers in children and have reached quite a bit but not enough insight — we must challenge possibly locked-in views and ought to look for new, promising avenues. Richard Feynman has stated this succinctly in 1966 [1], implying with his words prefacing this paper that positive results come from doubting that what is thought and taught is really true. With specific regard to leukaemia and other cancers in children, it certainly is reasonable to have doubts as to whether we identified the most important risk factors yet.

Hypothesis: visible light and the development of childhood cancers

To identify further *component causes* or risk factors, evidence from laboratory studies may guide epidemiology and vice versa. With regard to the latter, epidemiological studies have consistently shown associations between low-frequency non-ionizing radiation (NIR) in the range of 50–60 Hertz (exposure levels of at least 0.4 μTesla) and childhood leukaemia (CL; pooled analyses in [6]). They have thus provided the incentive for much experimental research into possibly causal links between this range of exposures and leukaemia [7]. Hitherto, these studies could not elucidate mechanisms to explain the epidemiological observations but many scientists feel that this potential lead has not been convincingly falsified either. Indeed, failure to identify a mechanism thus far does not negate the suggestion that a mechanism must exist to explain the epidemiological observations.

A particular research focus in coming years will be visible light. Indeed, the recent discovery of ''novel'' photoreceptors in the eye (for a review see [8,9]) which mediate a host of non-image-forming responses to ambient light, including the temporal organisation of our physiology, can be expected to inject increased interest and resources into ongoing research on a possible nexus of light, endocrine systems with melatonin as a key biologic intermediary, and the development of cancers. To possibly illustrate these expectations, please consider the following (see Fig. 2): rods and cones as our gates for vision have been noted as early as in 1684 and, in the following centuries, scientists from many disciplines investigated the secrets of colour, vision and light. Finally, in 1967, the Nobel Prize was awarded to Drs. Granit, Hartline and Wald as they were able to show how the pattern of this radiation with respect to frequency and intensity determines our awareness of the play of light in nature, of the multiplicity of forms and of the richness of colours. What researchers into photoreception and phototransduction are about to elucidate in these years can become a similar milestone: the discovery of the ''novel'' photoreceptors in our eyes has already been judged as a scientific breakthrough [9]. Indeed, these receptors and the dependent downstream cyclic events can be very important for health and disease in man [10], including the *protection against* or *susceptibility to cancers* — in children and in adults [11].

1684	rods and cones are observed	late 1990s	"novel" non-rod, non-cone photoreceptors in the eyes are discovered
thereafter	scientists from many disciplines investigate the secrets of colour, vision and light	thereafter	scientists study how "novel" receptors may play a key role for non-image forming processes, including the temporal organization of our physiology
1967	Nobel Prize to Granit, Hartline and Wald for their elucidation of the primary physiological and chemical visual processes	today ….	it can be expected that the "novel" photoreceptors and the dependent downstrea m cyclic events can affect the protection against or susceptibility to cancers – in children and in adults

Figure 2 One short history of our long-lasting interest in ''light''.

Testing the hypothesis

In principle, one would now want to rigorously test the hypotheses that visible light and/or low-frequency non-ionizing radiation contribute to the development of leukaemia and/or other cancers in children. Specific questions include whether and, if so, how one (or more) NIR exposure(s) and genetic constituents interact and thus cause the development of these childhood cancers. In theory, the recent suggestion of ''hallmarks of cancer'' [12] may provide research angles to do that systematically [13,14]. In practice, we would have to identify which of six common denominators ''shared by most and perhaps all types of human cancer'' [12, p. 57], in terms of defences against uncontrolled cell growth and distribution could be impaired by NIR, and thus lead to the diseases of interest here.

Principles

Hanahan and Weinberg [12, p. 57] have suggested that ''a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells''. According to them, anticancer defence mechanisms fail so that cells acquire some or all of the following six capabilities:

(i) self-sufficiency in growth signals,
(ii) insensitivity to growth-inhibitory signals,
(iii) evasion of programmed cell death (apoptosis),
(iv) limitless replicative potential,
(v) sustained angiogenesis
(vi) and tissue invasion and metastasis.

With regard to CL it appears already clear that several of these hallmarks, namely (i), (ii), (iii) and (iv) can be acquired by genetic changes, so that cell proliferation, cell differentiation and physiological cell death via apoptosis are affected [15]. While hallmarks (v) and (vi) are not applicable to the development of childhood leukaemia, they certainly are relevant for most other childhood cancers. The key questions will therefore include: which NIR exposure(s) could affect one or more

of these anticancer mechanisms? In other words [13], does non-ionizing radiation contribute to changes of cells so that they (i) provide growth signals on their own? (ii) ignore growth-inhibitory signals? (iii) avoid apoptosis? (iv) replicate without limit? (v) sustain angiogenesis? and (vi) spread by invasion and metastasis?

Of the distinct spectra of non-ionizing radiation, light is an important risk factor candidate because it could influence the ''hallmarks of cancer'' significantly. Indeed, light entering the eyes, powerfully controls circadian and neuroendocrine systems via our master biological clock, i.e., the suprachiasmatic nuclei at the base of our brain. Melatonin is a key biologic intermediary in the regulatory circuits of circadian organization. Its synthesis in the pineal gland in the centre of the brain is suppressed by visible radiation in a dose-dependent fashion [16]. With specific regard to the anticancer defence mechanisms, there is experimental evidence that melatonin may play an important role in all of them. Indeed, there is some indication that melatonin may affect proliferation processes (''hallmarks of cancer'' (i), (ii) and (iv): [17,18]), apoptosis ((iii): [19–21]), angiogenesis ((v): [22]) and invasive and metastatic cell properties ((vi): [18,23]).

Conceptually, the ''hallmarks of cancer'' have provided us with a more universal, rather than reductionist (i.e., focus on single cells and the genes within) approach. Cancers are regarded as complex tissues which are determined by a series of disrupted regulatory circuits [12] which, in effect, yields growth disorder or chaos. A further – related – conceptualization of carcinogenesis suggests that the coordinated interplay of biological rhythms could be important for protection against cancers in general and against childhood cancer in particular. That relevant disturbances of the timing of biological rhythms can lead to chronic processes and adverse health effects was authoritatively suggested in 1960 [2] and today it is conceivable that chronodisruption, i.e., a significant disturbance of the coordination and thus order of biological rhythms and effects – including the gene levels in individual cells – could contribute to the development of cancers [11]. With regard to cancer developments in children, the timing of biological rhythms, i.e., a physiologically determined sequence of cyclic events, could be disrupted (a) in either one or both parents before conception and/or (b) in the mother during pregnancy and/or (c) in the child in utero and after birth. Most recent publications lend support to possible links between disruptions of circadian rhythms and the development of malignant tumours in animals (the disruption of circadian rhythms in mice was associated with significantly accelerated growth of malignant tumours of two types [25]) and in humans (for a review see [26]). Moreover, it has been reported in September 2004, ''for the first time'', that constant exposures to light were followed by increases of the incidence of leukaemias in mice [27]. Our understanding of light's critical role for chronobiology is still emerging and further research will be fueled by the aforementioned discovery of ''novel'' retinal photoreceptors. That melatonin plays a key role in chronobiology is beyond debate and it even has been suggested that it ''is the only known chronobiotic, hormonal regulator of neoplastic cell growth'' [18].

In summary, a series of studies have directly examined possible relationships between melatonin and ''hallmarks of cancer''. Since melatonin is uniquely synthesized in response to ambient light exposures [28], we are also looking at indirect circumstantial evidence for biologically plausible links between light and these anticancer defences. The objective must be to identify further investigations that are warranted to add to the picture. In addition, other non-ionizing radiation emanating from electric power and any other biologic intermediary linked to such radiation should be examined systematically from the perspective of affecting the ''hallmarks of cancer''.

Pitfalls

The high prevalence of non-ionizing radiation – children and adults are exposed almost everywhere – may imply that if one or more spectra affect the development of cancers, NIR could be a ''strong'' risk factor in public health terms. The assumption that more than one spectrum may affect carcinogenesis would of course have profound implications for NIR research. In fact, unless investigations – be they epidemiological or experimental studies – control for all possibly relevant spectra, results may disallow appropriate interpretation. This dilemma applies already to NIR research. In the past 15 years, the so-called melatonin hypothesis (that excess exposure to environmental light and/or extremely low frequency electric and magnetic fields (ELF–EMF) may disrupt the function of the pineal gland and thus increase breast cancer risks [29]) has stimulated numerous experimental and epide-

[2] ''... circadian systems are inherent in and pervade the living system to an extent that they are fundamental features of its organization; and to an extent that if deranged they impair it. [24, p. 159].

miological studies. And yet, studies which relied on exposure assessments of low frequency EMF alone, ignoring the — probably important — exposures to light, may not be sensibly interpretable [30]. In fact, we may be unable to detect effects in experiments, and measure increased risks in observational studies, due to other spectra of NIR as long as we do not control for the possibly ''strong'' risk factor light. To illustrate this crucial point with a provocative analogy: we would be likely to miss possible effects of most known lung carcinogens if we do not control for smoking in study individuals.

Perspectives

Children develop cancer in general and childhood leukaemia in particular in much less time than it appears to take in adults for whom we often expect decades of development rather than the relatively few years in children. In fact, Hanahan and Weinberg [12] attributed the fact that cancer is still a rare event during an average human lifetime to the very multiplicity of defences. Weinberg therefore speculates that childhood cancers may require less ''hits'' than adult cancers (personal communication, 2004) and Greaves [2, p. 65] suggested ''that many cancers of early childhood require ... say only two ... genetic changes ...'' Nevertheless, the crucial questions remain: what hit(s) is (are) required to generate childhood cancers, including CL? And what — exogenous and/or endogenous — factors may cause these hits? With regard to exogenous factors it is important to bear in mind that environmental factors do not only appear to play a dominant role in carcinogenesis [4]; they also could be amenable to manipulation so that cancer risks be reduced.

In public health terms, it is common to think that some causes of disease are more important than others. This concept may be expressed by the strength of a causal effect. For epidemiologists, a strong cause can be defined as a causal contributor to disease in a large proportion of cases. Accordingly, a weak cause can be defined as a causal contributor to disease in a small proportion of cases. The strength of any given cause depends then, by necessity, on the prevalence of all causal factors that produce the disease [5,31]. Given these premises, for childhood cancer in general and CL in particular, we have identified only ''weak'' risk factors, viz few genetic disorders and some environmental exposures with low prevalences. The pervasive exposures to NIR in general and to light in particular, at work and in homes, could imply that one (or more) NIR risk factor(s) for cancer is (are) ''strong''. In this vein, from the public health point of view, light may be important for the development of cancers because the ubiquitous nature of visible radiation implies the possibility that even low risks could affect many individuals and thus contribute to a substantial proportion of the total population burden.

Moreover, the multifactorial complexities of carcinogenesis suggest that possible interactions between several components, including genes and environmental factors, may be critical. Without doubt, genetic research can and will be a key tool to understand mechanistic links. A convincing example to support this view is provided by research into photoreception and phototransduction of these days because much of our novel understanding of the adjustment of biological rhythms to light comes from an elegant series of studies with genetically engineered mice. And yet, *genetic manipulations* are unlikely to contribute to improvements of public health. To illustrate this crucial second — for at least some provocative — view please note the following example provided by the late David Horrobin in 2003:

> ''those familiar with medical research funding know the campaigns waged in the 70s and 80s by scientists hunting the genes for such diseases as cystic fibrosis. Give us the money, we'll find the gene and then your problems will be solved, was the message. The money was found, the genes were found — and then came nothing but a stunned contemplation of the complexity of the problem, which many clinicians had understood all along''.
>
> David Horrobin, 2003 [32].

With regard to the prevention of leukaemia and other cancers in children, it therefore seems much more unlikely in the nearer future to identify and manipulate relevant genes than to identify one or more environmental factors and then find ways to protect against effective doses via their inhalation, ingestion or percutaneous absorption [33]. Importantly, if genes and environmental factors interact to produce a risk greater than the sum of their independent effects, then such additional synergistic effects [5] could be eliminated by protecting against the environmental factors — which could include exposures to visible light in the context of this paper — alone [34].

With regard to intervention, one promising aspect to follow up is the suggestion from chronopharmacology that the effects of chemotherapy on childhood leukaemia may crucially depend on the timing of the treatment. In fact, data from Canada have suggested that when children with

acute lymphoblastic leukaemia received maintenance chemotherapy, the disease-free survival was better for those on evening chemotherapy [35]. Follow-up studies have reported similar findings from Canada [36,37] and Scandinavia [38].

Many more such insights are needed to better understand, prevent and treat these devastating diseases. And, beyond possibly improving our understanding of childhood cancers, we may learn from accelerated disease processes in children what can be more difficult to study in adults.

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