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DISCUSSION AND SUMMARY

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The presentations at this workshop demonstrate that, while there have been tremendous strides in the ability to cure childhood leukaemias, the understanding of the genetic and environmental causes of this class of diseases is limited. The epidemiological and the molecular evidence all suggest that childhood leukaemia derives from a multistage process where the initial event starting the process is either inherited or the result of a DNA damaging event during gestation[1]. From that initial event, the progression to disease has to occur fairly rapidly because the peak incidence occurs very early in life at around 1–3 y of age depending upon the type of leukaemia[2,3]. At later ages, the incidence drops off quite dramatically with a >90% smaller incidence beyond age 15.

As discussed at the workshop and in the articles in this special edition, a large number of studies have been conducted to identify risk factors associated with and possibly causal of childhood leukaemia. It is clear from the reviews in this special edition that the only environmental factor that is clearly linked to childhood leukaemia and most likely causes a fraction of the cases is ionizing radiation[4]. Extremely low-frequency electric and magnetic fields (EMFs) have also been associated with childhood leukaemia, but most reviews of this literature have found these studies to provide only limited evidence of an association, which is insufficient for a causal association[5]. Other environmental factors such as radiofrequency EMF, air pollution, smoking, pesticides, herbicides, persistent organic pollutants, radon gas and solvents, have all yielded either very weak associations or no association at all[4]. Indirect indicators of environmental exposures, such as proximity to nuclear power plants, have not provided any additional evidence of a causal exposure.

A number of socio-economic factors have also been associated with childhood leukaemias, with mixed results depending upon the metric used for assessing socio-economic status. Although many studies of other cancers have shown an increase in risk with decreasing socio-economic status, childhood leukaemia has mostly shown the opposite with risk increasing as socio-economic status increases. Also, studies evaluating kindergarten attendance and the frequency of interactions during early age have suggested that a lack of interactions with others in early childhood could contribute to increasing the risk. Somewhat consistent with these findings is an association between childhood leukaemias and increased birth weight in infants. Several theories have been brought forward to account for this. The first is that, in combination, these studies of socio-economic factors, birth weight and kindergarten attendance suggest the increased risk of childhood leukaemia occurs if the child lives in a high hygiene environment and has little chance to be exposed to a wide variety of germs and viruses[6]. The second suggests that in these more affluent environments, there is an increased exposure to growth factors during gestation and early life that exerts a proliferative stress on haematopoiesis that could clonally expand existing mutations that are either inherited or obtained in very early gestation[7].

Given the current knowledge and the relative risks seen in the numerous epidemiology studies of childhood leukaemia, my best estimate is that the attributable fraction has been accounted for by <10%. This means that, for more than 90% of the cases, there is no known or even suggested cause. There has been an increase in childhood leukaemias worldwide that cannot be explained by improvements in diagnosis and tracking alone. This increase strongly suggests an environmental factor (used in the broadest sense to include food, drugs, etc.) is influencing the rate of onset of the disease. But with all of these studies done to date, why have the major risk factors not been identified?

Although there have been a number of genetic markers that have been associated with childhood leukaemia, they are not very specific and are rather high penetrance in disease-free children. It is likely that the environmental risk factors for childhood leukaemia combine with genetic risk factors to increase the overall risk for the disease. The number of possible interactions between genes and the environment is virtually infinite and one would need to be extremely strategic if one is to move forward and actually find what is driving this increase in incidence. In that sense, it is necessary to look at what is already done and add to it based upon the knowledge gained from previous studies.

The high-hygiene theory of childhood leukaemia is one that should receive some serious follow-up at

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this point[8]. Some may argue that, if it were a virus or bacterial infection that was the largest risk factor for childhood leukaemia, it would have been seen by now. There is no doubt that considerable resources have been spent on looking into viruses and childhood leukaemia and nothing found. However, in addition to the theory outlined earlier, two additional issues suggest that a careful evaluation of viruses and childhood leukaemia would be beneficial at this time. First, many of the studies addressing viruses and childhood leukaemia are fairly old and did not have the benefit of modern technologies that may do a better job of identifying an underlying viral source. Second, the author has tried to find a virus that might cause the leukaemias when it may be the lack of an early lifetime exposure to a virus that is increasing the risk. For example, the countries with the greatest increase in childhood leukaemias over the last two decades are also the countries with the lowest prevalence of many common human viruses such as human papilloma viruses.

In the hunt for the causes of childhood leukaemias, size matters. As noted by many speakers, because of the low incidence of these diseases, it will take a worldwide consortium to gain sufficient sample size and power to identify risk factors that have small relative risks. The starting point in these consortiums should be the use of genome-wide association studies to provide a broader number of possible target genes for further exploration linked to complete evaluations of the environments of these children. Using these tools, one should be able to identify a host of new gene and environment links to childhood leukaemias that could then be explored in a broader array of research in smaller studies, laboratories and elsewhere.

Epigenetics is emerging as one of the major scientific advances of this decade. The understanding of the heritable control of gene transcription is opening new doors into the understanding of many cellular processes. Because the biochemical processes that are involved in epigenetics are subject to manipulation through environmental factors, this may be one of the most significant means by which the environment can alter disease rates including leukaemias. The degree to which some of the factors weakly linked to childhood leukaemias alter epigenetic control of gene transcription is an area that warrants additional resources in the search for the aetiology of childhood leukaemias.

Finally, the revolution in creating induced pluripotent stem cells also holds hope for understanding the root causes of childhood leukaemia. It is likely that this disease results from some form of heritable genetic change, either changes in base-pair sequence or changes in gene transcription, at a very early stage in the development of haematopoiesis. Having access to induced pluripotent stem cells opens a wide array of laboratory studies linked to existing or historical case–control epidemiology studies.

In virtually every society on this planet, children are valued and given high priority for protection. Using common scientific resources to address one of the major deadly diseases of childhood is reasonable as a means to prevent the disease. Also, because childhood leukaemias develop so rapidly from the first division after fertilization (<4 y), it is possible that a thorough understanding of childhood leukaemias could have important implications for the understanding and prevention of other cancers. Regardless of why this research is pursued, it is clear that a renewed effort in this area, and a much broader consortium of scientists pursuing the causes of childhood leukaemias is needed.

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