CHILDHOOD CANCERS AND THE IMMUNE SYSTEM

by

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Although the evidence is inconclusive there are some epidemiological studies whose findings are compatible with the hypothesis that the immune system is playing a defensive role in neoplasms as well as infections.  The authors of one such survey began by establishing a causal relationship between childhood cancers and pregnancy x-rays[12,13,20]; then used this association to show that the non-radiogenic cancers were initiated during the first half of foetal life[14], and finally showed that, even when there was no direct involvement of the immune system in the neoplastic process, resistance to infections might be at a very low ebb for at least two years before there were any signs of the cancer (Oxford Survey or OSCC data)[15].

Early foetal origins for childhood cancers would explain why, in these cases, there is so much involvement of typically embroynic structures such as the notocord (neuroblastomas), the lateral plates of the rhomboncephalon (cerebellar tumours), and the Woolffian ridge (Wilms tumours).  They would also allow fast growing cancers to prevent normal development of essential tissues and other cancers to reach a relatively late stage of development before encountering cells which might be capable of recognising and destroying small clones of mutants.

For a cancer which had caused maldevelopment of an essential organ such as the gut the most likely outcome would be an abortion.  However, in utero survival is not dependent upon normal functioning of the immune system and what happens thereafter is related to several factors such as the integrity of the immune system, the duration of breast feeding, the

nature of indiguenuous infections and the availability of antibiotics.
Therefore, the fact that slow growing cancers of the immune system
(lymphatic neoplasms) only became the commonest variant of childhood
cancers <u>after</u> antibiotics were discovered could be due to these cases
being unrecognised cases of infection deaths but also being less likely
to cause maldevelopment of the immune system than fast growing cancers
of the same cell system (myeloid neoplasms) and less likely to be the
cause of an early <u>in utero</u> death than cancers of other cell systems.

From the point of view of someone who is trying to discover
whether there is early involvement of the immune system in the cancer
process it is important that foetal survival should not dependent upon
the immune system and that childhood cancers should have foetal origins
because, given these conditions, the number of recognised cancers would
depend (i) upon the source of the malignant cells (with obvious differences
between the leucocytes and other cells) and (ii) upon the rate of cell
mitosis (with obvious differences between granulocytes and lymphocytes).
For cancers of the immune system the outcome would also depend upon the
nature of indiguenuous infections (with obvious differences between malaria
infested regions and other places), and the risk of any infection proving
fatal (with obvious differences between the antibiotic era and earlier
periods).

There have been two studies of interactions between childhood
cancers and infections.  The first one utilized three sets of official
statistics of mortality (U.S.A., Britain, and Japan) and examined the
relative frequency of leukaemia and pneumonia deaths in epidemic and
non-epidemic years[11].  The second one made use of the medical histories

of live and dead children in the Oxford Survey and related each illness to the date of the cancer death (cases) or a corresponding date (control)[15]. The mortality study showed that the risk of dying from respiratory infections was enormously increased for children who were (unknowingly) on the brink of developing leukaemia, and the morbidity study showed that changed reactions to other diseases preceded other manifestations of childhood cancers by several years. The changed reactions were in the direction of heightened sensitivity to infections; they affected children with leukaemia more than children with solid tumours and were most marked in the year immediately preceeding diagnosis of the cancer.

There has also been an attempt to discover whether the persistent rarity of myeloid leukaemia in younger age groups is an artifact due to these cancers having rapid growth rates and therefore being more likely to cause sudden death after cessation of passive immunity (due to maldevelopment of the child's own immune system) than more slow growing lymphatic neoplasms. The possibility that myeloid leukaemia might be an unrecognised cause of sudden death during infancy was suggested by the fact that, although the number of infants who are born each day is remarkably constant, the risk of dying from leukaemia between 1 and 6 months is twice as high for babies who are born in the first half of the year (January to June births) as for babies who are born in the second half of the year (July to December births)[18,19]. The peak incidence of cot deaths is between 1 and 6 months and in several series of these sudden deaths there were twice as many July to December as January to June births.

These mirror-image differences were explained by assuming
that it is possible for cot deaths to have respiratory infections as
terminal causes and maldevelopment of the immune system as an underlying
cause.  Therefore, infants with myeloid leukaemia would fit the bill but
would be more likely to experience a cot death if they were intensively
exposed to winter conditions between 1 and 6 months of age than if their
first experience of these harsh conditions was delayed until the second
half of infancy.  The first condition is met by children who are born
between July to December and the second by children who are born between
January to June.  In favour of this explanation of the rarity of childhood
cases of myeloid leukaemia are three observations: first, unlike other
leukaemia deaths (which are evenly distributed between the four seasons)
deaths between 1 and 6 months of age are summer biased, and cot deaths
are always commoner in the winter than the summer; secondly, the ratio
of myeloid to lymphatic cases is much higher for neonates than older
children; and thirdly, the world-wide increase in childhood leukaemia
which followed the discovery of antibiotics has everywhere affected
lymphatic more than myeloid cases, and older children more than infants.

There have been no formal tests of the hypothesis that non-fatal
infections can change the course of a childhood cancer.  However, in
regions where rapid development of some immunity to the malarial parasite
is a condition of survival, the commonest variant of childhood cancers is
not lymphatic leukaemia but an unusually localized form of lymphoma known
as Burkitt tumour[4].  Furthermore, in malarial regions - but no longer
elsewhere - children with myeloid leukaemia often have a peculiar tumour,
known as a chloroma, as the presenting symptom.  In Britain, chloromas used

to be a rare variant of childhood cnacer but no cases have been recorded since 1953[21]. However, in a recent study of Ugandan children the tumours were found in a majority of cases eventually diagnosed as myeloid leukaemia[6].

Acquired immunity certainly requires a post-natal environment and, in the case of malaria, it probably requires repeated exposure to the parasite. Therefore, there is no question of acquired immunity to malaria being a condition which can initiate a cancer with foetal origins. On the other hand, a single collection of cancer cells is much less of a threat to health than a metastatic cancer, and there is no doubt that Burkitt tumours are much easier to treat than childhood leukaemias. Furthermore, the diffuse disease is rare in regions where the localized disease is common and vice versa. Therefore, it is possible that acquired immunity can influence the behaviour of potentially malignant cells and is a factor to be reckoned with if it is acquired several months after the start of a cancer process.

In theory the discovery of immuno-suppressive drugs has made it possible to include adult cancers in studies of immune system effects. However, the main use of these drugs is in kidney transplant operations. Therefore, the situation is complicated by the fact that indications for these operations are not necessarily renal in origin. For instance, there is no reason why a cancer of the immune system should not develop in a patient who is already suffering from pyelonephritis and if this were to happen there could easily be deterioration in kidney function before the cancer had reached the stage of being clinically recognisable.

Therefore, although such cancers have been found in excess among recipients of kidney transplants[8,17] this does not necessarily mean that the drugs (or the operations) were the primary cause of the cancers.

In this connection, it is of interest to note how different were the long term effects of immuno-suppression in the following situations: following exposure to A-bomb radiation[2]; following treatment of ankylosing spondylitis with large doses of radiation[5]; and following renal transplants. In all three situations, the risk of an infection death was increased, but for persons who survived this hazard there was a risk of myeloid leukaemia or aplastic anaemia if the immuno-suppression was radiation-induced, and a risk of lymphosarcoma or reticulum cell sarcoma if the immuno-suppression was drug-induced. No explanation of this difference has ever been offered but it is a reminder that if there has only been exposure to low level radiation (or doses well below the level necessary to cause immuno-suppression) the long term risks are not leukaemia or aplastic anaemia but a more localized form of bone marrow cancer known as myeloma[9,16].

## Possible Nature of the Association between Cancers and the Immune System

Though it is doubtful whether circulating lymphocytes can recognise mutants as well as totally foreign cells, other components of the immune system known as tissue histocytes or macrophages are found in large numbers in malignant tumours. Therefore, there are cytological as well as epidemiological reasons for suspecting that the immune system is playing a defensive role in cancers as well as infections.

The evidence relating to pregnancy x-rays and other situations involving exposure to equally small doses of radiation suggests that the primary cause of a cancer is a disturbance of the controlling genes of somatic cells (somatic mutation). It is what happens thereafter that is difficult to visualize. However, the medical histories of children in the Oxford Survey have taught us that it is not only in patients with advanced cancers that the immune system is defective. We also know from screening tests for cervical carcinoma that a cancer in situ may regress spontaneously but is unlikely to do so if the patient is over 40 years of age[10], and, by including African children in cancer studies, we have learnt that common accompaniments of a sharply localized cancer of the immune system are chronic malaria and acquired immunity to the Epstein-Barr virus[7]. It is also becoming increasingly obvious that for everyone, but particularly children and old persons, there must be a direct connection between mortality from other causes and the proportion of recognised cancers. Therefore, it is possible that the immune system both influences the risk of non-lethal mutations having any delayed effects, and has an important say in whether later stages of a neoplastic process will progress beyond a cancer in situ or a benign neoplasm.

Every time a cell divides there is a risk of faulty allocation of the controlling genes between two daughter cells, and mitosis is such a frequent event that, even in children, the supply of new cells must be constantly exceeding the demand. Therefore, in all multicellular organisms there must be mechanisms for recognising and destroying damaged or surplus cells as well as foreign cells. An obvious tissue for generating such mechanisms is the immune system, and an obvious method of tissue-size control would be continuous selection against faulty products of mitosis (i.e. mutants).

An efficient fault detector should make it much harder for grossly abnormal mutants to survive than marginally abnormal cells. However, all mutants are less stable than normal cells. Therefore, the main cancer risk may be coming, not from fresh mutations, but from long standing clones of marginally abnormal cells whose only danger lies in the fact that they are more "mutation-prone" than normal cells. A cancer process which required the establishment of long lasting sources of fresh mutations (but only required a single exposure to a mutagen to establish such a source of future trouble) would go a long way towards reconciling the multiple hit theory of cancer causation[1,3] with the findings of cancer epidemiologists. The suggested process would favour long and uncertain intervals between induction and diagnosis and still allow the immune system to play essentially the same role in infections and neoplasms. Therefore, we would still be left with the possibility that the immune system is responsible for such things as the progressive increase in cancer prevalence with adult age, the high cancer detection rates in populations with low rates of infection mortality and the fact that young children are more cancer-prone than young adults.

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