Views on the Aetiology of Some Cancers

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Cancer is a collective term covering a variety of different diseases. Therefore, any consideration of the aetiology of cancer must be based on the separate consideration of the aetiology of each different type of cancer. It follows that there is not one cause, but a variety of different factors contributing to the aetiology of cancer. These factors can be broadly divided into environmental factors and factors attributable to individual variation, which could be called host or patient factors (Table 1). All of the environmental factors (chemicals, radiation and viruses)

Table 1. Factors known to be involved in the causation of cancer.

| Environmental Factors      | Patient Factors |
|----------------------------|----------------|
| Carcinogenic chemicals     | Immunological  |
| Ionising radiation         | Genetic constitution |
| Ultra-violet light         | Hormonal balance |
| Oncogenic viruses          | Age            |

have been clearly associated with many cancers in experimental and domestic animals. In man causation of some cancers by chemicals and by radiation is quite certain, but evidence for the aetiologic role of viruses in human cancer is still not conclusive even though in some cases the association between a particular virus and a specific cancer is very close (e.g. EB virus and Burkitt’s lymphoma). There is also good evidence that the host factors are important in the aetiology of both animal and human cancers. Over the many years that these factors have been studied there have been periods when one factor was studied almost to the exclusion of the others and this has slowed progress. It is generally accepted, however, that these factors may interact and that we must deal with these interactions if we are to understand the mechanisms by which cancer is produced.

The Nature of the Neoplastic Process

We have a reasonable understanding of the basic biology of cancer so that a general scheme can be proposed to describe the main stages of the process even though we do not fully understand the precise mechanisms causing each stage or leading from one stage to another (Fig. 1). An early stage is recognised, called initiation or in-

duction, which alters a cell (or cells) from a normal cell into one that has the potential of developing into a cancer. It is important to note that this initial change does not inevitably lead on to a clinically recognisable cancer. A long period often elapses between this initial stimulus and the eventual emergence of cancer. The reasons for this latent period are not at all clear. One factor is certainly cell death, which may, in part, be due to coincidental factors such as lack of vascularisation, but there is reasonably good evidence (very good in some animal cancers) that cell death is due to the recognition of the tumour cells as foreign, which leads to their deliberate elimination. This process is often called surveillance. It also seems probable that potentially malignant cells may remain quiescent for some time without progressing. Once again the mechanisms by which cells are held in check are not known. The best example of this quiescent state comes from a study of animal cancers induced by certain chemical carcinogens such as the polycyclic hydrocarbons administered at a dose below the threshold for tumour production. If at a later date a second chemical, termed a promoter, is applied which does not in itself have the capacity to produce cancers, cancers may be produced. Croton oil or the phorbol esters which it contains are often used as promoting substances[1]. The mechanism of action is related to the capacity of these substances to promote cellular proliferation, but it may not be as simple as that since these substances are known to have a potent effect on cell behaviour and differentiation.

When a population of potentially malignant cells begins to grow, it is not a matter of simple cellular proliferation. There is good evidence, particularly from cytogenetic
studies[2], that populations of cancer cells are extremely variable, and that quite rigorous cell selection may be occurring during the period of rapid proliferation. This cellular evolution is reflected at the histopathological level in loss of cellular differentiation and at the clinical level by the increasing aggressiveness of the neoplasm.

The Interaction of Causal Factors

Skin Cancer

From clinical observations and epidemiological studies it is quite clear that many different factors can influence the occurrence of skin cancer. These are set out briefly in Table 2. The occurrence of skin tumours is not random over the body; they occur particularly on areas exposed to the sun[3]. This effect is accentuated in people who spend large periods of time out of doors[4]. There is also a dramatic increase in the incidence of skin cancers in people of Caucasian origin living in countries where there is a high level of sunlight[5]. The effect is also influenced by the degree of skin pigmentation. Among Caucasians the incidence of skin cancer is highest in those with fair skin and fair or red hair. Skin cancers are extremely rare in races whose skins are heavily pigmented[6]. Albinos, regardless of race, tend to get skin cancers if they have a high exposure to sunlight[3]. It is the ultra-violet light in sunlight that is the important factor. This is an example of an interaction between an environmental factor, ultra-violet light, and a genetic factor, skin pigmentation. This well-known association is often not considered as a genetic susceptibility. However, it is from the study of another example of this interaction that the beginnings of an understanding of the mechanisms have become apparent. Patients with xeroderma pigmentosum who are susceptible to the development of skin cancer are also unusually sensitive to the effects of ultra-violet light[7]. Cells from these patients have been shown to be unusually sensitive to killing by ultra-violet light and they lack the ability to remove from DNA the damage caused by ultra-violet light[8]. Thus errors in DNA repair may be one of the likely mechanisms by which environmental agents exert their carcinogenic effects, though the chain of events leading from DNA damage to cancer is by no means clear.

However, there are a number of other risk factors in the genesis of skin cancers which have nothing whatever to do with exposure to ultra-violet light. It has long been recognised that exposure to certain polycyclic aromatic hydrocarbons contained in mineral oils used for lubrication is associated with a high risk of skin cancer[9]. The classic examples are the toolsetters' cancer and mule spinners' cancer. The later finding that patients who had had a primary skin cancer were also at risk of the subsequent development of other kinds of cancer, particularly of the upper respiratory tract or upper alimentary tract[10], has led to some speculation that those exposed workers who do develop skin cancer may represent a sub-group who are particularly susceptible to the effects of these polycyclic hydrocarbons. There is considerable evidence from experimental animals that variations in susceptibility to polycyclic hydrocarbons do exist and that they are under genetic control[11]. Attempts to demonstrate such effects in man have only been partially successful. We must bear in mind the possibility of specially susceptible populations and consider the far-reaching implications that this would have in industry if any attempt were made to pre-select those at risk to prevent them entering occupations where exposure was likely.

The only other chemical clearly associated with the development of human skin cancer is arsenic[12]. This is the one situation where a risk factor has clearly been identified, but where attempts to demonstrate the carcinogenicity of the material in animal systems have failed.

Patients who have received high doses of radiation for therapeutic purposes have a high incidence of skin cancers[13]. Often a long period of time elapses between the irradiation and the development of the skin cancer, but there is no doubt that radiation is a causal factor. Once again not all those people who are exposed to ionising radiation develop skin cancers. It has been suggested that this is due to the 'play of chance', but it seems more likely that some other factor is involved. Individuals may vary in their sensitivity to ionising radiation, for example patients with the genetically determined disease naevoid basal cell carcinoma syndrome (sometimes called Gorlin's syndrome) have a number of congenital malformations and tend to develop skin naevi that may progress into basal cell carcinomas[14]. Also associated with this disease is a tendency to develop brain tumours, particularly medulloblastomas. Patients with this syndrome who have received irradiation, either for the treatment of medulloblastoma or some other condition, may develop skin tumours in the irradiated field, which develop in very large numbers and after only a very short latent period, sometimes as little as one year[15]. This strongly suggests that in these patients there is an unusual sensitivity of a particular kind to ionising radiation and that we are once again considering an interaction between an environmental factor and the genetic constitution of the patient.

Evidence that viruses cause cancer in man is scanty, but both pox viruses and papilloma viruses cause benign
tumours. Planar warts are caused by papilloma viruses that closely resemble some animal cancer viruses. Under normal circumstances planar warts are completely benign tumours. In the rare inherited condition, epidermodysplasia verruciformis (EDV), the patients are unusually sensitive to the effects of human wart virus[16]. In these patients there is a tendency for the planar warts to develop into carcinomas. This is quite clearly in line with what we know about the behaviour of oncogenic papilloma viruses in animals. For example, the Shope papilloma virus in its natural host, the cotton tail rabbit, will produce only benign papillomas from which the virus can be recovered (c.f. warts). In the domestic rabbit, however, the virus produces carcinomas and in this situation the virus apparently becomes completely integrated with the cell and cannot be recovered[17]. The situation that exists in the EDV patient may be one of the few examples of tumour production by viruses in man, and another example of interaction between an environmental factor and the genetic constitution of the host. Till recently, experimental studies on human wart viruses have been difficult, but the development of in vitro culture systems for human skin epithelium[18] may now make this possible.

There may be many other factors that would influence the development of skin cancers. Quite clearly the age of the individual is vitally important. It could be that with advancing age it is more probable that a significant interaction will occur between the environmental factor and the potentially cancerous cells. On the other hand, it may be that older cells become more susceptible to the effects of the environmental agent or that once a potentially malignant focus has been initiated it is more likely to progress to a clinically recognisable cancer in an older individual. We cannot at present choose between these ideas.

Even for one particular cancer, therefore, there are many different factors interacting to create situations in which the disease can arise. At the very least, in the case of skin cancer, radiation and chemicals and viruses interact with each other and with both the genetic constitution of the individual and the age of the individual. It is also apparent that there may be many different routes by which a cell may be altered to give rise to the picture which we call skin cancer. Any one cancer may have a variety of different causes. It follows, therefore, that if we attempt to adopt preventive measures by concentrating on only one aspect, we may be dealing with only a part of the problem.

Other Cancers

While I have chosen to build this discussion specifically around skin cancer, the same sort of scheme could be built around any one of a whole variety of human cancers. For the commonest human cancers such as carcinoma of the breast in women and carcinoma of the lung in men the pattern of risk factors may not be quite so clear as it is for skin cancer, but I believe that a similar pattern will emerge in the future. In the case of carcinoma of the lung it was suggested in 1973 by Kellerman and Shaw[19] that susceptibility to carcinoma of the lung was due to variations in the ability of patients to metabolise the polycyclic hydrocarbons contained in cigarette smoke. Much work has since been done in this field, with somewhat equivocal results, but there are a number of other reports which tend to back up this idea, even if they do not confirm the detail. For example, the work of Emery and his colleagues[20], while it does not suggest that there is a single gene controlling the metabolism of polycyclic hydrocarbons in man, suggests that the level of inducibility of the aryl hydrocarbon hydroxylase enzyme system responsible for this metabolism may be greater in individuals who have got lung cancer than in a control population. It is quite clear in experimental animals that the inducibility of this system is under genetic control[11]. Most groups of workers have used lymphocytes for these studies. While it may seem rather far-fetched to make deductions about the susceptibility of lung tissue on the basis of studies done on cultured lymphocytes, a recent report[21] has shown that there is considerable variability between individuals in the capacity of lung tissue to metabolise polycyclic hydrocarbons. These studies are still at an early stage, but the far-reaching implications of the possible existence of a recognisable group of individuals who are susceptible to the effects of cigarette smoking need not be stressed.

A number of risk factors in carcinoma of the breast are now recognised. The age of having a first child, whether or not the child is breast-fed, and the fat content of the diet, have all been suggested as risk factors in human breast cancer. A number of studies, however, indicate that there may be a genetic element in some of those cases where there is a familial incidence of breast cancer. It has been suggested that the two particular factors associated with a familial incidence are early age of onset and the occurrence of primary cancers in both breasts[22]. If we can recognise those families in which there is an elevated risk of breast cancer we can not only concentrate screening procedures on them, but also give reassurance to those women whose families do not fall into this category which, of course, is the vast majority.

The Nature of the Initiation Process

Once again it is not necessary to look for a single mechanism. It is very important to recognise that a single clinical entity may not only arise as the result of the action of several different factors, but may depend on a number of quite different mechanisms.

Somatic Mutation

The idea that a cancer cell is a cell in which some change in the genetic structure has occurred is one of the oldest ideas in cancer research. For a long time the idea was out of favour, but recently a number of discoveries have cast new light on this possibility and it is now probable that this is one of the major mechanisms in the initiation of cancer. It has been recognised that there is a close association between those chemicals capable of
producing mutations and those capable of causing cancer[23], that the vast majority of cancers have abnormalities of the chromosomes and that some of these chromosome changes may be highly specific[2]. The best known example is the Philadelphia chromosome, which is characteristic of the majority of cases of chronic myeloid leukaemia, but is also found in association with other leukaemias, particularly some of the acute leukaemias in children that appear to be lymphoblastic, but in which the cells have cell surface markers of neither the B nor the T cell type. Recently, specificities have been recognised in a number of other situations. In promyelocytic leukaemia, for example, there is a highly specific translocation between chromosomes 17 and 15[24]. At a different level it has long been recognised that some patients with constitutional chromosomal abnormalities had an unusual susceptibility to developing leukaemia; patients with Down's syndrome are susceptible to developing leukaemia as children. Very recently, however, it has been shown that certain children with a specific deletion of the long arms of chromosome 13 are liable to develop retinoblastoma and that children with a deletion of the short arms of chromosome 11 are liable to develop Wilm's tumour. Indeed in this latter case the children with the deletion of chromosome 11 all have aniridia in addition to Wilm's tumour[25]. It seems possible that the presence of the chromosomal deletion in children with aniridia may be a predictive factor in determining whether or not the child will develop Wilm's tumour

All these facts tend to suggest that changes in the genetic material or some pre-existing abnormality in the genetic material may be important in the genesis of cancer. It has, however, been from the study of some of the rare inherited diseases that we have begun to get insight into more precise mechanisms at the molecular level. It now seems clear that in xeroderma pigmentosum the susceptibility to ultra-violet light is due to a defect in the capacity of the cells to remove from the DNA damage induced by ultra-violet light[8]. Thymine dimers require a specific enzyme for their removal and this enzyme appears to be either absent or malfunctioning in the majority of patients with xeroderma pigmentosum. There are at least seven different complementation groups in xeroderma pigmentosum[26], and therefore at least seven different genes that control the malfunctioning or functioning of this enzyme system. In addition, there are a number of patients who are not defective in this type of DNA repair, but who are defective in another DNA repair pathway, namely post-replication repair. It seems, therefore, that in the case of xeroderma pigmentosum the clinical entity is in fact a group of diseases all with slightly different causes which give the same clinical picture.

For some time it was considered that xeroderma pigmentosum might be an exceptional situation, but now there are a number of other situations where it is quite clear that defects in DNA repair may be critically important in the genesis of the disease. In patients with ataxia telangiectasia we have demonstrated a defect in the capacity of the cells to remove damage caused by ionising radiation from the DNA, and it seems very probable that this defect is in some way associated with the susceptibility of these patients to neoplasms[27,28]. It has become apparent in considering DNA repair that this could provide the common pathway for the action of both ionising radiation and carcinogenic chemicals. Both cause damage to DNA which requires the functioning of some repair pathway. If these repair pathways are defective in any way errors are introduced into the DNA and it may well be that a proportion of these errors are the basic errors responsible for the initiation of the neoplastic process.

Errors of Differentiation

There is now good evidence to suggest that for some tumours, particularly tumours occurring in childhood, errors of differentiation may be important[29]. There are many examples of association between the occurrence of tumours and the occurrence of congenital malformations which suggest that the occurrence of the tumour is part of the systemic upset. Wilm's tumour is a good example of this phenomenon. At the experimental level there is evidence that when tumour cells are placed in an environment that stimulates differentiation they may be able to differentiate normally, which suggests that the original cell changes were not of a mutational kind, but rather of a regulatory kind. Such examples come from the work of Illmensee and Mintz[30] on chimaeric mice, which are constructed by injecting a cell from one embryo into the blastocyst cavity of another embryo of different parental type. Cells of both parental types are involved in the formation of the animal. If teratocarcinoma cells are used as one parental type they can participate in the differentiation of normal tissues in the developing animal. It is not easy to get clear evidence that this is happening in the case of human tumours. However, it may be that the study of rare human tumours will give an insight into the mechanisms operating in the commonest cancers. Some cases of retinoblastoma occur sporadically, others occur in families. It has been suggested that retinoblastomas are due to the sequential occurrence of two mutations[31]. In the sporadic cases each mutation would be both post-zygotic and random and therefore the incidence would be low. In the familial retinoblastomas it is suggested that one of the required mutations occurs prezygotic and that the second mutation need only occur in any cell of the retina for a tumour to develop. The probability of this occurring is high. This fits very well with the earlier age of onset of the familial cases and the fact that familial cases are frequently bilateral and often with multiple tumours in the same eye. This idea is attractive but not entirely satisfying since it does not allow for the fact that the differentiation to retinal cells is clearly an important part of the process. Instead of a second mutation being required, the gene for retinoblastoma might result in a congenital malformation, namely an error in the differentiation of the eye; this creates a situation in which a neoplasm might develop. So, retinoblastoma may involve mutation, or errors of differentiation, or possibly both.
Conclusion

If studies of aetiology are to have any practical application we must try to avoid a number of errors of thinking that have obscured much work in the past. The need to consider each cancer independently is now widely, but not universally, accepted. The multiplicity of causal factors is well established. We must now recognise the interaction between different causal factors and we must accept the fact that a clinical entity may be heterogeneous as far as causation is concerned. If we can adjust to these ways of thinking we may do much more to prevent specific types of cancer and, incidentally, understand their basic biology more fully.

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Council Confounded

Time was when Council was empowered to nominate the candidates for the Fellowship and to present their list to Comitia for their votes. For some years individual Fellows grumbled about the unsuitability of some nominees and the neglect of worthy candidates. This matter suddenly erupted into crisis in 1864 when at Comitia, as The Lancet recorded, "circumstances occurred which must be of painful regret to all. 'A difference of opinion arose between the Council and the then Fellows present; and, as a consequence of the collision, reckless blackballing was resorted to.' Of the ten nominees of the Council only five were elected Fellows and The Lancet quoted the number of black and white balls cast for each, commenting that the names put forward had 'been used as skittles for other gentlemen to bowl at'. 'A more undignified, improper, and painfully unjust course was never adopted, and the whole proceeding is one which might fairly be characterised in the strongest terms of reprobation.' The Lancet suggested a change in the College bye-laws so that the Fellows themselves should nominate the candidates for Fellowship. The College Annals are discreetly silent on this episode but there was a resolution to consider whether the election of Fellows does not admit of improvement. In 1868 the bye-laws were changed so that individual Fellows could put forward their nominees for the Fellowship.