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The relationship between ageing and cancer: Somatic mutations or breakdown of host defence mechanisms

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Ageing has been defined as the sum of a number of physiological changes – to some extent independent of one another – which lead to an impairment of function (and adaptation) and a greater susceptibility to certain pathologies and ultimately to death (MAYNARD SMITH, 1962). Except for a peak in childhood, the incidence of cancer in the population rises steeply and progressively with age. The implication that there may be a causal – though not necessarily direct – relationship between age-associated physiological changes and the increase in occurrence of malignant disease with age is obvious and has frequently been suggested.

Two possibilities will be considered: 1. that the age-associated physiological changes facilitate the occurrence of cancer; 2. that the same sub-cellular lesions cause both ageing and cancer. The latter hypothesis has been advanced by the proponents of the somatic mutation hypothesis for ageing (cf. CURTIS, 1967).

1. Difficulties in facts and interpretations of the somatic mutation hypothesis for ageing

First let me emphasise that to question, that the occurrence of somatic mutation (i.e. changes induced in stem cells leading to the appearance of aberrant descendants such as leukocytes) makes a significant contribution to the sub-cellular processes that result in ageing in mammals, is in no way in conflict with the well established fact that the rate of ageing is genetically controlled.

The finding that radiations such as X-rays, which are capable of inducing mutations, shorten the life-span of animals constitutes the principal experimental evidence of the proponents of the somatic mutation hypothesis for ageing (HENSHAW, 1957). The fallacy in the argument is that an increase in the rate of mortality cannot *ipso facto* be equated to an increase in the rate of ageing. Physiological parameters (including the properties of collagen) have to be used to measure the rate of ageing and when this is done then no evidence has been found that radiation speeds up the normal rate of ageing

either in man (HOLLINGWORTH et al., 1962) or in experimental animals (ALEXANDER and CONNELL, 1960, 1963a).

Another criterion for the rate of ageing is the time of onset of age-associated pathologies. Superficially, radiation may appear to bring these on earlier but careful studies in which groups of irradiated and unirradiated mice were killed at different times and their pathologies studied showed that radiation did not speed up the various disease states uniformly (CONNELL and ALEXANDER, 1959; ALEXANDER, 1967a). This is particularly apparent from studies of the incidence of neoplasia. If irradiation accelerated the processes that lead to ageing, then one would expect that the latent period before pathological lesions (malignant or otherwise) become detectable would be shortened in the irradiated group but the incidence (i.e. the fraction of all animals affected) would be the same as in the control. In our experiment this was, in fact, the situation for lung tumours but the appearance of benign hepatomas – to which this strain is exceptionally prone (CONNELL and ALEXANDER, 1959) – was exactly the same in irradiated and unirradiated animals. Perhaps the most common effect of radiation is to increase greatly the incidence of malignancies and in some strains of mice the predominant cause of death after irradiation is a malignant condition that is almost wholly absent in unirradiated populations (UPTON, KASTENBAUM and CONKLIN, 1963). Here, radiation introduces a new pathology. In man cigarette smoking causes a contraction in the time axis of the normal survival curve but as the increased mortality rate is due principally to the induction of two diseases – lung cancer and chronic bronchitis, which are almost wholly absent in non-smokers – no one would claim that life-span shortening by smoking (7½ years on average for heavy smokers) is an acceleration of ageing. The occurrence of these diseases is not merely brought forward in time, but they are induced essentially *de novo* by smoking. Radiation-induced cataracts also fall into this group (ALEXANDER and CONNELL, 1963a) since they are morphologically quite distinct from senile cataract and their induction cannot be considered as a sign of premature ageing. Conversely, prolongation of average life-span does not constitute a retardation of ageing. The average life-span of different strains of mice varies widely but in general the short-lived strains have a high, and genetically determined, incidence of malignant disease which kills prior to senescence, and there is no evidence to indicate that the true rate of ageing varies.

On the other hand, a dose of 100 r of X-rays has been clearly shown to more than double the normal rate at which spontaneous somatic mutations occur in mice (RUSSELL and MAJOR, 1957). The radiation experiments, therefore, far from supporting the somatic mutation hypothesis can be interpreted as demonstrating the exact opposite, in the sense that exposure to X-rays which result in a large increase in somatic mutations does not accelerate ageing. These arguments rely on the contention that a shortening of life-span is not synonymous with an acceleration of ageing. More compelling are experiments in which the mutation rate has most probably been greatly

increased without there being any reduction in life-span in a strain of long-lived mice by treatment with mutagenic chemicals (ALEXANDER and CONNELL, 1963b).

The first mutagenic agents to be used were the bifunctional alkylating agents, myleran and chlorambucil (ALEXANDER and CONNELL, 1960) and they shortened life-span if applied in fractionated doses in a way akin to radiation. But there is no evidence at all to link the shortening of life-span to an acceleration of ageing for these treatments any more than for radiation. The capacity of these substances to shorten life-span need not be ascribed to their mutagenic properties since they have a wide range of biological activities and, in particular, are highly toxic to dividing cells, a property to which they owe their role in the chemotherapy of cancer.

The monofunctional alkylating agents and, in particular, ethyl methane sulphonate (EMS: $C_2H_5 \cdot O \cdot SO_2 \cdot CH_3$) are much more suitable for testing the somatic mutation hypothesis since they are highly mutagenic at dose levels where they show no cytotoxicity. EMS has been shown to produce mutations in *Drosophila*, *Neurospora*, barley, bacteria and bacteriophage (see ALEXANDER and CONNELL, 1963b) and recently BATEMAN (1963) has shown that it produces mutations in mice at a dose level of 50 mg/kg. But EMS even when given at very high doses in mice does not produce any detectable life-span shortening. If the reasonable assumption is made that there is a close parallelism between the induction of germ and somatic mutations then these results indicate that raising the somatic mutation rate many times above the normal does not affect life-span. Such a conclusion would appear to be irreconcilable with the concept that the accumulation of somatic mutations throughout life is an important factor in causing ageing (cf. ALEXANDER, 1967a).

2. The relationship between mutagenesis and carcinogenesis

The biological properties of cells obtained from cancers show that they have undergone a permanent and heritable transformation which has all the properties of a somatic mutation. Evidence is now accumulating that the rate of appearance in mammals of somatic mutations – or rather of the rate with which they give rise to phenotypic expression in the cell populations – is of the same order of magnitude as spontaneous mutations in germ cells, and an estimate for the spontaneous mutability of genes in somatic cells in man of between one in 10^{-5} to 10^{-6} per cell division can be made (ATWOOD et al., 1958; FRASER and SHORT, 1958). In man some 10^{11} cell divisions occur daily and in that time more than 10^4 cells that have undergone a malignant transformation would be expected if only one mutational step is required. Such potential cancer cells would, of course, be concentrated in those organs where cell division is most frequent.

Experimental evidence indicates that the occurrence of malignant cells is a relatively common event in populations of dividing mammalian cells. Thus normal (e.g. embryonic) cells when grown in tissue culture do not

multiply indefinitely; either the cell line dies out or the culture has turned malignant and its cells will give rise to cancer when injected into suitable hosts (cf. HAYFLICK and MOORHEAD, 1961). This phenomenon has been particularly well documented by FOGH and HOK (1958) with human amnion cells which, after culturing, cause cancer on injection into rats that have been rendered immunologically unresponsive. A similar phenomenon has been encountered *in vivo*. Embryonic mouse tissue that has been allowed to grow in millipore chambers placed within syngeneic hosts will cause cancer when removed from the chamber and transplanted subcutaneously (SHELTON et al., 1963). Yet a piece of skin has been transplanted successively from one mouse to another, genetically identical one, so that its total life-span greatly exceeded that of an individual mouse. Yet no tumours arose showing that under normal physiological conditions the anticipated malignant transformations did not express themselves as tumours.

Normal cells when growing under conditions where they are inaccessible to host defences, as is the case in tissue culture or within millipore chambers, appear to become heterogeneous and at least some readily acquire malignant potential. One is led to deduce that mechanisms exist in normal animals which eliminate cells that have undergone spontaneous transformations to malignancy.

While the basic requirement for cancer is the malignant transformation of a cell, in general this process is not the rate determining step in carcinogenesis (cf. ALEXANDER, 1967b). Cancer is seen when for one reason or another the cells with malignant potential, which are arising constantly, elude the physiological processes responsible for their containment. In a practical sense the genesis of a malignant tumour is not determined by changes in the character of individual cells, but is due to a failure of the organism. ALEXANDER and HORNING (1959) proposed that many carcinogenic stimuli acted in an indirect way by making it possible for malignant cells of spontaneous origin to establish themselves. This hypothesis was based on a study of the factors involved in the induction of sarcomata as a result of the subcutaneous implantation of plastic films - a phenomenon that had been discovered by B. S. and E. OPPENHEIMER. The key factor seemed to be that the film isolated some connective tissue from the controlling influences of the host. Two lines of arguments have frequently been advanced in support of the opposite view: namely that the occurrence of the cellular change (i.e. the transformation to malignancy) is the critical step which decides if and when a cancer will appear. These are:

1. *The alleged parallelism between mutagenic and carcinogenic agents.* Twenty years ago when very few chemical substances were known to be mutagenic the concordance was much more impressive than it is now when hundreds of diverse compounds have been found to have this property (see BURDETTE, 1955). Thus, evidence for the mutagenicity of the carcinogenic hydrocarbons and the carcinogenic azo dyes is not very strong and the cancer producing plastic films clearly cannot act in this way. Several power-

ful mutagens were shown by TRAINING et al. (1964) to be incapable of initiating skin carcinogenesis and the most potent mutagenic agent so far discovered, ethyl methane sulphonate, produces tumours only after a very long period even when given systemically in repeated doses (ALEXANDER et al., 1963b). For the induction of tumours and leukaemia by ionizing radiations time dose relationships do not fit a mutagenic process (MOLE, 1958) and suggest that the cause is one of the many other biological changes which radiations bring about. HADDOW (1938) pointed out thirty years ago that there was an impressive relationship between the carcinogenicity of chemical substances with the capacity to kill normal dividing cells. He stressed that a characteristic feature of the carcinogenic situation was continuous interference with normal growth.

2. The existence of a constant and significant mathematical relationship between cancer and age. - In man, the cancer death rate is said to increase with age at a rate corresponding to a sixth power law. This curve has impressed BURNET (1957) (see also ARMITAGE and DOLL, 1954) who speculates that six control mechanisms have to be abrogated by successive somatic mutations to give eventually a cell which is capable of "the initiation of frank cancer". A detailed study of the mortality statistics shows that the sixth power relationship is a mathematical artefact resulting from the pooling of data. If the mortality rates are analysed on a cohort basis for individual classes of cancers then they deviate significantly from logarithmic growth rate. But even if on a log-log plot the best straight line is drawn it is apparent that the exponent (i.e. the slope of this curve) varies widely from one situation to another and the average value of six is obviously without significance. This is brought out clearly in unpublished data prepared by my colleague, Prof. R. A. M. CASE, and quoted in detail by ALEXANDER (1967). There are not only great variations in the relationship between age and cancer for different sites, but that even for one site the exponent varies from country to country, between sexes, and between different dates of birth for the cohorts studied. There would appear to be no justification for giving a simple biological interpretation to the age dependence of cancer mortality (cf. ARMITAGE et al., 1965) or for linking this complex relationship to the induction of somatic mutations. Indeed, the facts would seem to be explained much more satisfactorily by an increase in the likelihood of a failure of a defence mechanism with age.

3. Immunological defence reactions against malignant cells

There may be more than one type of defence mechanism which can lead to the elimination of cells that have undergone a malignant transformation. Recent advances in the field of experimental cancer research has provided decisive evidence for immunologically mediated host reactions (HADDOW, 1965; ALEXANDER and HAMILTON FAIRLEY, 1967) and I will confine my remarks to these. Tumours arise when the immunological defence mechan-

Table 1

Mechanisms by which cells that have become malignant may avoid destruction by the immune reaction of the host directed against the tumour-specific antigens in the cell membrane

“Escape” mechanism	Examples
Tolerance to tumour antigen	Tumours arising from vertical transmission of oncogenic viruses
Insufficient antigen release	May be very common; demonstrated with chemically induced sarcomata
“Protective” antibody	Not yet demonstrated
Growth in “immunologically privileged” site	Possibly for sarcomata induced by plastic film
Non-specific depression of immune response	Increased susceptibility of very young animals or of thymectomised animals to oncogenic viruses

ism has been by-passed. There are several ways by which “escape” from immune surveillance can occur and it is the thesis of this lecture that the age associated changes in structure render “escape” of malignant cells more probable.

Evidence has been accumulated over the last ten years which shows that tumours which arise in experimental animals as a result of exposure to carcinogens – chemical, physical or viral – contain certain components in their plasma membrane which are different from those present in normal cells (cf. OLD and BOYSE, 1964). The existence of such substances was revealed by techniques involving transplantation within pure line animals (i.e. colonies in which each member is genetically identical and will accept skin grafts from one another). These tumour-specific antigens cannot be detected by normal serological techniques, but they cause a host reaction – predominantly cell mediated – which is selectively cytotoxic to the tumour cells and not to the host cells. The realisation that autochthonous tumours are, to some extent, foreign to the host in which they arise has given a great impetus to the search for immunological procedures that may be useful in the treatment of cancer (ALEXANDER et al., 1966 and 1968; DELORME and ALEXANDER, 1964).

The first point to be considered is why the parent cell (or small cluster of cells) derived by a transformation to malignancy *in vivo* survives to give expression to its neoplastic potential. Presumably the new and tumour-specific antigens arise at the same time as the malignant change and the transformed cell has therefore to “escape” from the host’s immune reaction before it can grow into a recognisable cancer¹. Tumour specific antigens may

¹ The “host-resistance” with which the experimenter is confronted occurs at the level of the macroscopic tumour and the question then is whether its growth is being

therefore only reach the immune system when the tumour mass is already too great to be capable of control by the host response. Clear-cut cases where there is no tolerance, but the host response is initially sub-maximal, because of insufficient antigen release, have been observed with tumours induced by SV 40 virus in hamsters (DEICHMAN et al., 1966) and by the Shope virus in rabbits (EVANS et al., 1962). In both cases exposure to "vaccines" made from tumour antigens leads to regressions of primary tumours.

Other "escape" mechanisms that have been considered are initial growth in an "immunologically privileged site" resembling the anterior chamber of the eye or the hamster cheek-pouch. Such a situation arises in the vicinity of plastic films that induce sarcoma.

The formation of immunoglobulin of the γ_1 type could also lead to "escape" since they bind to the surface of the "target cells" without being cytotoxic. This reaction may protect the cells against the lethal effects of cell-mediated immunity but as yet no experimental evidence exists to implicate this reaction in "escape".

There can be no doubt that malignant cells can "escape" and give rise to tumours in animals with completely normal immune responses and there is no need to postulate as has been done that carcinogenic agents have to be immunosuppressive.

HADDOW (1938) first showed that many carcinogenic agents and, in particular, the carcinogenic hydrocarbons were also highly cytotoxic *in vivo* to dividing cells and that, like radiation, they damage the lymphoid organs. It is therefore not surprising that the administration of relatively large doses of carcinogens, like methylcholanthrene, by such routes as subcutaneous injection, should be accompanied by a generalised depression of the immune response (PREHN, 1963). While this provides a possible "escape" mechanism it is not at all certain whether this is an important factor for chemically induced tumours. It must be emphasised that the amount of the carcinogenic agent which was required to cause immunosuppression was many times greater than the "threshold dose" for cancer induction. In our experiments (HADDOW and ALEXANDER, 1964) in which a pellet of carcinogen was placed below the skin no detectable immuno-suppression, as measured by skin grafting, or the formation of circulating antibodies occurred, yet this procedure is a very potent carcinogenic stimulus giving a high tumour incidence with a short latent period. Another point which must be emphasised is that grafting experiments have shown that frequently small inocula of cells from chemically induced tumours will give rise to tumours

opposed by an immune reaction. In the absence of spontaneous regressions it is obvious that any "host-resistance" is insufficient to cause the total elimination of the tumour, but it may cause the tumour to progress more slowly than its biological potential would allow in the absence of an immune response. Given the phenomenon of initial "escape" host-resistance even if present to a very marked extent would not be expected to cause the elimination of a rapidly growing tumour because the rate of production of new cells is likely to be greater than their rate of destruction.

in syngeneic recipients which have never been exposed to any immuno-suppressive agents. It is quite clear, therefore, that cells with tumour-specific antigens can "escape" in animals which have a completely unimpaired capacity to react against them.

On the other hand, there are situations where a relatively small decrease in immune reactivity greatly increases the number of tumours induced by a carcinogenic stimulus. A striking instance of this is to be found in viral oncogenesis. Tumour incidence is much greater if the virus is administered to rodents in the first few days of life. While the animals do not develop tolerance the fact that the immune reactivity is not yet fully developed in the very young animal facilitates tumour development. This illustrates the "knife-edge" situation which exists between the host response and the "break through" of cells with malignant potential to grow into a tumour. Similarly, removal of the thymus causes marked immuno-depression only if carried out neonatally and thymectomy of hamsters at 3 days of age leaves the immunological capacity of the animal virtually unimpaired – as measured by conventional tests. Yet it greatly enhances the carcinogenicity of polyoma virus (TING and LAW, 1967).

4. Immunity and age

The genesis of an immune response is a complex process involving many stages (see Fig. 1) and cell types. Age-associated lesion could occur at many points. Before considering the evidence for impairment, reference must be made to the hypothesis of WALFORD (1967) that ageing is an "auto-immune" disease due to the appearance of somatic cells with new surface antigens against which the host reacts. The appearance of new cell lines requires the occurrence of a permanent and heritable change and the theory is in fact a specific instance of the somatic mutation hypothesis. Critical experiments in my view failed to provide any support for it. Thus immuno-suppression does not extend life-span nor does the deliberate causation of a weak auto-immune reaction shorten it.

I would now like to turn to the experimental evidence that the capacity to mount a primary immune reaction decreases with age. Unfortunately the evidence for such a hypothesis is not convincing. In one particular strain of mouse (a hybrid between C3H and C57/B1) the capacity to produce haemagglutinins to sheep red cells fell progressively with age; both the number of spleen cells capable of responding to the antigen as well as their rate of proliferation was impaired by age (MAKINODAN and PETERSEN, 1964; ALBRIGHT and MAKINODAN, 1966). This phenomenon was not, however, general and METCALF et al. (1967) using the same test found a marked age dependence in C57/B1 mice but not in C3H mice. In view of the central role of the thymus in the development of the immune system there have been many speculations that the atrophy of this organ with age is a factor in senescence because it may reduce the capacity of an old animal to respond

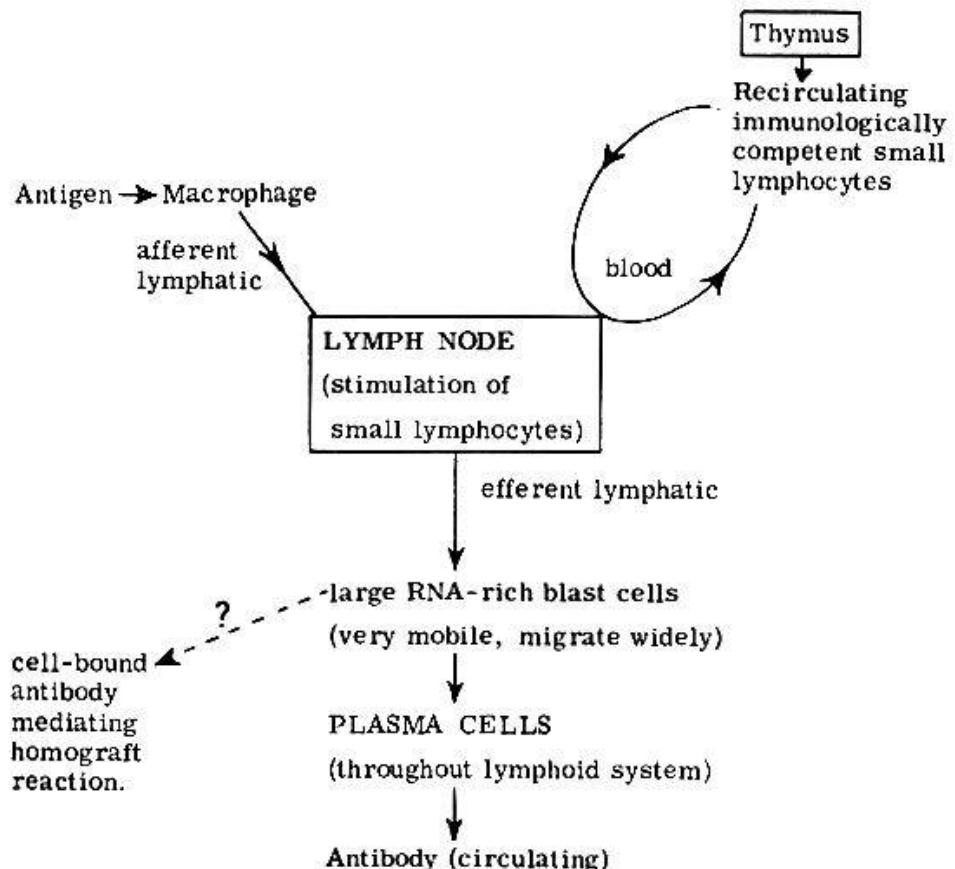


Fig. 1. Genesis of immune response.

to primary stimuli. METCALF et al. (1967) found that grafts of neonatal thymus did not restore the age associated depression in the immune response of C57/B1 mice. The spleen is the major site for the production of circulating antibody following i.v. administration of antigen and the fall in immune response with age when it occurs was found to be accompanied by histologically obvious degeneration changes (HANNA et al., 1967). A decrease in the phagocytic activity with age has been shown in rats (PATEK et al., 1967) and BEREGI et al. (1964) found that anaphylactic shock occurred more rarely in older rabbits.

The most thorough investigation into possible correlation between ageing, cancer and immunity has been carried out by TELLER and his colleagues (TELLER et al., 1964; AOKI et al., 1965; AOKI et al., 1966; TELLER et al., 1967). In the first paper they found in female "Swiss" mice a marked and progressive depression with age in the capacity to reject foreign cells - both skin and homograft tumours - and an increase in spontaneous tumours with age. In subsequent papers they found that aged Swiss mice also showed decreased phagocytic activity and produced only low titres of circulating antibodies against foreign (i.e. allogeneic) tumour cells. With commendable caution they did not conclude that the impaired immune response was necessarily a factor of ageing or in the appearance of tumours, since it was much more pronounced in "breeder" females than in virgins and they sug-

gested that hormonal factors might be involved. In their latest paper they carried out a critical experimental to test, if there exists a close relationship between ageing, immunity and cancer, by comparing six strains of mice with varying rates of incidence of spontaneous tumours. Old age was associated with a decrease in primary antibody response in four of the six strains but there was no correlation with cancer incidence. The authors concluded that a decrease in host immunity is not the primary factor responsible for the appearance of tumours in older animals.

LURIE (1964) made a careful study of the occurrence of spontaneous tumours in different strains of rabbits which varied in their susceptibility to tuberculosis. Tumours occurred much later in life in those strains of rabbits that were resistant to infection. LURIE had shown that the variation in resistance of the rabbits to tuberculosis was related to the capacity of the phagocytes to kill ingested tubercule organisms. It is tempting to correlate the relative cancer incidence also with phagocytic activity, although this has not, of course, been proved.

We are left with a confused picture. Thymus involution is perhaps the most characteristic anatomical feature of ageing yet thymus grafts appear to be without beneficial effect. When there is an impairment of the immune response with age, this would appear to be either at the level of the processing of antigen by macrophages or at the level of the production of immunoblasts. Whether these change effects are due to the "ageing" of the cells themselves or if they occur more indirectly for example as a result of connective tissue changes in the lymphoid organs is not known.

The limited experimental data does not allow the conclusion that there is a generalised decrease in immunological capacity in aged animals. This does not, however, necessarily invalidate the hypothesis that there is an age associated impairment of host defences against malignant cells which is - in part at least - responsible for the sharp increase in cancer with increasing age. There are many mechanisms of "escape" and in experimentally induced tumours generalised depression of the immune response appears only rarely to facilitate the establishment of an antigenic tumour.

One might speculate that some of the other "escape" mechanisms might be affected by age. Connective tissue changes and alterations in the permeability of vessels might increase the likelihood of a malignant cell establishing itself at a site initially inaccessible to a homograft-type reaction. Antibodies, particularly macroglobulins, may not be able to diffuse through the blood vessels in older animals and this may lead to a shielding of the tumour.

Summary

The hypothesis that somatic mutations constitute the sub-cellular lesions that result in ageing is discussed in relation to the effects of ionizing radiations and of mutagenic chemicals on the life-span of mice. From the data, it is concluded that somatic mutations do not play a major part in initiating

ageing. The role of somatic mutations in cancer is complex. The transformation of a normal cell to a malignant cell constitutes a somatic mutation but only a small fraction of such transformed cells appear to give rise to a tumour; the majority are probably eliminated and it would appear that there is a defence mechanism for the destruction of malignant cells. The rate determining step in carcinogenesis may not be the transformation of cells to a malignant state but the probability of eluding the host reaction. Carcinogenic agents may act by creating the conditions which allow transformed cells to establish themselves.

Most experimental tumours contain specific antigens in their plasma membrane and this suggests that immunological processes play a major role in the host defence against malignancy. While the evidence that there is a generalised depression of the immune response with age is not strong, other age-associated physiological changes may facilitate the "escape" of malignant cells in a number of indirect ways and contribute significantly to the rapid rise of cancer with age.

Zusammenfassung

Die Hypothese, daß den im Alter entstehenden subzellulären Schädigungen somatische Mutationen zu Grunde liegen, wird im Zusammenhang mit der Wirkung ionisierender Strahlen und mutagener Chemikalien auf die Lebensdauer der Maus besprochen. Die dabei erhaltenen Ergebnisse lassen darauf schließen, daß somatische Mutationen in der Einleitung des Altersprozesses keine wesentliche Rolle spielen. Die Bedeutung der somatischen Mutationen bei der Krebsbildung ist jedoch komplex. Die Umwandlung einer normalen Zelle in eine bösartige stellt eine somatische Mutation dar, aber nur ein kleiner Teil derart umgewandelter Zellen scheint sich zu einem Tumor zu entwickeln, die Großzahl wird wahrscheinlich ausgeschieden. Es sieht aus, als ob ein Abwehrmechanismus zur Zerstörung maligner Zellen bestünde. Der entscheidende Faktor in der Karzinogenese liegt möglicherweise gar nicht in der Umwandlung der Zelle in eine bösartige, sondern in der Möglichkeit, die Wirtreaktion auszuschalten. Karzinogene Stoffe könnten jene Bedingungen schaffen, die es den umgewandelten Zellen erlauben, sich festzusetzen.

Die meisten experimentellen Tumoren enthalten in ihrer Plasmamembran spezifische Antigene; dies führt zur Annahme, daß immunologische Vorgänge im Abwehrkampf des Wirtes gegenüber bösartigen Geschwülsten eine bedeutende Rolle spielen. Wenn es auch nicht endgültig bewiesen ist, daß mit dem Alter eine allgemeine Verminderung der immunologischen Abwehrkräfte einsetzt, so scheint es doch möglich, daß andere altersgebundene physiologische Veränderungen das «Entschlüpfen» maligner Zellen auf verschiedenen indirekten Wegen erleichtern und damit signifikant zum raschen Anstieg der Krebsbildung im Alter beitragen.

Résumé

L'hypothèse que des mutations somatiques constituent les lésions sub-cellulaires qui aboutissent au vieillissement est discutée en relation avec l'effet des radiations ionisantes et des produits chimiques mutagéniques sur la durée de vie de la souris. D'après les résultats obtenus, ce ne sont pas les mutations somatiques qui jouent le rôle principal pour engendrer la vieillesse. Le rôle des mutations somatiques dans l'origine du cancer est encore très discuté. Il est vrai que la transformation d'une cellule normale en cellule cancéreuse signifie une mutation somatique, mais il semble qu'une portion infime de ces cellules transformées donne lieu à une tumeur; la grande majorité est probablement éliminée, et il semble qu'il existe un mécanisme de défense qui assure la destruction des cellules malignes. Il est probable que le facteur déterminant dans la carcinogénèse n'est pas tant la transformation maligne cellulaire que l'élimination de la réaction de défense du porteur. Des agents carcinogénétiques pourraient bien créer les conditions nécessaires pour permettre à des cellules altérées de se développer.

La plupart des tumeurs expérimentales contiennent dans leur membrane plasmique des antigènes spécifiques, et cela suppose que ces processus immunologiques jouent un rôle de premier plan dans la défense de l'hôte contre les cellules malignes. L'on n'a pas pu mettre en évidence avec certitude, qu'avec l'âge, il y ait une diminution globale de la défense immunologique, mais d'autres altérations physiologiques séniles semblent faciliter la «suite» de cellules malignes par d'autres voies indirectes, ce qui expliquerait l'augmentation rapide du cancer en gérontologie.

Riassunto

L'ipotesi che le mutazioni somatiche rappresentino le lesioni sub-cellulari risultanti durante la senescenza viene discussa in relazione all'effetto delle radiazioni ionizzanti e delle mutazioni di sostanze chimiche durante la vita dei topi. Da questi dati si conclude che le mutazioni somatiche non hanno un'importanza determinante nel provocare la senescenza. L'importanza che hanno le mutazioni somatiche nel cancro è complessa. La trasformazione di una cellula normale in una cellula maligna rappresenta una mutazione somatica; sembra però che solo una piccola frazione di una tale cellula trasformata assicuri la formazione di un tumore. La più gran parte viene probabilmente eliminata e sembra che ciò sia un meccanismo di difesa per la distruzione delle cellule maligne. Il fattore determinante della carcinogenesi non è dato dalla trasformazione delle cellule in uno stato maligno ma dalla probabilità di evitare la reazione dell'ospite. Le sostanze carcinogene possono agire creando le condizioni che permettono alle cellule trasformate di fissarsi.

Molti tumori sperimentali contengono nella membrana del loro plasma delle sostanze antigeniche specifiche e ciò fa pensare che dei processi immunologici abbiano una parte preponderante nella difesa dell'ospite contro

i tumori maligni. Mentre non sembra molto probabile che esista una depressione generale della reazione immunologica con l'età, altri cambiamenti fisiologici dipendenti dall'età possono facilitare la sopravvivenza delle cellule maligne in maniera indiretta e contribuire in modo importante al rapido aumento della frequenza del cancro nell'età avanzata.

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