CANCER: AN IMMUNE RESPONSE THROUGH CELL EVOLUTION

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"All that can be asked of a theory is that it shall be concordant with developing understanding in related fields of knowledge and that it shall imply certain experimental consequences which can be tested."

F. M. Burnet, Science Journal, September 1965.

Lymphatic lymphocytes undergo a limited or controlled degree of multiplication for ordinary immunity, which is a defence mechanism. Lymphatic lymphocytes undergo unlimited or uncontrolled multiplication in lymphatic leukaemia. Therefore lymphatic leukaemia is, or can be likened to, an uncontrolled defence mechanism. But leukaemia is a cancer. So at least one form of cancer is, or can be likened to, an uncontrolled defence mechanism.

This being so, it would be reasonable to conceive of some other forms of cancer, if not all, as being uncontrolled or unlimited defence mechanisms — in other words, a form of immune response. (There is evidence for the existence of host-to-tumour response in the case of implanted tumours, but that is beyond the scope of this paper). The pure logic of the above seems unassailable. Whether the conclusion is indeed correct or not depends on further evidence. This further evidence is at hand.

What other features are there in common between cancer and immunity against ordinary bacterial infection? Conversely what are the contrasts between cancer and ordinary immunity and can the contrasts or paradoxes be explained away as exceptions that prove the general rule of similarity? What would be the factor in cancer corresponding to the bacterial antigen? It is here suggested that this is the carcinogen itself. With regard to similarities, the majority are already widely known; others will be explained and supported by reference to original articles. Antibacterial immunity being salutary, and cancer being definitely the opposite, a slight mental effort will be necessary to accept them as being essentially parallel processes.

1. *Immunity* is preceded by an incubation period. *Cancer* is preceded — certainly in some known forms — by a precancerous period. In other forms, the latter is not excluded.

2. Reaction to a single isolated dose of a vaccine may never become established immunity. *Cancer-in-Situ,* unless carcinogenic action is continued, might never become established cancer.

3. *Immunity* is strengthened with each new dose of vaccine. *Cancer* gets more active with each new application of carcinogen (cfr. shoe-shop girls and viewing boxes and the necessity of repeated applications in experimental carcinogenesis).

4. *Well-established immunity* is difficult to overcome by further infection. A tumour that recurs answers poorly to radiation.

5. *Immunity* is heritable (this is known). There is a linear transmission of immunity to bacterial infection. Asthma is also transmissible, and what is asthma if not another form of immune reaction? Therefore an analogy triad is formed by Immunity - Allergy - Cancer.

The tendency to cancer can be inherited, as is known in the case of mammary cancer-prone rodents. Sarcoma in mice is heritable (Richmond, 1959a). Murine leu-

kaemia is transmitted vertically, a low strain becoming a high leukaemia strain (Heston, 1965 and Salaman *et al.*, 1963).

6. In old age, *general immunity* is retarded (Court-Brown, 1963). *Cancer* is resisted by the very old.

7. All sorts of organisms, including viruses, can produce an immune response. All sorts of carcinogens, including viruses, can produce cancer. Here we have a link as well as a parallel. There is also, in a sense, a contrast. Bacteria and *infectious* viruses produce a type of disease which depends on the type of infecting organism. Chemical carcinogens and oncogenic viruses produce types of tumour which depend on the type of cell affected. This leads one to consider the possibility that in certain conditions when circulating specific antibodies cannot neutralize an antigen (here carcinogen) non-specific local tissue cells proliferate in an attempt to take on that function, the resulting tumour being a cancer. Tumour-producing viruses are by no means all related (Andrews, 1964) yet there is no essential difference between viruses that cause tumours and those that cause disease. This gives us not only an analogy but an actual overlap of antigenicity and carcinogenicity.

8. There is a cellular mode of immunity independent of circulating antibodies (Walter and Israel, 1965a). Children with agammaglobulinaemia still recover from measles, etc. Cancer can be induced by adding viruses to a tissue-culture medium (Berwaldy and Sachs, 1963)

9. Lymphocytes and antibodies are obviously parts of "Self". There appears to be enough evidence pointing to the fact that a primary, that is, carcinogen-induced tumour, is also part of "self", for instance: (a) No antibodies coat the cells of a spontaneous tumour (Harveitt, 1966); (b) Immune reaction to own growth is negligible (Everson, 1964); (c) Antibody to own spontaneous tumour is never found (Czajkowski *et al.*, 1967); (d) A protein antigen is absent in basal-cell carcinoma (Rothberg *et al.*, 1964).

10. Is a hormonal element involved in immunity? As is well known a hormonal element is certainly involved in cancer.

11. Irradiating the whole body deimmunizes. Irradiating the whole body produces remissions in Hodgkin's disease.

12. (Concluding the Analogy). Immunity is a protracted defensive response to bacterial infection. In view of the numerous similarities listed above, it would seem reasonable to regard cancer as an exaggerated and protracted defence mechanism or immune response against carcinogens. Unfortunately for the host, that is where the similarity stops. The highly beneficial character of antibacterial immunity is contrasted sadly and tragically with that of cancer, very understandably described as malignant or evil. Now why should two essentially similar processes, if this is what they are, both apparently starting off as a protective mechanism, develop so differently? An answer might lie in their contrasting features.

Contrasting features

1. In the early neonatal period, the body is, except for inherited antibodies, immunologically defenceless, the immune mechanism not being as yet in full function. Yet, also in the early neonatal period, polyoma virus and chemical carcinogens are more successful (Brit. med. J. 1963 and Walter and Israel, 1965). If as suggested by similarities, a cancer is a form of immune response ,how would it be explained that it is more active precisely at a period when circulating immunity is at its lowest ebb? One explanation would be that tissue immunity comes into play when and because circulating immunocytes and their antibodies cannot deal satisfactorily with those substances that have come to be called carcinogens. This may happen not only when circulating immunity, as in neonates, is not yet properly established, but also when the carcinogen is partly or wholely out of reach of the circulating immunocytes, or else because, having established contact, the latter are unable, for mechanical reasons, to dispose of them as they would of bacteria or of other foreign material The tissue cells nearest the invading particles attempt to do the work left undone by circulating cells, but, not being

anatomically constructed or suitably sited for the purpose, even if they did succeed in ingesting a minute proportion of carcinogen, they would find it physically impossible to remove it into the circulation. The line of cells directly in contact with the particles not only cannot remove the latter but themselves block the way for circulating cells to act.

Trentin and others since 1962 have shown that adenovirus of types 12 and 18 when inoculated into newborn hamsters or rats cause sarcoma in a high proportion of the animals (Documenta Geigy, 1964). Therefore these viruses, normally infectious, are carcinogenic when circulating immunity is in abeyance. Also, Gross (1961) produced lymphoid leukaemia only if the mice were inoculated within 12 days of birth (Gross, 1961). The reason would appear to be the same. The lymphoreticular system is more active in strains with low incidence of spontaneous tumours (Stern, 1960). This could be interpreted as meaning that, because of an active lymphoreticular system, local tissue cells are not called into action.

Even for lymphocytes to be of any use in immunity, they must be mobile (Burnet, 1962). A classical example is the condition in obstructive lymphoedema where the part is packed with extravasated lymphocytes and yet infection is very easily established. The reason being of course, that the cells are prevented from leaving the affected zone.

2. In late middle age circulating immunity diminishes. In late middle age cancer increases. Here again the apparent paradox is explained, if we accept that tissue immunity (i.e. the tumour) takes over when circulating immunity fails.

3. The lymphoreticular system is more active in established bacterial immunity. This is known for a fact. Lymphoid tissue as a whole is more active in tumour-resistant animals (Murphy, 1926); in other words, tissue immunity is strong.

4. The cells involved in bacterial immunity are "regular" circulating immunocytes. The cells involved in cancer are the "territorials", i.e. any tissue cells. With these we include bone marrow and the lymphatic tissues whose cells naturally overflow into the circulation. To carry the immunity-cancer analogy to a practical conclusion: Bacterial immunity may be suppressed or "paralysed" (Medawar, 1968a). Would cancer be inhibited by giving high doses of carcinogen? This aspect will be dealt with more fully later on.

When local tissue cells proliferate in a vain attempt to reject, encapsulate or phagocytose the carcinogen particles, repeated applications of the latter stimulate proliferation even further. Supposing healthy tissue cells normally produced mutants every so often, these would become suppressed. But if normal tissue cells were devitalized by carcinogen, this might create better conditions for the mutants to survive in and become relatively "successful" in the evolutionary sense. Without any need of departing from the original idea of an immune response, these mutants (or cancer cells) would be the immunocytes evolved to neutralize the carcinogen particles — if only they could reach them. As it is the larger the tumour grows, the further away from the carcinogen do the newest cells accumulate, their "success" having been absolute. It is a sort of static warfare with progressive building up on either side and very few casualties.

If, at a very initial stage, the mutated (i.e. cancer) cells could have overcome the carcinogen entirely, the small balance of uncommitted cancer cells could have been themselves suppressed — and another "cancer-in-situ" or "pre-cancer" would have resolved. As the body is being continually bombarded by carcinogens of all sorts, it is here suggested that "cancer-in-situ" is not only common but a regular physiological occurrence, which only exceptionally fails to produce an early resolution and proceeds to establish a cancer. We shall never know even the approximate number of precancerous conditions any more than we shall ever know the number of undetected crimes.

Carcinogenesis

It is now generally agreed that pure irritation or trauma, however often re-

peated, is *not* sufficient to cause malignancy. On the other hand, it is also generally agree that chronic irritation or trauma is a definite adjuvant towards malignancy in the presence of carcinogens.

Some carcinogens are notoriously strong and only a small number of applications of them are sufficient to produce malignancy; others are weakly carcinogenic and a large number of applications are required in their case. Still other substances, not normally regarded as carcinogenic at all, given certain conditions, produce cancer. In the paragraphs that follow an attempt will be made to show why this is so.

Tattooing, even if covering a large surface, or even the whole body, does not produce cancer, and the histological findings are only one layer of macrophages (Walter and Israel, 1965b). This is a form of foreign body reaction. Would it rest at that if tattooing were repeated over and over again at one and the same site? Tattooing is in one layer and one layer of macrophages can cope.

Certain chemicals, such as hydrocarbons, are notorious for their carcinogenicity, yet even these have to be applied at the same site repeatedly before malignancy is produced. Iron injections repeated at different sites in therapeutic doses never produce sarcoma (Haddow *et al.*, 1964). Even an Iron-induced tumour starts off with histiocytes containing iron (Richmond, 1959b).

This stage is analogous to a tattoo-reaction. Iron particles injected therapeutically (and therefore discrete) appear in phagocytes and *in connective-tissue cells* (Goldberg, 1960). Iron injected in large quantities at the same site produces sarcoma.

Obviously, then, Iron, though not carcinogenic in the ordinary way, at a certain concentration and repeated often enough can devitalize normal tissue cells sufficietly to encourage the survival of their mutants.

The fate of various types of inhaled particles in the lungs and the reaction they provoke also have something to tell us in relation to carcinogenesis.

Coalminer's Pneumoconiosis. Here, inhaled carbon particles are transplanted by macrophages to the lymphoid tissues in the lung, where they remain throughout life. "Coalminer's pneumoconiosis... probably produces little disability by itself; it is the associated chronic bronchitis which is crippling" (Walter and Israel, 1965c). So, it appears, cancer of the lung is not produced as a result of carbon inhalation although this is repeated regularly sometimes for most of a lifetime. A man can have lungs black with coal-dust yet die in old age from something quite different. The reason would be that macrophages, which are circulating cells, are quick enough in their action to cope with the particles as they settle in a fine layer on the epithelial surface, and carry them away before they get out of hand. The epithelial cells themselves are not then called into action, and there is no need for them to multiply unduly. What is more, any tobacco smoke in these cases would be dealt with by the *already mobilized* macrophages. As a matter of fact lung-cancer in tobacco smoking coal miners is rare. This is an extreme example of general and local immune responses being in inverse ratio.

Lung Silicosis produces an almost identical response. Not so *Asbestosis*. The asbestos fibres are large relatively to coal and silicon particles, and they form several local foreign body reactions, as they cannot be carried away by circulating cells. This involves rapid proliferation of surrounding cells, which is accelerated by the continuous supply of freshly inhaled particles. Local mutated cells, which would normally be suppressed become "successful" in their new way of life and proliferate unhindered in the shape of a malignant growth. The analogy here is between a foreign-body reaction and cancer, completing the chain as a *Foreign body-Allergy-Immunity-Cancer* analogy.

One can well understand mutation taking place as the result of direct interference by a virus with cell-chromosomes. It is not so easy to visualize how a relatively large extracellular object such as an asbestos thread can induce the same

change. But without the necessity for departing from the Immune Response Theory, the "Cellular Evolution Theory" suggested above would account for it.

Sawdust has recently been found to be the cause of nasal and sinus cancer in wood workers (Acheson *et al.*, 1968). The oncogenic mechanism might be the same as for asbestos.

Certain Viruses produce cancer (e.g. the Rous sarcoma). Here the individual viruses could very well act inorganically like any other particulate carcinogen, the "repeated application" being provided by their biological multiplication. It is known (Therap. Notes, 1960) that these viruses interfere very intimately with the genes probably causing mutation in this way, and therefore superadded on the mutation normally taking place.

Endogenous Carcinogens could be the cause of spontaneous tumours according to data by P. A. J. Bentvelzen and G. A. Zalay of Amsterdam (1965). According to the Local Immunity theory — or the cell Evolution theory — either is applicable — the mutated or cancer cells have now become immunocytes potentially better equipped than normal cells to deal with the invader, even though the younger generations are so far removed from the viruses themselves that they might never even make contact with them. This would be evolution at cell level analogous to that which Burnet (1965a) applied to immunity. It is known that a higher type of animal organism might evolve to fight or fly from a natural oppressor even though their respective future generations may never meet, for instance cetaceans and the descendants of their former land-dwelling enemies. Why should this not also take place at cell-level?

If cells susceptible to carcinogenic viruses are acted upon instead by a chemical carcinogen, or even by radiation, an identical type of cancer is produced. This means that any given tissue cell *can mutate in one way and one way only*, and the character of the causative agent, whether chemical, viral, or radiation, becomes somewhat insignificant once proliferation of the mutated cell is a *fait accompli*. The reader is therefore being asked to accept not one contention but two, each of which, however, lends support to the other:

(i) The anthropocentric view that normal tissue cells have changed into immunocytes and as such increase and multiply to a degree far beyond that required for ordinary and immediate body defence purposes. (This covers the pre-cancerous *reversible* stage) and

(ii) The *more detached, biological* view that ordinary tissue cells, forming part of an organized whole, when reacting to the presence of certain noxious parcles, whether chemical, viral or radiation, partly survive in a mutated form, in accordance with recognized laws of evolution, but completely relieved of all responsibility to the parent body, and in this form increase and multiply, the resulting tumour being not only a useless parasite but also a deadly one. It is now selfishly concerned only with its own survival and propagation.

Any good that might have been done by the mutated cells' first role (immunity), is therefore limited only to the precancerous period, and far outweighed by the harm done in its second role, that of struggling for its own primitive existence.

As an extreme *reductio ad absurdum* we may even go as far as to say that broadly and *biologically speaking*, malignancy does not exist. It is generally agreed that an epithelioma establishes itself as malignant when the basement membrane is pierced. There is no basement membrane where sarcoma is concerned, and this may account for its early malignancy.

When bacteriophage — a virus — attacks bacteria, either they are destroyed or new types of bacteria emerge. This is another example of immunity through evolution at cell level. Owing to the natural barrier at the tissue-carcinogen frontier, malignant cells grow mainly inwards, away from the carcinogen. This would explain the following apparently paradoxical observation:

(i) That "chemical carcinogen disappears as the tumour grows" (Rous, 1947). Naturally, the larger the tumour grows,

the less likelihood is there for carcinogen to be included in the biopsy material. Again "Chemical carcinogens attach themselves to neighbouring tissues but not to the cells of the cancer they have induced" (Walter and Israel, 1965d). The reason, of course, would be the same.

(ii) "Fe-induced tumours later lose their avidity for iron" (Richmond, 1959c). The avidity is still there, but contact is impossible.

(iii) "Viruses cause cancers yet are not demonstrable in cells" (Andrews, 1964). By the time a tumour is diagnosed it has grown out of all proportion to the causative viruses.

Radioactive substances produce cancer. Here again, it is not the type of radioactive substance that determines the type of growth, but the type of cell affected — as for chemical or viral carcinogenosis, the surviving mutated cells being identical with those from these latter causes. This should simplify treatment which could therefore, at least theoretically, be the same for all.

Something which may just be mentioned in passing at this stage is what Julian Huxley calls "multiple correlation". It is beyond the scope of this paper to go into its details. It can be said however that certain factors enhance the effect of the principal carcinogen; these are: temperature, primitivity of cells affected, pH, anaerobic metabolism etc. This aspect of the matter might lead to other lines of approach to the problem of cancer and its treatment, and could be made the subject of a further paper.

Carcinogens, therefore, are varied in nature being either chemical, viral, or the effects of radiation. To this list it is suggested *physical* be added as well. This would take in particulate foreign bodies like asbestos, sawdust, jute, etc. (Daily Telegraph, 5th July, 68, p. 21, col. 1) which are receiving more notice of late. What is it, then, that all these widely different agents possess in common which enable each of them, *if applied often enough at the same site,* to provoke cancer? At first sight, very little if anything at all. Yet if the negative aspect is considered, it will be seen where they agree: in that none of them can (I repeat, if reapplied often enough at the same site) be disposed of by the usual protective mechanisms of the body, which are:

(i) *Rejection,* an allergic reaction as for pollens, some other foreign proteins, homografts, etc.

(ii) *Immune Response,* as for disposal of foreign virus microorganisms and macromolecules by the reticuloendothelial system, and

(iii) *Encapsulation,* as for foreign bodies.

The survival and rapid multiplication of mutated cells is an attempt to substitute any of (i), (ii) or (iii), which unfortunately, is thwarted by local phyisical conditions.

The Theory

It is felt that enough has been said above to justify an enunciation. Cancer is a progressive and irreversible local immune response by static tissue cells against certain particulate substances which cannot be disposed of by the circulating immune mechanism. The response consists in a survival of mutated tissue cells, the mutation being caused in some cases by direct interference with the cell genes by carcinogens. The mutated cells (alias the cancer cells) have the potential nature of immunocytes, though this function is permanently frustrated owing to insufficient contact between cancer cells and carcinogen. The cancer cells increase and multiply for two reasons: firstly because, as immunocytes ,they cannot rest till all antigen (here the carcinogen) is disposed of ,and secondly because they have evolved into a successful colony of unicellular organisms which lives as a parasite on the body as its pabulum completely regardless of the host's economy.

As a "give away" corollary to this theory, by reversing the analogy, immune cells could possibly be regarded as mutated RE cells (as for tissue cells) each microorganism producing its own type of antibody (Burnet, 1965b). It is known that any macromolecule can produce an immune

response (Coombe, 1968). Is this not uncannily reminiscent of carcinogenosis?

Note that leukaemias are included here as local tissue tumours. In any malignant disease, however localized this may be, cells are always found in the blood. Owing to their origin in the haemopoietic system, leukaemic cells find themselves in the circulation more readily and more abundantly, but for the purpose of the present argument, this system is considered static. So any distinction would really be one of degree not of essential nature.

Treatment

Surgery for established cancer, though sometimes successful, is at best mutilating.

Regarding *Cytotoxics*, it is true that cancer cells are destroyed by them, but so are leukocytes, and no cytotoxic drug is really effective as such without also causing leukopoenia (Brit. med. J., 1965).

In *Irradiation* we have a long-tried ally. Deep X-rays penetrate into the depths of the tumour which is out of reach of the causative carcinogen. Radioactive gold cures established melanoma when injected into limb lymphatics (Jantet *et al.*, 1964) but X-rays travel in straight lines and, as is known only too well, might miss some peripheral cells. Also, ionizing radiation can inhibit growth of normal as well as neoplastic tissue (Starikova *et al.*, 1962). However, we are very grateful for radiation, in spite of its drawbacks. But is it the final answer? As far as the present line of argument is concerned X-rays do show beyond doubt that at least one type of carcinogen can be used to treat cancer.

Trypan-Blue, known to be cytotoxic, is also mentioned as an immuno-suppressive agent (Medawar, 1968).

"Hektoen used *Mustard Gas* (Dichlorethylsulphide) as an immuno-suppressive agent as far back as 1917, and the history of the use of X-rays for that purpose is even older" (Medawar P., 1968b). Here we have two agents both for immuno-suppression and as cytotoxics in cancer. So why not use the other immuno-suppressive, namely *Immunological Paralysis*, as a cancer inhibitor? We know what carcinogen particles do to normal cells — they turn their descendants into cancer cells. What would carcinogen particles do to cells already cancerous with which they came into contact? The following list seems to cover all possibilities:

(i) Nothing at all.
(ii) Cause a second abnormal mutation.
(iii) Revert them to the original condition of the normal parent cell.
(iv) Destroy them directly, or indirectly by cytostasis.

Let us consider these possibilities in turn.

(i) *No action at all.* This could well be, in which case this whole theory of an immune response falls through and there is nothing more to say for it. Therefore what follows is based on the theory being valid.

(ii) *Cause a second mutation.* This, though theoretically possible, is not borne out by present knowledge of cancer cells. Cells of a given cancerous growth, once established, have never been known to undergo a second mutation.

(iii) *Revert them,* i.e. mutate them back to normal parent tissue cells. This, of course, would be a very good thing, but is not very likely, as evolution is progressive.

(iv) *Destroy them directly,* or indirectly, the latter by cytostasis. This seems the only alternative left when the other three are eliminated. But it also has merits of its own. Having accepted the theory of immunity, we must also accept that the cancer cell, as an immunocyte, combines with the carcinogen particle in some way, perhaps even phagocytosing it. Carcinogens interfere with cell metabolism, sometimes, as in the case of viruses, by acting directly on the genes. It is therefore not unlikely that something similar would happen with cancer cells, whose biological mechanism would thus be seriously interfered with. This interference, as we have seen, does not produce a second 'forward" mutation, is not likely to cause a "reverse" mutation, and we are therefore left with direct destruction of the cell, or, the next best thing, cytostasis.

"Pre-cancer" and "cancer-in-situ" cells are cancer cells like any others, and yet, as in the case of the lung, they have been known to disappear when the subject, e.g. stopped smoking. The cessation of supply of carcinogen in this case might have allowed such an action as the above to take place and effected a complete cure.

The above, of course, can only happen if cancer cells can reach their targets, the carcinogen particles. Unfortunately the cells tend to multiply and spread deeply further and further *away* from the carcinogen and contact becomes well nigh impossible.

Now supposing fresh carcinogen — almost any one would do, not necessarily the causative one (it will be remembered that, once cancer is established, the nature of the cause becomes irrelevant) — could be introduced into the body in such a way that it reached each and every one of the tumour cells, the above result might be achieved. Owing to the compactness of the tumour we are here faced with the difficulty or perhaps impossibility of the particles pervading the intercellular spaces of the tumour as we would wish. This is where the spreading factor hyaluronidase could come to the rescue. If carcinogen particles could be administered systemically in solution in or with hyaluronidase, there is a possibility that they might reach the tumour before they could have any effect on normal body cells en route, and, once they reach the tumour, they would infiltrate (by virtue of the accompanying hyaluronidase) all its interstices to where they could be acted upon by, and act on the tumour cells.

The chances of the carcinogen particles harming normal cells en route would be minimal (though this, of course would have to be checked by animal experiment) because particles are discrete when given in this way; at the worst, the excess might be taken up by phagocytes and wasted. If they did get as far as the tumour it is hoped that they would be pounced on by the cancer "immunocytes", if there is any truth in the theory that after all these evolved with a view that one day they should neutralize their natural enemy the carcinogen.

The principle of bombarding cancer cells with carcinogen therapeutically would in effect only be an application of the Immunity Theory; for it is well known that one method of de-immunization is precisely to bombard antibodies with antigen.

In support of the above purely theoretical reasoning, there is some useful experimental evidence, which shows that:

(a) A well-known carcinogen has inhibited cancer growth; and
(b) Hyaluronidase could be a suitable vehicle.

(a) Starikova and Vasiliev (1962) experimented with rat sarcoma in vitro. They found that high concentrations of Dimethylbenzanthracene (DMBA) completely prevented the outgrowth of normal fibroplasts but they also found that the same carcinogenic hydrocarbon inhibits growth of normal *and of neoplastic* tissues. Small and moderate concentrations of DMBA were resisted by sarcomata whether HC-induced or cellophane-induced. (As suggested above, the causative carcinogen loses its importance once malignancy is established.) However, — and this is of great importance — DMBA, *in highest concentrations only,* caused partial or complete inhibition of sarcoma cultures.

The principle has therefore been established that a chemical carcinogen can inhibit the growth of a chemical-carcinogen-induced malignant tumour. This is, of course, a tremendous step forward. But, having established this principle, the next question is: why did the DMBA not inhibit the tumour *completely* and *every time*? The answer suggested here is that even the strongest concentration was not always able to find its way through the tumour's intercellular spaces to seek out each and every cell, the obstacle, of course, being the intercellular ground substances. This brings us back to the ground-substance liquifier *Hyaluronidase* which is found so useful clinically for the spreading of injected substances and for preventing the formation of haematomata. Dyes into the skin diffuse better with hyaluronidase Walter and Israel, 1965e) it can even be used subcutaneously with opaque substances for I.V.P.'s. Hyaluronidase is safe

to administer systemically (Popper, 1967) and anyway its action on tissue is reversible. As is well known, an allergen *alone* applied to the skin of a sensitized person causes a severe allergic reaction. If the allergen is applied to the sensitized skin together with hyaluronidase, not only is there no side-effect, but it desensitizes the existing allergy (Potter, 1967). This shows:

(i) that spread of hyaluronidase through the body can reach the sensitized zone (nose, bronchi, etc.); and

(ii) also applicable to cancer, that selectivity takes place at a distance, also as in this case producing a form of immulogical paralysis.

What is more, there also actually exists an association between cancer-cells and hyaluronidase; it is known that cancer cells tend to lose their attachment and stick to foreign substances (Abercrombie *et al.*, 1963). Also extracts of malignant tumours show the presence of hyaluronidase (Walter and Israel, 1965f). Could this possibly mean that an attempt is being made by the tumour itself towards natural treatment on the very same lines here suggested as artificial therapy? With regard to the use of hyaluronidase a sobering thought is that in bladder cancer from certain aromatics hyaluronidase can actually be an adjuvant towards tumour formation (Walter and Israel, 1965f).

Should the carcinogen-hyaluronidase combination show any therapeutical promise, there seems to be no reason why it should not be used together with more orthodox methods. Should the working theory of carcinogenesis and subsequent cancer treatment here presented warrant the time and expenditure, it is open to testing by animal experimentation. It should not take long to accept or discredit it.

Postscript

The conclusion arrived at from pure reasoning, that an attempt should be made to cure cancer by carcinogen administered systemically with hyaluronidase, is strongly supported by the work of Starikova and Vasiliev. Popper's experiments with hyaluronidase in allergy are equally encouraging. As both these articles came to the author's attention when this paper was already drafted they give even stronger support to what might otherwise have appeared to be mere fantasy.

Summary

It is suggested that cancer might be the body's immune response to particulate noxious substances (hence "carcinogen") which the ordinary defensive systems are unable to deal with. The response would consist in the survival and proliferation of mutated local tissue cells (cancer cells); on the principle of Darwinian evolution, which become actual or potential immunocytes against the carcinogen. Owing to a physical barrier, carcinogen can never effectually come in contact with these new cells, which therefore proliferate indefinitely as a parasitic colony of unicellular organisms.

Should it be considered that there are sufficient grounds for accepting cancer as an immune response, it is suggested that treatment might take the form of immunosuppression. Large doses of carcinogen administered systemically might be able to produce immunological paralysis with disappearance of cancer cells. In the hope of liquefying the tumour's intercellular spaces to facilitate spread of carcinogens, it is suggested that the latter be administered together with hyalurodinase.

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