IMMUNITY AND RESISTANCE IN CLINICAL CANCER*

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In spite of the intensive search for chemotherapeutic remedies, clinical cancer management is, in practice, still limited to surgery and radiotherapy. While both these methods are more or less efficacious in eradicating the primary lesion, and perhaps also the first phalanx of regional spread, most patients so treated still die of disseminated malignant disease. It seems unlikely that the principles of surgical and radiotherapeutic practice could be extended so as to cure those cases for which our current techniques are not adequate. Indeed, far from improving our results, attempts to extend the treated zone frequently diminish the probability of cure. The prognosis seems to be largely determined at the outset by the extent of the tumour at the time of treatment, its rate of growth, and its tendency to metastasize. This suggests that the next important step in the control of clinical cancer is to investigate those factors by which the mammalian host influences the rate of growth and dissemination of tumours.

RESISTANCE IN EXPERIMENTAL CANCER

The history of experimental cancer research is dominated by the rude fact that autogenous growths, including human cancer, will not respond to those simple procedures by which transmitted animal tumours are readily cured. Except under specially controlled conditions, transmitted tumours are genetically and antigenically foreign to their hosts, maintaining a precarious existence in the presence of circulating isoagglutinins.[1] All transplanted tissue, including experimentally transmitted tumours, has been shown to carry specific antigens[2] which, like the human blood-groups, correspond to definite 'histocompatibility genes'[3] in the host. Only in a thoroughly inbred strain of animals, bearing a tumour which arises regularly in that strain, avoiding prolonged serial passage of the tumour which may permit diversification from its host, can we be reasonably sure of a tumour-stability approaching that operating in human cancer. Otherwise tumour transplants are virtually 'incompatible' with the host, and are easily cured by almost any form of non-specific trauma or intoxication. Almost all chemical agents developed for cancer therapy have been selected on the basis of their non-specific action in mice bearing incompatible tumours and, for this reason alone, cancer chemotherapy as currently practised is unlikely to contribute effectively to human medicine.

On the other hand, a most valuable contribution of animal tumour research to the problem of human cancer lies in the fact that the resistance of the host against its tumour can be modified by many physical, chemical and physiological factors. Murphy[4] first proved that the reticulo-endothelial system, in particular the lymphocyte, exerts a controlling influence on tumour growth. Agents stimulating the production of antibodies were able to enhance the host's tumour-resistance, often to the point of absolute immunity.[5] This effect can be evoked by spontaneous regression of unstable tumours,[6] vaccination with attenuated tumour strains,[7] injection of non-specific antigens such as embryo skin[8] which may, however, contain antigens in common with the tumour,[9] implantation of spleen from normal animals,[10] injection of formaldehyde into the tumour,[11] temporary ligation of the blood-supply to the growth,[12] and implantation of radiation-attenuated tumour fragments.[13] The effect of antisera[14] and of splenic fragments from immune animals[15] was also demonstrated against tumour tissue-cultures *in vitro*. None of these manipulations, however, has conferred a lasting immunity to implants of compatible or autogenous

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tumours, or succeeded in destroying such tumours when established, nor have they had any beneficial effect in human cancer cases.

The converse effect—abrogation of natural or acquired resistance to tumours—is easily produced by factors inhibiting reticulo-endothelial function, such as total body irradiation,[16] blockade of the RE-system with colloids,[17] administration of cortisone and allied drugs,[18] overwhelming doses of antigen in the form of lyophilized tumour,[19] neurogenic stress,[20] or local trauma,[21] irradiation,[22] or intoxication.[23] All these agents can promote the onset of tumours, facilitate their growth and dissemination, and inhibit their response to treatment, suggesting that immunological processes might affect the pathogenesis of cancer in man and its prognosis.

IMMUNOLOGICAL MECHANISMS IN THE PATHOGENESIS OF CANCER

The mechanism of immunity must have appeared early in the course of evolution of metazoal organisms, when it became necessary to maintain the integrity of the cell-population by selective elimination of all extraneous cell-types, be they invading parasites or aberrant body-cells. Apparently 'normal' and 'foreign' cells can be distinguished by their characteristic protein structures: genes, enzymes or antigens, which carry identifiable patterns, 'markers'[24] or 'information'[25] analogous to the cybernetic mechanisms of modern communication theory. Homeostasis can then be maintained by the elimination by the reticulo-endothelial system, through antibodies and phagocytosis, of all cells carrying markers other than those to which the body is adapted. This mechanism resembles the automatic radar defence-system IFF ('identification-friend-foe'), in which friendly craft are fitted with a radar reflection circuit returning a characteristic signal pattern, and the receptors so coded that this pattern alone fails to actuate the defensive missiles. In the vertebrate host the RE-system receives its discrimination-code during foetal life, when it actively acquires a specific tolerance to all antigens present at that time.[26] Examples of this effect are found in the human blood-groups, cross-transfusion reactions in dizygotic cattle-twins, intra-uterine grafting experiments, and probably too in the so-called milk-factor of newborn mice. There is, apparently, a critical period in early life before which any proteins present are classified as 'friendly' for future reference, but after which the reaction is reversed and all unrecognized antigens are treated as 'foreign'.

Whether the proximal causation of cancer is a somatic gene-mutation,[27] a virus-like transmissible agent,[28] or an enzymatic[29] or antigenic[30] adaptation, is no longer of practical importance, since it now seems probable that these various concepts are merely different facets of the same physical process, initiated either by intrinsic thermodynamic events,[31] or as a result of endogenous or exogenous chemical or physical agents.[32] Cancer cells, whatever their origin, contain genes,[33] antigens[34] and enzymes[35] other than those found in normal tissue, and are consequently subjected to immunological homeostatic control. For this reason single cancer-cells or isolated small groups cannot in themselves give rise to malignant tumours, a certain critically large number of cells being required before tumour growth can commence.[36]

The subcritical dormant tumour-cell colony, however, can suddenly adjust to the presence of antibodies, escaping from homeostatic control, by deleting marker-genes or de-differentiating.[37] Multiplication of these mutant cells produces an excess of foreign protein, which will then neutralize circulating antibodies and inhibit their further production.[38] In this way an excess of tumour antigen will suppress the resistance of the host sufficiently to permit unrestrained tumour-growth,[39] invasion and metastasis.[40]

It would seem to follow that most adults must possess many small groups of isolated neoplastic cells persisting for long periods as 'subcritical colonies',[41] which only occasionally reach critical size and become clinically overt. This situation is recognized in solar hyperkeratoses, small rodent ulcers, intraduct papillomata of the breast, adenomata of thyroid and prostate, intestinal polyposis, and papillomata of the bladder, all of which have been observed in the quiescent 'precancerous' state for many years before active growth supervenes. Presumably a similar phase also occurs in tumours of other less accessible tissues, especially in cases where a precipitating injury such as incomplete excision preceeds the overt disease.

There is evidence, too, that the host may continue to exert some restraining influence on the growth of established tumours. A frequent finding at autopsy in cancer cases is the presence of many tumour-cell emboli which have evoked a surrounding inflammatory reaction and are in the process of dissolution.[42] Similarly, one not infrequently observes a patient who develops distant metastases 15-40 years after removal of the primary growth.[43] Apparently tumour-cell emboli can be restrained in a dormant state for extremely long periods, and suddenly become active when the host's resistance is diminished as a result of age, debility or intercurrent disease.

Both, therefore, in the healthy adult carrying subcritical or precancerous foci and in the locally cured patient with subcritical or dormant metastases, those factors which might affect local or systemic resistance are of the first importance in determining future survival. Since these factors are readily influenced by trauma, stress, radio-diagnostic procedures, and medication, they fall within the scope of everyday medical practice.

EXTRANEOUS FACTORS INFLUENCING GROWTH AND DISSEMINATION OF CANCER

An almost unlimited range of materials have been shown to induce tumours in experimental animals,[44] and an equally wide range of common agents to which the human population is habitually exposed in industry,[45] medical treatment,[46] social ritual,[47] and the atmosphere of both town and country,[48] have been incriminated as probable carcinogens. Carcinogenic agents may, in general, be shown to act in one or more of 3 possible ways:

1. *Initiating agents* are weakly carcinogenic in themselves but become potent in combination with certain 'promoting' factors.[49] This group of agents are all effective mutagens, and presumably act through mutation of genetic 'marker' protein, giving a profusion of subcritical tumour-cell foci which, however, can proliferate only if local resistance is suppressed by the action of promoting factors. Examples of this type of action include ionizing radiation, polycyclic hydrocarbons like benzpyrene, and mitotic poisons like triethylene-melamine, which have in common the ability to deliver to the relevant protein molecule a quantum of energy in excess of 3 electron-volts.[50] Included in this group are many agents with which contact is not easily avoidable, such as the hydrocarbons in smokes, fogs, industrial fumes, pitch, and cigarette tars;[45,47,48] radiation by cosmic rays, atmospheric radon and uranium dusts, medical and industrial X-rays, and the products of atomic-energy enterprises;[51] and, of special importance in the Transvaal, ultraviolet solar radiation,[52] to which the skins of all outdoor workers are regularly exposed.

2. *Local promoting factors* or 'co-carcinogens'[49] are themselves unable to induce cancer, but are very effective in stimulating subcritical precancerous foci into active growth. Almost any form of trauma, chronic irritation, or stimulation of hyperplastic growth, has this effect. Application of croton oil, surgical incision, and injection of foreign material, have all been used experimentally as co-carcinogens.[49] In the same category are the growth-stimulating hormones, such as oestrogens[53] acting on uterine and mammary epithelium, and androgens acting on the respiratory and alimentary tracts, which probably accounts for the sex differences in the susceptibility of these organs to identical carcinogenic stimuli. Promoting factors are of special importance in the management of tumours arising in sites known to harbour other precancerous foci, as in the case of solar hyperkeratosis with skin cancer, or multiple papillomatosis with carcinoma of the bladder. In these cases excision of the primary lesion is often followed by several new primary tumours (sometimes erroneously thought to be recurrences) arising in the surgical scar. In such cases, presumably, a non-traumatic form of treatment without co-carcinogenic effects, such as radiotherapy, might have been preferable. Similarly it is frequently observed that a plastic surgical procedure, which would certainly have been successful for the treatment of skin cancer in, say, an office worker in Europe, means a slow and painful death if indiscriminately applied to a Transvaal farmer or bricklayer.

3. *Systemic promoting factors* comprise that large group of agents which inhibit immunological mechanisms. They include injection of colloidal materials which mechanically blockade the RE-system, such as india-ink, trypan-blue, ferric saccharate (recently marketed for intravenous iron medication), and thorium dioxide sol (radiodiagnostic contrast medium);[54] agents producing lymphopenia, such as total body radiation[55] and virus infections like influenza;[56] mitotic poisons and similar drugs used for cancer palliation, including mustard-gas derivatives, folic acid, purine and amino-acid antagonists (aminopterin, azoguanine, and sarcolysine), and synthetic vitamin-K analogues (menadione or 'synkavit');[57] excessive doses of anti-reticular cytotoxic sera;[58] hormones, like pituitary corticotrophin and possibly certain adrenal steroids;[59] and all severe injuries, debilitating illnesses, pregnancy, and major surgical procedures, collectively classified as 'stressors'.[60] Although many of these agents have been observed to inhibit temporarily the growth of established tumours —hence their repute as palliative agents—they tend, in general, eventually to accelerate tumour proliferation and dissemination.[61]

The 3 levels of carcinogenic action described are not entirely independent categories, and some of the agents enumerated may work at more than one level. Powerful carcinogens like methylcholanthrene and radio-active materials, for example, are known to act at all 3 levels, others apparently at 2, and many behave more or less in the manner indicated. From the practical point of view, it is the obvious duty of every physician to prevent, as far as possible, the onset of cancer by minimizing exposure to suspected or potential carcinogenic agents, eliminating all inessential diagnostic radiographic examinations in younger members of the community, avoiding all forms of radiotherapy or administration of radio-active isotopes for non-malignant conditions unless a serious threat to life or health makes such exposure essential, ensuring adequate protection of the community from radio-active products, including atmospheric and oceanic contamination by atomic bombs, discouraging smoking and similar suspect habits, and urging control of smoke, soot, and motor exhaust fumes. The older members of the community, who presumably already carry precancerous foci, and in particular apparently-cured cancer cases who may carry dormant tumour-cell rests, should especially not be exposed to promoting factors such as corticotrophic, gonadotrophic and sex hormones, any of the cancer-palliative drugs known at present, avoidable trauma, and stress-inducing operations, although chronic irritative or inflammatory conditions should be corrected. Many of the drugs mentioned are useful in the palliation of incurable malignant disease, but it is obviously important to avoid their use in curable cases, even long after the tumour has apparently been eradicated.

HOST RESISTANCE AND THE RESPONSE TO THERAPY

The significance of systemic immunity in clinical cancer control is nowhere better illustrated than in the response of tumours to radiation. The doses used clinically are known to have little direct effect on the tumour cells *per se*, and doses from 10 to 100 times greater are found necessary to destroy cancer cells irradiated outside the host in tissue culture.[62] A tumour irradiated *in situ*, however, undergoes a subtle antigenic change rendering it susceptible to immunological and phagocytic processes in the host, which can then effect its destruction. Any factor tending to isolate the tumour from the vascular and cellular elements in its bed will prevent its regression following otherwise on adequate irradiation.[63] Tumours in avascular scars and ulcers, particularly the devitalized scars and necrotic ulcers from previous irradiation, are notoriously radio-

resistant. Similarly factors inhibiting systemic immunity, such as total body irradiation or mitotic poisons, including cortisone and other cancer-palliative drugs like nitrogen mustard and azoguanine, will all render tumours incurable by radiotherapy.[64] Even the so-called radiosensitizing agents such as menadione or 'synkavit' will in fact prevent complete regression of adequately irradiated tumours.[65] It would seem that practically all *palliative procedures automatically preclude the possibility of cure.*

Further, when extensive or deep-seated tumours are irradiated, the correspondingly large volume-dose itself induces a leukopenia and inhibits reticulo-endothelial function, with the result that such tumours often fail to respond to ordinarily curative doses. The systemic resistance factor thus sets the upper limit for size and depth of tumours curable by conventional radiotherapy.

The converse of this effect, that is the enhanced radiosensitivity of tumours when host-resistance is stimulated, has only recently been demonstrated with homozygous tumours grown in genetically modified heterozygous hosts,[66] with a mutant tumour grown in homozygous hosts, and with tumours grown in hosts specifically immunized against them.[67] These effects point to the future possibility of specifically immunizing the human host against his own tumour, thus enhancing its curability by radiation and possibly also preventing or delaying the growth of metastases.

CLINICAL EFFECTS OF ENHANCED TUMOUR RESISTANCE

The response which might be expected were it possible to enhance the patient's resistance to his tumour, is exemplified by those rare cases when the tumour is genetically or antigenically distinct from the normal tissues. The testicular seminoma, for example, arising from haploid germ-cells in a diploid host, is the most radiosensitive human tumour known and can be cured by radiation even when widely disseminated.[68] Another example, the chorionepithelioma, arising from foetal cells and growing in the maternal host, is exceptional in that, even in the presence of metastases, it frequently regresses spontaneously after removal of the primarily affected organ.[69]

All too rarely one encounters in the follow-up clinic a patient who, owing to some obscure and fortuitous combination of circumstances, develops an unusually effective resistance against his tumour.

Case 1. Miss W., a 60-year-old European spinster, presented at the Johannesburg Hospital in 1948 with a Stage-II carcinoma of the upper outer quadrant of the right breast of 9 months' duration. The primary growth was 7 cm. in diameter, not attached to deeper structures, but there was an enlarged hard mobile lymph-node in the right axilla. She was treated by radical mastectomy and routine post-operative roentgen therapy. Histologically the tumour was a high-grade, rapidly proliferating, spheroidal-celled carcinoma. In 1950 the patient developed widely-dispersed skin metastases over the whole trunk, head and neck. Although no treatment was necessary, the patient being free of symptoms and having what was considered a hopeless prognosis, some of these skin nodules were irradiated experimentally, purely in order to corroborate the minimum lethal dose after Friedman's method.[70] Using small fields of superficial radiation, 24 separate nodules were given a series of successively smaller single doses over a period of 4 years. Of the 24 nodules treated, 17 disappeared completely after doses ranging from 2000 r down to as low as 300 r. Since the lethal dose of the average breast-cancer and its satellite nodules, under the physical conditions used here, is not less than 1200 r,[70] this result indicates a greatly increased radiosensitivity. Nodules given 250 r or less or left untreated, reached a size of 10-15 mm. in diameter and then remained stationary for the 5-year observation period (Fig. 1). Biopsy of one such stationary nodule showed the same high-grade, rapidly growing,

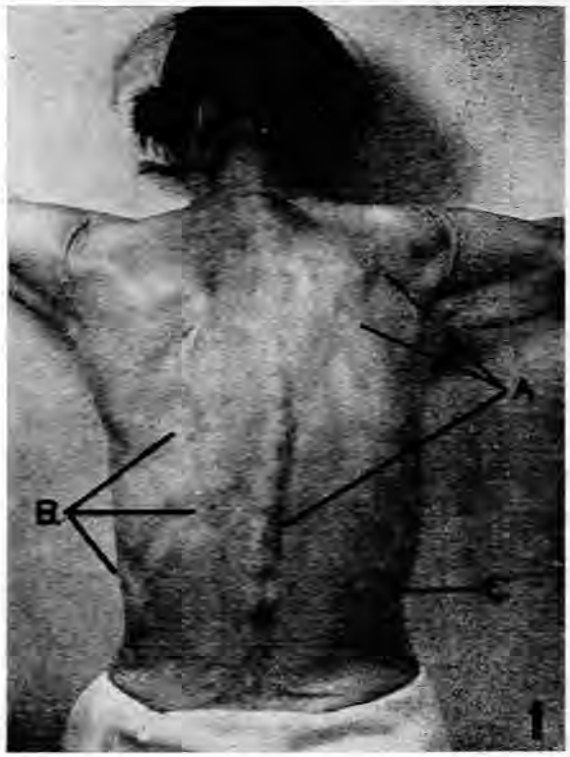

Fig. 1. Metastatic cutaneous carcinomatosis, showing, (A) nodules cured by moderate dosage ranging from 500-2000 r in a single exposure, (B) nodules persisting unchanged after doses of 200-300 r, and (C) untreated nodule remained static for a 5-year observation period.

spheroidal-celled carcinoma as the primary growth. The patient has remained symptom-free without any further extension of the tumour, and except for poor nitrogen balance, has remained physically healthy for 8 years after the onset, and 5 years after overt dissemination of her tumour. As in the experimental animals, a markedly increased radiosensitivity is here associated with a degree of anti-tumour resistance in the host. Whether this resistance was built up by irradiation of the series of small deposits with progressively diminishing doses, or whether the patient had the good fortune to possess a strong tumour resistance *ab initio*, is a matter for future investigation.

Apart from systemic immunity, the effect of *local* resistance on the growth of metastatic tumour is well-illustrated by

Case 2. Mr. L., a 59-year-old European mechanic, presented at the hospital in 1948 with a 6-cm. diameter squamous carcinoma of the dorsum of the left hand of 2 years' duration. This was treated with superficial radiotherapy. Seven months later there was an obvious local recurrence, and involvement of the epitrochlear and axillary lymph-nodes. All three sites showed squamous carcinoma on biopsy, and were treated by intensive irradiation. For the succeeding 6 months the patient was well except for a small necrotic ulcer at the primary site. He then suddenly developed a febrile constitutional reaction with a generalized macular

rash. The skin rash faded within a few days, except for those lesions inside the irradiated areas which persisted and increased. Some weeks later each macule within the irradiated skin-fields

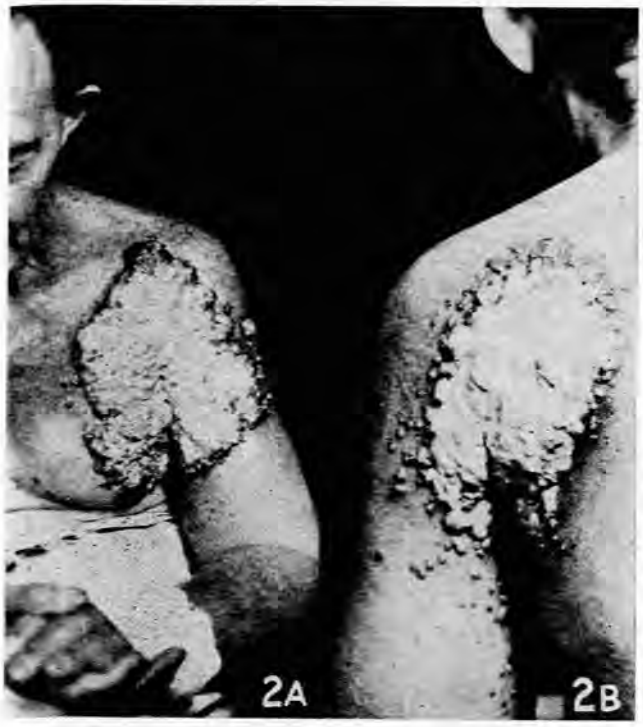

Fig. 2. Metastatic cutaneous melanomatosis confined to two irradiated axillary skin fields. There is obviously a resistance-factor operating in the unaffected skin.

had developed into a palpable tumour. The lesions became confluent, forming two rectangular tumour-masses exactly demarcating both axillary treatment-fields (Fig. 2). Biopsy of these lesions showed unpigmented malignant melanoma! Although the primary melanoma was not found, the patient dying shortly afterwards without necropsy, there can be no doubt that widespread melanoma-cell embolization had occurred, but that all tumour emboli were effectively suppressed except in those tissues where local resistance had been impaired.

CONCLUSIONS

Both local and systemic tumour-resistance factors have been identified in the human being, shown to determine the appearance of certain tumours, and to affect profoundly the prognosis of treated cancer. It behoves the physician to remain aware of these effects, particularly in relation to the existence of precancerous or subclinical tumour-foci, and to avoid local trauma, stress-inducing manipulations or medication which might embarrass the resistance mechanism and thus promote the onset of overt cancer.

In the management of established growths it is essential to decide at the outset between palliative and curative treatment, since all palliative therapy or medication interferes with local or systemic resistance-factors and thus precludes cure.

Follow-up of successfully-treated cancer cases also requires special care in avoiding procedures which may release residual tumour-rests from the local restraint imposed by cellular or fibrous reactions, and avoiding traumatic or surgical stress, use of cancer-palliative drugs, or administration of growth-stimulating hormones, all of which may possibly activate dormant metastatic deposits.

The converse of these processes, i.e. immunologically-induced sensitization of the tumour, has been shown to be feasible, at least in one experimental species, and would, if applicable to humans, probably result in increased radiocurability of the tumour and delayed onset of recurrence or metastasis in the partially controlled case.

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