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SYSTEMIC FACTORS IN CARCINOGENESIS*

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IN 1874, at a meeting of the Pathological Society of London, the question was raised whether cancer should be regarded as a local or a systemic disease. While Sir James Paget thought that cancer was a "disease of the blood," Sir William Gull, Hutchison and others maintained its strictly "local" origin.[26] An almost cyclic alteration of these thoughts can be traced in cancer research of the past 80 years. Experimental chemical carcinogenesis, although it contributed greatly to our understanding of the neoplastic processes, has swung the balance of the scale towards local or cellular factors and emphasis has been placed on the search for carcinogenic agents. Advances in biochemical and biophysical sciences made possible a more detailed analysis of the properties of the malignant cell and so diverted attention from the investigation of the nature of the systemic factors affecting neoplasia. Although so-called "cancer susceptibility" or "resistance" has always been mentioned as an important factor, the tendency was to regard the local action of chemical carcinogens as a model for the causation of spontaneous tumours. The nature of factors responsible for the development of spontaneous tumours in man was implied, on the basis of the effects of experimental carcinogens in animals. We were tempted to forget that apart from industrial carcinogenesis there is little evidence to implicate either chemicals or viruses in the etiology of common cancers in man, though Cook[10] a long time ago warned that the demonstration that chemicals can act as carcinogenic agents does not mean that they constitute a common tumour-inducing factor.

Only recently do we appear to have slowly reached the point where it is evident that both local and systemic factors are operational in neoplastic diseases, although obviously any systemic factor will finally act through a local medium. Many investigators have ceased to view cancer as an autonomous entity. This is largely the result of the demonstration that neoplastic growth can be modified by hormonal factors. By means of these factors, dependent and independent tumours were differentiated, the latter being those in which no factors able to modify growth have been demonstrated as yet. This has been an important development, which contributed to the disparagement of the concept of autonomy of cancer. However, probably no tumour is completely autonomous, since it is dependent at least on nutrition and possibly on other factors, known or unknown. The division into dependent and independent tumour is probably artificial and certainly meaningless without specification of the particular factors concerned.

The objective of our studies was to correlate the evidence available on the action of various systemic factors affecting the malignant process with our experience in chemical carcinogenesis. The term "systemic factors in carcinogenesis" was introduced in 1927 by Kreyberg,[40] who suggested the possibility of an indirect action of external carcinogens through a "systemic" (vascular) factor in addition to a local effect on the cells. The following discussion includes hormonal, neurotrophic and immunological factors; this appears to be the most obvious grouping of demonstrated and suggested factors. Confirmed experimental findings lead us to believe that systemic factors are involved in all phases of neoplasia in addition to the local ones. The word "systemic" denotes, probably more appropriately than other terms, the nature of these factors, implying both the "host" and a particular "system".

HORMONAL FACTORS

The participation of hormonal factors in the neoplastic process has long been recognized. One might refer here to the observations of Beatson[3] at the turn of the century on the effects of ovariectomy on breast cancer. However, it has only been during the last few years that the importance of endocrine factors in the development of malignant tumours has been appreciated to an increasing extent. The basic reorientation in the consideration

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of hormonal factors in neoplasia is probably directly related to the evidence that endocrine glands are principally involved in the etiology of several varieties of tumours. In 1932, Lacassagne[43] showed experimentally that œstrogens increase mammary tumour incidence in mice. Since then œstrogens have been demonstrated to participate in the induction and progression of a wide variety of tumours, including mammary, uterine, prostate, renal, vesical, adrenal, testicular, ovarian, pituitary, bony, and connective tissue tumours, lymphomas and leukæmias. The fact that the tumours not only of effector tissues, but also of other organs, are influenced by œstrogens brings up the question of a direct or indirect role of hormones in the neoplastic process. Ingle[39] has introduced the concept of "permissive action of hormones", suggesting that the action of some hormones may be only adjuvant to other factors permitting the effects to take place. Several instances of "permissive action" of hormones have been confirmed subsequently in experimental carcinogenesis. Griffin, Rinfret and Corsiglia[22] reported complete inhibition of liver damage and hepatoma formation after administration of 3′-methyl, 4′-dimethyl-aminoazobenzene to hypophysectomized rats; feeding of the dye to normal rats for 10-12 weeks was sufficient to induce a high percentage of tumours. Inhibition of liver tumour formation by 2-acetyl-aminofluorene in hypophysectomized animals was reported by us in 1953.[62] The interpretation of the inhibitory effects of hypophysectomy on hepatic tumour formation is difficult. Our results indicate that the inhibitory effect concerns not only the initial lesion in the liver, but also conversion of pre-existing lesions into malignant tumours. Two possible mechanisms might be considered: (1) A direct hormonal effect caused by removal of hormonal regulation of a target organ. Such an endocrine relationship with pituitary gland has not yet been demonstrated. (2) An indirect effect mediated through factors regulating liver metabolism. This includes pituitary factors regulating liver regeneration, such as those described by Glinos and Gey[18] and those regulating sex hormone metabolism.[9]

The concept of permissive action of hormones added weight to a postulate expressed by Gardner[16] that "the possibility that abnormal endocrine environments can create or destroy cancer seems remote – the hypothesis that abnormal endocrine environments may result in the expression of potentialities of the tissues, less likely to be expressed under a 'normal environment', seems tenable." Observations on animals with spontaneous tumours of endocrine glands show that tumours of non-endocrine organs may be dependent on some hormonal imbalance. For example, rats with spontaneously developed hypophyseal tumours showed thymomas, hepatic adenomas, carcinomas of the oral cavity, bronchial carcinomas, leukæmias and lymphosarcomas.[15] The incidence of these types of tumours in normal rats is low. An etiological relationship must be entertained.

The voluminous literature on the effects of hormones in neoplasia contains many contradictions. Some of them are explainable by the differences in specific conditions in which the experiments have been carried out; others are based on variability of interpretation; still others may be only apparent and will be resolved by further investigations. At present a systematic integration of the experimental and clinical findings appears to be impossible. Gardner[17] considered four factors in the analysis of hormonal responses in carcinogenesis: (1) variations in hormone production; (2) variations in the end organ sensitivity; (3) differences in the utilization, destruction or excretion of hormones; (4) presence or absence of augmenting or inhibiting influences. Suffice it to say that in many instances the interdependence of factors is not completely understood. The variations in hormone production are not always evident, and the hormones maintaining the neoplastic process might operate at physiological levels. Bethune,[4] for instance, reported normal œstrogen excretion levels in hypophysectomized patients, in whom the operation brought an objective remission of the tumour. No differences might be apparent in the end-organ sensitivity, though the responses vary. The importance of variations in the utilization or excretion of hormones, and the action of nonspecific promoting or inhibiting factors, have also been stressed.

The development of hormonally "dependent" tumours usually requires a long period of time and passage through successive phases of hyperplasia and benign neoplasia. Undoubtedly a long "critical" period of hormonal dependence exists. The hormones maintaining the tumour growth in this phase might differ from those hormones which induced it. The progression of cancer, i.e. transformation of less malignant cells into more malignant ones, appears to be gradual and usually continues if the abnormal hormonal situation persists. In each instance any hormonal factor is apt to have its antagonist. This may be functional (such as a particular re-setting of events in the hormonal system), or chemical (such as steroid compounds originated by simple changes in the molecule of the original hormone, with subsequent acquisition of antagonistic action).

The perplexing combination of hormonal effects on tumour growth can be illustrated by the studies of actions of the adrenal cortex: its variety of hormonal functions affects to a certain degree the neoplastic process in any location. If adrenal cortical hormones are necessary for the function of all tissues (such as metabolism, secretion, growth),[59] one might expect that these hormones would also be involved in neoplasia. The variability of the effects of cortisone on tumour growth actually reflects the widely divergent effects of cortisone upon tissues. Its administration has been

reported to inhibit the inflammatory reaction, decrease the permeability of capillaries, possibly depress the formation of new connective tissues, suppress mitotic activity, inhibit phagocytosis, exert antihistamine activity, and diminish or prevent immunological responses.[59] It is likely that cortisone does not directly affect the vitality of cancer cells, but the various mechanisms affecting it.

Clinical use of cortisone in treatment of neoplastic diseases produced contradictory results. It is virtually impossible today to trace a common denominator for these findings. In experimental work cortisone was found by some to inhibit the induction of tumours by benzanthracene and methylcholanthrene; others reported that cortisone accelerated tumour production by methylcholanthrene. The dissemination of metastases can be promoted by cortisone administration, even when the primary tumour decreases in size, a result which was called the "paradoxical effect" of cortisone on tumour growth.[35] It was attempted, with some success, to prevent the unfavourable effects of cortisone on neoplasia by administration of anterior pituitary lobe preparations, on the basis that pituitary growth hormone antagonizes the principal effects of cortisone.[36]

The effects of adrenalectomy in experimental animals have been studied in a variety of tumours. With reference to the polyvalent effects of adrenal hormones, it is significant that the growth rate of Walker carcinoma 256, a transplantable, carcinoma-sarcoma of rats, has been found to be considerably diminished (38%) in adrenalectomized animals.[66] The effects on other tumours, such as hepatic tumours induced by azo dyes, are not uniform.

The original observation of Huggins[36] on the effects of castration on prostatic carcinoma formed the basis for modern investigation of the effects of surgical removal of endocrine organs. Later Huggins and Scott[37] suggested combined orchidectomy and adrenalectomy as a logical step to abolish the additional endogenous source of steroid sex hormones. Adrenalectomy has been tried in many centres, and it seems that approximately 40% of patients with breast cancer show remissions lasting for months or years. In the series reported by Stanford Cade,[8] objective improvement was observed in 30% of cases, with a higher rate of subjective improvement. However, as stated by Huggins,[38] the response to adrenalectomy is not uniform and occasionally the growth of a malignant lesion may be accelerated by the procedure. The important question of the etiology of malignancy after adrenalectomy has been asked by Graham,[2] who has demonstrated accessory adrenal tissue in the cœliac region in 32% of autopsies. The presence of such accessory tissue may partly explain the failure of adenalectomy in some cases.

The anterior lobe of the hypophysis as a regulator of endocrine glands and a link with higher nervous centres plays an important though indirect role in neoplastic diseases, being the central relay in preparation of the complex event of hormonal imbalance. Several anterior hypophyseal hormones have been found capable of inducing and maintaining the growth of tumours of target glands; gonadotrophins in the ovaries or testes, thyrotrophic hormone in the thyroid gland and adrenocorticotrophin in the adrenal glands. Growth hormone was shown to favour the occurrence of various tumours in rats, though it did not seem to enhance tumours of mice or the induction of tumours by chemical carcinogens.[22] There is no evidence at present that any particular tumour is "dependent" on growth hormone, which appears to increase the growth rate of tumours only in proportion to the increase in body weight. However, the recent studies of Pearson and his associates indicate that growth hormone may stimulate metastatic growth.[54]

The wide range of metabolic changes controlled or affected by hypophyseal hormones is demonstrated by the physiological effects of hypophysectomy. Here again, as in studies with adrenocortical hormones, many of the experimental results are not in complete agreement and apparently reflect the particular conditions under which the experiment was conducted. Moon, Simpson and Evans[49] have observed inhibition of the formation of sarcomas in hypophysectomized mice which were injected with moderate doses of methylcholanthrene; this inhibitory effect was absent when high doses of the carcinogen were used. The major discussion regarding the effects of hypophysectomy has centred around the question of whether or not the inhibition of tumour growth is based on decreased food intake of hypophysectomized animals. In our studies the caloric intake of the control rats fed 2-acetyl-aminofluorene has been restricted to the levels of intake of hypophysectomized animals; the difference in tumour incidence between these groups remained statistically significant. The experiments of Talalay, Takano and Huggins[67] with tube-fed hypophysectomized rats also indicate that hypophyseal ablation produces its inhibitory effect on tumour growth also in force-fed animals.

The clinical experience with hypophysectomy originated by the series of Luft and Olivecrona[45] seems to warrant use of the procedure in advanced cancer cases of endocrine organs. The largest series reported so far in Canada are those of the Dalhousie University-group.[4] The results indicate that hypophysectomy is amazingly successful in bringing about objective remissions in about one-third of patients with breast cancer. Major problems are the selection of cases which will respond favourably to hypophysectomy and the difficulty of radical removal of the pituitary gland.

Hormonal treatment may produce pronounced growth-inhibitory effects, especially in tumours whose etiology is linked to an endocrine background. The original observations of Haddow, Watkinson and Paterson[24] on the influence of syn-

thetic œstrogens upon advanced breast cancer has formed the basis of œstrogen treatment in breast cancer. A recent observation of Segaloff[58] indicates that the beneficial effects of œstrogens might actually be due to depression of pituitary activity.

Testosterone has some definite antagonistic effect upon the role of œstrogens in neoplasia. The inhibition of the promoting effects of œstrogens on mammary cancers by administration of androgens has been demonstrated. It is interesting to note that testosterone has also been reported to cause regression of metastatic thyroid adenocarcinoma.[33] Although biopsies showed the presence of atrophic tumour cells at the site of the metastases, no evidence of progression was observed. This inhibitory effect was observed to be closely related to the adrenocortical function and anabolic activity of the individual.[33]

These examples of the effects of exogenous hormonal therapy on neoplasia demonstrate not only the complexity of the problem, but also the fact that intricate balances rather than individual hormones are of primary importance. The disruption of orderly equilibrium maintained by these mechanisms seems to play a part in the induction of tumours in the hormone-regulated organs. Generally, if a given hormone affects a target tissue, it produces growth and changes in functional activity, and finally influences the differentiation. The suppressive action of some hormones on functional activity of target cells might be related to cancer induction in the sense of Haddow's view[26] that chemical carcinogens act more readily on cells following such depression. Single hormones usually participate in the induction of neoplastic processes accompanied by other factors or conditions (such as species specificity, degree of cellular responsiveness and territorial sensitivity). The division of tumours into dependent and autonomous seems to be both useful and desirable to delineate the known dependency relationships. However, one might question whether, with the steadily increasing number of demonstrated dependencies in relationships, all tumours will be shown eventually to depend at some phase of their development on some growth-regulating hormonal factors.

The development of tumours of endocrine glands following prolonged hormonal imbalance provides an excellent example for the suggestion that any condition of functional imbalance of an organ may be followed by the development of malignant neoplasm.[31] For instance, prolonged functional imbalance imposed upon the liver by choline deficiency first induces fatty metamorphosis, which is followed by cirrhosis and eventually by tumour formation.[31]

The prolonged functional imbalance may be primarily responsible for many tumours occurring in man. The complexity of involvement of endocrine glands in the neoplastic diseases complies with the general rule in endocrinology that complex balances rather than single hormones are responsible. It is to be expected that a physiological regulating mechanism of each particular organ or tissue will be demonstrated as playing an important part in the carcinogenesis of that structure, a concept outlined by Horava[29] as "situations antitumorales". The fact that some effort of the functional unit to counteract any imbalance is always evident offers possibilities in cancer prevention.

NEUROGENIC FACTORS

The information available on the role of neurogenic factors in the etiology of neoplasia is difficult to integrate. Cancer research workers in the late 'twenties were impressed by the possibility of inhibiting tumour growth by a change in neurotrophic control of tissues. Ewing,[14] referring to the experiments of Remond[56] and of Pearce and van Allen,[53] stated: "I regard these observations as of considerable importance in pointing out a possible factor in tissue predisposition to tumour growth." Unfortunately many of the older reports have to be discarded as purely speculative. Of possible significance might be the experimental observations of Mellanby,[48] who concluded that hyperplasia and metaplasia of epithelium in animals kept on a vitamin A-deficient diet is due to loss of neurotrophic control, as evidenced by the development of degenerative changes of medullated nerves in the central and peripheral nervous systems.

For a time the main point of discussion in cancer research was focused on the question of whether or not defective or absent neurotrophic control of tissues is one of the factors predisposing to the formation of malignant tumours. During this period several well-controlled experiments were reported on the subject of denervation and role of blood vessels in the etiology of neoplasia. Although the conclusions drawn frequently exceed the limits of the experiments performed, in quoting them one might follow the motto of Keynes (*Treatise on Probability*) that part of our knowledge is obtained directly and part by argument. Itchikawa, Baum and Kotzareff, and Remond, Bernardbeig and Sandrail[57] subjected rabbits to neurectomy (auricular nerve section) with simultaneous or delayed application of crude tar to the ear and reported an accelerated growth of tumours on the denervated side. Lorin-Epstein and Bodnartschuk[44] performed cervical sympathectomies under similar conditions and reported acceleration of the formation of papillomas and carcinomas. Pearce and van Allen[53] describe a series of experiments including cervical sympathotomy, complete sympathectomy, and superior and inferior sympathectomy, on rabbits bearing transplanted Brown-Pearce sarcoma. Statistically significant differences in the growth of the inoculated tumour were observed between animals whose sympathetic system had undergone operative interference and controls, the distribution of metastases being greatest after complete sympathectomy and sympathotomy. Well-controlled experiments were performed by Tsunoda,[68] who

reported an increased "take" and rate of growth of transplanted tumours of both epithelial and connective tissues after transection of the sciatic nerve. Cervical sympathectomy in rabbits caused increased epithelial growth and invasiveness of tumours produced by tar application.

Cramer[11] entertained the feasibility of segmental loss of sympathetic innervation leading to an increased network of capillary loops around the transplanted tumour, as well as lack of contraction of tumour vessels upon sympathetic stimulation. Shapiro and Warren[60] more recently conducted studies on transplants to the anterior chamber of the eye of Brown-Pearce carcinoma and reported no evidence of rhythmical active motion in the tumour vessels, though response to stimulation was maintained.

In our studies[61] we have attempted to investigate the effects of autonomic blocking agents on experimental carcinogenesis. Two groups of drugs have been considered for use in this investigation.

1. *Ganglionic blocking agents.*—These, as is known, partially block the transmission of both sympathetic and parasympathetic impulses in the autonomic ganglia. Suppression of the sympathetic vasospastic reflex results in peripheral vasodilation, which might have been important in this type of investigation. However, in experimental animals the blocking effects are of short duration and are therefore not suitable for experimental carcinogenesis.

2. *Adrenergic blocking agents.*—The mechanism of inhibition of vasoconstriction by these agents is not perfectly understood; according to newer concepts[51] their action is due to disturbance in equilibrium between the mediator and blocking agent. An alkylamine was added to the diet of male rats kept for 17 weeks on 2-acetyl-aminofluorene administration. In the majority of animals receiving high doses of alkylamine (0.5 mg./g. body weight) tumours appeared earlier. This was particularly well observed in sebaceous-gland carcinomas of the head. The difficulties and limitations in interpretation of the results obtained are fully realized. However, it is of interest to note that Stone[65] observed adrenergic blocking properties in a derivative of fluorene. The relation of the vascular changes produced by adrenergic blocking agents to the absence of the chemical mediator at the neuromuscular junction does not appear to be justified. As stated by Nickerson,[51] the alkylamines do not inactivate epinephrine in tissues, "neither can they prevent a sympathoadrenal discharge by blocking nervous impulses at the ganglionic level".

In his early work on the vascular bed of tumours, Goldmann[19] attempted to establish the hypothesis that human tumours elicit an abundant vascular supply with permanent vasodilation and consequent slowing of the blood stream. Recent observations of Zulch[70] on structure and the formation of blood vessels in glioblastomas appear to be of significance. Zulch[70] found pathological changes in the vessel formation of these tumours, including large lacunar vessels, closed capillary nets with widening of the lumen, glomerular systems and organized vascular systems resembling cavernous formations. He concluded that these changes might in some way be induced by a specific vascular stimulus present in the area of tumour formation, which causes rapid proliferation of new vessels and widening of the vascular lumen. Zulch[70] has also pointed out that brain tumours represent a particularly suitable subject for investigation of endogenous factors, as no exogenous carcinogens, viruses, irradiation effects or chemical substances can be implicated in the causation of these tumours.

The loss of autonomic vasomotor control of a tissue segment could be considered as an etiological factor in the development of neoplasia if some mechanism could be demonstrated to account for permanence, if not irreversibility, of the malignant process. One might postulate that the growth rate of the neoplastic focus depends upon the degree of pre-static hyperæmia, causing concentration of growth-regulating hormonal factors. Simultaneous existence of an ischæmic condition of the surrounding tissues would increase the susceptibility to invasion.

The extent and reversibility of these vascular changes depends, among others, upon the regulating influence of sympathetic vasomotor units and ganglionic transmission. Supposedly this connection is interrupted for some reason and new vasomotor fibres regenerate along the arterioles; the contractibility in a growing vessel is related then to the rate of growth of nerve fibres. The "autonomic balance" of a tissue segment can be maintained by the complex interrelationships with the neighbouring segments. Ray and Console[55] have demonstrated that the return of sympathetic activity after any sympathectomy is not necessarily due to regeneration of nerve fibres, but may be effected through "re-adjustment" by invasion of fibres from an adjacent area. Existence of some pathological process at the ganglionic level, which would impair these processes in a morphogenetic field, would therefore be of importance in determination of extent and permanence of newly formed tissue. Since the nerve cells have no power of regeneration, a ganglionic lesion could be permanent or possibly progressive.

The pathological studies pertinent to these considerations refer to morphological changes in the autonomic ganglia and are difficult to interpret for three reasons: (1) difficulties in establishing a reliable morphological basis; (2) wide range of normal variations; (3) inadequacy of present staining methods of neurogenic elements. Extensive studies in this respect have been conducted by Kuntz.[41] Kuntz studied histological variations in human autonomic ganglion cells obtained at autopsy, using methylene blue and Cajal silver staining techniques. He concluded that heavy

melanotic pigmentation was generally more extensive with progressing age. (The age range of cases studied varied between five weeks and 78 years.) Kuntz[42] can be quoted as stating: "The excessive pigmentation of the autonomic ganglion cells in this group of patients (younger) undoubtedly is associated with the malignant process." No parallel observation in experimental carcinogenesis exists. In our own colony of rats fed 2-acetyl-aminofluorene, no serial studies were performed; however, in several sections of the sympathetic ganglia obtained from rats with malignant tumours hyperpigmentation and necrosis of ganglion cells were evident.

IMMUNOLOGICAL FACTORS

Although the operation of immunological factors in neoplasia has been discussed for a considerable period of time, it is only in recent years that the emphasis in studies of tumour immunology has shifted from diagnostic serology and attempts to induce resistance, to the investigation of immunological aspects of growth. The actual progress in immunobiology of neoplasia has profited by advances made in the basic sciences of genetics and microbiology. The field of immunology of cancer includes such broad subjects as immunogenetics, biophysics and immunochemistry. Many findings in these fields with no apparent relation might eventually prove significant in the immunology of malignant transformation. To give an example, one might quote Pauling's demonstration of the influence of molecular architecture of proteins on their antigenic properties.[52] The biochemical aspect of immune reactions brought immunology closer to the subject of antimetabolites, which forms the basis of Martin's theory of biological antagonists.[46]

On the other hand, two recent clinical developments have contributed significantly to the renewed interest in the immunological factors affecting neoplasia: (1) possibility of an immunological reaction in the verified cases of spontaneous regression of human cancer; (2) homotransplantation of human cancer cells into volunteer recipients.

In some of the cases of spontaneous regression of malignant tumours an immunological type of reaction seems apparent, as in some cases of the well-known series of Stewart.[64] Discussing spontaneous regression, Boyd[5] observed that some of the facts in cases of regression of human cancer "seem to fit the concept of an immunological relationship between tumour and host, activated possibly by some change in the protein complexes of the malignant cells". Upon analyzing the significance of previous treatment in such cases, he drew attention to the fact that in many cases external causes inadequate to eradicate the disease completely, such as incomplete removal, low-dose irradiation, or acute febrile conditions, are frequently encountered in the histories of these patients.[5] In that sense it is possible that good results obtained with radiotherapy of tumour tissue not normally responding to it, or occasional favourable response to a chemotherapeutic agent, might be based not on actual destruction of tumour cells, but on change in the antigenic properties of the tumour. The clinical picture of tumour regression frequently suggests that some alteration occurs in the immunological set-up of the tumour cells and the autologous host.

Southam, Moore and Rhoads[63] recently reported the results of homologous transplantation of tumour cancer cells into subcutaneous tissue of volunteer recipients with and without malignant disease. The survival and quantity of the tumour tissue were increased in cancer patients. In two cancer cases the growth of the implanted grafts was unrestrained as long as the patients survived (six and nine weeks). In one case, metastatic formation in the lymph nodes was observed. After regression of the first transplant, the second implantation of the same cell type was accompanied by increased reaction of the recipient's tissue.[63] Obviously it is too early to draw any conclusions from these experiments. However, if further studies confirm these observations, the practical implications are obvious.

For a non-immunologist, the studies of immunological factors in neoplasia appear to be biased by two conclusions: (1) application of findings obtained with transplanted tumours to all spontaneous tumours. (2) The proposition of immunoreaction as a theory of carcinogenesis. Such a trend is unavoidable; it is also advisable in cancer research to integrate the particular aspects of the problem with the general picture; the critique usually provides the necessary adjustment.

Burnet and Fenner[7] introduced the "self-marker" hypothesis which holds that at a late stage in embryonic life the reticulo-endothelial system becomes capable of recognizing potentially antigenic constituents of the expansible cells of the body as "self-components". Some foreign antigens present at the time may also be recognized as "self-markers" and incapable of acting as antigens on the conditioned animals. In later work Burnet[6] has suggested that cells of many types may be continually liberating "self-markers" into the systemic circulation and that these may exercise a control function.

Medawar and his associates[47] have developed the concept of immunological tolerance as a specific suppression of reactivity induced by exposure to antigenic stimuli before the development of ability of immunological response. These antigens were shown to be of tissue, bacterial or hæmatogenous origin. Immunological tolerance was found to be limited to the antigen in question, thus differing from the so-called immunological paralysis, such as suppression by cortisone or irradiation.

Green[21] has suggested that specific protein complexes characteristic for the tissues in question are modified by action of the carcinogens, the modified complex being capable of self-duplication. According to this theory, the loss of identity proteins (self-

markers) is responsible for the development of adaptation, after initial antibodies production has occurred. The malignant transformation would then be caused by antigenic loss.

Although the search for specific neoplastic antigens continues, present evidence exists only with regard to quantitative differences in the antigenic components of normal and malignant tissues. These were demonstrated by elution techniques, selective absorption studies, metachromatic differential fluorochroming and radioisotope-labelled antibody-antigen systems. As stated by Hauschka,[27] no qualitative antigenic aberrations typical for malignancy have been found so far, and on the whole, the isoantigens of tumour cells are of the same type as those of normal tissues. The findings of Amos, Gorer and Mikulska[1] on the antigenic systems in the mouse lymphomas suggest that malignant leukocytes could be weakly antigenic.

Some of the properties of malignant tissues are more likely than others to be explained by antigenic loss in tumour cells. The ability to metastasize might be linked to the diminution of the isoantigenic differences between the tumour and the autologous host. Immune mechanisms of antigenic loss might also be applied to explain the genetic simplification of cancer cells—the anaplasia. The potentiality to evoke immunological reaction in the host might be expected to decrease with the progression of cancer; however, the increasing simplification of antigenic constitution of tumour cells might occasionally lead to an increased response on the part of the host.

Horava[32] explained the nature of the malignant transformation from the immunological point of view as follows: a cancer-inducing agent disrupts the antigenic mechanism which maintains the tissue integrity. A chromosomal variant of antigenic nature and equal to a somatic mutant occurs and its survival results in appearance of a viable cell equipped with new abnormal potentialities. That tumour tissue might possess tumour-inhibiting properties has been demonstrated by Horava[30] by systemic administration of tumour exudate, derived from the so-called "tumour pouch", to rats bearing transplanted Walker carcinoma of the same types as the tumour producing the exudate. The histological changes observed in the Walker tumour[30] consisted of vasodilation with multiple hæmorrhages, degenerative changes and necrosis of tumour cells. Although several factors might have played a role in this experiment, the inhibitory effect of tumour tissue extracts on the tumour of the same type under the specific conditions of this experiment cannot be doubted.

It has been shown by several investigators that the tumour cells do not exhibit uniform properties, but vary in their response to radiation, drugs, antibodies or viruses. Haushka[28] has further developed these ideas and defines the picture as "neoplastic cell population". According to his diagrammatic representation of important biotypes, a wide range of variant cell types exists within each tumour with a relatively stable equilibrium, resulting from competition between cellular biotypes and "bioselection" by exogenous factors. Hauschka[27] has shown that the variants can be selectively concentrated by propagation in a partially compatible host. Burnet[6] considered the possibility that this selection is confined to cell types not resistant to the immunological destruction, while Hauschka[28] believes that the selection is based on loss of antigenic properties amongst the available variants.

Studies of the immunological factors in neoplasia represent one of the most promising fields in research. As has been mentioned above, the phenomena accompanying spontaneous regression of human tumours are suggestive of an immunological response. It is possible that the reason why we do not observe regression more often in the fully developed cancer is that the capability for regression diminishes with the duration of the process. The fact that cancer is not seen more often may be due to spontaneous regression of minute collections of malignant cells before they become perceptible by diagnostic means. To decipher the immunological factors in tumour susceptibility seems to be one of the most important tasks in cancer research.

CONCLUDING COMMENTS

Investigations of the nature of etiological agents in neoplasia indicate a wide variety and diversity of inducing factors which, under suitable conditions, may induce malignant changes. The term "carcinogen" does not convey the interplay of factors which frequently appear necessary to initiate malignant growth. We have suggested previously (1950) that the development of malignancy depends on the presence of three separate conditions: (1) injury of the cells in question; (2) susceptibility of the tissues; (3) imbalance of hormones regulating growth of the tissues concerned. The non-specificity of factors of etiological significance in tumour induction is probably based on the fact that they affect only one of these conditions and require coincidental presence of factors affecting the other two co-ordinates for induction of cancer. Accordingly, the combination of the etiological factors, rather than the factors themselves, would be specific for induction of neoplasia.

The injury to the cells can be interpreted in the widest possible sense. We have numerous examples of actions of injurious agents in human neoplasia which do not lead to malignancy *per se*, but contribute in some way to its development. Many of the so-called pre-cancerous lesions fall into this class. Chemical carcinogens, such as 2-acetylaminofluorene, produce tumours *per se*, probably because, in addition to the injury, they cause some changes which bring about a breakdown in tissue resistance of the host. It can only be speculated that factors affecting neurotrophic control of morphogenesis and immune response might be of importance in

this breakdown produced by an environmental agent. The extent to which such agents can overcome the defensive host mechanisms determines the incidence of tumours produced. A classical example of a "complete" carcinogenic action is the irradiation effect of radioactive strontium on bone, which in our experience is capable of producing an almost 100% tumour response if an appropriate time-dose relationship is used.

The participation of a third factor—imbalance of growth-regulating substances—appears to be quantitative. Foulds has pointed out that the "progression in malignant characteristics" is a more typical property of neoplasm than the growth itself. It is unlikely that abnormal hormonal conditions play a qualitative role in the induction of neoplasia; nevertheless their presence seems necessary for the expression of some of the properties of malignant tissues. A number of such factors have been demonstrated experimentally to be hormonal in origin, in the ordinary sense of endocrine secretion; they appear to be organ or tissue specific, though obviously any systemic hormonal imbalance is likely to result in focal or local pathophysiological conditions. The future will undoubtedly demonstrate infinitely more complex aspects of hormonal control of growth, including many unsuspected endogenous secretory elements.

To account for the fact that in the majority of common human cancers there is no evidence of action of specific carcinogenic agents, we have previously introduced the term "carcinogenesis without carcinogens", implying a co-ordinate action of neoplastic factors. If cancer is a negative condition, "a manifestation of the breakdown in one or more aspects of the positive control that welds the cells of the body into a single functioning unit", then the investigation of factors which normally control the growth processes seems to be of primary importance. Burnet,[6] from whom this quotation comes, divided the process of control of a collection of living cells into the following components: (1) a pre-existing plan of action; (2) a feed-back mechanism for transmission of information about the state of cells in question; (3) a central control mechanism for regulation of the response to the information transmitted; (4) a reception mechanism in the cells for induction of corrective reactions. We have sufficient evidence to conclude that a number of local and systemic factors participate in maintenance of the processes of control and act at various levels of this scheme.

As far as local factors are concerned, Burnet[6] concluded that the primary requisite for malignant transformation is a loss of the control mediated by physiological contact with adjacent cells. Weiss and Andres[69] have contributed significantly to the understanding of these factors by demonstration that injection of embryonic melanoblastic cells into chick embryos of non-pigmented strain produces proliferation of donor melanoblasts and appearance of melanin granules in the host locations corresponding to the donor site. Moscona[50] has shown that chick-embryo cells, dissociated into separate units by treatment with trypsin, can produce tissue-like associations in tissue culture.

As far as systemic factors are concerned, the participation of hormones in neoplastic processes is sufficiently confirmed, experimentally and clinically. The evidence of participation of factors of immunological and neurotrophic nature is only suggestive. The significance of the systemic factors has been emphasized by generations of surgeons, pathologists and zoologists, the professions which see cancer. To mention only the more recent ones, Dunphy[12] concluded in a review of changing concepts in the surgery of cancer that the traditional notion that cancer is an autonomous growth is untenable in view of "regression of metastases after removal of primary growth, late metastases, great variabilities in the growth rate of various nodules of the same cancer, regression of skin metastases and indisputable evidence of natural defence against cancer." Delarue[13] emphasized the susceptibility and biological growth-control factors in his work on concepts determining the treatment of breast cancer. These clinical observations cannot be disregarded in cancer research. Further investigation of the role of systemic factors in neoplasia and growth control will determine more precisely the factors affecting susceptibility to cancer, which have heretofore been overshadowed by the concept of autonomy of malignant growth. The important studies on cellular constituents and possibly existing chemical differences between normal and cancer cells should not distract us from the major issue of factors controlling growing processes.

The analysis of the presented material suggests that malignant neoplasms develop as a result of interrelated local and systemic processes. In most instances, none of these factors is absolute; all are of only relative etiological importance. On the basis of the concept of progression and the demonstration of the variety of complete and incomplete carcinogenic agents, carcinogenesis emerges as a process depending upon the interaction of carcinogenic, local and systemic factors, a process not completed when the tumour first appears, but one which may continue throughout the course of the disease. The control of this process is effected by several mechanisms. It is possible that among others such systemic factors as an endogenous deficiency or some form of abnormal immune reaction are of etiological significance in the genesis of malignant neoplasms.

SUMMARY

The significance of systemic factors in carcinogenesis is analyzed. The word "systemic" seems appropriate to denote the nature of these factors, implying both the "host" and a particular "system". The most obvious grouping of these factors includes hormonal, neurotrophic and immunological factors. The data available on the participation of hormonal factors in the

neoplastic processes are sufficiently confirmed. Suggestive evidence seems to exist for the action of neurotrophic and immunological factors. The available data are reviewed and our own experimental studies interpreted. It is noted that considerable evidence has accumulated indicating the vast multiplicity and diversity of agents, which under suitable conditions may induce neoplastic changes in tissue. The absence of specific causative agents is stressed in the etiology of the majority of common cancers in man. It is suggested that, with some exceptions, probably none of the factors affecting neoplastic growth is absolute and all are of only relative importance. It is concluded that the process of carcinogenesis is dependent upon the interaction of local and systemic factors, a process not necessarily completed when the tumour first appears, but one which may continue throughout the course of the disease.

REFERENCES

A list of references is not published, for lack of space. Enquiries should be directed to the author.

RÉSUMÉ

L'auteur analyse l'importance des facteurs systémiques dans la carcinogénèse. Le mot *système* semble convenable à décrire la nature de ces facteurs évoquant à la fois l'hôte et l'un de ses systèmes en particulier. Les groupes de facteurs les plus évidents comprennent les facteurs hormonaux, neurotropiques et immunologiques. Les données sur la participation des facteurs hormonaux dans les néoformations ont reçu une confirmation suffisante. Il semble y avoir des preuves suggérant l'existence des facteurs neurotropiques et immunologiques. Les données recueillies à date sont passées en revue et l'auteur interprète ses propres données expérimentales. On doit remarquer que des preuves nombreuses sont accumulées montrant la multiplicité et la diversité des agents, qui dans des conditions propices, peuvent produire des changements néoplastiques dans les tissus. L'auteur souligne l'absence d'agent causateur spécifique dans l'étiologie de la majorité des cancers communs de l'homme. On suggère, qu'à quelques exceptions près, aucun de ces facteurs affectant la croissance néoplastique n'est absolu et tous ne sont que d'importance relative. On conclut donc que le processus de la carcinogénèse dépend de l'interaction de facteurs locaux et systémiques; ce processus n'est pas nécessairement complet lorsque la tumeur paraît au début mais il peut se poursuivre au cours de l'évolution de la maladie.

MITRAL VALVE SURGERY* SIXTY-FIVE CONSECUTIVE CASES TREATED BY MITRAL COMMISSUROTOMY WITH NO OPERATIVE MORTALITY

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MITRAL VALVOTOMY is well established as a valuable surgical procedure, but not all physicians may appreciate how safe the procedure has become.[5, 6, 8] New diagnostic aids, such as left heart catheterization, with or without dye curve studies, are proving to be very valuable in the careful selection of cases.

Before these new aids became available, some complicated cases (i.e., patients with combined aortic and mitral valve disease, or patients with combined stenosis and regurgitation) were subjected to an ineffective operation which resulted in a more stormy postoperative course, high operative mortality and a poor end result. Moreover, some patients who could have been helped were refused operation.

INVESTIGATION

The investigation should include a complete history and careful physical examination. The two most useful additional procedures are taking an electrocardiogram to demonstrate right ventricular hypertrophy or dominance, which so commonly accompanies important mitral stenosis, and fluoroscopy with barium swallow to outline the left atrial enlargement, which is almost always a feature in hæmodynamically important mitral stenosis.

Rheumatic activity must be ruled out by a careful record of the temperature for a few days, together with white blood cell count and erythrocyte sedimentation rate.[1]

Right heart catheterization should be performed where congenital heart disease, such as atrial septal defect or tricuspid stenosis, must be ruled out.

Left heart catheterization* has been a very valuable addition to the armamentarium. It is a certain and safe procedure[2, 3, 9] which provides more information than "wedge" pressure tracings obtained on right heart catheterization ("wedge" pressures are a reflection of left atrial pressure obtained by passing a right heart catheter out into the smallest branches of the pulmonary artery). The specially designed needle is passed through the posterior chest wall under local anæsthesia to enter the left atrium; then a fine nylon catheter is threaded through the needle to pass across the mitral valve into the left ventricle. A pressure gradient across the valve during diastole is the *sine qua non* of mitral stenosis. If aortic valve disease is suspected, pressure in a peripheral artery is recorded simultaneously. The systolic gradient between left ventricle and aorta is then measured, to indicate the severity of aortic stenosis. Mitral or aortic valve stenosis with associated regurgitation is a more complex problem, which cannot be assessed accurately without special techniques, such as the use of dye dilution curves.

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*Performed on 350 occasions to date with low morbidity and no mortality.