Papers on Cancer by M L Kothari et al

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Reprinted from the "Journal of Postgraduate Medicine",
Vol. XIV, No. 2, April 1968.

GENESIS OF CANCER

(A temporal approach)

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I

Several theories have been advanced to explain the genesis of cancer, but they fail to encompass all facets of the process. A glaring drawback of most of the concepts is their inability to impart a temporal perspective—a time dimension—to the phenomenon of tumorigenesis. Any satisfactory theory must account for the fact that cancer, both spontaneous and induced, occurs generally at a specific time in the life span of the organism. As Burnet[6] aptly states: 'At every stage in scientific development, it is necessary to provide the best available generalisation as a guide to effective work.

A brief review of some of the biological aspects of cancer might enable us to evaluate any new concept regarding carcinogenesis.

Latency: A remarkable feature in the development of cancer is the existence of time lapse, or a latent period, between exposure to a carcinogen and the occurrence of a cytologically and clinically recognisable neoplasm.[23, 28, 52, 73] The varying time-periods which intervene between the exposure to carcinogens such as benzanthracene compounds,[52] or irradiation,[43] and the occurrence of skin cancer are well known.

With regard to the above, Kark[28] has posed some pertinent questions which may be quoted to advantage at this juncture:

(a) Is latency due to changed cells suspended in a state of dormancy until further stimuli evoke frank malignant properties?

(b) Is the process one of gradual progress over a number of years to a final morphologically evident cellular change?

(c) Does latency represent time taken by malignant cells to overcome host resistance?

(d) Advancing age is accompanied by an increasing incidence of neoplasms. Is this an expression of the culmination of malignant transformation after latent intervals following earlier tumorigenic influence?

Spontaneity: A large majority of tumours in animals[12, 37, 40, 68, 72] and man[60, 68] cannot be ascribed to any known cause and, therefore, are termed naturally occurring, or spontaneous. Spontaneous malignant transformation of cells in tissue culture is extensively documented.[17, 18, 70, 71]

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Received for Publication: 5th March 1968.

Multiplicity of Carcinogenic Agents: Viruses, parasites, hormones, chemicals, physical agents such as ultravoilet and other irradiation as well as chronic irritation are accepted as likely causes[5, 28, 60, 75] of both, experimentally produced animal cancers and some naturally-occurring animal and human cancers. However, all these different agencies lead to a common end result—a cancer cell.[31, 60] It would appear that a normal cell of the body reacts to these insults in a rather stereotyped manner by unfolding one of its inherent characteristics—'a cytodifferentiation which is a part of its repertoire'.[83]

Multiple Cancers: Moertel et al[47] have reported a total of 1909 patients diagnosed as suffering from multiple primary malignant neoplasms which occurred simultaneously and/or subsequently. The second cancer occurs most frequently in the same organ as the first; next, in order of frequency, is affection of the same organ system (occurrence of cancer colon at another site), while the least frequent is involvement of unrelated tissues.[28, 31]

Tissue Resistance or Susceptibility: In both natural and experimental cancers, tissue susceptibility is a *sine qua non* of the genesis of cancer.[8, 80] Under experimental conditions, the same carcinogen induces different types of tumours in different animals.[28] In humans, cancers arising in particular organs do so with a much higher frequency in certain communities as compared to others.[61] In the same individual and in the same organ system, e.g. the gut, an outstanding example of both tissue susceptibility and tissue resistance, is afforded by the high frequency of cancer in areas just proximal to the pylorus and distal to the ileo-caecal valve. The above high-cancer zones are separated by a considerable length of gut almost "immune" to cancer.

Host Resistance: In a high risk cancer environment not all exposed develop cancer, i.e. all smokers do not develop carcinoma of the lung.[14, 28, 31] Likewise, a small percentage of non-smokers do not escape it.[14, 28] In experimental tumours host susceptibility is a prerequisite to the induction of cancer.[60]

Age Distribution: Cancer affects all ages, although its incidence increases with increasing age.[16, 19, 75, 79] The type of cancer changes with age. Soft tissue tumours, leukemias and neuroblastomas are tumours of the younger age groups whereas epithelial tumours occur at later ages.[60] However, reports of oesophageal cancer at 14, 40 and 80 years of age[61] show that such an age-distribution is not rigid.

Sex Distribution: Cancer of the breast and uterus in the female and cancer of the prostate in the male can, of course, be considered sex specific, but not so the malignancies of other organs whose incidence shows wide variations.[60]

Geographic and Racial Variations: Penile cancer is exceptional in Jews, rare is Moslems but common in Hindus, Chinese and Latin Americans.[28] That customary early post-natal circumcision is not the sole factor conferring

this racial immunity can be judged from the fact that amongst the uncircumcised the incidence ranges from 0.95% amongst British males[22] to 18% amongst the Chinese.[48]

Though the anatomical distribution of tumours in different parts of the world is extremely varied,[7, 15, 75] the age-specific death rate from all neoplasms at all sites is remarkably constant.[75]

Heredity: Maud Slye,[74] in as early as 1914, showed that the susceptibility of mice to the development of spontaneous tumours, including breast cancer, was passed on as a heritable factor in successive generations. Throughout the history of research on mammary cancer in mice, the aetiologic importance of genetic factors has been recognised.[26] The occurrence of tumours in the same organ in pairs of monochorial twins suggests a hereditary basis.[28] There are a number of conditions, either initially frankly malignant or predisposing to malignancy, which are clearly related to heredity.[5, 39, 60] These include retinoblastoma, xeroderma pigmentosum, von Recklinghausen's neurofibromatosis, hereditary polyendocrine adenomatosis and tylosis with oesophageal cancer. Other malignant neoplasms including carcinoma of the breast, stomach, uterus and urinary bladder do occur in families but the hereditary basis is not clear.[5, 31, 60]

Aging and Carcinogensis: The association between the increasing incidence of cancers in man and animals with increasing age is well documented.[16, 19, 79] In primitive racial groups with low life expectancy, the recorded incidence of cancer is reported to be remarkably low[7]. Excluding cancer in children, a survey in the United States in 10 metropolitan areas showed the following incidence per 100,000 population: 40 at 25 years of age, 475 at 50 years and 1900 at 75 years.[16] In random-bred Swiss mice, the incidence of cancer increases cumulatively with age, and tumours are not solely of any one type.[79]

Smithers[75] has pointed out that most people dying of neoplastic disease also show many senile changes which would have otherwise killed them fairly soon in any case. A country with a high cancer death rate is likely to be one which has good standards of living and good medical services which ensure longevity.[75] As a colleague aptly puts it, "Well! You must be around before you can get it!"

Rate of Growth: A wide variation exists in the following:

(a) The rate of growth in different tumour types:

(b) that of the same tumour type in different individuals; and

(c) that of the same tumour type in the same individual but at different sites.

Tumour Recurrence: Recurrence of cancer after surgical removal or destruction by radiotherapy is well known.[5, 60] The cancer-free interval may vary from a few months to several years. What permits this cancer-free existence? Did the residual tumour remain dormant during this time or did

some normal cells manage to turn malignant? Why is it that when cancer recurs, it, more often than not, assumes a more malignant form?

Precancerous States: Many conditions are now recognised as being precancerous. These are, in themselves, not malignant, but are quite likely to undergo such a transformation;[5, 60] examples are benign hyperplasia (breast, colon, skin), mucosal changes of leukoplakia, squamous metaplasia in the gall bladder or in the pelvis of the kidney. A precancerous state is characterised either by a state of benign hyperplasia or of metaplasia.

Though not usually labelled precancerous, embryonic malformations do predispose to a cancerous change and also merit consideration here, e.g. undescended testis and teratoma. In teratoma one or more of the constituent cell types undergoes malignant change.[60] Misplacement of cells at early stages of development renders them susceptible to a future neoplastic change.[60]

Cancer *Versus* Inflammation:

"Is it possible that the neoplastic reaction is, in fact, nothing more nor less than the intracellular counterpart of inflammation and represents a general reactive process in response to a variety of agents?" (Shubik).[73] Both cancer and inflammation are cellular processes almost universal in occurrence[5, 60] and are deemed responses to an external agency—an irritant.[5] However, there are some fundamental differences between the two processes. Inflammation is an immediate response to an injury or an irritant. Cancer is believed to be a delayed response; it 'does not leap to life'.[75] Inflammation usually has a detectable basis while cancer, in its natural form in both man and animal, is "spontaneous".[3, 12, 40, 68, 72] Inflammation can occur predictably, can assume a predictable form and terminate predictably. Cancer remains unpredictable in its occurrence, manifestations and termination. Inflammation, in many ways, is more universal in character than cancer. Individual, sexual, racial, geographical, hereditary or species variation do not affect its manifestations, nor do the tissues exhibit any selective resistance to it. Inflammation is a process which, like repair, can be assigned a definite purpose;[60] it is a homeostatic mechanism.[5] Cancer appears to be purposeless[60] and constitutes 'a great menace to human life'.[28] On removal of the irritant, inflammation usually subsides, while cancer, once established, is independent of the provoking agent.[60]

Characteristics of the Cancer Cell: No structural or metabolic characteristic has yet been found which can definitely distinguish between normal and neoplastic cells.[10, 23, 38, 51, 59, 60] Cancer research, todate, has done little to alter the opinion of Bayne-Jones et al,[2] expressed in as early as 1938, that there are no fundamental differences and no striking variations in chemical make-up, enzyme content, metabolism or structure between normal and malignant cells of the same tissue type. While what has been said above regarding the distinction between cancer and inflammation is generally true, it appears

equally true that the former cannot be completely differentiated from certain reparative, regenerative and inflammatory processes in which cell multiplication is a prominent feature.[60] In malignant cells, deviations from normal mitotic divisions do occur, but none of them is characteristic, and all may be found in non-cencerous conditions.[28] In Boyd's[5] words, 'the microscopic features may be as equivocal as the clinical manifestations'. These obvious structural and metabolic overlaps between cancerous and non-cancerous cells led to Potter's *Minimum Deviation Postulate,*[63] that only those changes which are found in all cancer cells are really fundamental to the development of malignancy. The only characteristic that may be considered common to almost all cancer cells is their progressive, often disruptive proliferation.[19, 60] One cannot resist quoting Nicholson[49]: 'Tumours in their structure, their functions and the manner of their growth do not differ essentially from other tissues, and obey the laws that govern their behaviour.'

The Time Dimension in Carcinogenesis: Massive statistical data in humans and equally voluminous experimental work in animals have given us the 'what', the 'who' and the 'where' of cancer. The 'why' is the bone of contention for all theorists. However, the 'when' of both human and animal cancers (spontaneous or induced) has remained relatively unexplored and unexplained!

Two facets of carcinogenesis outlined above point imploringly to the time dimension. The first is latency; the second is the increase in the incidence of cancer with increasing age. Aging is the process that occurs with the passage of time.[76] Is it possible that the passage of time inflicts upon the body cells either the process of aging and/or the process of cancer?

Cancer: The Normal Potential of Every Cell! Except the mature nerve cell, most cells in the body appear to possess an inherent capacity for undergoing a neoplastic change.[60] Cancer is not any evil, it is merely a variant of biological behaviour of cells.[75] It occurs in many vertebrates, some insects and plants,[82] and, in all these it occurs spontaneously. Neoplasia is a universal cell potentiality[60] and that potentiality has been expressed in tissue culture wherein spontaneous[17, 18, 70, 71] and induced[62] malignant transformation is known to occur. Nicholson[50] has accredited a normal dividing cell with a neoplastic potentiality, in a dramatic, yet succint manner, "I regard tumour formation as a reaction to stimulation comparable with every reaction of the organism or cell, which differs from these in degree, but in principle not at all. Its visible anomalies or peculiarities of structure are, for me, commensurate with the expressions of those of behaviour; they are effects of tumour formation and not its cause: tumour formation is a reaction—an innate, physiological 'potency' or 'capacity', if you please—of every dividing cell, and represents and is the innate, physiological function of growth by division."

From the foregoing, there are two generalisations which can be inferred:

(i) Cancer, a process that affects almost all cells of the body, at all ages, assumes a myriad forms, occurs apparently without any provocation and is

governed by the time dimension, can be safely assumed to be a normal potential of any normally dividing cell.

(ii) Any new hypothesis on cancer must be sufficiently broad-based so as to account for the wide spectrum of the biological behaviour of cancer. In particular, it should impart a temporal perspective to carcinogenesis and should explain why ageing and cancer go hand in hand in both animals and man.

II

NEW CONCEPTS ON CANCER

The present hypothesis on cancer makes the following assumptions:

1. Cancer is an eventual, normal phase in the life cycle of a dividing cell in postnatal life.

2. A cellular clock, the *Cytochron** governs the expression of the neoplastic potential of a dividing cell. This implies that all naturally occurring tumours are a normal biologic expression of cell behaviour for which no carcinogen need operate. A carcinogen merely sets the cytochron in advance so as to force a premature occurrence of the cancerous change. A death due to a non-cancerous cause precludes the appearance of cancer.

3. Cancer, like the biological processes of ageing and senescence, is a time-governed phenomenon evolved through the process of natural selection as a means to terminate the life of the organism.

In the present communication, assumptions (1) and (2) will be elaborated upon. The assumption that ageing, senescence and cancer are 'a biologic triad governed by time' is a subject of a separate communication.[30] The first assumption necessitates a study of the kinetics of cellular proliferation in postnatal life which, in turn, necessitates a 'classification of cell populations on the basis of their proliferative behaviour'.[34]

III

CLASSIFICATION OF CELL POPULATIONS IN POSTNATAL LIFE[33, 34]

Leblond has suggested a convenient classification of the cell populations in the body into three groups. The following account is essentially based on his publications[33, 34].

1. **Static Cell Populations:** These are the perennial or the permanent cells of the body and comprise the nerve cells, both central and peripheral.

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* The term *cytochron* is here suggested as an abbreviation for a hypothetical, built-in, cytochronometric device. It appears to be a suitable alternative for the term "biological clock."

In rats, these have been found to be incapable of division after the age of seven days. They persist till the death of the organism and can be said to possess the same life span as that of the organism.[11] It must be mentioned, however, that Altman,[1] from his work on young adult rat and cat brains has suggested that neuronal multiplication may be a normal postnatal phenomenon in the mammalian brain.

2. **Expanding Cell Populations:** These are 'homogeneous groups of cells showing scattered mitoses in numbers that account for the increase in the total DNA content'. The life span of each cell is co-extensive with that of the individual and new cells are produced only to cover the growth of the tissue.[11, 34] Contrary to former belief, the dividing cells are fully differentiated cells.[11, 34]

Examples of expanding cell population are the various glands, the muscular tissue, kidneys and neuroglial cells. The mitotic index of expanding cells dramatically increases with appropriate stimuli. Hunt and Hunt[27] have reported, in the hypophysis and the adrenal cortex of young female rats, a cellular turnover much greater than has so far been accepted. They have suggested that these two glands might be placed in the group of renewing cell populations.

3. **Renewing Cell Populations:** These are 'homogeneous groups of cells where mitosis is abundant and exceeds that required for the total increase in DNA content'. A very high production of cells is balanced by a corresponding cellular loss. The high magnitude of cell production is exemplified by certain renewal systems in man. About eight billion mitoses occur in the bone marrow at any given moment so as to maintain a proper stock of erythrocytes. In a three-month-old rat about three thousand million cells are shed daily from the gut lumen—a number that is a twenty- second part of the entire cell population of the rat.[11] The epidermis shows a fairly rapid turnover; about ten thousand cell doublings occur in man during a life span of a hundred years.[77]

Examples of renewing cell populations are: the epidermis, various mucosal linings, bone marrow, lymph nodes, thymus, testis, all haemopoietic organs and all skin appendages. An adequate explanation for such high cellular turnover is not available. The reasons must be both intrinsic, i.e. the inherent capacity of the parent cells to divide at certain intervals, and extrinsic, i.e. those external agencies which produce a cell loss.[33, 34] All mucosal linings and the epidermis are at constant interaction with the *milieu exterieur* and 'the constant influx of new cells anticipates damage and prevents occurrence of weakened areas or gaps in the epithelium'.[34]

A Working Scheme For Cellular Proliferation In Postnatal Life:

Certain broad generalisations regarding the three types of cell population described above may be made. The static cell population has all cells which do not divide. Both the expanding and renewing cell populations have cells

which are capable of division[33, 34] (stem cells) and are, therefore, destined to divide.[4, 67] Except for a few epithelia,[46] all the renewing cell populations have cells which are differentiated[33, 34, 56] and, therefore, 'destined to die'.[4, 67] Whether the expanding cell populations have a percentage of cells which are incapable of division and, therefore, 'destined to die' is not certain.* The following scheme, therefore, applies essentially to the renewing cell populations. It is felt, however, that it could possibly be applied to the expanding cell populations, as well.

Certain important terms merit definition here:

1. **alpha cell**[55, 56, 57, 58] **or stem cell:**[20, 33, 34, 69]

This is the undifferentiated cell, destined to divide.

2. **n Cell**[55, 56, 57, 58] **or daughter cell:**

This is the differentiated, mature cell with a finite life span.[53, 54] It is incapable of division and, therefore, destined to die.

3. **Differential,**[34] **asymmetric**[34, 78] **or alpha-n**[55, 56, 57, 58] **division:**

When an alpha cell divides into another alpha cell and an n cell, differential division is said to have occurred. This division leads to an arithmetic increase in cell number. (Fig. 1).

4. **Non-differential,**[34] **symmetrical**[78] **or (alpha—2 alpha)**[55, 56, 57, 58] **division:**

This type of division is said to have occurred when an alpha cell gives rise to 2 alpha cells. This leads to an exponential increase in cell number. (Fig. 2, 3, 4).

5. **(n-2n)**[55 66] **division:**

This type of division is said to have occurred when an adventitious (*vide infra*) alpha cell divides symmetrically into two n cells, both destined to die. (Fig. 3).

In the subsequent discussion, the following terms will be used: alpha cell; n cell, differential division, non-differential division, n-2n division.

Attributes of the alpha cell: The alpha cell is a direct descendent, in the evolutionary process from the unicellular organism.[56]. It has also retained the capacity of the parental unicellular organism for non-differential division.[56] With the emergence of the multicellular organism, it has also developed a capacity for differential division. The life span of the alpha cell may either be defined as being infinite[56, 58] or as one doubling (generation) time.[57] The latter does not imply death of the cell but, rather, a change of state.[24]

"The primary unit of growth is the expressible gene complement of the alpha cell. Each gene complement not only will determine the protoplasmic mass and composition of this cell, but will also carry with it, a fixed number and composition of n cells. There is a maximum capacity for alpha—2 alpha

* Pure proliferative populations are rare in the mammalian organism—Quastler.[65]

(differential) divisions and for alpha-n (non-differential) divisions inherent in the genetic make up of the alpha cell ... Every alpha cell division gives some risk of genetic alteration." (Osgood).[56] Only an alpha (stem) cell can initiate a colony in tissue culture, or a transplant or a tumour.[20, 56, 57,58,62] Needless to say, the ability to divide is a necessary prelude to abnormal division in a neoplastic manner.

The Concept of Steady State: This implies a steady state, quantitative as well as qualitative. Quantitatively, a renewing cell population is said to be in a steady state when the number of cells produced is balanced by an equal number of cells lost.[33, 34, 64] By about the age of one year in rats, a steady state is reached and is subsequently maintained despite a very rapid cell turnover.[34] Qualitatively, a steady state implies a constancy of the n: alpha cell ratio. Normal cell proliferation is characterised by a transient decrease in the ratio of n: alpha cells.[56] This is followed by an over-compensation with a transient increase in the n: alpha cell ratio.[56] This follows Le Chatelier's principle[36] which states that when a system at equilibrium is subjected to an additional constraint, the position of equilibrium moves in a direction which tends to neutralise the additional constraint. Malignant proliferation is characterised by a constant decrease in the n: alpha ratio.[56]

The steady state concept is easily applicable to a renewing cell population. In the rat, after the third month of life, the rate of addition of nuclei to expanding cell populations continues to decrease and towards the age of one year no further addition can be detected.[34] This would imply that even in an expanding cell population, after the growth period, a steady state is reached. Such a state is, however, more of a resting type in contrast to the steady state dynamically maintained in renewing cell populations.

Type of Cell Division:

(a) **Differential Division:** (Fig. 1) It is this type of cell division (leading to an arithmetic increase in cell number) that occurs almost exclusively in postnatal life.[45, 53, 54, 56] Any decrease in the number of mature or n cells due to any cause promotes such division of the alpha cells.[9, 56] An increase in the number of mature cells decreases alpha cell division[9, 56]

(b) **Non-differenital Division:** In a healthy adult, such divisions are exceedingly rare[32, 53, 54, 56] and occur only in order to replace alpha cell loss.[56] A non-differential division not only doubles the population of the alpha cells but also potentially doubles the number of the n cells.[56] Even twenty such divisions can increase the total mass by a factor of million.[56]

The concept that mitotic divisions in renewing systems are differential is popular as well as convenient. Unfortunately, there is no evidence for an exclusively differential mitotic division in renewal systems.[34, 35, 41] Leblond and co-workers have reported non-differential cell division normally occurring in the basal layer of the stratified squamous epithelium of the oesopha-

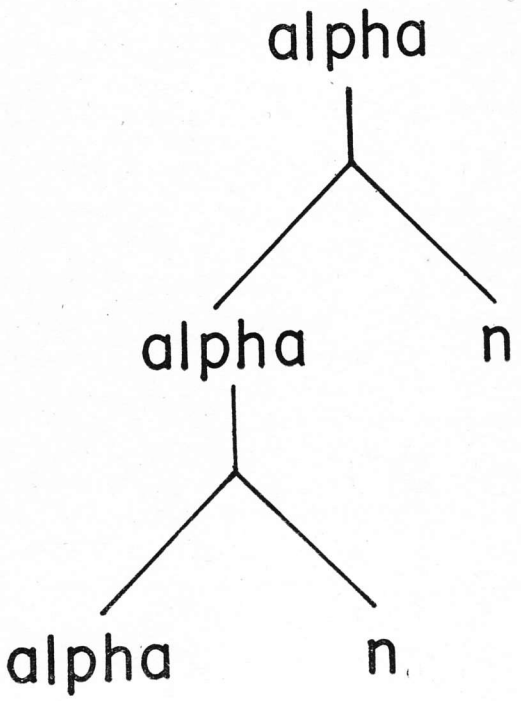

Fig. 1:
Differential division.

gus[35, 41] and the intestinal crypts of rats.[34] Leblond has provisionally concluded that, at both these sites, the decision as to whether alpha cell will differentiate or continue dividing depends on the environment.[34]

However, while comparing renewing cell populations with neoplastic ones, Lebold[34] observes that 'renewal systems give rise to cells which lose the ability to divide and eventually die, so that the increase in cell number is not exponential and indeed, the size of the population tends to stabilise, just as in expanding cell populations.' Moreover, the concept of steady state necessitates that the ratio n : alpha remains constant.[56] It is felt that the patterns of non-differential divisions which occur in a normal or a cancerous cell population may be defined in clearer terms.

(i) A true non-differential division occurs only to replace alpha cell loss. Both the alpha cells formed from such a division continue to function as alpha cells (Fig. 2).

(ii) An apparent non-differential division occurs, without any alpha cell loss having occurred, and assumes a course whereby it becomes a variant of differential division. Of the two so-called alpha cells, one may be termed adventitious, since it soon ends in two mature daughter cells by n-2n division. The other continues as an alpha cell. The number of alpha cells, therefore, remains more or less constant. This type of apparent non-differential division regularly punctuated by n-2n division helps in maintaining a steady state (Fig. 3).

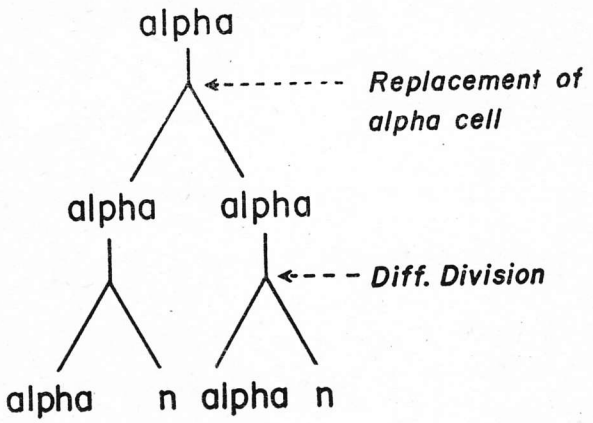

Fig. 2:
True non-differential division for replacement of alpha cell loss.

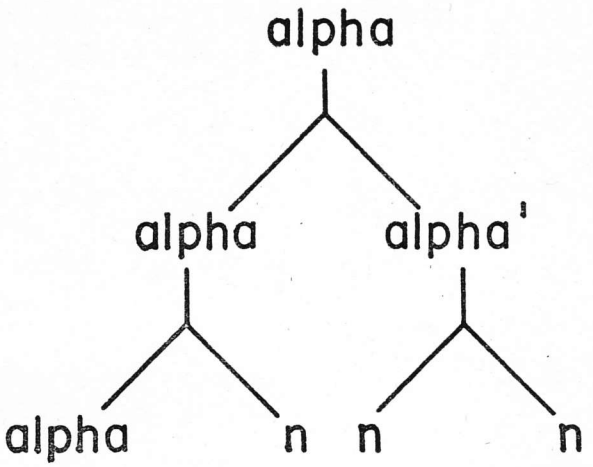

Fig. 3:
Apparent non-differential division. The adventitious alpha cell (alpha') divides into two n cells, thereby maintaining a constant number of alpha cells.

(iii) In a cancerous cell population, non-differential division occurs rather as a rule than an exception. A majority of cells produced retain the ability to divide.[3, 44] This leads to a sustained, exponential increase in cells (Fig. 4).

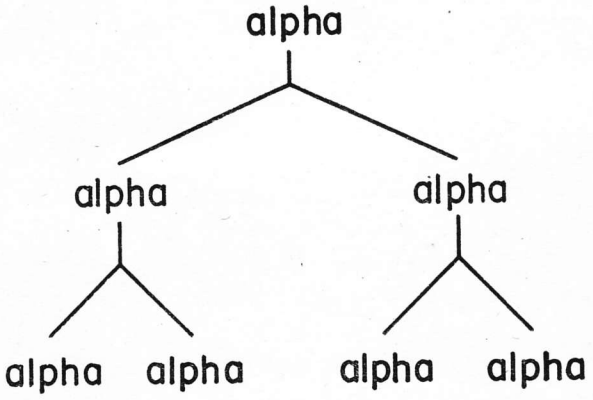

Fig. 4:
Non-differential division in a cancerous cell population.

IV

1. **Cancer—an Eventual Phase:**

All biological systems must reproduce themselves in order to ensure their survival; the reproduction of biological systems involves reproduction of cells.[42] To the 'why?' of cell division, the answer is that the cell must divide or die.[42] The fundamental process of cell division thus becomes the basis of life: In a unicellular organism, it is necessary for the continuation of the species. In a multicellular organism, it is necesary for its reproduction (embryogenesis) and for growth and maintenance in postnatal life. A dividing cell is, therefore, the main star in the galaxy of biological existence.

"Every animal appears as a sum of vital units, each of which bears in itself the complete characteristics of life" (Virchow).[80] Taking a dividing cell (alpha cell, stem cell) as one of these vital units, it is interesting to follow its life cycle in the various stages of existence of the parent multicellular organism.

There are three phases in the life cycle of a dividing cell:

i. the prenatal or embryonic,
ii. the postnatal differentiated,
and iii. the postnatal dedifferentiated.

i. **The Prenatal Phase:** This is characterised by the cell undergoing very rapid non-differential divisions, leading to an exponential increase in cell number, with production of various clones for the purpose of forming cell types (organogenesis) and, *pari passu* with this, the establishment of certain immunological patterns.

ii. **The Postnatal Differentiated Phase:** The proliferative activities (differential divisions) of the dividing cell (alpha cell) lead essentially to an arithmetic increase in cell number. The continued cellular proliferation ensures growth and maintenance. The ability of any cell for undergoing divisions is fixed at a certain maximum (*vide infra*). As and when this capacity comes to an end, i.e. is exhausted, the dividing cell reaches the end of its fidelity span* and now enters the third phase. Depending upon the genetic set up, some cells enter the third phase earlier than others.

iii. **The Postnatal Dedifferentiated Phase:** At the end of the second phase, the dividing cell, having spent its fidelity span, reverts to the first phase: It resumes non-differential division which leads to exponential growth in cell number, establishes new clones of cells, initiates new immunological patterns, but fails to serve the needs of the parent organism. This independent primitive existence of a system of dividing cells in an otherwise disciplined cell community is what we call cancer.

* During this span, the proliferative activities of the dividing cell serve the needs of the parent organism.

2. **The Fixed Cell Division Capacity (FCDC) and Carcinogenesis—the 'Cytochron':**

The material to follow is based on Osgood's postulates[56] that

(a) Every alpha cell division involves a genetic change in the alpha cell.

(b) There is certain fixed maximal capacity for both differential and non-differential divisions inherent in the genetic set up of the alpha cell.

Both these concepts necessitate assigning to the alpha cell a mechanism which must operate so as to satisfy the assumptions stated above.

The Cytochron: The existence of a fairly accurate clock-work mechanism as a universal feature of cellular organisation has been recognised.[21, 66] The huge handbook of biological data[25] confirms the prevalence of a palpable mathematical exactitude regarding both time and number, in the animal and plant kingdoms. Each animal has its own natural life span, a species specific pulse-rate and respiratory rate in health. If the life span and the pulse rate of the animal at different ages are known, it is possible to compute the total number of times its heart could beat during postnatal life. It was felt that this concept of time and number could be extended to the process of cell proliferation in postnatal life. Osgood's postulate that there is a fixed maximal capacity for both differential and non-differential divisions in the alpha cell expresses this in part. The type of cell division that is under immediate consideration is of the differential type. It is proposed that the hypothetical **cytochron** (cellular clock, cytochronometric device) resides in the genetic set up of any alpha cell and is concerned with two fundamental operations:

(a) The determination of the total number of times that the alpha cell will divide in a normal, differential manner. This is stored as coded information in the cytochron.

(b) The registration of the number of divisions undergone by the alpha cell. With each such division, a marker on the clock moves once. Walker[81] has suggested that the number of mitoses, rather than chronological time, may be responsible for the timing factor in cellular differentiation and ageing.

In order to graphically present the above concept, a curvilinear recording system is suggested (Fig. 5). Along its entire length, the total number of times the alpha cell can normally divide is charted. This has a genetically predetermined basis. Furthermore, into the same recording system is incorporated a marker which moves unidirectionally over a fixed length (between any two marks), each time indicating one particular division of the alpha cell. It may, therefore, be stated that with such a recording system, the alpha cell, after any single division, is no longer exactly the same cell it was just prior to that division.

Such a clock mechanism incorporates, primarily, biological and, secondarily, chronological time into its working. The number of divisions that the alpha cell undergoes will be registered as a denominator or indicator of

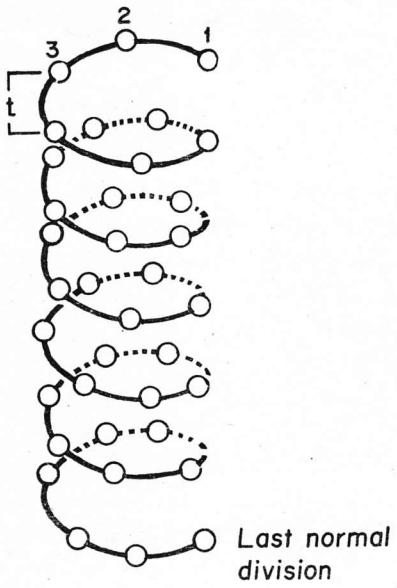

Fig. 5:
The cytochronal helix. Each circle denotes one differential division. t is the average time between any two divisions.

the biological time. The chronological time over which these divisions are spread out may be correlated with the biological time. "The organism is sometimes spoken of as a time-binding machine... I prefer to say that the organism carries with it the history of its life." (Dobzhansky).[13]

The second postulate, that there is a certain maximal capacity for differential and non-differential divisions in every alpha cell, raises a question as to the exact relationship between the differential and the non-differential divisions of an alpha cell. It is suggested that, since differential division is what occurs almost exclusively,[56] it should be considered the funamental attribute of the alpha cell which, as and when needed, undergoes non-differential division at the cost of a part of its total capacity for differential division. This total capacity for differential division, fixed at a certain maximum is the Fixed Cell Division Capacity (FCDC) of an alpha cell and resides in its genetic set up. The FCDC, fixed at a certain maximum during cytodifferentiation in embryonic life, is carried into postnatal life as an inherent biological property of every alpha cell.

A question arises as to the importance of the FCDC of an alpha cell with reference to its role in the postnatal life span of the parent organism. It is proposed that so long as the FCDC of any alpha cell is not completely exhausted, it will continue to divide in a normal manner so as to serve the needs of the parent organism. The chronological time over which the entire FCDC is spread out will constitute the fidelity span of the alpha cell in postnatal life, which is the second or the 'postnatal differentiated' phase in the life cycle of such a cell.

Strehler[77] has reported the findings of Hayflick and Hay that chick and human embryonic fibroblasts are capable of only a fixed number of doublings

in vitro: The human cells can be subcultured about fifty times, after which they degenerate and eventually die. A question arises as to what happens to an alpha cell after it exhausts its FCDC! Does it, like the fibroblast described above, degenerate and die or does something else happen to it? It is postulated that as and when the FCDC of any alpha cell is exhausted a metamorphic mechanism is triggered off by the cytochron (Fig. 6) and the

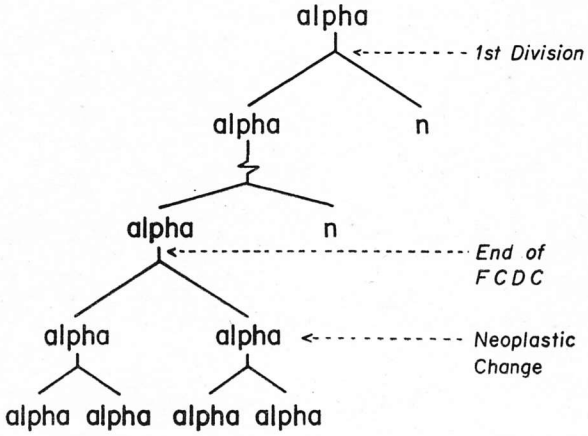

Fig. 6:
The exhaustion of FCDC and the occurrence of neoplastic change.

cell now enters into its neoplastic or 'postnatal dedifferentiated phase'. One recalls here Burnet's[6] statement: "The real problem of cancer is, then, to understand the process of control by which normal cells, from fertilised ovum to the end of life, are maintained in morphological and functional conditions appropriate for the needs of the organism at the time. . . . Cancer is a negative condition — a manifestation of breakdown in one or more aspects of the positive control that welds the cells of the body into a single functional unit — the organism as a whole." The alpha cell was under positive control as long as its FCDC was not spent out. It escaped such positive control when a negative state of 'no more FCDC' came into being. Cells in tissue culture undergo very rapid alpha-2 alpha (non-differential) divisions.[58] As postulated above, each non-differential division occurs at the cost of a part of the FCDC. The FCDC of the cells would be very rapidly exhausted, promoting thereby a malignant change, as often observed in tissue culture.

The suggestion that it is the exhaustion of the FCDC which leads to a neoplastic change may perhaps be stated in mathematical terms as follows: Let

T = The life span of the animal

C = FCDC of any alpha cell

t = The average generation (doubling) time for a differential division of the alpha cell

T_1 = The time over which the FCDC would be spent — the fidelity span of the alpha cell.

Then

$C \times t = T_1$

If $T \leqslant T_1$

no neoplastic change can occur. However, if

$T \geqslant T_1$

the alpha cell undergoes a neoplastic change. T_1 can be reduced by a reduction of C and/or by reduction of t.

Having boldly postulated that it is the FCDC of an alpha cell that determines the 'whether' and the 'when' of a neoplastic change, it is essential to also postulate factors which may govern or modify the quantum of the FCDC.

The FCDC Postulates:

1. In postnatal life, each (dividing) alpha cell has a fixed maximal capacity for differential divisions which is its FCDC.

2. The FCDC is a function of the genetic set up of the cell.

3. In a particular cell population (a group of morphologically similar cells with, presumably similar function, e.g. the acinar cells of the pancreas or transitional epithelium) the FCDC of all cells is generally the same.

4. Cells in the same cell population may have different FCDC.

5. In cell populations with a rapid cellular turnover (e.g. mucosa of the small intestine, the haemopoietic system), the FCDC of the cells is proportionately high.

6. The FCDC, for the same cell types in different animals, is a species-specific number and is usually proportionate to the life span of the organism.

7. Gametic or somatic mutation or 'genetic loads'[13] can alter the FCDC of any cell.

8. Viruses, chemicals, carcinogens, irradiation, hormones and chronic irritation, in short, any carcinogen may reduce the FCDC of a cell.

9. Any demand for rapid and/or excessive cellular proliferation forces the affected cells to expend their FCDC at a faster rate than that of other cells.

10. The concept of FCDC is applicable to the different cell types found in embryonic malformations such as teratomata and dermoids.

11. Any embryologic abnormality, either of form or position, tends to reduce FCDC of the cells involved.

12. Any metaplastic change tends to reduce the FCDC.

13. Cells in tissue culture may lose their FCDC rapidly and thus be predisposed to a malignant transformation.

14. The chronological time over which the FCDC of a cell is spread out constitutes the fidelity span of that cell.

15. When the FCDC is exhausted, the cell metamorphoses into its neoplastic phase.

The FCDC concept incorporates into it both biological and chronological time. These dimensions when applied to the life cycle of a dividing cell permit one to account for the genesis of cancer. The concept explains why any normal (alpha) dividing cell is potentially malignant. The concept also permits stochastic considerations in the genesis of cancer: heredity, mutations, carcinogens and time can all focus, singly or collectively, their influences so as to bring about a neoplastic change in a normal cell. To the question, 'Is cancer a sudden change?' it provides the answer that genotypically it is a gradual process whereas phenotypically it is a sudden change. The application of the FCDC concept in the understanding of the various biological aspects of cancer (outlined in Part I) has been attempted elsewhere.[29]

SUMMARY

A biological approach, with a temporal bias, to the process of carcinogenesis has been presented. It has been emphasised that cancer is a "normal" potential of any dividing cell and that a hypothetical cellular clock, the *cytochron,* governs the expression of this potential. A concept of cell division regulated by the *cytochron* has been elaborated so as to impart a temporal perspective to the problem of carcinogenesis.

ACKNOWLEDGEMENTS

The author wishes to thank Prof. S. M. Bhatnagar for his constructive suggestions and Miss Neela Kothari and Miss Poorvi Rajdeo for their help in the preparation of the manuscript.

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TOWARDS SEMANTIC CLARITY IN CANCEROLOGY

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There exists, in all scientific disciplines, a certain indifference towards its constituent terms and difinitions so that there remains a chasm between the progress made by the science itself and the progress made in creating *pari passu*, precise terms and the definitions. To quote, for instance, Weiser *et al*[39] on immunology: "Though the science of immunology has made rapid strides, the terminology unfortunately has grown without suitable guidance so that terms which are unsuitably descriptive and confusing have been employed." In the field of cancer, a similar situation exists. We neither have a precise definition of cancer nor do we have a clear, relevant, parlance.

It was Lavoisier[24] who first recognised the need for precise terms in any science: "As ideas are preserved and communicated by means of words, it necessarily follows that we cannot improve the language of any science without, at the same time, improving the science itself; neither can we, on the other hand, improve the language or the nomenclature which belongs to it. However certain the facts of any science may be, and however just the ideas we have formed of these facts, we can only communicate false impressions to others while we want words by which these may be properly expressed."

A classification of the various terms used in cancerology will yield five basic groups as shown in Table 1. The etiologic, the operational, and the last five behavioural terms have been discussed elsewhere.[20] We shall presently deliberate over the important terms in the Morphologic and the Behavioural groups and evolve a scheme whereby we may, in the words of Humpty Dumpty, mean just what we choose to mean. In short, the present chapter is an attempt at Eusemantics*[13, 14, 15, 16, 21, 23] in cancerology.

CANCER

The confusion that prevails over this fundamental entity may be realised from a recent statement by Foulds:[7] "Cancer research will have reached an outstanding landmark when it becomes possible to define neoplasia in biological terms." One fails to understand why Foulds should

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Received for publication: January 1, 1971.

* This term has been coined by the authors from two Greek words, *eu* meaning "good" and semantics meaning "pertaining to meaning of words". Cf. eubiotics meaning "the science of healthy living", and euphenics, coined by Joshua Lederberg,[25] meaning "the science of producing better phenotypes". Eusemantics, then, is the science of evolving appropriate, meaningful terms and definitions.

TABLE 1

Main Sematic Groups in Cancerology

Morphologic	Cytologic Histologic	Aetiologic	Operational	Behavioural
Cancer	Hepatoma	Viral cancer	Initiation	Benign
Carcinoma	Lymphoma	Radiational cancer	Induction	Malignant
Sarcoma	Meningioma	Kangri cancer	Promotion	Innocent
Leukemia	Nephroma	Dhoti cancer	Progression	Dormant
Polycythaemia	Adenoma	Embryonal cancer	Regression	Incipient
Tumor	Glioma		Precancerous	Latent
Round cell carcinoma	Melanoma		Carcinogenesis	Occult
Spindle cell carcinoma/ sarcoma	Schwannoma		Cancerogenesis	
Squamous cell carcinoma	Plasmacytoma		Carcinogen	
Oat cell carcinoma	Various blastomas		Cancerogen	
Adenocarcinoma			Neoplasia	
Carcinoma simplex			Anaplasia	
			Secondary cancer	
			Primary cancer	
			Spread	
			Metastasis	

have, himself, complicated the problem by using the terms cancer and neoplasia to mean the same thing.

The terms cancer and carcinoma appear to have the same origin (L. **cancer,** Gk. **karkinos,** and Sanskrit **karkarata** meaning a crab; Gk. **onkoma** a swelling). "The claw like venous pattern and the tenaciousness of malignant tumors suggested to the ancient the analogy of a crab or cancer" (Lewin[26]). Dorland's dictionary[6] draws a distinction, based more on usage than on logic, by defining cancer as "a cellular tumor the natural course of which is fatal and usually associated with formation of secondary tumours", and by defining carcinoma as "a malignant new growth of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases."

TUMOR

Virchow[37] is reported to have remarked that no man, even under torture could exactly say what a tumor is. Nicholson[30] also maintained that "it is impossible to define a tumour". According to Boyd,[2] "A tumor or neoplasm is a growth of new cells which proliferate without relation to the needs of the body. The essence of the process is loss of control over two fundamental functions of the cells, namely, reproduction and differentiation." Willis[40] *"essays"* the definition of tumor as "an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimuli which evoked the change."

Despite the fact that the loss of differentiation does not occur in a "benign" tumor or neoplasm, but does occur in cancer, Boyd's[2] definition groups them together. Willis[40] makes the prior presence of "stimuli" as an integral part of tumorigenesis, an assumption ill-supported by the occurrence of a variety of spontaneous tumors in man and animals as well as the extensively documented cancerous transformation of cells, spontaneously, in tissues culture. Whereas Boyd[2] and Willis[40] have despaired of any law and order in tumor development, Foulds[7] is fairly optimistic: "...most tumours have histological patterns by which they can be recognised and named. Tumours, in general, are not formless, chaotic conglomerations of cells but have an organised structure which sometimes approaches in perfection that of parent tissues." It would be evident from Foulds' definition that he, too, equates tumor with cancer.

The term tumor (L. **tumere**, to swell) indicates the presence of a swelling due to any cause (cf. tumefy, tumefaction, tumesence). Celsus[4] (30 B. C.) used the term tumor to indicate the swelling associated with any inflammation. Commenting on the title of the classic work on cancer by Willis,[40] Fould[7] states that the author has "taken a retrograde step using the much less comprehensive and adaptable title *The Pathology of Tumours*." Garb[8] has been quite frank about the meaning/s of the term tumor: "The word **tumor** strictly speaking merely means a swelling; thus, a boil or blister could be called a tumor."

NEOPLASM

The term neoplasm (Gk. **neo**, new; **plasma**, formation) means newly formed tissue. Such a general term, though embracing both normal and abnormal new tissue formation, cannot be considered an improvement upon the term tumor. Yet Foulds[7] has entitled his recent monumental work on cancer as **Neoplastic Development.** Cells are constantly formed anew, at a rate exceeding even the fastest growing cancers, in the renewing cell populations in the alimentary epithelium and bone marrow. Healing of a wound*, by primary or secondary intention, occurs only because of

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* *The Neoplasm in Wound Healing*

With the touch of the knife
The tissues depart;
A breach is created
Void of vessels and cells.

No sooner this happens
Cells spring into action:
Comes fibroblast, comes angioblast
Laying a weave of collagen as well.

The wound heals,
The gap is bridged,
The cell participants disappear,
Leaving behind a fibrous seal.

a very rapid development of **neoplasm.** A scar or a keloid are but examples of neoplasm. Qualifying every neoplasm by appellation benign or malignant fails to clear the confusion.

SARCOMA

The term sarcoma (Gk **sarx, sarkos,** flesh), like cancer and carcinoma, is only a morphologically descriptive term and it is just possible that the term cancer or carcinoma (crab) was first applied to a "sarcoma" showing the "claw like venous pattern", seen more commonly in sarcomata than in carcinomata. In contrast to the Latin root **cancer** or the Greek root **karkinos,** the root **sarcos** has wide physiological and pathological usage: **sarcoplasm, sarcolemma, sarcostyle, sarcomere, sarcoid, sarcoidosis.** To a person uninitiated in cancerology but well versed in etymology, the occurrence of sarcoma would appear natural and be causally related to muscle fibre which rarely undergoes a cancerous change.

LEUKEMIA

The etymology of the term leukemia (Gk. **leukos,** white; **haima,** blood) has poor scientific merit. We have yet to see a patient of leukemia with white blood. It is not realised that leukemia (excess of leucocytes in the peripheral blood) is an epiphenomenon* which may or may not reflect, qualitatively and/or quantitatively, the main phenomenon of "abnormal widespread proliferation, in bone marrow and often in other blood-forming tissues, of the precursors of one of the types of leukocytes." (Moore[29]). Our deliberate neglect of the main phenomenon and excessive dependence on the epiphenomenon leads us into such, unfortunately widely accepted[28, 29, 34] semantic adventures, as "subleukemia", "aleukemia", and "preleukemic leukemia".

POLYCYTHEMIA

Polycythaemia (Gr. **poly,** many; **kytos,** a vessel, as if a cell; **haima,** blood) implies increased number of cells in the blood, physiological or pathological. Dorland's dictionary[6] defines polycythaemia as "excess in the number of red corpuscles in the blood". Why should the term refer to the red blood cell only is not understood for the term merely signifies increase in the number of cells in the blood. Monti[28] defines polycythaemia as "an abnormal increase in the number of red cells in the circulating blood". However, according to the same author: "Primary polycythaemia is a disease ..... characterised by an increased proliferation of erythroid, myeloid and megakaryocytic elements with resultant numerical increase of erythrocytes, leukocytes and platelets in the peripheral blood."

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*"*Lymphatic leukemia* is lymphosarcoma with a circulating metastasis". (Willis[40])

—OMA

The terms such as hepatoma, lymphoma, etc., are noncommital, sitting-on-the-fence terms which only indicate that there is a tumor of the liver or the lymphoid tissue, without indicating the presence or the absence of a cancerous change. The hepatoma in question may be a cavernous hemangioma without a single cancer cell or it may be highly anaplastic,* liver cell carcinoma. "It is the **tissue** of origin not the **organ** of origin, of a tumour on which its peculiar properties depend." (Willis[40])

The microscopic classification of cancers into round celled, spindle celled, etc., is misleading for two reasons: the same tumor may show all the varieties; and the behaviour of the cancer cells are so often independent of whether they belong to **adenocarcinoma** (most "differentiated") or carcinoma simplex (highly "undifferentiated").

BENIGN/MALIGNANT

The behavioural qualities of any lesion—benignancy or malignancy—should be clearly understood. Benign to whom? Malignant to whom? Benign means harmless, but not so, for a non-cancerous, **"benign"** ependymoma of the aqueduct of Sylvius, that kills a patient. In cancerology, clinical or pathologic, malignant is taken synonymous with cancerous.[2] However, we know of malignant arterial hypertension. Malignancy indicates "the tendency to go from bad to worse" or to cause death. A benign parathyroid adenoma can set up a chain reaction whereby the individual goes from bad to worse and eventually dies. This is an example of **death due to the malignancy of a benign parathyroid adenoma!** On the other hand a frank cancer of the prostate may be most benign** for it may remain silent for years together without ever killing the patient, who may die of a "malignant" heart failure or hypertension. Every senescent process goes from bad to worse and may therefore deserve to be called malignant.

Benignancy or malignancy should be strictly determined by what the tumor does to the patient rather than what it looks under the microscopes, for these two qualities do not always correspond to each other. It cannot be denied that most cancers are malignant in their behaviour. However, not every cancer is malignant, nor is every non-cancerous lesion a benign one.

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*Anaplasia (Gr. *ana* backward; *plassein* to form) indicates loss of normal differentiation, organisation and specific function[38] and appears acceptable as a histologic criterion of cancer.

**Even when left untreated, every cancer does not proclaim *"vini, vidi, vici."* Nor can you say for every cancer, *"abiit, excessit, evasit, erupit."* Nor need you use for every cancer cell, the words (of Shakespeare) adapted by Foulds[7]:

"The cell is out of joint; O cursed spite
That ever I was born to set it right."

SUGGESTED TERMINOLOGY

Despite inherent etymological handicaps and/or semantic overlaps, the terms, cancer, carcinoma, sarcoma, tumor, neoplasm and such terms as hepatoma and adenoma have become ingrained in cancer parlance. Instead of rejecting any of these terms, we shall judiciously exploit them by suitably defining each of them so that both of our thinking and statement enjoy a measure of clarity. In this, recourse shall been taken to the more common implication of each term. There is, however, no escape from replacing the most illogical term leukemia by a more rational term leucosarcoma (or leukosarcoma).

Tumor: A clinical term which, without committing about the cancerous or non-cancerous nature of the lesion, implies the existence of abnormal aggregate of cells, which exhibit abnormality either of number (so-called benign tumor) or type (cancer). For example, a patient has a brain tumor, or a hepatic tumor or a uterine tumor.

Neoplasm: A "microscopic" term that implies abnormally increased population of normal cells or the presence of cancer cells. If the cells look normal and are normally arranged, the neoplasm is an **eucytoma.** If there are cancer cells, it is a cancerous neoplasm.

—oma: The suffixing of **oma** to any organ or cell must imply a non-cancerous lesion consisting of increased number of normal cells, e.g., hepatoma, adenoma, melanoma indicate "benign", non-cancerous lesions made up of normal cells. "All benign" neoplasms genuinely constitute a lump or a tumor and hence the suffix oma (Gr. **-oma**, from **onkoma** a swelling) is highly suitable.

Cancer: The term cancer is a generic term for all carcinomata sarcomata, leucosarcomata, or any other form of cancer (Fig. 1).

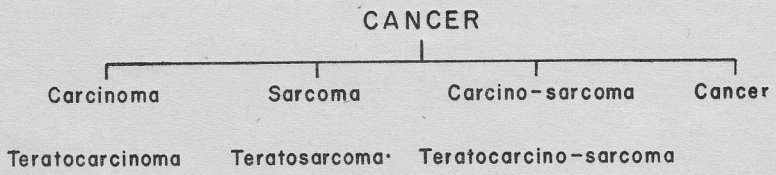

Fig. 1.

Carcinoma: All cancers of epithelial (glandular, surface lining), neurectodermal and chorionic tissues should be referred to as "carcinoma", used as a separate term or suffixed to a cell-type or an organ e.g., choriocarcinoma or carcinoma of the chorion.

Sarcoma: All cancers of hemopoietic and non-hemopoietic mesenchymal tissues (leuco-, erythro-, lymphopoietic tissues; connective, skeletal, vascular tissues) should be called sarcoma, used as a separate term or suffixed to a cell type or an organ e.g., osteosarcoma or sarcoma of bone. We may recall here Willis'[40] statement: "It has not been customary

to think of the leukaemias, Hodgkin's disease and plasma cell tumours as 'sarcomas', or to speak of malignant meningeal or synovial tumours as 'meningiosarcoma or synoviosarcoma'; but it is quite justifiable to do so, for these are all malignant non-epithelial mesenchymal neoplasms." Hence, leukosarcoma (± leukaemia as an epiphenomenon); myelosarcoma; plasmacytosarcoma; erythrosarcoma and panhemocytosarcoma.

A Note on Embryonal Tumors

Not all intranatal cancers are derived from "immature" embryonic tissues nor do all of them present a similar picture. The suffix **blastoma** is used by some to indicate the origin from immature embryonal tissues, and by others to indicate this and/or marked anaplasia. Moreover, "we commonly use the name 'fibroblast' to apply not only to immature connective tissue cells in the embryo but to proliferating connective tissue cells in granulation tissue and other proliferative lesions in adults. So also we speak of 'osteoblast', 'lymphoblast', 'myeloblast', and so on, in reference to proliferating cells of the adult body; so that to such names as 'obteoblastoma' or 'lymphoblastoma' strong objection can rarely be sustained." (Willis[40]). The use of "blastoma" as a suffix for denoting embryonal tumor should be dropped. Instead, one should state "ganglioneurocarcinoma" or "retinocarcinoma" of infancy, childhood or prenatal life, as the case may be.

DEFINING CANCER

Just as Virchow[37] and Nicholson[30] have expressed their hopelessness in any attempt at defining a tumour, Smithers[36] has maintained that cancer is just a shortened way of saying something which cannot be simply defined. He is, however, more certain when he proposes that "cancer is a disease of organisation", a proposition as broad and noncommital as any other. Further, he considers the term "cancer" an undesirable one for the emotional overtones, attached to it which, according to Foulds,[7] have been "a bar to accurate communication and the cause of severe avoidable human suffering."

The handicaps that beset any one who wants to define "cancer" are many: 1. There is no such thing as **the cancer cell**, for each cancer is a species by itself, with cells structurally and functionally unique. 2. Cancer cells have architecture and behaviour arbitrarily defined as cancerous. Cancer is a stage in the lifecycle of a dividing cell. A cell in this stage is an organ of behaviour, not a precise structural entity. 3. The cytoarchitectural and behavioural spectrum presented by different cancers is unimaginably wide, ranging between near-normality to the grossest abnormality. "Any future precise statement of the essential nature of cancer in molecular or other terms must take into account and integrate a large array of structural and behavioural differences as well as similarities." (Leighton[26]).

Some Current Definitions

Burnet:[3] "A cancer results from the multiplication of cells within the body which are alien in the sense that they are not adequately subject to the controls that ensure the morphological integrity of the body"— essentially a behaviouristic concept.

Khanolkar:[11] "Any abnormal, uncontrolled malignant growth is cancer."

Roe:[33] "Cancer is a disease of multicellular organisms and is characterised by the seemingly uncontrolled multiplication and spread within the organism of apparently abnormal forms of the organism's own cells."

Peller[31] gives (in his own words) a "somewhat bulky and clumsy description" of cancer: "Cancer is a process evoked by the great variety of stimuli, and persisting also after their cessation. After an asymptomatic period of greatly varying duration, there ensues an uncoordinated, excessive cell proliferation combined with some or much dedifferentiation. The process is usually irreversible. The proliferation is void of features of specific inflammatory, reparative, or malformative growth, and is capable of disturbing the balance of the body to the point of death, regardless of mechanical disturbance and of the spread of cellular manifestations of the disease."

All the definitions cited above present cancer as an evil springing from within the body—an emotional overtone that must, according to Smithers[36] and Foulds,[7] be avoided. For that very reason, Foulds[7] has quoted a part of the memorandum prepared by a committee of Scottish physicians in 1902, which according to him, is fully justified even today: "It is much to be wished that we had an exact definition of cancer, those of the nosologists being very imperfect and insufficient... If a just and exact definition of cancer cannot yet be formed, we must be satisfied with such a description as a correct history of the disease will afford. This, it appears has never yet been judiciously and accurately done... It is much to be wished that we may no longer be deceived by ambiguous words or phrases or consider them as conveying to us any essential or practical knowledge."

To the so many sweeping generalisations made in the definitions cited above, Dawe's[5] rejoinder serves as a useful moderator: "For example, many definitions include the phrase, 'uncontrolled growth,' which certainly requires some qualifications with regard to many tumors, e.g., some prostatic cancers and mammary cancers that respond sharply to endocrine control factors, sometimes for years. 'Uncontrolled' therefore comes to mean more or less controlled as compared with certain other proliferative processes, and depending on physiological conditions existing in the host. Even the property of serving no useful function to the host is not without exception as, for example, in a functioning thyroid neoplasm that restores the euthyroid condition to a host previously in a hypothyroid

state. Besides, the 'no useful function' character does nothing to distinguish neoplasms from hypofunctioning or hyperfunctioning conditions involving no threat to the host on a cell-proliferative basis. Data on cell kinetics in normal tissues and in neoplasms reveal that tumor cell populations may proliferate at rates higher than, lower than, or equal to those of their normal counterparts, and that the lifespan of proliferating tumor cells and size of the nonproliferating pool of cells in neoplasms can vary widely and overlap the normal ranges."

Smithers,[36] while trying to evolve a definition of cancer, alludes to and defines life as: "Self-reproducing groups of changing organic material which maintain their integrity by reacting with and by counteracting the effects of their environment." This definition of life, as those from many dictionaries, equates all living forms so that by this definition Aristotle is equal to ameba, Newton to nematoda and Buddha to bacteria. Unicellular as well as multicellular organisms are composed of cells that themselves have not undergone any significant change in the evolutionary process which is truly the story of the evolution of the cell's repertoire. Any definition of life is incomplete without qualifying at what level of evolution it is being defined and with reference to which particular individual organism. A higher organism (man) is, biologically, an aggregate of cells, which as a unit of behaviour, has species-specific and individual-specific cognitive, cerebrative and conative repertoire or faculties. Einstein, Newton or Buddha can never be divorced from their species-specific and individual-specific behaviour. Each cancer, like each individual, is unique and possesses its unique affective* and effective** behaviour which can be defined with a certain precision at the general level of the phenomenon of cancer and on a probabilistic basis at the level of a particular cancer.

Cancer, like life, must be defined at various levels. It is an integral part of biology, "a process as inevitable as evolutionary progress and of the same general nature"; it, therefore, deserves a general definition at the level of biology. It is an eventual phenomenon in the lifecycle (cytomorphosis) of a dividing cell,[12, 17, 18, 19, 20, 22] and it must, therefore, be defined in terms of cytomorphosis. It involves a metamorphosis of the cell and therefore should be defined cytologically. Such a metamorphosed cell —cancer cell—affects its surrounding, hence necessitating a histologic definition. Finally, the cancer cell/s affects the host, and hence the ontogenic definition. Smithers[36] has rightly stated that the characteristic picture of cancer as affects an individual is the terminal event in a long progressive chain of circumstances. We might recall here the words of Perez-Tamayo[32] on inflammation, that are equally applicable to the study of the development of cancer in an individual: "The inflammatory process must be analysed to be described, but in this dissection there is danger of overlooking the fact that the resulting parts are meaningless without

*What can be done to the cancer cell by the host and by medical measures.
**What the cancer cell/s does to the host.

continuous reference to the whole." It would be equally advantageous to quote a clinician, Lewin[27] who while defining cancer, emphasizes the same theme as Perez-Tamayo. "The term cancer has been used to describe abnormalities at three levels: host, tissue, and cell. At the host level, cancer is usually associated with a poor prognosis and includes a great number of diseases which, in regard to etiology, clinical course, and treatment, may differ as widely from each other as does, for instance, a boil and miliary tuberculosis. At the tissue level, the term cancer is reserved for those proliferations characterized by uncoordinated, invasive, or metastatic growths. Finally, the concept of the cancer cell possessing characteristic morphologic, functional, immunologic, or genetic features has proved useful in the laboratory and in exfoliative cytology. The manifestations of neoplasia at any of these three levels may be distinctly abnormal or may merge imperceptibly with the normal." (Lewin[27]). Set below are the definitions of cancer at various levels.

Biologic Definition of Cancer

Cancer is a mode of protoplasmic behaviour, built into the dividing* cells of a metazoic organism as one of the senescent mechanisms evolved by Natural Selection to bring about the death of the organism at a specified time thereby subserving the Gompertz phenomenon of increasing mortality with increasing age at the level of the species and the phenomenon of finite life-expectancy at the level of the individual organism. Cancer serves the Gompertz function throughout the lifespan of a particular species and hence occurs from intranatal life to the oldest age in that species. This concept of cancer as one of the built-in senescent processes accounts for its high incidence in a species spared of other death producing hazards. The occurrence of cancer in insects, plants, all animal species and even in tissue culture highlights its universal biologic character.

Cytomorphotic Definition of Cancer

Cancer is an eventual stage in the lifecycle (cytomorphosis) of a normal, diploid, dividing cell in a metazoic organism, consequent upon the entry of the cell into the senescent stage on exhaustion of the finite cell-doubling capacity of the cell, provided the cell possessed cancer-genome. A cancerogen does not cause cancer but merely advances temporally the stage of senescence of the cell by reducing its finite cell-doubling capacity.

Cytologic Definition of Cancer

A cell in the stage of cancer is characterised by possessing suitably altered cytoarchitecture including an adaptation of its antigenic structure

*Undividing haploid (gametic) cells and undividing diploid (neurones) cells are incapable of manifesting the stage of cancer, illustrating the principle that the faculty of dividing abnormally necessitates, *a priori*, the faculty of dividing normally.

which favours its survival, multiplication and migration. Such a cell, at random, may "read out" any part of the total cell genome so that the cell may exhibit some function which is never beyond the repertoire of some normal cells of the host organism. Each cell in the cancerous stage is a species by itself and possesses its specific cytoarchitecture, mitotic behaviour and affective and effective repertoire and hence exhibits wide spectra of structure and function which range from near-normality to gross-abnormality and which may not be related to each other.

With acronyms* forming the order of the day, it may be profitable to use the term CANCER as an acronym and list the possible cytoarchitectural and functional alterations that distinguish a cell in the cancerous stage from a normal diploid, dividing cell (Table 2). The expanded acronym reads as Cellular Abnormalities of Nucleus, Cytoplasm, Emigration and Reproduction.

Histologic and Ontogenic Definitions of Cancer

These definitions of cancer hinge on the important principle that the significance of cells in cancerous state lies not so much in what they look like as in what they do to the host tissue and the host organism. What the cells do (effective behaviour) is inseparably linked with what the host tissue and the host organism do to these cells (affective behaviour of cancer cells) so as to hold in check or promote the activities of the cells in the cancerous state. According to Leighton,[26] the definition of cancer in behavioural terms only have demonstrable relevance today, and that "local and distant spread are the behavioural qualities that are essential in the identification of cancer." Smithers' statement[35] is more elaborate: "Cancer is a word for a selection of extreme behaviour patterns within the class of tissue malformations, being normally contained within the subdivision tumours. Tumours are arbitrarily classified as cancerous or not by the number and degree of behaviour characteristics which happen to be observed, none of which are peculiar to them, but all of which, when they occur together, may form a characteristic picture. The word, by common usage, has come to represent the terrors of the more dangerous end of a variable scale of growth abnormalities in the same sort of way that the term 'galloping consumption' was once selectively applied to severe pulmonary tuberculosis. This has at times been carried to the extreme of using the word cancer only for those growth disorders which are fatal so that, as some dictionaries still affirm and some writers imply, the disease is lethal by definition. We might, they allow, be able to reduce the incidence, we could not otherwise affect the mortality."

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*cf. WISH = Wistar Institute Susan Hayflick[10]—a cell line; HIID=Hemo Iso-Immune Disease;[39] CIS=Carcinoma In Situ; SRS-A=Slow-Reacting Substance of Anaphylaxis[39]; SCRAM= Suspended Cells in Robotized Agitated Medium.[9]

TABLE 2

Some Perspectives of Cancer at the Cell Level.

Cancer: Cellular Abnormalities of Nucleus, Cytoplasm, Emigration and Reproduction

C	A	N	C	E	R
Cancer a stage of	Assemblage of Aberrations	Nuclear/cytoplasmic ratio increased	Cytoplasmic membrane altered	Eragastoplasm reduced	Rate of multiplication high
Cytomorphosis of a dividing cell	Antigenic adaptation leading to changed	Nucleolus enlarged, multiple	Cytoplasmic organelles reduced; degenerate	Endoplasmic reticulum reduced	Rhythm of multiplication irregular
Cloning efficiency variable	Antigenic profile	Nutritional needs simplified	Cytochemistry changed	Ectobiology/ ectoplasm altered	Responsiveness to host influences, hormones, drugs etc., variable; usually nil
Cell morphology ameboid, epitheloid, mechanoid or fibroblastoid	Antibodies secreted against immunocytes	Numerical explosion of cell number	Cell adhesiveness diminished	Enzyme-pattern variable	
			Cell cohesiveness diminished	Energy-release through glycolysis	Respiration anaerobic
Cell-to-cell consciousness lost	Allegiance to host tissues and host organism lost	Nitrogen trap Nihilisitic nature	Caryotype usually abnormal	Eliminative repertoire powerful	Repertoire wide; can mimick any aspect of any normal cell
			Chromosomes aneuploidic, polyploidic		
			Cell kinetics (lifespan, mitotic time, intermitotic time, size of non-dividing cell-pool) altered		
			Contract inhibition of movement lost		
			Contact inhibition of division lost		

Histologic Definition

Cells in cancerous stage, with alteration of surface properties and the probably consequent partial or complete loss of contact inhibition of multiplication and movement, exhibit progressive multiplication leading to increased population-pressure of altered cells, eventually resulting locally into loss of polarity and invasion of neighbouring tissues, and distantly into emigration of the cells to form secondary foci of cancerous cell growths. The histologic features present a wide spectrum, ranging from features which are distinctly abnormal to those merging imperceptibly with the normal.

Ontogenic Definition

Cancer, a part of the individual's overall senescence, like rest of the senescent processes, silently (asymptomatically) progresses to the manifest (symptomatic) stage, consummating singly or severally (with other senescent processes) into the death of the organism. It may not occur at all or may remain silent despite widespread involvement of the individual's body. In the young, its nature is more virulent and more rapidly lethal, unaided as it is by other senescent processes.

General Working Definition

Cancer is one of the built-in senescent mechanisms—an eventual stage in the lifecycle of normal diploid dividing cells in a metazoic organism. It is a time-governed process manifest on aging of the organism and terminates the life of the organism on its own or with the help of other senescent forces. It may not occur at all or may remain silent despite its definite presence in the organism.

Clinical Definition

A clinician is most intimately associated with the various facets of cancer behaviour. Offered a multiple choice of terms such as benign/malignant neoplasm, benign/malignant tumor, or cancer, he uses one or more of these without being able to define any of them satisfactorily because of the lack of a clear concept (Fig. 2).

The clinical definition may be stated as follows.

Cancer is a mode of cell behaviour expressed as Cellular Abnormalities of Nucleus, Cytoplasm, Emigration and Reproduction, and the consequences thereof focally, locally or systemically, with or without the occurrence of symptoms and/or signs.

Each cancer is a syndrome; not a specific lesion. Locally it may present as a lump or a tumor, an ulcer, an area of induration, fixity to neighbouring tissues, or rarely, there may be no clinical abnormalities at all. Focally it may involve the lymph nodes which themselves may form a

Morphology	Whether Tumor ?	Suggested Terminology
Swelling	Yes	Cancerous tumor
Lump or mass	No	Cancerous mass or lump
Infiltration	No	Cancerous infiltration
Ulcer	No	Cancerous ulcer
Ulcer	No	Areolar ulcer because of cancer (Paget's disease)
Metastases	No	Cancer metastases or spread
Cells with abnormal cytoplasm and nucleus	No	Cancerous aneuplasm, Cancer, Carcinoma

Fig. 2.
The fallacy of using the term tumor.

lump, ulcerate, or invade other structures. Systemically, a cancer may metastasise, cause toxaemia, hormonal imbalance or some immune disorder. The cancer may not cause any symptoms or signs, or any physiological disturbance thus behaving in a truly benign manner. All that may or may not happen should be assumed, anticipated or indicated by the general term cancer or the more specific terms carcinoma, sarcoma or leukosarcoma.

Writing about hypernephroma, Ian Aird[1] comments that of its numerous names, "hypernephroma" is the most commonly used; "nephroma" is the most logical; while "Grawitz tumor" is politely noncommital. In clinical cancerology, tumor is a very commonly used term; cancer is the most logical; and neoplasm is politely noncommital. It is suggested that in formulating or stating the diagnosis of a cancerous condition, the terms tumor or neoplasm should be avoided. Consistent use should be made of one of the three qualifying terms carcinoma, sarcoma, leukosarcoma, or when

in doubt, or as a general measure, cancer. The appellations benign and malignant should be avoided. The word "benign" is usually employed not so much to indicate the benignity of behaviour as to imply eucytomorphism under the microscope. The term malignant can be dispensed with since it would be, *ipso facto*, implied in terms cancer, carcinoma or sarcoma. It may be remembered that while most cancers can be highly or moderately malignant, a few of them can indeed be as benign as far as their behaviour goes.

SUMMARY

An attempt has been made towards **eusemantics** in cancerology. The numerous terms have been classified and their semantic propriety evaluated. It has been pointed out that the terms **tumor,** and **neoplasm** cannot be substituted for the term **cancer** which as a generic term encompasses **carcinomata, sarcomata, leukosarcomata** (in place of the wrong term **leukemia),** and other forms of cancer. The term **eucytoma** has been suggested in place of the so-called benign neoplasm or tumor. The fallacy inherent in the use of the appellations **benign** and **malignant** has been pointed out. Biologic, cytomorphotic, cytologic, histologic, ontogenic and clinical definitions of cancer have been given. It has been suggested that the term CANCER is a good acronym which, when expanded, reads as Cellular Abnormalities of Nucleus, Cytoplasm, Emigration and Reproduction.

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Reprinted from the Journal of Postgraduate Medicine",
Vol. XV, No. 2, April 1969, *pp.* 53-63

FINITE LIFETIME OF SOMATIC CELLS—A BASIS OF FINITE LIFESPAN OF ANIMALS

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The lifespan of various animal species is fixed but the basis for this constancy is not known.[9, 12, 13, 18] The lifespan of man, despite all the medical advances, has remained the same throughout recorded history.[12, 13, 18]

A clear concept of the lifetime of the various somatic (diploid) cell-types in a multicellular organism such as man may lead to an understanding of the problem of the fixity of lifespan of animals in general. It may also provide an insight into such problems as cancer.

It is obligatory that the concept of lifetime* of body cells should be so evolved as to be applicable to every single cell in the community of billions of cells which form the organism. A higher, multicellular animal is made up of widely diversified cell-types, a situation that calls for classification of cell-types in the adult organism.

Classification of Cell-types

In a vertebrate, such as man, the sensory receptors, the neurones, and the muscle cells constitute the 'specialised cells'.[9] All the other cell-types may be classified as non-specialised. The former constitute the SENSORIUM,[20] the NEURONIUM[20] and the MOTORIUM[20]—the SNM COMPLEX of the body which has two components, the somatic and the visceral. 'The world to us' and 'the world because of us' is a function of the somatic component of the SNM complex which mediates the cognitive and the conative aspects of an individual's existence. The visceral component of the SNM complex is concerned with homeostasis of the body. The cells of the SNM complex are the fixed,[9] static[33, 34] perennial,[19] non-dividing[18] or the non-replaceable[55] cells which show no mitotic activity in postnatal life.[17] The rest of the body tissues, including the neuroglia, the endocrines and the sex organs, are grouped together as the SUPPORTING TISSUE COMPLEX (ST COMPLEX) of the body. The ST complex has undergone very little change during evolution and its role is to subserve the SNM COMPLEX. The ST complex is composed of mitotic (dividing) and postmitotic cells and includes both the expanding and the renewing cell populations of the body.[33, 34]

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Received for publication: 18th January 1969.

* The term lifespan is referrable to an animal and the term lifetime to its body cell or cells *in vivo* or *in vitro*.

Such an unorthodox but comprehensive classification has been presented (Table 1) consequent upon the realisation that the SNM complex is essen-

TABLE 1
A comprehensive classification of cell-types in postnatal life

Basis	Classification	
I. Function	SNM Complex	ST Complex
II. Proliferative behaviour	Non-mitotic (Non-dividing; Non-replaceable; Fixed; Static)	Mitotic (Dividing; Renewing cell population and expanding cell population)
III. Lifespan	Perennial	Intermitotic Postmitotic

tially perennial, whereas the ST complex is mortal. The timed mortality of the individual is essentially a function of the mortal cell clones[31] which form the ST complex which has been timed to maintain the organism over its life-span and then to kill it. "The same cellular mechanism would prove morphogenetic in the embryo, defensive in the adult and destructive in senescence" (Metchnikoff).[38] An ageing mechanism which automatically brings life to an end is built into the cells as an essential feature of their construction, a kind of biological clock with time-scale characteristic for each species.[9]

Lifetime of the Non-dividing Cells (SNM Complex)

The alternative term "perennial cells" suggests that these cells live as long as or longer than the individual.[1, 19] Brody,[6] however, has shown that 20% of the neurones in the human brain are lost by the age of 70 years. Similar findings have been reported in the brain of the honey-bee.[46] Assuming that some neuronal atrophy occurs daily in postnatal life, it may be stated that the nerve cells, each of which has a biological life of its own,[21] have a lifetime from the time of neuronal differentiation to the time beyond the life-span of the individual. In the majority of human beings the larger portion of the neuronal mass remains unatrophied till late age suggesting that the majority of neurones can justifiably be called the perennial cells. The same holds true for the cells of the sensorium and the motorium.

Lifetime of the Dividing Cells

In any community of dividing cells in an adult organism, there are cells capable of division called the stem[33, 34] or alpha cells[41, 42, 43] and cells incapable of any further division called the n[41, 42, 43] cells, or postmitotic cells. The doubling-capacity of any dividing cell is finite both *in vivo* and *in vitro* and

this is its FCDC (Finite cell-doubling capacity which is preferable, though equivalent, to fixed cell-division capacity as described earlier.)[30] The work of Hayflick on human foetal and adult fibroblasts, *in vitro,* has illustrated this beautifully, and beyond any doubt.[23, 24]

A dividing cell undergoes a change with every division[43] and, therefore, in a manner of speaking has as many lives as the number of divisions undergone. The average time between any two successive divisions is its intermitotic lifetime. Its total lifetime (also called its fidelity span)[30] is the time over which its FCDC is spent. The divisions undergone by the cell may be differential or non-differential which together with their inter-relationship have been discussed in an earlier publication.[30]

It would not be out of place to recall Osgood's generalisations[43] regarding the lifetime of a dividing (alpha) and postmitotic (n) cell in postnatal life: 'for each cell series in each species, evolution has probably provided the optimal range of lifespan for the n cell and the range of generations times for the alpha cell, both for non-differential (alpha, 2 alpha) and differential (alpha, n) divisions for that specific cell-type in that specific species at that specific stage of growth and for the type of environment to which the species has been most recently required to adopt, in terms of evolutionary history. There will be wide variations in generation time and n cell lifespan inherent in different alpha cells of the same tissue and species, in the same individual and between individuals, but for each of these factors there will be a mean value as well as a probability distribution'. The possible variations in the FCDC for body cells have already been presented elsewhere as the FCDC postulates.[30]

The lifetime of the n cell or the postmitotic cell lasts from its birth until such time as it is cast off, gets destroyed, atrophies, or outlives the individual. The lifetime of certain postmitotic cells is known: platelets—4.3 to 4.5 days,[40] R.B.C.—120 days,[1, 5] epidermal cells—3 weeks.[1]

Differential versus Non-differential Divisions

The controversy as to which of these is more common in postnatal life is not yet settled. The work of Leblond and his co-workers[34, 36] has been responsible for upsetting a popular and convenient concept[32, 37, 41, 42, 43] that mitotic divisions in postnatal life are largely differential in nature. The following observations, however, prompt the present authors to once again support Osgood's assumption that it is the differential division which in essence predominates in postnatal life, and that non-differential divisions occur only for stem-cell replacement, and are therefore uncommon, if not rare:

(i) Only 32 non-differential divisions are needed for the entire foetal growth in man. The total cell mass can be increased by a factor of a million by even 20 such divisions.[41]

(ii) Muggleton and Danielli[39] have shown that, contrary to accepted views, even amongst the protozoa (Amoeba proteus) differential divisions occur under certain experimental conditions. In type A clone of amoeba, after any division, one of the daughter-cells retained the capacity to divide whereas the other had lost it.

(iii) Osgood[44] has made the important observation that cells in tissue culture undergo rapid non-differential divisions. This may be due to the absence *in vitro* of autobiotic substances[51] such as retine and promine, secreted *in vivo* by the general cell mass of the body through the agency of which cellular proliferation is regulated.

A generalisation might be made that the lifetime (T_1)[30] of a dividing cell is equal to C x t where C is the FCDC of the cell and t the average intermitotic time. Whenever a non-differential division occurs *in vivo* or *in vitro*, it occurs at the cost of a larger number of potential differential divisions. The genetic set-up of the cell in which the FCDC resides has been described elsewhere as the cytochronal helix.[30]

CYTOMORPHOSIS

The term cytomorphosis[1] denotes the series of successive changes undergone normally by a cell during its total lifetime.

It has already been mentioned that a dividing cell is the main star in the galaxy of biological existence.[30] Apart from being responsible for growth and reproduction of the organism, it has built into it a process of ageing and death. "Every animal appears as a sum of vital units each of which bears in itself the complete characteristics of life" (Virchow).[52] A dividing cell is obviously one of these vital units and it exhibits a series of successive stages during its existence in the parent organism. These stages collectively constitute the cytomorphosis of a dividing cell. Cytomorphosis *in vitro* does not differ from that *in vivo*, but, for the sake of convenience, it is said to consist of 'Phases' instead of the 'Stages' described *in vivo* (Fig. 1).

1. Embryonal Stage:[1, 2] This stage is characterised by extremely rapid cell divisions accompanied by progressive differentiation leading to the formation of an embryo, a miniature form of the adult organism.

Cytodifferentiation[54] may be said to have been well established at the end of the embryonic stage and at the beginning of the foetal stage.[2]

2. Stable, Differentiated Stage: This is characterised[2] by progressive functional specialisation of cells and growth, maturity and maintenance of the organism. This stage dates from the time of cytodifferentiation to anytime upto or beyond the death of the organism. This stage embraces Phases I and II *in vitro* described by Hayflick.[23, 24] His demonstration of the essential biological similarity[24, 25] between fibroblasts derived from foetal and from

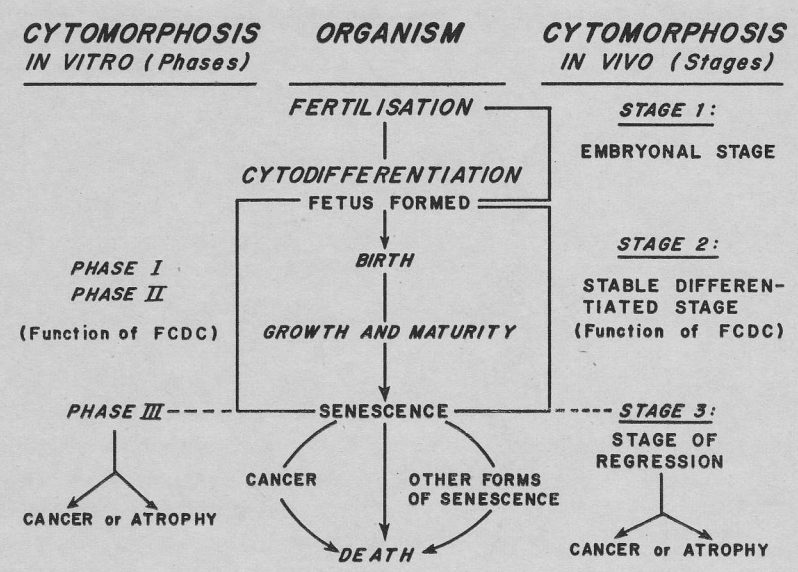

Fig. 1: Cytomorphosis *in vivo* and *in vitro*.

adult human tissues permits the assumption that this stage begins *in utero* at the end of the embryonal stage when cytodifferentiation has been achieved. It is from this time that the biomechanics of the genetic set-up of the cell governing its FCDC starts operating. The duration of this stage is a direct function of the FCDC quantum. The next stage of regression may make its appearance even while the FCDC is not completely expended.

3. Stage of Regression:[1] The cell during this stage exhibits senescent changes typified by chromosomal abnormalities. It enters this stage either in the postmitotic state of the last of its normal divisions or while a part of the FCDC still remains. This change is increasingly noticeable with increasing age and has been the basis of the somatic mutational theory of ageing.[18] This stage when seen in culture of normal diploid cells *in vitro* has been termed Phase III by Hayflick.[23, 24] He has correctly observed that this phase may bear direct relation to the problem of ageing and senescence.[23, 24] Attempts at reversing this phase have been uniformly unsuccessful.[23]

4. Stage of Atrophy or Cancer: The senescent cell either atrophies[1] or continues its senescence[30] in a modified form by undergoing a cancerous change which is the postnatal dedifferentiated phase[30] in the cytomorphosis of the dividing cell.

Atrophy or Cancer?

Cancer has been claimed a universal cell potential.[26, 30, 45] However, it must be noted that very few of the numerous dividing cells of an adult

organism undergo a cancerous change. Cells after exhibiting Phase III *in vitro*, commonly atrophy and only uncommonly turn malignant. Hayflick[23, 24] while culturing foetal and adult human fibroblasts, uniformly observed atrophy of the cells on exhaustion of their FCDC. Spontaneous occurrence of cell line[23, 24, 25] (i.e. conversion *in vitro* of normal diploid cells called cell strains into cancerous cells called cell lines) is a rare event in the cultivation of most animal cell strains.[23] The remarkable exception to this generalisation is the behaviour of mouse cells which when cultured almost always spontaneously alter from cell strains to cell lines and acquire the ability to multiply infinitely.[25] Chick cells, in contrast, never become cell lines.[25] Graded scales of tendency to or immunity to a change from cell strain to cell line must be existing.[25] Hence, the statement that cancer is the potential of every dividing cell needs modification. A better expression may be that cancer is an attribute of every type[11] of dividing cell, a probability distribution governing its frequency *in vivo* and *in vitro* so that any normal dividing cell at the end of its FCDC, either atrophies or turns malignant. Goldblatt and Cameron[22] have hinted at such a distribution by stating that 'in all embryonic and even adult normal tissues there may be scattered cells or groups of cells potentially malignant. . . .!'

Carrel's success in perpetuating fibroblastic cells *in vitro* led to the concept[23, 31] that somatic cells are immortal, a view still held by some workers.[18, 19, 48] Unicellular organisms have been regarded as immortal.[43] Jennings[27] has, nevertheless, pointed out that death from intrinsic causes is common to these as well. On the other hand, vegetative clones of protozoa can multiply indefinitely.[27] Muggleton and Danielli[39] grew "spanned clones" (types A and B) of amoeba in which the number of divisions was finite. It has long been felt that the finite lifespan of the animal ought to be reflected in the finite lifespan of the body cells,[23, 24, 25] an assumption elegantly confirmed *in vitro* by Hayflick with human foetal and adult fibroblasts.[23, 24]

The so-called immortal clones[10] of somatic cells *in vitro* are accepted as resulting from an unrecognised cancerous change.[23, 25, 31] Infinite capacity to multiply is, therefore, a quality acquired only on neoplastic transformation. A somatic cell can be considered immortal only in the sense that it can produce a cancerous progeny which due to its capacity to divide infinitely can claim to be immortal. The immortal cancer cell *in vitro* is at an advantage over its fellow *in vivo* since the *in vitro* milieu can artificially be maintained *ad infinitum*[10] whereas the *in vivo* cell kills the host organism and with it its ownself.[26] Infinite capacity to divide is both an *in vivo* and an *in vitro* phenomenon, only potential in the former and demonstrable in the latter.

Implications of Finite Cell Lifetime

Controversy continues as to whether the non-dividing cells (SNM complex) or the dividing cells contribute to the process of ageing and death. The

consensus is in favour of the former view.[4] We feel, however, that the cells of the SNM complex are essentially perennial and ageless. The dividing cell, though evidently devoid of age-changes, definitely ages with each division and at the end of its lifetime either atrophies or undergoes a cancerous change. The finite lifetime of diploid cells *in vitro* may be a cellular expression of senescence so well known at the organismal level.[23, 25]

The stage of regression in the cytomorphosis of body cells heralds either atrophy or a cancerous change. This assumption is supported by the increasing chromosomal abnormalities[18] and increasing incidence of cancer with advancing age[26, 45, 50] in both man and animals. With the eventual fate of every dividing cell *in vivo* and *in vitro* towards either atrophy or cancer, the cell with each of its divisions marches a step closer towards atrophy or cancer, and in this manner ages without showing any structural change until it enters the stage of regression (Phase III). A cancerous change has been considered an escape from senescence.[8, 14] Cancer certainly is no escape from senescence but a variant of senescence itself. Weiss considers senescence[54] (ageing) and cancer[53] as variants of cellular differentiation and this justifies the statement that cancer is senescence. In fact, cancer is the only senescent process which can assert itself from intrauterine life to the oldest age of the organism. It will, therefore, be appreciated that a normal dividing cell can positively contribute to the death of the organism by intrinsic, time-governed changes:

(i) in the form of cancer which definitely contributes or

(ii) atrophy which contributes rather poorly.

The process of early atrophy of certain cell types may account for such diseases as idiopathic cirrhosis, diabetes mellitus, pernicious anaemia, atrophic rhinitis or atrophic gastritis. The postmitotic cells of the ST complex may contribute to senescence by early atrophy but never by cancer.

The non-dividing cells, in our opinion, contribute insignificantly to natural death. Their carcinogenic potential is nil.[7, 19] Some of these cells are prone to malignancy in early life e.g. retinoblastoma, neuroblastoma, but these are, more often than not, hereditarily governed. Early atrophy of a large number of cells in focal areas occurring at a particular age may account for the various heredofamilial neuronal and muscular dystrophies. It is strongly felt that many dystrophic diseases of the nervous system e.g. Friedrich's ataxia, and myopathies are due to hereditarily transmitted short lifetime of respective neurones or muscle cells. These are often accompanied by cardiomyopathies,[49] the basis for which is the same.

The assumptions outlined above account for a number of hitherto unexplained facts: cancer is a universal cell-type potentiality; some cells of the body readily form cancer both spontaneously and experimentally while some rarely undergo a cancerous change; cancer occurs increasingly with advancing age; hyperplastic states often terminate as cancer; skin grafts from younger

animals live longer;[29] cells grown in tissue culture either degenerate and die or assume a cancerous form; atrophic diseases of the specialised cells (SNM complex) tend to be heredofamilial in nature. Barret-Brown[3] has cited an instance where a homotransplant of the nose survived until the death of the donor after which it shrivelled up and died.

Lifetime of Cells and Lifespan of individual

The SNM complex in each organism has at least evolved to the extent of outliving that organism.[1, 14, 19] The immediate corollary is that the lifespan of the individual organism is deterministically governed by the lifetime of the ST complex formed by the intermitotic and postmitotic cells and the intercellular substance. In a utopian state of public health wherein diseases due to environmental causes are almost completely eliminated[8] and the death in the humans is caused exclusively by diseases intrinsic in origin,[8] the behaviour of the ST complex would account for a very large proportion of all these deaths. About half of these would be in the form of an intracellular phenomenon of cancer and the rest in the form of intercellular phenomena generically termed atherosclerosis. The species-specific lifespan thus becomes the function of the ST complex, the lifetime of which is governed by the FCDC of its constituent stem cells as well as the rate at which the process of atherosclerosis occurs. It may be mentioned that the existence of glands secreting 'a death hormone' responsible for ageing has been postulated.[28] Since ageing is essentially the function of the ST complex such a hormone would presumably operate by altering the lifetime of some target cells and by affecting the rate at which atherosclerosis occurs.

Heredity modifies the factors (genes) governing the lifespan by evidently introducing shortevity,[13] or longevity[13] which often manifests itself as a heredofamilial phenomenon. It is well known that longevity runs in families.[13] Shortevity is exemplified by heredofamilial neuronomyopathies in the SNM complex, and the very few heredofamilial cancers and probably some of the hereditary cardiovascular diseases in the ST complex.

Prolonging of Lifespan

With the advent of spare-part surgery, hopes may have been raised that the human lifespan can now be increased. This, however, does not appear likely[15] for various biological reasons. The time of ageing, its rate, and the occurrence of death are essentially intrinsic phenomena controlled by the genes and hardly modified by environmental factors. Nor will it be possible to alter them by all the medical advances put together. One could not possibly change all the billions of cells of the body, and till a few centimetres of bronchial, gastric or cervical mucosa are left, nature will have enough of an

armamentarium up its sleeve for bringing life to an end at its predestined time.

The length of animal lifespan has been most acceptably correlated with the Brain weight/Body weight (BrW/BW) ratio,[12, 16,47] which is the highest in man. However, as has been elucidated, lifespan is a function of lifetime of the ST complex. We already know of the finite lifetime of certain cells and organs of human body. Attempts to increase the R.B.C. survival in peripheral blood beyond 120 days have not met with any success.[5] The ovary has a precise mechanism for terminating its active life[13] and, in different age chimeras in experimental animals, it is not the lifespan of the host but that of the ovary which determines the fate of the transplant.[29] The relationship between the BrW/BW ratio, the lifespan of the animal and the lifetime of the ST complex points to the possibility that animals with a greater ratio also have an ST complex with a correspondingly greater lifetime either as a concomitant feature or as a consequence of the greater ratio.

This predetermined, gene-dependent species-specific finite lifetime of various cells and organs is bound to frustrate any attempts at altering it for the better. As an alternative to transplant surgery it has been suggested that with suitable alteration in the gene structure of man (euphenics)[35] individuals with greater lifespan of the ST complex can be created, thus promising increased lifespan as a natural 'built-in' mechanism.

SUMMARY

A concept of finite lifetime of somatic cells has been evolved in relation to the finite lifespan of the animal and the occurrence of certain abnormalities such as cancer. It is suggested that the finite lifetime of the dividing cells of the body subserves the mechanisms of ageing of which cancer is an integral part.

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Reprinted from the "Journal of Postgraduate Medicine", Vol. XV, No. 3, July 1969, pp. 101-105

MODUS OPERANDI OF CARCINOGENS: MERE TEMPORAL ADVANCEMENT

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A halo of awe and mystery surrounds the term carcinogen and the mode in which it may induce cancer. All carcinogens, identified or postulated, lead to a rather common end result—a cancer cell. A common pathway is probably exploited by all carcinogens to bring about such a change. This has prompted us to postulate that all carcinogens act, both *in vivo* and *in vitro,* on a common target in the cell machinery, in a common manner. The purpose of this communication is to pinpoint the target and the nature of the change induced therein by a carcinogen.

Biologic Actions of Carcinogens:

All carcinogens, including oncogenic viruses, induce a cancerous change in only a susceptible dividing-cell.[7, 9, 11, 18, 22] The cancer so induced does not differ in any way from a cancer spontaneous in origin[20, 21]. Synergism exists between chemical carcinogens and viruses,[14, 19, 20] tumorigenic or non-tumorigenic. Tumors from joint chemical and viral action do not differ from those induced by chemical action alone.[19] Once a cancerous change has been induced, the carcinogenic agent, chemical or viral, is no longer needed for the perpetuation of the cancerous process and is not invariably recoverable from the induced cancer.[7] The same viral[4, 19, 20, 21] or chemical[6] carcinogen can cause a variety of cancers in the same animal or in different animals.

A definite latency characterises the induction of cancer both *in vivo*[14, 17, 18] and *in vitro*.[7, 20, 22] A period of 12 to 56 years (average 33 years) may elapse between exposure to ionising radiation and the occurrence of cancer in man.[17] *In vitro,* the cells, after exposure to even an effective dose of a carcinogen, can continue to divide normally[7, 22] (Phase II),[12, 13] apparently retaining all the while their normal parent-cell characters. The duration of this phase is, however, reduced with a concomitant reduction in the number of finite cell-doublings (the FCDC)[15] which leads to a reduction of lifetime of the cells.[16] Just prior to the neoplastic conversion (induced or spontaneous), cells, *in vitro,* exhibit marked depression of mitotic activity[5, 7, 10, 22] reminiscent of Phase III[12, 13] or the senescent phase as described previously.[16] This senescent phase in the life cycle of a cell is exhibited, *in vivo,* by increasing chromosomal abnormalities seen

From: The Department of Anatomy, Seth G. S. Medical College, Bombay-12.
Received for Publication: 18th January 1969.

with advancing age, both in animals and man.[9] After entry of the cell into the senescent phase (Phase III *in vitro,* Stage 3 *in vivo*),[16] the cell undergoes either atrophy or cancerous change, depending on a probability distribution.[16] Hayflick observed that human fibroblasts, *in vitro,* uniformly atrophied after entering Phase III.[12, 13] Too large a dose of carcinogen may forthwith kill the cell precluding all the changes described. The action of carcinogens may be summarised as reduction of the normal lifetime (Phase II, Stage 2) of a dividing cell, and therefore, an early entry into the senescent phase, the cell thereafter following its predetermined fate—atrophy or cancer.[16]

Irrepressible Cell Behaviour:

Carcinogens are effective only on the susceptible dividing-cell both *in vivo* and *in vitro,* which means that not all dividing cells turn cancerous under carcinogenic influence. Moreover, carcinogens have no influence on the non-dividing cells[2] (SNM complex)[16] or even on the postmitotic cells of the less evolved organisms such as insect imagoes.[8] A carcinogen may kill the cell forthwith, failing which the cell shows no immediate conversion to malignancy. It continues its normal divisions, albeit with a reduced FCDC. The cell thus stands firm against the carcinogen, exhibiting, a shortened lifetime. Its activities continue as they would have otherwise, except that the lifetime shows a temporal contraction. At the end of this shortened lifetime, the cell enters the senescent phase. A carcinogen is effective only in accelerating the entry of the cell into the senescent phase. Thereafter, the cell, depending upon its genotype, turns cancerous. The newly formed cancer cell, like a resistant bacterial organism, often exhibits increasing resistance to the cytotoxic action of the same carcinogenic agent.[7]

An Interpretation:

What has been described thus far permits a generalisation regarding all carcinogens: A carcinogen acts on a dividing-cell, expediting its normal cytomorphosis[3,16] by shortening Stage 2 or Phase II, by reducing the FCDC either directly[15] or through precancerous hyperplasia of normal cells,[19] thus hastening the appearance of senescence in the cell subsequent to which the cell pursues its predetermined fate. The ability of the same carcinogen to induce different cancers in the same individual or different cancers in different individuals suggests that it acts on some specific but common component of the genetic machinery (cytochron)[15] regulating the FCDC. (Fig. 1)

"A cellular clock, the cytochron, governs the expression of the neoplastic potential of a dividing cell.....A carcinogen merely sets the cytochron in advance so as to force a premature occurrence of the cancerous change."[15] A speeding up of the internal clock leads to early appearance of lung cancer in experimental animals.[2] Irradiation hastens the process of ageing, promotes

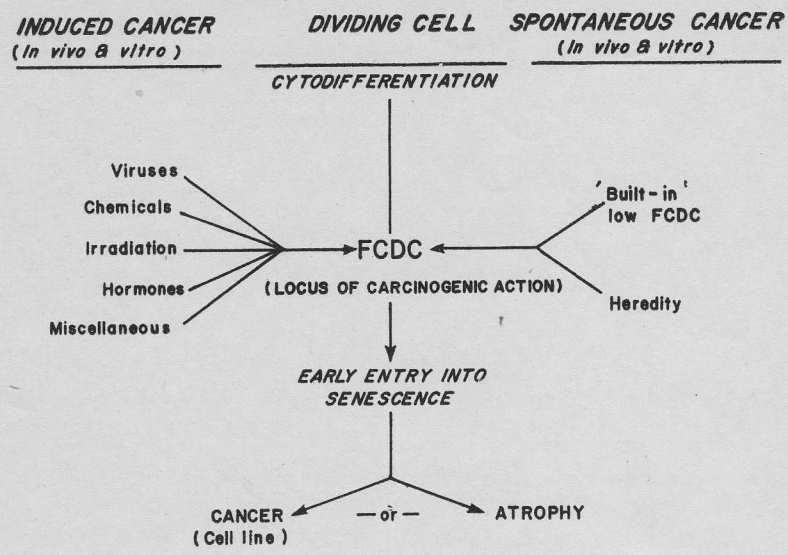

Fig. 1: FCDC as the determinant of spontaneous and induced cancer.

early appearance of tumors and reduces the lifespan of experimental animals.[2, 8] Potential chromosomal abnormalities remain latent for many months as seen by their appearance in liver cells following stimulation of mitosis months after irradiation of the organ.[1] This is easily explained by stating that radiation in this case reduced the FCDC but preserved, as would be expected, the cell normality otherwise. Subsequent mitotic demand brought about an early entry into Stage 3 or the senescent phase.

DISCUSSION

No explanation has yet been advanced as to why the various carcinogens should be so impotent against the non-dividing cells of the body, despite the fact that all diploid cells carry the same genome. Nor has an explanation been forthcoming for the time-lag seen both *in vivo* and *in vitro*. These two phenomena point to an inevitable inference: a carcinogen acts only on the FCDC of the cell reducing it but never completely eliminating it. As described earlier, the sequence of events both in spontaneous and induced *in vitro* neoplastic transformation remains the same, the difference being temporal rather than qualitative. Spontaneous neoplastic transformation *in vitro* occurs after prolonged culture,[12, 22] while such a change occurs rapidly under the influence of a carcinogen. A carcinogen is a mere link in the chain of events, often a chain completable without this extrinsic intervention.[23] That cells, even after exposure to adequate doses of carcinogens, merrily continue their normal life for a definite time points to the heartening fact that even a

dividing-cell is quite resistant to the effects of the various carcinogenic agents, whose only pertinent action is on the FCDC of the cell. At the end of FCDC, the cell chooses whether to turn cancerous or to atrophy.

SUMMARY

The *modus operandi* of carcinogens, in general, has been presented. It has been suggested that a carcinogen does not induce cancer but merely promotes its premature appearance, in a cancer-prone cell, by reducing its finite cell-doubling capacity (FCDC) and thus its lifetime.

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Reprinted from the "Journal of Postgraduate Medicine", Vol. XV, No. 4, October 1969, pp. 147-158

THE PROBABILITY OF CANCER

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Cancer, a universal process[18,34,45] and a potential of every cell[19,31] does not appear **prima facie** to obey any rule with regards to its distribution. Certain generalisations based on available data permit the formulation of principles that govern the probability* distribution of cancer in animals, in general, and in man, in particular. The probability of developing cancer,[16] as discussed below, is the risk of cancer at all ages, to a species, a race, an individual, an organ or a cell.

Species:

Cancer occurs in many invertebrates[18,45] and in all the vertebrate species.[18,39,45,46] Its incidence in a particular species may be stated as almost inversely proportional to the other natural hazards lethal to that species. Tumours therefore, have, in general, a low incidence in animals other than man.[5,26,46] Certain laboratory animals e.g., mice, reared in a sheltered environment, offer an enlightening contrast to this by exhibiting a high incidence of cancers including leukemia.[9,25,26] Man exhibits the highest incidence of cancer because of his ability to survive other hazards.
This is, in a way, illustrated by the fact that the incidence of cancer in children in the Western countries such as U.S.A. has exhibited a marked increase following the elimination of infection and deficiencies as causes of death.[2] Loutit[26] may be quoted here to advantage: "Nature red in tooth and claw sees to it that in the wild most individuals fall to predators when they are young and inexperienced or as soon as their physical faculties of strength and cunning begin to decline. In contrast, man and laboratory animals live a relatively sheltered life and are preserved to enjoy an old age. Death comes as a result of degenerative or malignant disease."

Type of Cancer:

Schlumberger,[39] in an extensive coverage of cancer in animals, showed that certain types of cancer predominate in certain animals: adenocarcinoma of kidneys in frogs, carcinoma of nasal sinuses in dogs, melanoma of the skin in grey horses, etc. Such exclusive involvement of a particular organ is seen even in man: 75% of cancer deaths in males and 48% of can-

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Received for publication: 19th April 1969.

* 'Probability' is being used for the relative frequency of the occurrence of a random event (Stone).[41]

cer deaths in females in the Japanese are accounted for by gastric carcinoma[1,19,46] whereas the incidence of leukemia in Japan is the lowest in the world.[9] This indicates that there could be a species-specific and race specific (e.g. man) senescent mechanism[21,22] expressing itself by cancer of a particular organ.

Congenital Anomalies:

There is a high coincidence of congenital anomalies and cancer.[2,4,36,37] This would appear to be a mechanism of Natural Selection whereby those unfit to survive are eliminated more effectively. Ectopic organs, otherwise normally formed, e.g. testis, exhibit a high incidence of an early malignant change.[1,3,4]

Age:

Cancer increases with increasing age in man and other animals[5,8,12,13,16,40] and this is consistent with the principle of increasing mortality with increasing age.[7, 8, 42] Aging— the changes attendant upon the passage of chronological time following ontogeny[29,48] —is characterised by a progressive loss of vitality as a result of senescent changes in multiple systems.[7,8,42] Hence more rapidly growing and rapidly lethal cancers, acute leukemias, sarcomata and glial tumours, tend to occur at a younger age[2,4,9,46] when such aiding factors as diabetes and/or atherosclerosis are absent. It has been experimentally shown that transplanted malignant tumours grow more rapidly in young animals.[4] Clinical and pathological observations indicate that the same holds true in man.[4] The 'acuteness' of leukemias declines with age.[9] Carcinomas, occurring at older ages, are aided by senescence affecting multiple systems.[8,29,42] These observations offer an explanation for the statement by Ariel and Pack[2]. "The reason for the differences in type between cancers in the very young and cancers in older individuals is not understood." Cancer, a disease of middle and old ages in man[5,46] is as well a disease of middle and old ages in animals such as mice[9] and dogs.[18]

Sex:

In the distribution of both cancer[5, 9, 12, 34, 46, 47] and atherosclerosis[33, 43] females sharply differ from males, the difference tending to decrease after the female menopause.[28, 33, 43, 46, 47] Even in children, a definite sex difference exists regarding the incidence of various cancers except those governed hereditarily.[2, 9] The reason for the low incidence for certain cancers in the adult females in contrast to their very high incidence[5, 34, 46] in the males, e.g. tongue, lung, stomach, is the fact that Nature exploits for the genesis of cancer in the female, certain areas which are characterised by periodic regular proliferation such as the breast, ovary and genital tract. Another important aspect is that these organs, especially the ovary, have a finite lifetime

of about 45 years after birth[7], at the end of which the cells either undergo atrophy or carcinogenesis. The overall incidence of ovarian tumour is 4-5 times higher than testicular tumours.[17]

Geography and Race:

Leukemia in Denmark,[9] gastric cancer in Japan,[1, 19, 46] cancer colon in the U.S.A.,[27] Burkitt's tumour and Kaposi's sarcoma in Africa[5, 9, 19, 34, 46] and oropharyngeal cancer in India[35] suggest underlying geographical and racial factors. The postulated geographical factor is the presence of a virus causing these sarcomata.[2,4,5,9,46] The virus theory is doubtful.[9] It would appear that racial factors far outweigh the geographical factors. Leukemia is highest in Denmark,[9] and fairly high in other European countries[9] and U.S.A.[9] The American Negro population is less affected than white[9,12] the former exhibiting a higher incidence of carcinoma stomach and cervix. The incidence of leukemia is lowest in Japan[9] (cf. carcinoma stomach) and significantly low in an allied non-Caucasian race viz. the Chinese[9], who as a racial characteristic, lack the occurrence of chronic lymphocytic leukemia.[9] That a particular cancer should affect a race much more than other races is probably due to multifactorial inheritance[36] because of which certain cells come to have a reduced lifetime[21, 22] as well as the presence of a cancer genome[14, 22] as a racial characteristic whereby that particular cancer affects a majority of the population. Though the anatomical distribution of tumours in different parts of the world is extremely varied, the age-specific death-rate from all neoplasms at all sites is remarkably constant.[40]

Heredity:

There is no primary gene for cancer in general.[5] Very few neoplasms, therefore, have a definite hereditary basis.[2,4,5,36,46] These are familial polyposis coli, generalised neurofibromatosis, retinoblastoma and xeroderma pigmentosum. A single autosomal gene, usually dominant[27,36], determines the heredofamilial nature of these tumours. The incidence of retinoblastoma in the offspring of parents cured of the disease is 50% or more if the latter are from a family subject to retinoblastoma.[4] In experimental animals, where inbred strains can be easily obtained, the ease of tumour induction depends on the genetic make-up of that animal strain.[5,9] Carcinoma of the breast, stomach, rectum and urinary bladder tend to occur in families but the basis is not clear.[5, 27, 34, 46] According to Willis,[46] most of the "cancer families" exemplify the laws of chance. The presence of a hereditary factor in leukemia is highly suggestive when multiple cases occur in close relatives.[9]

The risk of developing leukemia or other malignant tumours is many times higher than in the general population, in patients with mongolism, Down's syndrome, Bloom's syndrome, Fanconi's anemia, etc., conditions characterised by chromosomal abnormalities.[4,36]

Twins:

In homozygous twins, the incidence of the occurrence of cancer in one increases the probability of cancer in the other.[19,34] Symmetrical and simultaneous occurrence of gastric cancer at the same age of 70 years has been reported in monochorial twins.[1] A similar coincidence has been observed with carcinoma cervix and leukemia.[19]

Exposure to a Carcinogen:

A short-lived or a chronic exposure[5, 34] to carcinogen/s—physical, chemical, biological—predisposes to a cancerous change earlier than would have occurred in its absence.[20,22] Nevertheless, a definite latent period, longer **in vivo** than **in vitro,** intervenes before the neoplastic change occurs.[19,22,34] Children irradiated during infancy develop a marked excess of neoplasms when compared with the general population of their untreated siblings.[4] Chronic ulcerations, such as dental ulcer, peptic ulcer and skin ulcer following burns tend to prematurely exhaust the FCDC of the cells[20, 21, 22] at the margin of the ulcer, thus precipitating the change of ulcer-cancer.[5,34,46]

Cell-type:

i. Functional classification: Cells of the sensorium, neuronium and motorium (SNM complex)[21,22] with their inherent indivisibility[11] rarely undergo a cancerous change. Even when such a change occurs as in retinoblastoma, it is hereditarily governed and occurs at a younger age.[2, 4, 5, 36] Cancer is a prerogative of the cells of the supporting tissues (ST complex)[21, 22] of which neuroglia is a part.

ii. Proliferative behaviour: Cancer predominantly occurs (Fig. 1) in the renewing cell population[11,23,24] (RCP), e.g. leukopoietic tissues, and various epithelia which are characterised[11,23,24] by regular and fairly rapid cellular production and loss. Lest it be mistaken that the rapidity of cellular turnover and cancer always go together, it must be pointed that the small intestinal epithelium having a rate of cell reproduction as fast as the fastest growing Walker's sarcoma[23] rarely develops a cancerous change.[1,5,34,46] The expanding cell population[11,23,24] (ECP), characterised by cell production only for replacement of stem cells has, comparatively, a very low incidence of cancer. Perennial[11] (static)[23,24] cell population (PCP) with the loss of ability to divide normally in postnatal life losses the faculty of dividing abnormally as well.

iii. Germinal layers[3]: Embryological classification of tumours has been attempted unsatisfactorily in the past.[46] Ectoderm, mesoderm and entoderm contribute differently to cancer in human females and males (Table 1). Skin and oropharyngeal cancer account for most of the ectodermal cancers (23%) in males. Breast cancer in the female, accounting for more than 29% of all female cancers, overshadows the involvement of ectoderm in

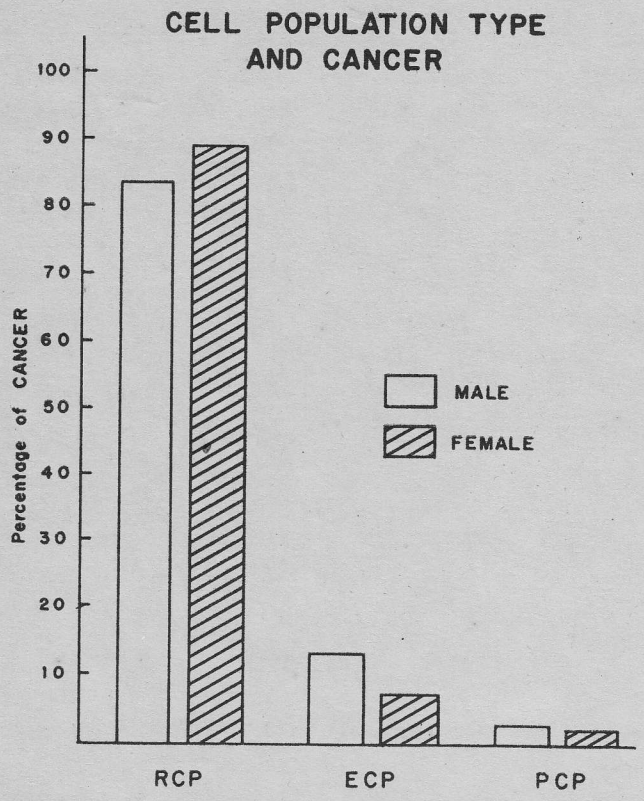

Fig. 1: Cell population type and the incidence of cancer. RCP—renewing cell population; ECP—expanding cell population; PCP—perennial cell population.

(Adapted, on the basis of proliferative behavious,[23, 24] from the data by Harnett,[17] in Kark[19]).

males. The dominance of mesodermal cancers in females is owing to the fact that the ovary, uterus and the Fallopian tubes—the sites selected frequently for cancer are mesodermal in origin.[3] It is interesting that more than two-thirds of cancers in males are attributable to entoderm[3] being largely contributed to by the bronchus, stomach and rectum (Table 1). With the high incidence of leukemia and sarcomata in children, it would appear that mesodermal tumours are the commonest in children.

TABLE 1

Contribution of germinal layers to cancer in man

Germinal layer	Male	Female
Entoderm	68%	33%
Mesoderm	5%	25%
Ectoderm	23%	39%
Total	96%	97%

(Adapted from Kark[19], after Harnett[17]).

Organ:

Though common in the renewing cell population (RCP), as shown above, cancer affects the surface lining of the visceral tubes in preference to the skin which not only belongs to the RCP but is subject to repeated trauma, external irradiation, etc. The immense wear and tear of the palmar skin does not predispose it to cancer.[45] The involvement of the visceral tubes offers certain advantages to the killing potential of the cancerous process:

(a) Centripetal growth leads to luminal obstruction thus affecting the supply lines (oesophagus) or exit channels (rectum). This is comparable to atherosclerosis which, too, invades the lumen.

(b) Because of proximity to other vital organs, local spread by centrifugal growth involves them as well.

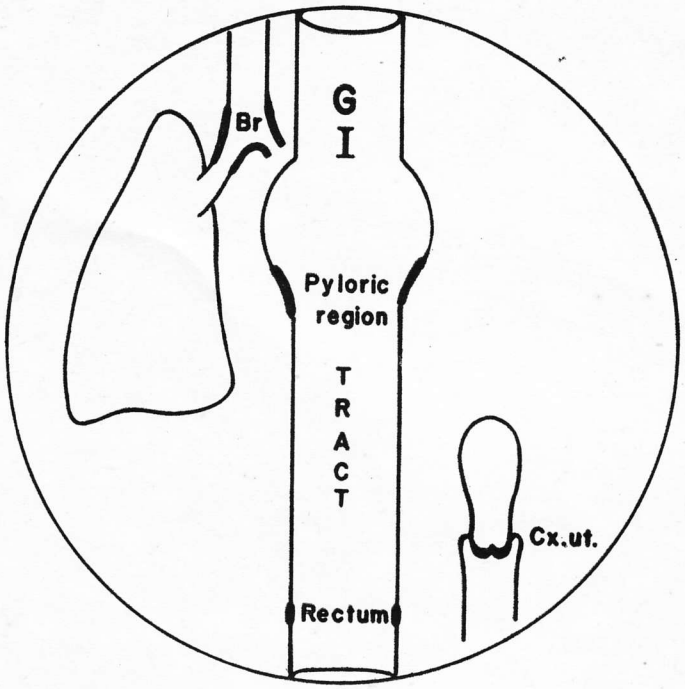

Fig. 2: Epithelial sites most commonly affected by cancer—pylorus, bronchus, cervix, and rectum, wherein "less than 20 gms. of epithelium is the source of about one-quarter of all malignant tumours in man." (Payling Wright).[34]

Figure 2 shows how a few grams of mucosa in select areas account for more than 25% of cancers in man.[34] All these sites have multiple important relations all around and hence a high killing potential exists. The arteries have already been equipped with the potential of being occluded by patho-

logical processes such as atherosclerosis and hence the paucity of tumours arising in the arterial lumen.

The leukopoietic tissue is another important site in the RCP commonly affected by cancer. By its very nature, this organ permits a multifocal origin of cancer[9] and is tantamount to the protector turning a persecutor, a killer.

Cancer genome:

"For studying the natural history of neoplasia, the concept of mutation is less useful than the concept of capacity based on a facultative genome." (Foulds).[14] Carcinogen or no carcinogen, cancer only occurs if the cells carry the cancer genome.[21,22] This is applicable to both **in vivo** and **in vitro** carcinogenesis and is the basis of both cell-resistance and host-resistance against carcinogenesis.[20, 21, 22]

Precancerous States:

The probability of cancer increases in the presence of certain conditions affecting the cells.

(i) Hyperplasia:

Many have emphasized the role of benign hyperplasia in increasing the probability of cancer.[14, 27, 34] Notable hyperplastic benign growths turning malignant[1,2,4,30,34] are familial polyposis coli, gastric polyposis, von Recklinghausen's disease, and benign breast hyperplasia. Many carcinogens initially induce benign hyperplasia which eventually changes into cancer.[34]

(ii) Metaplasia:

Metaplastic changes such as leukoplakia in the oral cavity, senile keratoses in the skin and squamous metaplasia in the pelvis of the kidney often terminate as cancer.[1,5,34]

(iii) Ectopia:

Notable are ectopic testis, kidney, bladder and thyroid, in that order.[1, 34]

Atrophy:

It has not so far been realised that diseases characterised by premature atrophy of cells are often complicated by a cancerous change. To name some: atrophic gastritis *per se* or in pernicious anaemia,[1, 5, 34] xeroderma pigmentosum,[2,5,34,46] atrophic dermatitis following radiational injury,[1] cirrhosis of liver.[1] The placenta, having the shortest lifetime of any human organ[2], shows all the changes of senility at birth[2] and during its lifetime is subject to the malignant change of choriocarcinoma.[2] It has been mentioned that timed atrophy of the gonads and the genital tract in the female renders them unduly susceptible to a neoplastic change.

Multiple cancers:

The existence of any malignant neoplasm implies increased susceptibility to the development of a simultaneous or subsequent second 'primary' lesion in the same organ, in a similar paired organ (kidney), in the same organ system (colon), and in another unrelated organ in that order of frequency.[19,31,32,34,44] This is not to be confused with the multicentric origin[9, 34, 46] of the same cancer. Warren and Ehrenreich[44] deduced that multiple cancers occur 11 times as often as expected by chance alone. Most reports give a rate less than 11, 6 being a more general estimate.[19] In a particular series, Moertel *et al*[33] reported primary cancer of the breast in 27% of patients with cancer cervix, 34% of patients with cancer uterus, 27% with cancer ovary and 29% with cancer colon. Lynch and Krush[27] have observed an increased occcurrence of multiple cancers with cancer colon. The multiplicity of cancer is comparable to atherosclerotic process at multiple sites contributing algebrically to overall senescence and eventual death.

Recurrence:

"Many of the most histologically malignant neoplasms (retinoblastoma, Wilm's tumour, neuroblastoma and others) are being cured in infants and children by proper surgical and/or radiological treatment" (Ariel and Pack).[2] On the other hand, leukemia, a disease of young age, is fatal in 100% of cases.[9] It would appear that a prognosis of 'no recurrence' may be made only in certain malignancies, amenable to treatment in infants and children in whom the nature of the pathological process cannot be distinguished from other congenital abnormalities[2, 4, 35, 36] which, like cancer,[2, 4, 5, 46] are often amenable to treatment[2] and even undergo spontaneous regression.[4,5,46] Since each cancer is an individual species by itself,[18] except for the conditions cited above, it is difficult to predict the possibility or otherwise of recurrence.

DISCUSSION

There has been no attempt made to present anywhere the probability of cancer in exact numbers. Cancer being a senescent process, dependent upon multifactorial inheritance (Fig. 3) which also includes environmental factors,[36] any attempt at giving exact figures would be hazardous.

One recalls Willis' statement:[46] "The most voluminous and in general the least reliable of the main sections of the literature on neoplasms is the statistical." The rather subordinate role played by genetics makes Gibbon's remark[15] on the laws of probability so applicable to the chances of inheriting cancer 'so true in general, so fallacious in particular.'

The probability of cancer is dictated by the purpose cancer is called upon to serve. Cancer has been declared useless,[34] purposeless,[9] menaceful.[19] However, as Smithers[40] has pointed out cancer is no special evil, it is

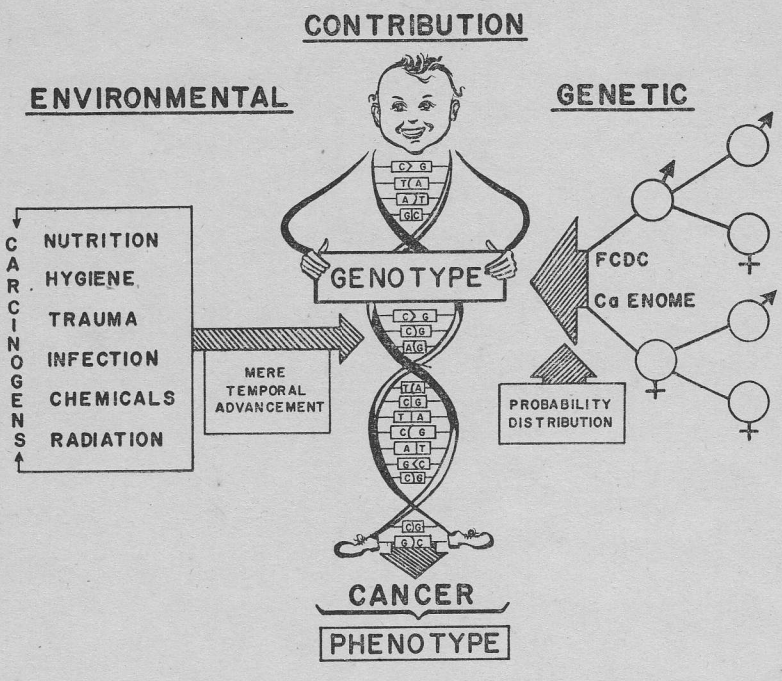

Fig. 3: Factors determining the occurrence of cancer (Adapted from Porter).[36]

just a variant of biological behaviour. Cancer, like the biological processes of ageing and senescence, is a time-governed phenomenon evolved through the process of Natural Selection as a means to terminate the life of the organism.[20] If the non-cancerous mortality is high, the incidence is low and **vice versa.**[16] The incidence of cancer has gone up in children in affluent countries such as U.S.A., spared as the children are of infections and deficiency diseases.[2] Even in adults, a rise in cancer mortality has been related directly to the fall in non-cancer mortality.[16]

Atherosclerosis and cancer account for the largest number of deaths in an affluent society.[10] It would appear that both these processes ('intrinsic causes'—Burnet)[6] are maximally operative in man who with his very high brain-weight/body-weight ratio[7, 38] (which is the highest amongst all animals)[7, 38] enjoys the longest adaptability to external environment and hence the lowest incidence of death due to 'extrinsic causes' (Burnet).[6] It has been rightly stated that cancer in man is the legacy of preventive medicine.

The data outlined above explain the species-wise, sex-wise, organ-wise, and cell-wise probability distribution of cancer. It is noteworthy that leukemias of younger age are 'acute' just as juvenile diabetes tends to be much more severe than diabetes of later life. Nature apparently appears ruthless in eliminating young individuals not very fit to survive. At a younger age of the organism, Nature depends on a mechanism single yet severe. At a later age, the cumulative effects of many senescent processes, individually

not very severe, kill the organism. Such a concept would appear to impart a 'purpose' to cancer; its purpose, indeed, is to manifest the inherent destructive power of protoplasm, a part and parcel of its total repertoire, and thus to serve the Gompertz[7, 8, 42] phenomenon of increasing mortality with increasing age in all animals, including man.[7,8,42]

SUMMARY

Various factors governing the probability distribution of cancer have been outlined and explanations advanced for the same. These factors, singly or severally, may permit the prediction of the incidence of cancer organwise and cell-wise in a given species of vertebrates, especially man.

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Cancerology: Science or Non-Science

(A plea for cancerrealism)

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Reprinted from the "Journal of Postgraduate Medicine,"
Vol. XXIV, No. 2, April 1978, pp. 68-90

Reprinted from :—
Journal of Postgraduate Medicine (1978), 24 (2) 68-90

CANCEROLOGY: SCIENCE OR NON-SCIENCE?

(A plea for cancerrealism)

By

M. L. KOTHARI AND LOPA A. MEHTA

SUMMARY

Cancerology is, by all counts, a non-science, which may be defined as a so-called scientific pursuit in the teeth of obvious proofs to the contrary. Not one facet of current cancerology—etiology, diagnosis, therapy, prevention, and its latest fad, immunology—enjoys any clear, rational basis. No wonder that the outcome of the whole gargantuan effort is "precisely nil", with possibly more people living on, than dying of, cancer. The pathway to the logically acceptable and comprehensible science is simple—to give cancer its due place in biology, to give the cancer cell its rightful place of but a form of cytodifferentiation, and to give the cancer therapist the supremely relevant role of a palliator. To talk of cancer cure is to deny the cytosomatic reality that cancer is one's own flesh and blood. Being a part of one's self, cancer need not always be treated. If a therapist has the right and obligation to diagnose, treat, and prognose upon a cancer patient, he has, hitherto unrecognized, equal right and obligation, not to do one or all of these. Cancerrealism offered in this article can guide a therapist to this often necessary path of inaction.

Cancer, paranoically personified, is continuing to have the last laugh, after being attacked on all possible fronts. Bier's[14] summing up many decades ago—"There is a tremendous literature on cancer, but what we know for sure about it can be printed on a calling card."—found itself fully revindicated recently when Burnet[28] declared that the outcome of the entire cancer research has been "precisely nil." Coronary heart disease, the doubly greater killer, stands a poor second to cancer in being funded, politicized, and paranoically symbolized.

Breast cancer as a paradigm typifies the colossal cancerologic failure. A *subcutaneous* cancer, the natural history of which has been studied for centuries,[60] most amenable to self/clinical examination, -graphies, staging, grading, -ectomies, hormonization, dehormonization and the most varied therapeutic combinations, has stubbornly refused to yield even a wee bit in the last 70 years;[81] it has, in fact,

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Received for Publication: 6th June 1977.

gone worse.[125] Yet research establishments refuse to prune their anticancer claims, for "It just doesn't pay to rock the boat."[81] *Cui bono?* The lay—the media—do not lag behind. A promethean prophesy, a book, *No More Dying*[117a] envisions drugs to cure or prevent cancer, heralding the emergence of the eternally non-dying *Homo longevus.*

Cancer research is based not on *science,* but on *non-science,* an epistemologic revelation that explains the cancerous proliferation—"now more people live on cancer than die of cancer"[7]—of research,[45] in the teeth of the writings on the wall. Putting it in Ardrey's[6] style, the whole cancer fiasco represents "the disastrous consequences of applying utter logic to a false premise." The many false premises on which the cancer edifice rests need analyses, as follows.

NON-SCIENCE OF CAUSALISM

Bertrand Russell[167] delvered, in 1918, a devastating judgment against causalism: "All philosophers, of every school, imagine that causation is one of the fundamental axioms or postulates of science, yet, oddly enough, in advanced sciences, ...the word 'cause' never occurs. The Law of Causality, I believe, like much that passes among philosophers, is a relic of a bygone age, surviving like the monarchy, only because it is erroneously supposed to do no harm." The gains of cancerologic causalism have been nil; the harm done is global phobia of "cancerogenesis" should people eat, drink, breathe, or copulate. *The medical finger accuses*—almost everything as cancerogenic[141]—*and having accused, moves on to accuse still more.*[58] Such anxiety-making—the curious preoccupation of the medical profession[38]—reaches its apogee when PUFA, which is supposed to *prevent* heart attack, is declared as *causing* malignant melanoma.[79, 122, 143] Editorially, Ingelfinger[101] rightly described cancerophobia as a social disease as serious as cancer, and morally far more devastating.

Cancerogenism[30, 56]—the obsession that a *-gen* causes cancer—has not for once satisfied the fundamental tenet[71] of causalism: *an invariant relationship of events in which the cause must precede its effect and the effect must follow its cause.* "It is this sense of *must* which distinguishes causal connection from coincidence."[71] Any *-genic* postulate that *A* causes *B,* must in the same breath, explain why *A* occurs without, and refuses to occur despite, *B.* The causalism of modern medicine is incapable of complying with the foregoing, be it coronary, or cancer. Further, causality cannot jump gaps in time; the *effect* must immediately follow the *cause.*[71] The concept of "latency"[105, 141] that allows as many as 12 to 56 years between the exposure to the postulated cause and the occurrence of cancer is, because of the irreconcilable temporal gap, clearly against the causalism of cancerogenism. The current epidemic of epidemiologic studies[46] on cancer was triggered by a search for *Mr. Cause that never was,* a wild-goose chase powered by the application of utter logic to a nonexistent premise.

The noble aim behind the cause-hunt is the prevention-promise.[56] "Since so little is known about the origin and development of neoplasia, it is not surprising that many cancers can be neither prevented nor cured."[66] What if much is known? Reviewing a book ambitiously titled *The Prevention of Cancer,* Jellife[103] concluded that, although the various authors provide an excellent analysis of the large amount of data related to the *causation* of different

cancers, no reasonable means are provided anywhere for prevention. "For example," Jellife[103] remarked, "after twelve erudite pages on breast cancer, the reader can discover no practical alternative to prophylactic bilateral mastectomy at an early age." Harvey Cushing[50] exclaimed that, like many other catchwords, *prevention* can be overworked: "There is only one ultimate and effectual preventive for the maladies to which flesh is heir, and that is death."

A la Koestler,[110] scientismic perversity reaches its climax when patients are purportedly "cured" by the very agents known as causing cancer—irradiation, chemicals, and hormones. Viruses and immunity had hitherto escaped this cancerologic diabolism of *what causes, cures* cancer. However, viruses have been mooted as curative[198] while immunity,[34] our last hope against cancer, has been incriminated[159] as cancerogenic and cancerotrophic. Diagnostic procedures (mammography,[9, 23, 141, 142] right now) are not exempt from the cancerogenic edge. All that is done to cure cancer, manages to cause cancer.

The truth in all probability, is that cancer is causeless. Cancer, the primeval broth of pre-life that spawned organized life,[51, 95] is a property of all living systems[52, 200] *ab aeterno,* being but a way of cytodifferentiation that is part of the normal cellular repertoire.[157] It is an integral part of the human biologic trajectory, a bioevent that can't be *caused.* In this light, cancerogens have been rightly held as agents that are "accelerators of some process that is inherent in the animals."[47,175,184] Neologistically, cancerogens, not excluding the recently notorious polyvinyls, should be called *cancer-preponers.*[113] The invention of the new science of ecogenetics[149] is the last-ditch effort of the causalists to somehow incriminate our *milieu* for what programmedly is, in Shakespearean words, "an ill-fated thing, Sir, but my own."

THERAPEUTIC NON-SCIENCE

Glemser,[75] from his globe-trotting survey of cancer research and treatment, gathered, from the scientists themselves, that radiotherapy is obsolete, chemotherapy is an absolute farce, and that surgery ought to be dispensed with, sooner the better. The reasons are not far to seek: If even the doubtfully helpful[147] mammograph threatens to cause "as many cancers as it is picking up"[9, 23, 141, 142] by increasing the natural risk of breast cancer, by *one-one-one-one* mechanism (*one* mammogram gives *one* rad to *one* breast to increase the risk by *one* per cent),[23] then sure enough any form of therapeutic radiation[28] would increase the risk of iatral (so-called iatrogenic)[25] cancer much more.

Chemotherapy is another story: Karnofsky,[106] lately of the SKI, in his chapter on experimental chemotherapy gave the directive that "if an agent has certain biologic effects such as carcinogenic, mutagenic, or bone-marrow depressant activity, it merits testing for chemotherapeutic activity." Each agent used *against* cancer, was "cancerogenic" to start with, a farce that has not changed from nitrogen mustard to adriamycin.[135] The situation is similar to that in Anthony Burgess's *A Clockwork Orange*:[27] "Our subject is, you see, impelled towards the good by, paradoxically, being impelled towards evil." The too-generously funded cancer chemotherapy research programs provide an "anticancer" drug which, by a semantic alchemy, turns anti-psoriasis when used by a dermatologist, anti-

immunity when employed by a Barnard, and anti-rheumatoid-arthritis when given by an internist. Cancer chemotherapeutic agents prove to be *anti-everything*, including the patient. (Cf. "The aggressive chemotherapeutic approach used ... is often lethal to the patient with LRE."[127]) The chemicals provide cent per cent failure against autochthonous[74, 183] cancer and, sometimes, cent per cent success against the so-called transplanted cancer[74] which is not a cancer at all but a borrowed mass of mitotically active cells. The singular, and outstanding, success of cancer chemotherapy against gestational choriocarcinoma is a function of the transplanted (fetus to mother) nature of the cancer, rather than any special qualities of the drugs. As back as 1947, Woglom[206] described the quest for cancer drug as much difficult as finding an agent that will dissolve away the left ear and yet leave the right ear unmolested; "So slight is the difference between the cancer cell and its normal ancestor."[206] Haddow[84] has compared the search to the biological equivalent of squaring a circle. Regardless, cancer chemotherapy continues to be defined as "essentially the science of discovering exploitable difference between malignant cells and normal cells."[183] Farce, in science, seems to have its own reasons.

Surgery's dispensability stems from the closely comparable successes of measures ranging from tylectomy (which tantamounts to *nil-ectomy*), for breast cancer on the one hand, and supraradical mastectomy on the other. "Each of these diverse treatments has its fervent advocates," the BMJ[60] editorialized, "and yet despite a plethora of reports there is little evidence on which to recommend the 'best buy' for the patient." Radicalism is however the preferred course, either because it is approved by the majority of breast surgeons,[188] or because it is more dollarogenic.[49] Be as it may, cases for which *nothing* is done, fare no worse.[17, 104, 209] The *we-must-operate/treat* diehards insist so on the ground that not enough is known about untreated cases. "On the contrary, if one bothers to scan the literature, there are ample articles on just this subject."[186] If it is Dowian *do and be damned, and do not and be damned,* then why do anything at all? Why not allow many a woman to die with her own breasts on?

All other measures—hormones, immunotherapy, Isselsism, thermotherapy, and all other nostra—are used *faut de mieux,* when the three bulwarks of surgery, radiation and chemotherapy have failed, or are *prima facie* useless. Malleson's diatribe *Need Your Doctor Be So Useless?*[132] could be paraphrased to read *Need Your Cancerologist Be So Useless?*

Notwithstanding the foregoing, cancerology reeks with treatment, nay, overtreatment, probably because, *it is better to believe in therapeutic nonsense, than openly to admit therapeutic bankruptcy.*[8] What happens when a doctor—a cancerologist—is at the receiving end of such therapeutic nonsense? He doesn't want it, for he can't trust it. Solzhenitsyn portrays this poignantly in *Cancer Ward.*[179] Erik Erikson's[63] invocation *Doasyouwouldbedoneby* does not strike a responsive chord in the heart of medical therapists, for they know too well of the therapeutic non-sense.

A word about controlled clinical trials, the most important condition for which—namely, that *even cancer* must be left untreated to serve as control[166]—is rarely obtained.[166] The failure of such trials *vis-a-vis* many problems including cancer therapy is too well-known,[65] and large-

scale international trials only serve to highlight their futility.[39] Foulds,[70] as it were, ruled out the scope of controlled trials when he generalized that "no two tumours are exactly alike." Connors and Ball[42] enlarged on this by declaring that this behavioral unlikeness reigned amongst "morphologically similar tumors" as also amongst "tumors obtained by the same means and in the same pure line of animal." How come controlled trials, when no two humans, nay, no two cancers, nay, no two cancers in the same human, nay, no two clones in the same cancer are exactly similar to each other?

THE DATE DOGMA

Today, the recurring theme in writings medical[13, 73, 190] or lay[23] is the war cry *Diagnose And Treat Early (DATE).* *DATE* has been tirelessly advanced as the cure-all promise against cancer; the motto takes for granted that treatment applied sufficiently early is or should be successful treatment. While the outcome of *DATE* program has remained ill-defined, it has certainly bred a widespread *I/we-did-not-seek-DATE* neurosis among cancer patients and their relatives. The iatral nature of this neurosis is dependent upon statements such as these: "In no other disease does the patient himself bear so large a share of responsibility...In no other disease does the patient alone influence the outcome to a great degree."[32] The title to the foregoing text is dramatic: THE BIG IF. The ending is no less incriminative: THE RESPONSIBILITY IS YOURS. The author[32] heightens the impact by figures: "Ninety thousand American lives are lost needlessly every year. These are the deaths which early diagnosis could have prevented—and can prevent." The *DATE* concept, as has been presented to the public and patients so far, puts the therapist in an enviable and inculpable position. Should the therapy fail—and it must, so often—it is only the patient who has to admit *mea culpa, mea culpa.* The patient has no escape, for he/she has been categorically told: "The choice is yours—and wholly yours." (Cameron).[32]

The medical naivete,[190] that the *earliness* of a cancer is synonymous with its curability, is laid bare the moment a definition of the elusive *earliness* is asked for. Cytokinetic studies, apart from dispelling the myth of faster multiplicability of cancer cells,[11, 183] have revealed, (a) that it takes years before a cancer marches from inception to detectability and (b) prior to being detected, a tumor enjoys a formidable number of cancer cells. "Unfortunately, gross or microscopic tumor cell identification in man or animals is probably, at best, limited to between 1 million and 1 billion tumor cells."[172] An average cancer cell, like an average normal mammalian cell, has a diameter of around 10 microns[120] and gives rise, through 20 exponential doublings, to around 2,500,000 cells comprising a lesion only a millimeter in diameter,[59, 129, 196] a size smaller than "an 'o' on this page."[23] Cheatle[35] declared, in 1927, that the appearance of a lump in the breast meant advanced cancer beyond the hope of cure. Cytokinetic studies have done the disservice of proving that this is so even when it is a microlump, undiagnosable by any *-graph.*

"Early diagnosis of breast cancer operates on a fast track these days and better results in survival statistics are appearing."[73] This robust optimism has to be tempered by a global survey revealing the worsening of breast cancer mortality.[125] We can continue to hope, but the *DATE*

drive, damned by so many cancer-realities, has failed. As Macdonald[129] puts it for breast, the fixed rates of incidence, mortality, and survival following diagnosis—"that discouraging and almost parallel line"[164]—allow only one conclusion that early diagnosis, small size of the primary lesion, long meticulous or extended surgery, with or without adjuvant radiotherapy have not been of any value in our battle against a biologic complex formed by mammary carcinoma; even metastasis and recurrence of breast cancer have not been found to be influenced by earliness or lateness of treatment. All the inconvenient data[130] from the various *DATE* programs can allow the generalization that *no cancer,* that can be labeled—microscopically, endoscopically, or clinically—as a cancer, is an "early" cancer and that the so-called earliness of a cancer is no guarantee for a late death, nor the lateness a passport for early demise. Moertel,[145] citing Palmer, convincingly drives home the *DATE* debacle: "It might be hoped that earlier diagnosis could brighten the surgical picture, but even this road seems blocked. In a group of sixteen cases in which esophageal cancer was diagnosed prior to the development of symptoms while the patient was under active medical surveillance, Palmer could demonstrate no improvement in survival."

PRAGMATISM OF PRECANCER

Virchow cited by Ewing,[64] declared that no man, even under torture, could say exactly what cancer is. Yet, while cancerology continues to ail from the spinelessness of definitionlessness *vis-a-vis* cancer,[116, 181] it has chosen to establish the burgeoning science of *precancer,* that boasts of the ability to doubtlessly diagnose[37] precancer—*earlier-than-early cancer*—and to grade[173] it from 0 to 10, unmindful of the fact that the microscopic grading of even a *fait accompli* cancer—which may be "cytologically indistinguishable"[93, 115] from the parental normal tissue—depends so often on the barometric pressure and the bowel tone of the pathologist.[148] What is *carcinoma in situ* below the umbilicus, becomes with equal, characteristic equivocation *minimal cancer* above it. To wit, listen to Hutter,[98] concluding a conference on minimal breast cancer. "The great aspiration for the future is to have the pathologists identify any lesion which is significant threat to the future health of the patient so that it can be treated...I have carefully chosen my words to avoid specifying whether the significant lesion is actually cancer or what the preferred treatment should be. Nevertheless, if we can consistently identify an obligate precursor to metastasizing cancer we can establish a cure rate of 100 per cent."

The rank uncertainty of what *is* precancer, breeds, what Park and Lees[156] called long ago, *pragmatism* that thrives on "probably not cancer but safer away"[156] type of diagnostic and therapeutic approach. As early as 1923, Bloodgood,[16] from his experiences with breast cancer, at the Johns Hopkins over 33 years in retrospect, wrote of "Benign Lumps Diagnosed Cancer or Suspicious of Cancer." He remarked that such pragmatism increased the cure-rates. Sheep-slaughter presented as wolf-slaughter has managed to create the mysterious "paradox of increasing incidence and decreasing mortality"[46] of two most sought-after precancers—cervical[46] and mammary.[22] Bloodgood's[16] highly objective generalization is as relevant today: "As this element of error has been present in my own investigations for years, I feel justified in the

conclusion that it is present in all statistical studies throughout the world."

The precancer pragmatism reminds one of Voltairs: *Si cancer n'existait pas, il faudrait l'inventer.* Such cancerous invention explains the sudden four-fold leap in cancer rates for the year 1975, [141] the demoralizing cancerophobia,[101] and the *fright, confusion, and panic*[23,130] that plagues womankind. It also accounts for 690,000 hysterectomies performed in the USA in 1973,[26] (a number equivalent to the global publications on cancer per year),[173] many of these carried out "unnecessarily," and as such useless towards preventing cancer.[26] It is a measure of sanity that the worth of Pap Smear is being questioned,[13, 90] and it may not be too long before precancerology dies a natural death, like many an advance in modern medicine.[174] The poor public response to cytologic screening[193] could be looked upon as an evidence of, what Comfort[38] calls, "the astounding resilience of human common sense against the anxiety makers." May be, that is what makes more and more people—60 million Americans[141]—smoke dsepite the Surgeon General's warning on every cancer stick.

THE LAST CANCER CELL

Wilcox,[202] writing on "The last surviving cancer cell: The chances of killing it" generalized that "a minimum requirement for a cure is the elimination of the last cell." The presupposition here is, as it is in *DATE* drives, that *canceration* of normal body cells is a kind of *once-and-for-all affair* so that the demon can be completely exorcised, provided the multidisciplinary exorcists arrive in time. The cytokinetic concept of "clonogenic cells,"[177, 182] advanced to explain the failure of chemotherapeutic exorcism also suffers from the illusion of canceration as a once-and-for-all process. What foils the exorcists, however, is not the last cancer cell but the neighbouring *normal* cell waiting to turn cancerous. *Le roi est mort, vive le roi*—so the heralds proclaimed the death of one French king and the coming to the throne of the other. The body playing host to a cancer, on removal or destruction of the latter, proclaims *Le cancer est mort, vive le cancer,* by asking some normal cells to turn cancerous, be it stomach, lung, bowel, or brain.

Canceration is a fundamental prerogative of every normal, divisible cell. A cell that turns cancerous afresh could be said to *neo-cancerate.*[113] The human body's propensity for neo-canceration rules out the possibility of any therapeutic—surgical, radiational, chemotherapeutic, or immunologic—triumph against the hypothetic "last" cancer/clonogenic cell, and, therefore, against cancer. It may be emphasized that neo-canceration is not equivalent to "cell recruitment,"[66] which presupposes the ability of a cancer cell to seduce a normal cell into cancerhood. Neo-canceration is canceration once more, independent of the cancer that already exists or that has been treated. Even if the *DATEists* manage to grab a cancer before it has jumped the fence—metastasized—neo-canceration is a force that may thwart their curative aims.

An exception to the above cellular scare is presented by gestational choriocarcinoma. This cancer, being a transplant from the fetal tissues to the mother, has no would-be-choriocarcinomatous normal progenitor cells in the mother so that a chemotherapeutic agent administered in the right dosage at the right time manages to achieve a total cell kill, thus accounting for its much celebrated cure.

IMMUNOLOGIC ILLUSION

Surveying the field of tumor immunology, a science-writer[75] hit upon the generalization that immunology is now so advanced that one immunologist cannot comprehend what another is talking about. Medical obfuscation[48, 102] never had it so good. Tumor immunity hasn't been defined, and is unlikely to be in view of such learned editorial double-speak: "This article illustrates that under proper circumstances, tumor immunity can stimulate tumor growth."[61] Yet, today's most dominating form of cancer research is *tumor immunity,*[44] threatening to usurp the top place enjoyed by the disproportionately overfunded[28, 29, 151] tumor virology, already declared as "a major disappointment."[28, 29] Tumor virology presses on regardless, rejuvenating itself by virologic obfuscation—"misevolution" of protoviruses[187] or virogene colliding with oncogene[94]—keeping alive thus the unending promise of immunologic *bullets* against "specific tumor proteins"[160] and the ultimate bonanza of a vaccine program.[62, 138]

While the obfuscatory going is good, anticancer going is otherwise. Burnet,[28, 29] writing on cancer antigens, stated that "Nothing of value for either prevention or cure has come from the laboratories," adding that lab-oratorial immunology, bred from inbred strains, has had nothing to do with human cancer. Tumor immunity ambitiously aims at diagnosis, treatment, prevention and prognosis of cancer and precancer[13, 22, 37, 41, 77, 89, 163, 168] but a review[137] of a book on tumor immunity's "Scientific Basis and Current Status" ends up with unsuccess, disappointment, frustration, and difficulties, the latest one being that a circulating cancer antigen may in fact protect the parent tumor. The typical double-speak of cancerology reaches one of its high, when the talks of the prevention of cancer by tumor immunity, get matched by the promotion[22, 68] of the use of potent "oncogenic"[87] immunosuppressors as prophylactic against recurrence of cancer.

Tumor immunity itself does not seem to have decided on which side of the tumor it is. The betrayal by antibodies[163] is a thing of the past; now even the cell-mediated immunity is turning a leading suspect in the initiation and promotion of cancer.[159, 168] May be it is decided by "Immunostaging as a guideline to immunotherapy."[2] May be it depends on immunity's moods: It is antitumor if it is malignant melanoma, lung or colon carcinoma, but blatantly protumor if it is carcinoma cervix or bladder.[88, 168] Immunity may, however, betray to enhance malignant melanoma.[153] Oettgen and Hellstrom,[154] writing a chapter in the current Bible, *Cancer Medicine,* raise enough anticancer hopes before and after the few lines that follow: "Thus, it is not simply a matter of deciding whether 'immunity' inhibits or fosters cancer. Only if means can be devised to shift the balance between inhibitory and enhancing immunologic forces in either direction can we hope to find a clearer answer." BCG immunotherapy of cancer, apart from "frequent complications"[136, 139, 153, 180] assumes, in the light of the foregoing a procancer edge.[18] *A la* Peter Principle, BCG immunisation has reached its level of incompetence and is paving way for a wormicidal drug—levamisole—that has proved to be an "immunostimulant" with its own unpredictable efficacy and side reactions.[136]

Let us face it: The cancerous proliferation of highly fundogenic tumor immunology is a comic verification of the

principle of applying utter logic to a false premise. No autochthonous cancer has believed in being non-self.[114] It is for everyone, to borrow words from Mr. Doolittle in *My Fair Lady,* "Me own flesh and blood." For gastric carcinoma, for example, the suture line *takes* even when the knife runs "actually through the cancer"[131] amply proving the *self* nature of cancer cells. The elaborate studies on "How Lymphocytes Kill Tumor Cells"[4] in culture has little to do with the self-sameness of cancer cells and lymphocytes in the same individual.

LAB NON-SCIENCE

Were hindsight to help, we would realize that the unmitigated failure[28, 29, 40, 185, 189] of cancer research can be attributed to the fact that cancer is, by its very nature, unresearchable. Burnet's[29] candor that the contribution of lab-science to medicine has come to an end is not even applicable to cancerology, for the contribution has never begun. Huxley[99] generalized that *each cancer is a species,* being like the human owner, unhelpably unique.[29] The individualistic character of every autochthonous cancer[70, 99] animal or human, coupled with the unique biologic trajectory of the individual, rules out any structural or behavioral comparison, prediction of therapeutic outcome, or disease-death correlation. The little emphasized benignancy[195] of malignancy—that cancer does not always kill—questions the very *raison d'être* of cancer therapy. In fact, Hardin Jones[104] went to the extent of concluding that treatment, more often than not, shortens the lifespan of a cancer patient. A biologic, non-anthropocentric approach to cancer reveals it as is no error, but an integral part of cellular/organismal behavior, that will not yield to "the basic-science route to a medical nirvana"[82] regardless of the fact that such "research is still the lifeline of medicine."[111] Non-medical sciences have started admitting the *trans-science*[121] nature of problems. Cancer is trans-science and trans-two-billion-dollar-NCl-budget. The "light-at-the-end-of-the-tunnel" thesis[81] of Vietnam war days is only relevant to the point that there is certainly dark at the end of the cancerous tunnel.

The use of *transplantable cancer,* because of the sheer incapability of using autochthonous animal cancer,[74] is an intellectual compromise that has spawned little good. Any immunologic/therapeutic data obtained using cancer transplants cannot be extrapolated for the simple reason that it is *cancer* only when it is autochthonous and with the owner; otherwise it is a borrowed mass of mitotically capable cells that, multiplying in a test tube or a biotube, can only prove that MOPP,[165] POMP[170] or TRAMPCOL[86] are "terribly toxic drugs"[86] that form "the blind artillery which cuts down its men with the same pleasure as it does the enemy's,"[179] making hitherto unknown infections "now the major cause of death in patients with leukemia."[96] It is a sad comment on the perversity of lab-science that cancer transplantation and organ transplantation were born as twins in the womb of inbred mice,[97] and that cytotoxic agents prove friendly for graft-survival and inimical to cancer-survival, purely because of their cytotoxicity against the mitotically capable lymphocytes on the one hand and the cancer cell-lines on the other.

All that the transplantable *L* 1210, *B* 16 *melanoma, osteogenic sarcoma HE* 17304 and so on have done at The Cancer Chemotherapy National Service Centre (CCNSC)[78] (now, Drug Research and

Development)[78] and elsewhere is to show, animal after animal, and year after year, the naggingly prototypal *-cidal* efficacy of the "drugs" against dividing cells. The dependence of all forms of life on the cardinal biologic phenomenon of cellular division[12] constitutes the most unabrogable obstacle to the present or future success of cytotoxic (chemical and/or radiational)[207] agents. The human body is dotted from head to foot with renewing cell populations many of which exhibit far more consistent and faster cellular proliferation than the fastest growing *Walker carcinoma* 60.[123] As and when a patient is exposed to the CRAB[183] aims of a cytotoxic agent, the damage to normal cell populations is a certainty while the damage to the cancerous cell population is only a probability.

Cancer research has now entered the cell-surface,[150, 185] *cell-enzyme*[199] *era*,[150, 185] entailing a massive research effort that has provided an enormous catalogue of differences between normal and cancerous cells. The compromise here too, is no different. "These *'in vivo'* approaches are complicated by the fact that most tumor cells arise from unknown precursors, making comparisons with other cells difficult. Because of these problems and the limited availability of uniform cell populations, the main tools of the cancer-cell biologist have thus been model systems employing untransformed/transformed tissue-culture cell lines, frequently of rodent or avian origin."[150] Koestler's fourth *Pillar of Unwisdom*[109] could not be more relevant than to cancer lab-science, ever ready to reduce a complex phenomenon to simple quantifiable elements without worrying at all that the specific characteristics of the complex phenomenon—cancer—are lost in the process.

FROM NON-SCIENCE TO SCIENCE

We can visualize a parallel-problem here: *diabetes mellitus*.[112] Boyd[20] concluded that "the more we know about diabetes, the less we seem to understand it;" the more we treat the patient, the less we seem to benefit the patient;[108, 204] the more we research on it, the more we replace certainties by uncertainties.[144] Nevertheless, eminent diabetologists[31] in "an exercise of mass delusion"[133] blatantly "propose as 'truth' a concept that remains to be proved.[133] May be, this is the way modern medicine works. A 4-page color-ad on clofibrate[1] promotes lipid-lowering therapy with an apologetic box that renders clofibrate a non-drug; but the color carries the show and doctors universally prescribe the drug notwithstanding the two columns, in small print, on its hazards.

The burden of the foregoing is to draw attention to a malady that afflicts modern medicine—the connivance of the dividing line between *what we know* and *what we know not*. Holmes,[92] while pointing out the "Border Lines of Knowledge in Some Provinces of Medical Science," observed that "The best part of our knowledge is that which teaches us where knowledge leaves off and ignorance begins." Finding or erecting such an epistemologic watershed, in cancerology, is not difficult provided we abjure non-science (which in the current context can best be defined as *arrogance despite ignorance*) in favor of science pregnant with the humility to accept ignorance. "Science," Holmes[92] declared, "is the topography of ignorance." Let us see where, in cancer, does knowledge leave off, and ignorance begin.

What follows should be perused with Arcadian humility, which the *Homo*

sapiens (?), preparing now to be *Homo longevus*,[117a] appears in no mood to have. With the aid of his "optimistic ignorance"[79a] on cancer, he hopes to "square the circle", and boldly declares right away, that *YOU CAN FIGHT CANCER AND WIN*.[22a] A saner 1977 survey[189a] of the "Science and Technology of Medicine" leaves no scope for such *Homo*-hopes. The simple realities of cancer—cancerrealism—that follow assure an easy change from the non-science to the science, of cancerology.

Tumor = Lump: The Border Line

The *raison d'etre* of cancer therapy is that the chief manifestation of cancer is *mass-ive*—a celluloma called a tumor or a lump. (Imperatively, the *synonymy* between *cancer* and *tumor* is avoidable obfuscation.[113, 116]) A cancer clinician's knowledge begins with a tumor and ends with it. By a variety of lumpectomic and/or lumpolytic measures, the neoplasm is made to disappear. The whole cycle of detection/destruction of lump is repeated with the reappearance of the tumor.

Tumor = Lump, is thus the clinical border line between the blissful ignorance of what did happen and the unhelpable uncertainty of what will. *Vis-a-vis* a patient, a cancerologist only knows of the tumor—how to diagnose/treat/retreat it in n-tuple ways. It is a sobering thought that cancerology is nothing more, or less, than lumpology. The logic of such curt summing up can be understood by considering, (a) the preclinical or pretumor phase, and (b) the clinical phase—the tumor and after.

Canceration to Tumor: Preclinical Phase

Let the setting of the story be the body of an eminent cancerologist—the pancreas[21] or the stomach[10] of Armand Trousseau, the great clinician of *Hotel-Dieu de Paris*, the stomach[36, 113, 206] of William Mayo, Sir D. P. D. Wilkie, or Ernest Borges of Tata Memorial Centre, Bombay, the lung[54] of David Karnofsky, the kidney[100] of Harold Dorn the cancer-epidemiologist or the colon[126] of Leslie Foulds. Whether it be these luminaries or their patients, canceration—the inception of cancer—starts as a very small, silent event that tardily marches over several years to the stage of being detected, by a -graph, -scope or clinical/self examination, the starting point being a few cells in a single focus or in many foci as in leukemia. Before hitting the eye of the clinician or causing symptoms in the patient, each cancer takes a pretty long time—computed as ranging from $2\frac{1}{2}$ years[43] for a rapidly lethal cancer as of the lung to as much as 17 years or more for such cancer as of the breast.[43, 128, 130] During this time, even the cancerologist-patient is blissfully unaware of the cancerous happening. Considering that the average duration of survival after the diagnosis of cancer is 3 years,[33] this preclinical silence of cancer speaks for the quiet, benignant behavior of cancer over a greater part of its stay in an individual. This is probably true of a number of pathologic processes: "Thus, the myocardial infarction, the cerebral infarction, or the gangrene of leg which terminates a patient's life may be seen as the final episode of a series which remain silent over a long period of the patient's life before they obtrude into his experience and finally terminate it." (Pickering).[158] While the cancerous silence is kind to the patient, it rings the death knell for the *DATE* dogma, as was editorialized[59] over a decade ago, and almost concurrently echoed by Macdonald[130] when he declar-

ed that two-thirds of the life cycle of breast cancer is completed by the time "early" clinical discovery becomes possible.

Furth and Kahn[72] could experimentally produce "leukemia" in a healthy mouse by transplanting a single "cancer" cell. This may drive home the point that a cancer to become generalized—undetectably to begin with—does not require more than the first few cancer cells. The clinican, then, is too late when the first few normal cells turn into the first few cancer cells. A mammographically detectable "tumor" has to be at least a cubic mm in size, and worth at least 1000,000 cells[119] before it could be detected; such a lump over the silent years has had on each day "twenty-four hours for metastasis to occur."[59] Let us, for once, admit cancerrealisatically that *from canceration to tumor is from ignorance to tumor.*

Tumor and After

Eureka, the tumor is found. This *eureka*-euphoria can last no longer than the time Archimedes was in the bathtub on that fateful day, for uncertainty plagues every move. The incurable individuality of each tumor and its owner makes unpredictable, (a) what the tumor will do to the patient, and (b) what the treatment will do to the tumor. Regarding the former, it may be, as for Mayo, Wilkie, Borges, Foulds and Dorn, "the discovery of a hard tumor,"[203] and an inexorable downhill course, despite all attempts at treatment. Left untreated, as stated earlier, the tumor may not bother, choosing to go to the grave with the patient. Treated, as for the pathologist-author Boyd,[21] the tumor may not reappear for a lifetime. In short, a tumor treats the patient the way it likes, in a predetermined fashion regardless of the therapist. Treatment, in fact, may ill-treat the tumor: Even after the most painstaking application of the criteria of operability, there are women in whom surgery manages to accelerate the evolution of breast cancer.[130] "Some patients with breast cancer in early, operable stages have very short survival after surgical intervention."[107] The authors[107] introduced the concept of acute evolutive onset (*AEO*) attending some cases of breast cancer as could be judged by clinical examination, mammography, skin thermometry, and provoked hyperglycemia test. Surgical intervention markedly precipitated distant spread in cases with *AEO* as compared with the control *AEO* group untreated by surgery. The authors[107] concluded that "surgical intervention must be excluded as the first therapeutic step, even in stage I breast cancer." We do not know how many other cancers have *AEO* so that this or that form of therapy may only serve to fan the fire of a smoldering early cancer. The foregoing uncertainties are complicated by what treatment does to the patient, for all cytotoxic agents—chemical or radiational—are accelerators of aging,[3, 161] all with a "marrow-devastating"[86] "oncogenic"[87] potential.

Tumorectomy (or -lysis), in a manner of speaking, is symptomectomy/signectomy, but not cancerectomy. Treated, *the tumor is out, the cancer is not,* much less cancerability of normal tissues. Over a century ago, Billroth[15] aphorised that surgery removes a tumor, but not the patient's *diathesis* for cancer. "Unfortunately it must be admitted that all cancer surgery is in large measure palliative, given the occult spread of the disease before treatment in a high percentage of cases."[192]—an observation not denied by

the most diehard *DATEists.*[13, 91] The much-celebrated victory over leukemia must contend with the fact that, although in complete remission the peripheral blood picture and the bone marrow are *normal,* 10^8 to 10^9 leukemic cells still remain, making relapse virtually inevitable.[201]

Whither Cancer Treatment?

Thus, all told, prior to the detection of and after the detection/treatment of a tumor, clinicians are essentially *know-nothings*—a gnoseological bitter pill served sweet in Shelleyan style:

> We look before
> And after, a tumor
> And find that
> We know naught.

Glemser's worldwide survey of *Man Against Cancer*[75] only revealed that the realistic title of his book could have been *Man Helpless Against Cancer*: Surgery is dispensable, radiotherapy obsolete, and chemotherapy a farce. Any talk of treating cancer tantamounts to Ecclesiastes' *Vanitas vanitatum*: "Nothing is worth doing, no way is better than another."[205] The foregoing finality may smack of a deliberate offense—a Nietzschean "devaluation"[205] of all therapeutic values. But the reality is different, more about which, *anon.*

"At the present time," Brooke[24] generalized in 1971, "cancer treatment appears to have reached a culmination, a peak beyond which we have not moved for several decades." This means that cancer therapy did reach its (whatever) zenith of perfection which has plateaued ever since then. But as none of the therapeutic measures against cancer has been, as yet, held as not rejectable, we are forced to conclude that cancer therapy reached its Peterian zenith of imperfection "several decades" ago, and all that we have been doing is to move in circles and call it as "progress" and "recent advances" and so on. Such euphemismism may be justified on the geometric ground that all circular motions are made up of a series of motions in a straight line, and straight line motion is progress.

Cancer therapy has, all along, betrayed the application of utter lumpolytic logic to the false premise of a cure. Watts[197] has described the peculiar and perhaps fatal fallacy of modern times: *the confusion of symbol with reality.* Such fallacy dominates cancerology so that what is diagnosed and treated is not cancer—"a disease of the whole organism"[162]—but its most evident manifestation, a lump or an *-oma.* The consoling cures obtained in "certain rare neoplasms"[183] such as gestational choriocarcinoma, neuroblastoma, retinoblastoma, Wilms' tumor or even "low-grade malignant bone tumor (s)",[19, 134] are a function of the nature of the cancer, rather than any ingenuity of the hit-and-miss treatment. The cure of solar-plexus cancer—"the 19th neoplasm cured by chemotherapy"[140]—by *MIRACL* makes the curable list impressively big enough, yet scientifically too hollow for cancerology to survive its current intellectual crisis.

TOWARDS CANCERREALISM

At the very outset, the indispensable role of cancer therapy must be underscored. Despite the accepted impotency of all therapies (Fig. 1) against autochthonous cancer, one and all measures are useful when employed to ease a dis-eased cancer patient. Cancer is, as Foote[69] observed, "a mysterious plague that cries out not for philosophy but for a pallia-

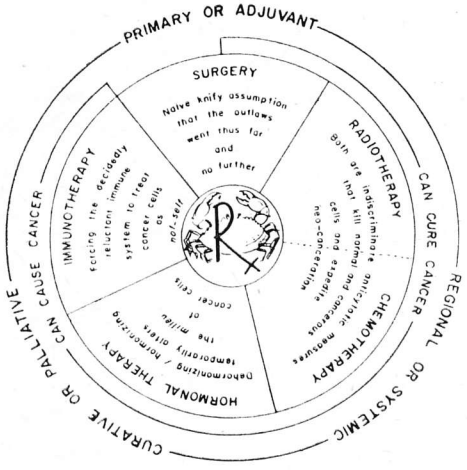

Fig. 1. The gestalt scheme, above, sums up the aims, types modes, and the limitations of the various therapies for cancer. The scheme may smack of therapeutic nihilism, but, a dispassionate, cancerrealistic appraisal of it can offer a physician, therapeutic realism that may help him and his patients. The high praise for surgical therapy, all along in this article, would appear more justified on realizing that it is the only mode of therapy that is devoid of a cancerogenic edge, being the only mode of treatment that destroys the tumor, often the whole tumor, and if exercised with restraint, nothing but the offending tumor. Veronesi[191] lends a historic perspective to surgery's undying worth: "The surgical removal of malignant tumors is the oldest form of treatment for this condition, has retained its leading role in the course of centuries, and is still the treatment of choice in a high percentage of cases."

Everyday some new way of treating cancer is announced, bewildering the therapist and his patient alike. The therapist had better bear in mind an appropriate paraphrase of Shakespeare's advice, given by Polonius to his son Laertes, in Hamlet (Act 1, Scene 3, Lines 62-65), as follows:

Those therapies thou sast, and their adoption tried,
Grapple them to thy soul with hoops of steel;
But do not swell thy bag with the burden
Of each new hatch'd, unfledged remedy.

tive." A cancer patient with esophageal/colonic obstruction, symptomatic SOL in the brain, a massive ungainly jaw from Burkitt's tumor, fungating mass in the breast, or a large osteosarcoma of the humerus cannot be bored with the philosophy of whither cancer therapy, but must be eased immediately with an appropriate palliative measure. Cancer will be with mankind forever, being part, and progenitor of it. Cancer therapists will be needed to play their vital *easing* role as long as mankind survives.

As a science, cancerology has been a do-goodistic crusade, devoid of biologic scholarship,[28, 178] that has anthropocentrically made an enemy out of a biophenomenon. Despite all its bizzare demeanors, cancer is contradictionlessly[171] comprehensible[113] as an *intrinsic, age-dependent, senescent* process. Its *intrinsicality* does not permit of cause/s, nor of its cure/control by any extrinsic agent; its *age-dependence* permits it to subserve obligatory herd mortality;[104] its *senescent* nature allows it to be present and progress without being necessarily symptomatic or lethal, making it *a la* Dobzhansky,[55] a part of an organism's continuing development. We still know not whether cancer really kills a patient, or is merely an incidental manifestation of a larger thanatogenic reality.[104] At whatever age it occurs and whatever time it is diagnosed and treated, cancer-death-rate has characteristic constancy,[57, 104, 208] rendering the five/ten-year-cure rates mere fallacies of confounded countdowns.[124]

On the basis of vast survival data of cancers treated and untreated, Waterhouse[195] was inspired to suggest that the diagnosis of cancer should not necessarily deprive a person of the benefit of insurance. That cancer is not[152] the villian-of-the-piece can be appreciated even when compared with other diseases. Zumoff *et al*[208] analyzed the mortality statistics

for series of patients with hepatic cirrhosis, metastatic breast cancer, chronic lymphatic leukemia, and myocardial infarction. "It was found that the four diseases analyzed shared an unexpected relationship of mortality rate to duration of disease: the basic mortality rate remained constant during the course of disease; prognosis was neither better nor worse for the patient late in the disease than for the patient early in the disease."[208] The authors[208] concluded that all the above diseases have a common alteration of "the undefined physiologic systems" that govern susceptibility to aging and dying, producing thereby an elevated and constant increase in this susceptibility.

Cancerrealism can be a good guide in outlining the scope and limitations of the clinician, engaged in cancer diagnosis, treatment and prognosis. The appreciation, that rank ignorance and uncertainty rule the *fore* and *aft* of the crude dividing line of our tumorous knowledge, compells the formulation of and the adherence to a therapeutic[76, 113] dictum: Treat to ease the patient ill at ease, and to this end spare no measures, including those for the relief from pain, and anxiety. Cancerrealism does not permit of treating those who are at ease, at peace with their lumps. The need and the wisdom to treat the patient *symptom/sign-far and no further* leaves out radicalism, superradicalism and cytotoxic cocktailism, knowing that a cancer patient needs, above everything, *joie de vivre* which greatly depends on healthy bowel mucosa and cellular bone marrow. Such restraint is not rare; CML, CLL, breast and rectal cancer are examples[49, 80, 83, 146, 194] in point. The Hippocratic ideal of *primum non nocere* could not find a better place than in clinical cancerology. Dunphy[57] has recently underscored the hazards of prognosing; many a cancer manages to make a mockery of carefully considered clinical prognostications. The better course is "I do not know," the best course is to emphasize that *No one knows,* no matter how benign or malignant looking, localized or widely spread, early-treated or late-treated, ill-treated or well-treated, the cancer is.

The needlessness[118] of treating asymptomatic cancer takes us a step backwards to the needlessness of diagnosing cancer, and more so precancer, thus avoiding diseasing an individual fully at ease. Diagnostic iatrality is a potent dis-easing force of modern medicine thriving on DATE drives. A Fischerism[67] very well describes the lethal potential of a diagnosis: "Do you ever ponder the advisability of not making a diagnosis and thereby avoiding a death sentence?" With the pronouncement of the diagnosis of cancer, the bird of fear—as Norman Mailer would describe—builds a nest in the patient's throat. Cancer-diagnosis inevitably induces[53] overwhelming anxiety, paralyzing fear, universal panic "akin to an animal response with witchcraft powers,"[53] not sparing even the physicians and surgeons "thoroughly acquainted with the facts of curability."[53] The antidote to this iatrality is the cancerrealistic restraint—not to *diagnose* a cancer that has, hitherto, not bothered the patient. Some cue is currently available in this direction: "The benign behavior of an occult thyroid carcinoma (which cancer, when considered as a systemic process, is not occult?) makes the risk of not diagnosing one during life of no consequence."[169]

The greatest service that a clinician can render, apart from diagnosing lumps and treating cancer, or giving poppy[5] for pain, is to teach a patient to live, zestfully and

productively, with cancer. Such enlivening approach is consistent with the little emphasized benignancy of malignancy *viz.*, that all cancers do not kill rapidly. A favorite theme of William Osler[155] was *to live in daytight compartments.* Osler did not direct his positivism to some cancer patients, for whom time is supposedly running out. He, like Kipling and Stevenson, pleaded that time is running out for everyone afflicted, as Cowley put it, with "an incurable disease" called life. And since everyone so incurably afflicted with a killer disease lives, there is no reason why the presence of another killer disease, e.g., cancer, should mar an individual's zest for living, her or his *joie de vivre.* And if the physician can teach the patient how to live with cancer, could he not as well teach how to die, with dignity, of cancer?

If life should be regarded as essentially good, Ardrey[7] avers, *then death must be revered as its foremost angel.* Death has its own reasons a thing thanatologists are urging us to accept.[57, 117] If we accept death as natural, should we not also accept the bodily processes that lead to it? "After all," Pickering[158] emphasized, "it is these diseases which kill and make way for the new life."

JBS Haldane[85] paid a tribute to his rectal cancer that killed him by the poem *Cancer's a Funny Thing,* the message being "cancer can be rather fun" provided one faces the tumor with a sufficient sense of humor. *Tout comprendre cancer, c'est tout pardonner cancer, c'est tout pardonner mort.* Let us accept cancer as a part of living, and a way of dying.

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