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THE UNITARIAN OR TROPHOBLASTIC THESIS OF CANCER

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It is veritably impossible to find, among the hundreds of valid experimental contributions to our knowledge of cancer made during the past half century, an experimentally established datum that would controvert the thesis of the basic biological uniformity characterizing all exhibitions of cancer.

THE CRITERIA OF UNIFORMITY

To the experimentalist who does not overtly accept an unitarian thesis of cancer, such a thesis is still implicit in the commonplace facts of his science. The classic experiments of Warburg on the respiratory pattern of cancers of various species and tissue origins reveal a high uniformity from tumor to tumor.[1] Correlatively, the Coris find the lactic acid and sugar content of the various exhibitions of cancer to be highly uniform.[2] Williams and his co-workers report a pronounced degree of uniformity in the concentration of eight B vitamins in a great variety of animal and human tumors, regardless of the tissue of origin or the manner of their induction.[3] Robertson makes similar observations for vitamin C.[4] The addition of various substrates to malignant tumors of various types yields highly uniform respiratory responses.[5] Shack describes an almost complete uniformity in cytochrome oxidase content in a number of mouse tumors. [6] Greenstein finds that the presence of any exhibition of cancer uniformly results in a depression of the liver catalase. [7,8] Maver and Barrett describe substantial evidence for an immunological uniformity among malignant tumors.[9] Greenstein reports an impressive degree of uniformity in enzyme concentration among malignant tissues, regardless of their means of induction, tissue of origin or species of origin. [10] Others describe a uniformly low content of such aerobic catealytic systems as cytochrome, succinic, and d-amino acid oxidases, cytochrome-c, catalase and flavin.[11,12,13,14,15,16,17]

Further phenomena of uniformity are observed in the elevated water and cholesterol content of malignant tumors as well as other primitive tissues.[18,19] The induction by a single steroid carcinogen, such as methylcholanthrene, of malignant exhibitions as diverse as leukemia and malignant melanoma, attests to a basically uniform etiology. The uniformity of various exhibitions of cancer in respiratory properties, lactic acid production, vitamin content, enzyme content, action on a given substrate, effect on liver catalase, cytochrome oxidase content immunological properties, and many other characteristics is correlative to an uniformity of

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malignant tumors in the ability to metastasize, in their amenability to heterotransplantability,[21, 22] and in their autonomy, invasiveness and erosiveness. Indeed, there is no known basic property unique to any single exhibition of cancer---the only variation being a morphological one partially conditioned by admixed benign or somatic components.

The degree in the uniformity of the factors described increases with the increasing malignancy with which the tumor is exhibited. Thus with an increasing degree of malignancy, all malignant exhibitions converge toward a common tissue type. For this reason the cells of the most malignant of all exhibitions of cancer should epitomize the properties of the malignant component in all other exhibitions of cancer. That this is the case, we shall observe in the pages that follow.

We have glanced briefly at data that are commonplace to cancer research. The logical consequences of these data have, however, seldom been examined. Since the phenomenon of cancer is truly an unitarian one, then, of logical necessity, the variations in the biological malignancy of different exhibitions of cancer must be a function of the *concentration of a cell of an intrinsically uniform malignancy.*

POSITION OF THE CANCER CELL IN THE LIFE-CYCLE

In accounting for the nature and origin of the single cell type comprising the constant malignant component in the varying morphological exhibitions of cancer, we find one of two alternatives open. The definitively malignant cell either has its normal counterpart in the life-cycle or the malignant cell is without a normal cellular counterpart and, therefore, arises as a spontaneous generation. Since spontaneous generation is an untenable postulate, the only alternative is that the malignant cell has its counterpart in the life-cycle. The question then arises whether this counterpart is a relatively developed cell or the most primitive cell in the life-cycle. Since the primitivity of the cancer cell is a commonplace, in looking for its cellular counterpart in the life-cycle we turn to the most primitive cell in this cycle. This is the trophoblast cell. Then as a logical corollary of the unitarian thesis, we should find the trophoblast as the constant malignant component in all exhibitions of cancer: the malignancy of the cancer varying directly with its concentration of trophoblast cells and inversely with its concentration of somatic cells.

If the unitarian thesis is valid, then the most malignant exhibition of cancer possible should be comprised almost completely of *frank* trophoblast cells; and, in being so comprised, should epitomize the cellular and other phenomena shared by exhibitions of a lesser malignancy. The most highly malignant exhibitions of cancer known are the chorionepitheliomas comprised of frank *trophoblast cells,* cytologically, endocrinologically and otherwise indistinguishable from normal pregnancy trophoblast cells. If cancer is an unitarian phenomenon whose malignancy is a function of the concentration of trophoblast cells within a given tissue, then the greater the concentration of such cells within a tissue the higher the malignancy

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of the tissue and the more profound its cytological deviation from the cytology normal to the tissue. If the unitarian thesis is valid, then the single exception to this generalization would comprise the most malignant of all exhibitions of cancer: that involving the pathologic exhibition of the normally or "physiologically" malignant pregnancy trophoblast. It is, therefore, most significant that when pregnancy trophoblast is malignantly exhibited as primary uterine chorionepithelioma there is no *ascertainable cytological, endocrinological or other intrinsic change whatever from the normal trophoblast cell.* As Boyd has phrased it, "microscopically the chorionepithelioma is an exaggeration of the condition normally found in pregnancy."[23] All other tumors represent an attenuation of the condition of their normal tissue of origin.

PROPERTIES OF THE TROPHOBLAST CELL

But if cancer is, as an unitarian phenomenon, trophoblastic then we should expect to find occasionally in the male---where trophoblast never normally exists---at least some cases in which the failure in somatic resistance to the definitive malignant cell (trophoblast cell) is so complete that the trophoblast is frankly exhibited as such in the fiercely malignant testicular or primary extra-genital chorionepitheliomas.[24, 25, 26, 27, 28] The chorionepitheliomas are unquestionably the most malignant tumors in either sex, and the degree of their malignancy is routinely determined by measuring the gonadotrophin their trophoblast cells excrete.[29, 30, 31]

If the trophoblast cell, presented outside the normal canalization or checks of pregnancy, is truly the cancer cell, then it must be impossible for the trophoblast cell or its hormone---"chorionic" gonadotrophin---ever to be found in the male or, aside from the canalization of normal pregnancy, in the female except in a malignant fashion. *Neither the trophoblast cell nor its hormone has ever been so found except as cancer.* And whenever the trophoblast cell or its hormone has been found in the male or the non-pregnant female, the associated malignancy is observed to vary directly with the urinary excretion of trophoblast cell-produced gonadotrophin.

Even a superficial examination of the trophoblast cell indicates that it possesses such properties of the cancer cell as invasiveness, erosiveness, autonomy and ability to metastasize throughout the organs of the host.[32, 33] Indeed, though normally canalized to physiological ends, the pregnancy trophoblast in carrying the conceptus from anatomically outside of the maternal host to implantation within the uterine wall must behave in a profoundly malignant fashion. No malignant cell invades any tissue any more rapidly and completely than the pregnancy trophoblast does the human uterus in the first few weeks of gestation.

If the trophoblast cell, then, is *instrinsically* malignant, this malignancy should become especially apparent when the trophoblast is removed from the normal extrinsic checks and controls surrounding it in its normal canalization of pregnancy. Maximov is among those who have observed normal pregnancy trophoblast in tissue culture *pari passu* non-tropho-

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blast.[34] He describes as follows a tissue culture preparation of a normal rabbit embryo *plus* the contiguous trophoblast:

> "From the very first moment of their formation *in vitro,* the trophoblastic elements, whose function under normal conditions is to destroy, resorb, and penetrate into the uterine mucosa, attack the growing embryonic tissues. They glide between cells through the intercellular spaces, along blood vessels, gnaw large holes in epithelial sheets....Wherever they appear they dissolve, destroy and resorb everything surrounding them. The picture sometimes bears a striking resemblance to *chorionepithelioma malignum.* As *in vitro* there is no maternal tissue, the destructive tendencies of the trophoblast are directed toward the net and only available---the embryonic tissue itself. This is rapidly destroyed and totally used up for the nutrition and growth of the trophoblast."

Maximov's description of the nutritive utilization by the trophoblast of somatic or embryonic tissue *in vitro* bears a striking parallelism to the following observation of Greenstein[35] on the nutritive behavior of the cancer cell:

> "It is, indeed, astonishing that a tumor can thus attach itself to an organism already running downhill in negative nitrogen balance and subsequently grow at the host's further expense."

Parasitization is eloquently clear in the description given by Maximov and it is implicit in Greenstein's observation. Normal pregnancy trophoblast represents, of course, a parasitization of cells of one genetic constitution by those of another. If cancer is an unitarian and thereby a trophoblastic phenomenon, its parasitic behavior is very easy to understand.

Were pregnancy trophoblast *in vivo* or *in situ* to lack the humorally mediated checking influences that are lacking *in vitro* then such tissue would expectedly behave as it does *in vitro* and be exhibited in the fiercely malignant fashion of primary uterine chorionepithelioma.

Rather than pause here to review in further detail the points of identity between the cancer cell and the trophoblast cell, of which the senior author in a review of over 17,000 papers has been able to catalogue 43, let it suffice to say that we have been unable to find a single point of dissimilarity between the cancer cell and the trophoblast cell. The points of identity, of course, are those shared exclusively by the cancer cell and the trophoblast cell and not shared by any somatic cell.

THE CELL OF ORIGIN AND THE MEANS OF ITS DIFFERENTIATION

If cancer is a truly unitarian phenomenon, then its cellular origin as well as its cellular nature are exemplified in the origin and nature of the most malignant exhibition of cancer---primary uterine chorionepithelioma.

Pregnancy trophoblast arises through the *differentiation* by meiosis of a diploid totipotent cell in response to *organizer stimuli* (afforded through the sex steroids). The meiosis of the diploid

totipotent cell results in a haploid gametogenous cell whose only alternative to death is division (sexually or parthenogenetically induced) with the consequent production of trophoblast. The only cell from which the most primitive cell in the life-cycle, the trophoblast cell, can arise is the most undifferentiated or

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most potent cell in the life cycle: the diploid totipotent cell. It is this cell alone that is competent for meiosis. In fact, aside from the explanation of spontaneous generation, only two alternatives exist for the origin of the malignant cell. Like all other growth phenomena, it may arise as the result of the differentiation of an undifferentiated cell in response to organizer stimuli; alternatively, it may be ascribed to the ontogenetic "reversion" of normal cells to a primitive state. Even though the very notion of such reversion is a thermodynamic fantasy inadmissible by modern biology, if a normal cell *could* revert, the most primitive cell in the life cycle toward which such reversion could occur is still the trophoblast cell. Hence, aside from the errors of spontaneous generation or cellular reversion, *only the phenomena of cellular differentiation are tenable in accounting for the origin of the cancer cell---though the stimulus to such differentiation may, of course, be diversely mediated*.

It is thus a simple embryological fact that the malignant component of the most malignant of all exhibitions of cancer---primary uterine chorionepithelioma---represents the unchecked growth of normal trophoblast that has arisen through the differentiation of a diploid totipotent cell, by reduction division, and the division of the consequent haploid gametogenous cell to produce trophoblast. We have seen the proof of this in the fiercely malignant behavior of rabbit trophoblast removed from the checking influences of the maternal host and placed in tissue culture. This trophoblast, of course, came into being through processes normal to the production of all trophoblast in normal gestation. This is true also of the trophoblast of primary uterine chorionepithelioma.

It is necessary that we emphasize here the fact that our description of the origin of *any* trophoblast cells is merely a recapitulation of commonplace, universally accepted embryological data. We must not permit terminology to obscure this fact. Let us add that it has been experimentally established that in mammals the haploid gametogenous cell in either the male or the female may be nonsexually activated into division with the consequent and inevitable production of trophoblast.

Because the trophoblast cell of primary testicular chorionepithelioma is indistinguishable from that of the normal pregnancy trophoblast cell[36, 37, 38] or a trophoblast cell of primary uterine chorionepithelioma,[39, 40] the general consensus in pathology that chorionepitheliomas arise from the division of a gametogenous cell (non-sexually activated), derived through the normal meiosis of a diploid totipotent cell, is biologically and logically sound. It is likewise generally recognized that *primary extra-genital* chorionepitheliomas occurring in both sexes represent trophoblast that shares a common cellular origin with all other trophoblast; an origin from an haploid gametogenous cell (through fertilization or non-sexually) that has arisen through the meiosis of a diploid totipotent cell. This principle is congruent with the axiom that cells which are alike arise from pre-existing cells that are alike.

INDEX OF MALIGNANCY

If cancer is an unitarian phenomenon in which all morphological exhibitions share, in varying degrees, the known malignant component of the chorionepitheliomas, then it follows (1) that the malignancy of a growth will vary directly with its concentration of trophoblast cells and inversely with its concentration of body or somatic cells; and (2) the trophoblast cells comprising a malignant lesion must possess the capacity for being morphologically masked or obscured by the tissue in which they primarily occur or to which they metastasize. Testicular chorionepitheliomas afford an interesting vantage point for the examination of these possibilities. In screening over 900 testicular cancers in the Army Institute of Pathology, Friedman and Moore (1946) reported, in part, as follows:[41]

> "*Nearly twice as many metastases which exhibited chorionepitheliomatous structures arose from primary tumors containing no chorionepithelioma as from pure chorionepitheliomas or neoplasms containing focal chorionepithelioma.* While only 0.4 per cent of the primary testicular tumors were pure chorionepitheliomas and 6.4 per cent showed focal chorionepitheliomatous tissue, *27 per cent of all metastases which terminated fatally contained chorionepitheliomatous elements."* (emphasis ours)

Thus, not only may the trophoblast, when frankly exhibited as such in the primary site, metastasize to be morphologically masked in the secondary site, but the primary trophoblast itself may be morphologically masked by the soma and be frankly exhibited only when metastases occur into tissues of relatively lower reactivity in which the trophoblast is not morphologically masked but is frankly exhibited as such. The masking of the trophoblast by the reactivity of the somatic cells is a measure of the resistance of the host: the degree to which such somatic resistance against the ectopic trophoblast fails determines the malignancy with which the trophoblast is exhibited. Thus, the greater the incidence of a chorionepitheliomatous exhibition (trophoblast) in the metastases, the greater the degree of malignancy.

COMPETENT CELL AND ORGANIZER

The origin of every new cell is the result of the apposition of a competent cell and an organizer stimulus. All new cells arise as the result of cellular differentiation, which is a process by which a new cell type of a higher degree of individualization and a lower degree of developmental competence is produced. There are no exceptions to this generalization---not even the cancer cell. While a differentiated cell may become plastically deformed or necrobiotic, it can never form a new cell type through any means except the forward-moving course of cellular differentiation. Cellular reversion is a thermodynamic impossibility; it has never occurred and can never occur. Water does not run uphill---not even in cancer. The cancerous cell is neither a deformed one nor a necrobiotic one. Its lethality resides in the very fact that intrinsically it is a normal cell---though its spatial and temporal relationship to the organism-as-a-whole is an abnormal one. The trophoblastic or unitarian thesis simply recognizes that: (1) the can-

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cer cell is contained within the life-cycle and (2) that it is the most primitive cell in that life-cycle.

Though the diploid totipotent cells which give origin to trophoblast are known to be very abundant in the gonads, the question next arises as to their occurrence extra-genitally. Most modern pathologists [42, 43, 44, 45, 46] recognize the existence of so-called ectopic germ cells (diploid totipotent cells) and Bounoure [47] has, in an extensive monograph, recently reviewed the conclusive observational and experimental evidence for the dispersion of such cells throughout the soma. Of course, embryologically, these cells are nothing more than totally undifferentiated cells that have not, as Arey phrased it,[48] participated in body building but have reserved their total potency or competency since the initial cleavage of the zygote. Cells of various degrees of undifferentiation exist within the soma as a reservoir from which tissue repair and regeneration occur. *But only the totally undifferentiated cells of the soma are competent for meiosis;* these cells are the diploid totipotent cells. Of course, all cells in the soma are diploid, but only those that are *totally undifferentiated* are totally potent or *totipotent*---hence competent for meiosis. That such cells exist as well as function in the soma is further proved by the occasional occurrence of primary extra-genital chorionepithelioma in the male in such regions of low tissue reactivity as the pineal gland[49,50] and the anterior mediastinum.[51, 52, 53, 54] The frankly exhibited trophoblast cells are correctly attributed to the only progenitor of trophoblast: a diploid totipotent cell that has undergone reduction division or meiosis to form a haploid gametogenous cell that has trophoblast formation as the only alternative to death.

Carcinogenesis is thus seen to be a phenomenon involving a spatially anomalous *differentiation* in response to organizer stimuli. (Primary uterine chorionepithelioma---as well as normal pregnancy trophoblast---while involving precisely the same differentiation in its origin does not, of course, involve it anomalously.) The differentiation involves the phenomenon of meiosis with the consequent production of trophoblast, which, presented ectopically, is inevitably exhibited as cancer---the malignancy of which depends upon the extent to which such ectopic trophoblast is resisted. Thus in the unitarian thesis we see the malignant component in *all* exhibitions of cancer deriving from precisely the same cell type from which the chorionepitheliomas arise. We see all producing the same cell type---trophoblast. We see this cell doing ectopically precisely what it does in its normal canalization: eroding, infiltrating, and metastasizing.

"One of the most important problems in cancer research," Greenstein[55] points out, "is concerned with the question of why primary tumors metastasize." If cancer is trophoblastic, the problem of metastases is resolved: the normal pregnancy trophoblast is the *only* cell in the life-cycle that regularly metastasizes, doing so throughout the maternal host in the early months of pregnancy.[56, 57]

The stimuli to malignant differentiation are exemplified in the sex steroids which induce the meiosis of diploid totipotent cells in their normal

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canalization. In view of the relatively specific organizer action of steroids, it is significant that practically all of the carcinogens are either steroids or, like diethylstilbestrol, possess the physiological properties of steroids. Though carcinogenesis may be mediated by highly diverse means, the ultimate common pathway involves the apposition of competent cell and organizer stimuli. The competent cell is always a totally undifferentiated cell (diploid totipotent cell) and the organizer stimulus ultimately involved appears to be a steroidal compound.

Agents producing a chronic inflammation can also prove indirectly carcinogenic, since chronic inflammatory sites have a marked capacity for localizing or concentrating steroidal sex hormones as well as other substances.[58] Certain chemicals may also prove indirectly carcinogenic through impairing the somatic detoxification mechanism for steroids.[59, 60] That under special and very limited circumstances viruses may also contribute to the common pathway by which malignant differentiation is accomplished in birds* and rodents is recognized. Virchow, however, pointed out 90 years ago that no stimulus can elicit from a tissue potencies not inherent within the tissue. The general consensus is that the role of the cancer virus is evocatory, eliciting from the organism an inherent potency; rather than creative, conferring *de novo* the cancer cell upon the organism.

ESTROGENS

Since the meiosis of normally canalized diploid totipotent cells is accomplished in both sexes through the organizer action of steroidal sex hormones, a review of the formidable literature on the carcinogenic properties of estrogen correlated with the unitarian thesis would be most pertinent to a complete elucidation of the thesis. Space will not permit this, and it must suffice to say that the normal estrogens bear as crucially a basic relationship to the origin of malignant cells, under ordinary circumstances, as chorionepithelioma bears to their cellular identity.

VIRUSES AND SOMATIC MUTATION

Since the virus theory is subsumed under the unitarian thesis---as a specialized contributory means** of eliciting the malignant differentiation---the chief remaining theory is the somatic mutation hypothesis. This hypothesis explains nothing and is, in fact little more than a circular definition: cancer is due to a change; a change is a mutation. This change occurs in the body or soma; therefore, cancer is due to a somatic mutation. On the other hand, the trophoblastic or unitarian thesis does embrace a very definite genetic "mutation." This "mutation" is expressed as meiosis

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* The phylogenic homologue of the trophoblast (extra-embryonic blastoderm) in birds is known to exhibit, under certain conditions, malignant properties: e.g., anidian formation[61].

**Joseph Needham[62] has cogently remarked: "It is an instructive exercise to read through the writings on the virus theory of cancer, substituting the words 'active agent' or 'active extract' for virus wherever it occurs. The results are illuminating."

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whereby, with the division of the consequent gametogenous cell, the ectopic trophoblast (cancer) cell presented to the soma is, through the necessity of meiosis, *of a genetic composition unique from the soma;* and, therefore, in the most literal genetic sense a *neo*plasm.

Even were one uncritically to accept the somatic mutation hypothesis[63] or the virus theory of cancer,[64] it would be necessary either to seek their resolution in the unitarian or trophoblastic thesis or to turn to a non-unitarian explanation. In which case it would be necessary, then, to postulate an indefinitely large variety of unknown cancer viruses or a similar variety of unknown somatic mutations to account for the origin of the cancer cell. But not even these would suffice since neither hypothesis could account for the fiercely malignant behavior of

normal trophoblast *in vitro*---nor for the fact that this cell has never been found in a non-pregnant organism except as cancer.

MEIOSIS

We have observed that the extra-genital dispersion of diploid totipotent cells is a commonplace fact. We have specifically ascribed the origin of all morphological exhibitions of cancer to the meiosis of one or more such diploid totipotent cells with the consequent production of a gametogenous cell whose only alternative to death is division with the resulting production of trophoblast.

In the normal reproductive canalization the *only* way in which trophoblast can arise is through the meiosis of a diploid totipotent cell and the consequent division (non-sexually or by fertilization) of the resulting gametogenous cell to produce trophoblast. Therefore, one question alone remains here: can the same diploid totipotent cell in an extragenital site undergo meiosis to eventuate in trophoblast production?

As early as 1879 Arnold observed gametoid (meiotic) mitosis in malignant tissue. About twenty years later Farmer, Moore and Walker reported the occurrence of meiosis (heterotypic mitosis) at the border of malignant tumors.[65] In 1929 Evans and Swezy described in inflamed somatic tissue changes "strikingly similar to those of meiotic mitosis."[66] In 1936 Hearne observed meiotic changes in tissues cultured with methylcholanthrene[67] and Molendorff made similar observations in 1939 with estrone.[68]

Diploid totipotent cells are dispersed throughout the soma. Meiosis occurs within the soma. Frank trophoblast cells occur within the soma---though inevitably in a malignant exhibition. They can arise only through the division of a gametogenous cell produced by the meiosis of a diploid totipotent cell. Frank trophoblast cells have never been found in the soma except as the most malignant exhibition of cancer---with the exception of pregnancy.

Indeed, the difficulty is no longer one of accounting for the origin of the definitive malignant cell through the phenomena discussed, but rather one of seeking *any* explanation of how the meiosis of ectopic diploid toti-

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potent cells, exposed to adequate organizer stimuli, could invariably be averted so as to preclude their normal differentiation to trophoblast, whose ectopic exhibition has never been known except in a malignant fashion. Frankly exhibited, such trophoblast comprises the most malignant exhibition of cancer possible, though when morphologically masked by the somatic response of the hostal cells the malignancy of such trophoblast is moderated.

UNITARIAN VS. NON-UNITARIAN THESIS

The body of experimentally established facts comprising modern oncology is formidable. It is not possible for any explicitly defined thesis to stand unless it is congruent with, or at least not contradictory to, such facts. Only the unitarian thesis finds such congruence. To the unitarian thesis in general and in particular to the preceding data outlined for it, it is especially instructive to apply Herbert Spencer's criterion of truth---the inconceivability of the opposite. The thesis opposite or alternative to the unitarian one is that each morphological exhibition of

cancer represents a biologically distinctive phenomenon, each with a malignant component different from all others. This would mean literally hundreds of basically different types of cancer cells---each type being normally unrepresented in the life-cycle; therefore, each being spontaneously created. Not only would it become necessary to postulate the existence of hundreds of distinct species of cancer cells, but also a postulate of an almost infinite number of subspecies of each type of cancer cell would be required to account for the varying degrees of malignancy exhibited by a given malignant lesion in the course of its evolution. Since a single chemical carcinogen can evoke practically any malignant exhibition, then it would become necessary---according to any non-unitarian concept---to conclude that causes which are alike produce effects that are unlike. On the same basis, the occurrence of the frankly exhibited trophoblast cells of extra-genital chorionepithelioma in the male (identical with those of the primary uterine form) would necessitate the unbiological conclusion that cells which are alike arise from cells that are unlike. The logical negation of *any* non-unitarian hypothesis is further apparent in the experimentally defined uniformity of cancer cells in every one of over twenty factors studied to date. (p.1)

In contrast to the alternative non-unitarian hypothesis, the unitarian thesis holds that the malignant component in all exhibitions of cancer is the same; that this component is not spontaneously created but represents the most primitive cell in the life-cycle; that this cell arises not through "reversion" but through differentiation; that the varying morphological exhibitions are simply conditioned by the nature and resistance of the tissue in which the ectopic trophoblast finds itself; and that the malignancy of the exhibition is, roughly, expressed in the degree of deformation of the somatic tissue by the ectopic trophoblast---and that this is reflected in the morphology from which histological diagnoses derive.

The unitarian thesis and the trophoblastic thesis are of logical necessity synonymous: the most malignant exhibition of cancer (chorionepithelioma) comprises cells intrinsically identical with pregnancy trophoblast cells.* Then, if cancer is an unitarian phenomenon, the malignant component of the varying morphological types must be trophoblastic; for, two quantities equal to a third are equal to each other.

Finally, were we to set aside all else evidential of the unitarian or trophoblastic nature of cancer, and scrutinize but a single datum, we should find that neither experimental fact nor scientific reasoning can offer any alternative to the trophoblastic nature of cancer in explanation. This one datum is the fact that many authors over the past half-century have described frank trophoblast (chorionepithelioma) metastasizing from a primary site to appear at the secondary site in an adenocarcinomatous or other exhibition.[69, 70, 71] And the converse has frequently been seen.[72] Moreover, frankly exhibited trophoblast (chorionepithelioma) often has been described as merging by imperceptible degrees into an adenocarcinomatous or sarcomatous exhibition. In their comprehensive monograph on chorionepithelioma, Park and Lees (1950) write:

> "There is no doubt that in many instances of testicular chorionepithelioma, certainly in several of our sections, characteristic trophoblast merges imperceptibly with areas of undifferentiated tissue whose hostal origin would never be questioned."[73]

TROPHOBLAST AND THE PANCREAS

John Beard, a lecturer in embryology at the University of Edinburgh, first published on the trophoblastic thesis of cancer in June, 1902.[74] By February, 1905 he reported, on embryological grounds, the antithesis of the pancreatic enzymes to the trophoblast cell;[75] and, a few years later he specifically pointed out that the cancer or trophoblast cell protected itself against pancreatic enzymes through the production of specific antitryptic substances.[76] The occurrence of tryptic inhibitors in cancer sera has, during the past forty years, been described by at least fifteen different workers,[77-92] though not within the context of the trophoblastic thesis.

In 1947 Krebs, Krebs and Gurchot first pointed out the specific antithesis of chymotrypsin to the malignant (or trophoblastic) cell.[93] In 1948 Clark, Cliffton and Newton further confirmed the specific and antitryptic antithesis of the cancer cell and offered evidence for the diagnostic and prognostic utilization of the phenomenon. In 1949 West and Hilliard, in the study of sera of over 3,000 cancer patients, reported the specific antithesis of the malignant cell to chymotrypsin by showing that 15 grams of crystalline chymotrypsin would be necessary--in a single dose--to neutralize all of the *average excess of* chymotrypsin inhibitor in the serum of the advanced cancer patient. The latter workers proposed the utilization of the specific antichymotryptic titer of the serum for prognostic but not necessarily diagnostic purpose.[88, 91]

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*The malignant exhibition of the trophoblast of the placenta is the expression of a lack of *extrinsic* growth restraints against the trophoblast; this fact was demonstrated in the tissue culture of normal rabbit trophoblast.

It is noteworthy that West and Hilliard, as well as others, have described a quantitative relationship between the concentration of cancer cells and the titer of specific chymotrypsin inhibitor. This titer was observed to fall after the surgical removal of the malignant tumor and to rise linearly with its recurrence. Thus the data on the antitryptic properties of cancer sera are not only proof of the antithesis between the cancer cell and the pancreatic enzymes, but are further evidential of the unitarian--and thereby trophoblastic--nature of cancer.

Since the malignant cell is not spontaneously created but has its normal counterpart in the most primitive cell of the life-cycle, each organism in the span of its own gestation destroys the cellular counterpart of cancer. This destruction is accomplished through the pancreatic enzymes, notably chymotrypsin and amylase.

When the mammalian organism totally fails in this, the pregnancy trophoblast overgrows as chorionepithelioma.[94] A partial failure is reflected as a toxemic pregnancy,[95] and/or a hydatidiform mole accompanied by an abnormally high excretion of chorionic (trophoblastic) gonadotrophin. For this reason hydatidiform moles are most frequently associated with toxemic pregnancies, while the risk of sequent chorionepithelioma is 2,000 to 4,000 times greater after hydatidiform mole than after normal pregnancy.[96] The reason for "the much higher curability rate of choriocarcinoma preceded by hydatidiform mole," as reported by Park and Lees,[96] is that the precedent hydatidiform mole represented at least a partially successful antithesis on the part of the maternal host to the trophoblast.*

The reason why primary uterine chorionepithelioma can within a few weeks arise and kill the patient is that this most malignant tumor simply represents a *hyperplasia* of normal trophoblast cells freed from their extrinsic restraint---just as the *in vitro* culture of the rabbit trophoblast freed from the maternal environment yields a fiercely malignant exhibition.

It is well established* (1) that pregnant diabetics exhibit a greatly increased incidence of the pregnancy toxemias; (2) that the severity of such toxemias varies directly with the overgrowth of cellular trophoblast as reflected in the abnormally elevated excretion of chorionic gonadotrophin; (3) that the phenomenon involves a non-insulin deficiency of the pancreas gland; (4) that the predisposition to pregnancy toxemias is noted as early as five years[97,99] prior to the clinical onset of diabetes; (5) that the administration of steroidal sex hormones in such pregnancy toxemias frequently ameliorates the condition; and (6) that this amelioration is reflected in a proportionate depression in the urinary excretion of chorionic gonadotrophin.

Since such steroidal sex hormones as estrogen depress the proliferation of the cellular trophoblast both in normal and toxemic pregnancies, as reflected in a depression in the urinary excretion of chorionic (cytotropho-

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* The complete bibliography for these data is given by Krebs & Bartlett's (1949) monograph on "The Pregnancy Toxemias, the Role of the Trophoblast and the Pancreas."[122[sic]]

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blastic) gonadotrophin, it is significant that Kullander (1948) found in primary uterine chorionepithelioma that the administration of stilbestrol resulted in a clinical improvement that paralleled the decline in the urinary excretion of chorionic gonadotrophin.[100] Though Kullander did not cure his patients, so long as stilbestrol controlled the excretion of chorionic gonadotrophin, they improved.

It is a commonplace observation that the administration of estrogen or testosterone during pregnancy will often depress the production of chorionic gonadotrophin sufficiently to cause the Ascheim-Zondek test or its Friedman modification to become negative.

In listing the criteria of malignancy, Oberling and Woglom write: "...Above all is the impudent independence called autonomy."[101] Certainly, no other property is more characteristic of the cancer cell than autonomy; *yet in the most malignant exhibition of cancer possible we find the trophoblast cells showing the same susceptibility to the checking influence of sex steroids as is found for the normal pregnancy trophoblast.*

If cancer is trophoblastic, and as such an unitarian phenomenon, it would seem that the steroidal sex hormones should suppress the growth not only of pregnancy trophoblast and chorionepithelioma but all other exhibitions of cancer as well. That this would be the case were sufficient localization of the steroidal sex hormones possible at all malignant sites is shown in the fact that these hormones do act to suppress the growth of mammary cancer, prostatic cancer, and their metastases involving the skeletal system. Morphologically, the difference between a primary mammary cancer and a prostatic one is much less pronounced than the difference between either and a primary chorionepithelioma.

The placenta, the prostate, and the mammary gland are notably capable of the selective localization of steroids; hence, trophoblast in any of these areas will show a like response to the injection of steroidal sex hormones. In the case of prostatic and mammary growths the use of the physiologically antagonistic steroid is rational, since such causes the somatic elements in the growth to atrophy. That the palliative effect is dependent upon the ability of the *somatic* elements in the tumor to localize the steroids is shown in the fact that the skeletal metastases from the prostate as well as from the mammary gland are responsive specifically to estrogen

and testosterone, respectively. Yet this amenability is lost as, with increasing malignancy, the original somatic elements in the skeletal metastases are lost. That such a loss is not directly due to the increasing malignancy but indirectly to the loss of the specific somatic cells responsible for the localization of the steroids is indicated by the fact that in the placenta, while the localizing somatic elements remain, the growth of the vastly more malignant chorionepitheliomatous exhibition is checked.

Thus we find the unitarian principle of cancer implicit in the sex hormone therapy of cancer, as in *all* other useful forms of cancer therapy. Moreover, in the unitarian principle the use of steroidal sex hormones in cancer finds its first rationale.

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Since a non-insulin pancreatic deficiency has been identified with the overgrowth of pregnancy trophoblast, which overgrowth has been shown amenable to steroidal sex hormones, two questions arise: (1) what is the nature of the deficient pancreatic factor, and (2) is the deficiency of this factor associated with the overgrowth of *all* trophoblast? About half a century ago John Beard[102-119] found a concomitance between the commencing function of the fetal pancreas, as indicated by the appearance of zymogen granules in the gland, and the precipitate degeneration of the trophoblast or its phylogenetic homologue. Broad comparative studies confirmed his thesis that, in the span of normal gestation, the pancreatic enzymes are responsible for checking the growth and ultimately destroying the gestational trophoblast or its homologue. In fact, Beard's studies were so carefully performed that he was able to state half a century ago that in the 56th day in the span of human gestation the cellular trophoblast undergoes a sudden degeneration. Some 30 years after this work, the trophoblast cell-produced chorionic gonadotrophin was discovered, and only recently has the quantitative technic for the estimation of chorionic gonadotrophin been sufficiently perfected to show that a composite[102] excretion curve for chorionic gonadotrophin made through the span of human gestation coincides[120] precisely with the curve predicted half a century ago by John Beard.

If the urinary excretion of chorionic gonadotrophin persists at the original level after the 56th to 70th day in the span of human gestation, the process is inevitably exhibited as chorionepithelioma. In fact, if the abnormal elevation of chorionic gonadotrophin found in pancreatic dysfunction in pregnancy exceeds a certain level, again the process is exhibited as chorionepithelioma.

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In view of the antithesis of the pancreatic proteases to the trophoblast cell, it is clear why both pregnancy and cancer are associated with high titers of trypsin and chymotrypsin inhibitors: antithesis is a two-way street, so to speak.

If the pancreatic enzymes are antithetic to the cancer cell, if they resist the cancer cell as the cancer cell is known to resist them (through the specific antitryptic inhibitors) why does cancer of the pancreas gland occur? Why is it that cancer is not only primary in this gland but

that this gland itself may be subject to secondary growths through metastases or direct invasion?

The pancreatic proteases exist in the pancreas in the form of their *inactive* zymogens. These are not converted into the corresponding active enzymes until they are acted upon by the kinases of the blood or, especially, by those of the small intestine. In view of this, one may ask why the small intestine, then, is not practically immune to cancer. Woglom answers this question well in his commentary in an abstract of a paper by Raab:[120,122,123]

> "One of the most striking features about the pathology of malignant disease is the almost complete absence of carcinoma in the duodenum and its increasing frequency throughout the gastro-intestinal tract in direct proportion to the distance from this exempt segment."

It is noteworthy that the small intestine is not only practically immune to primary tumors but also to metastases. A fulminating malignant growth may exist in the pyloric end of the stomach a few millimeters from the immune small intestine, but, as William Boyd points out, "The duodenum is never invaded, the tumor stopping short at the pylorus. Spread to neighboring organs usually involves the liver or the pancreas."[124] The incidence of malignancy is, of course, high immediately distal to the ileocecal valve.

The pancreatic enzymes not only normally occur in the active state in the blood stream, which possesses an optimum *p*H for their action but the clinical determination of serum amylase and trypsin are standard procedures, especially in pancreatic diseases.

THE PANCREAS AND CARCINOGENESIS

The fact that pregnancy occurs in the presence of a normal concentration of pancreatic enzymes indicates that trophoblast can exist for a while under such conditions. It must be remembered, however, that such trophoblast is: (1) held in check until the 56th day of gestation and almost completely destroyed shortly thereafter (with the commencing function of the fetal pancreas) and (2) that implantation occurs *after* the trophoblast has had about a four-day period of growth anatomically exterior to the host.

The trophoblast carries with it its own anti-tryptic enzymes against the pancreatic proteases. As we have seen, *carcinogenesis involves ectopically precisely the same basic mechanisms involved in the production of canalized trophoblast.* The prolonged exposure of a tissue to carcinogens results in a prolonged depression in its respiratory mechanisms.[125] This may result in the appearance and persistence of ectopic trophoblast in the exposed tissue. The trophoblast or cancer cell is autonomous of the hostal respiratory system and is obligatively anaerobic, undergoing [an]aerobic glycolysis even in the presence of a free oxygen supply.[126] The trophoblastic thesis explains the long-known identity of trophoblast cell metabolism with that of the cancer cell: [127, 128, 129] an obligative anaerobic system is obviously a necessity in a primitive parasitic cell like the trophoblast (or cancer) cell.

When cancer is elicited experimentally from a normal laboratory animal, the lesion usually does not metastasize, but attains a large size and is almost completely somatic. Herein reside the scientific limitations of artificially induced or transplanted animal tumors in the scientific study of chemotherapeutic agents. Such tumors are practically benign in the biological sense.

Because the pregnancy trophoblast regularly and normally metastasizes in the early phase of gestation, we must expect metastases ultimately in any "full blown" cancer.

While a low-grade malignant growth (primarily somatic tumefaction) can be induced ultimately by sufficient carcinogenic stimuli in the presence of normal pancreatic function, a highly malignant exhibition is invariably accompanied by at least a relative pancreatic insufficiency implicit in the

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correspondingly high serum titer of antitryptic and antichymotryptic enzymes.

That the induction of the ectopic trophoblast is usually accomplished against great difficulty---regardless of pancreatic adequacy---is indicated in the fact that non-chorionepitheliomatous exhibitions in man usually have a latent period of years, while a chorionepithelioma in pregnancy may arise from the preexisting trophoblast and destroy the host within a few weeks.

The extent to which the soma resists malignant involution is reflected in the fact that only two cellular differentiations---meiosis of the diploid totipotent cell and subsequent division of the resultant gametogenous cell---divide the malignant cell from the benign one. This explains the all-or-none suddenness classic to the malignant change---and the absence of true transitional cells.

CANCER A COMPOSITE TISSUE

The malignant lesion is a composite tissue comprising (1) trophoblast plus (2) somatic elements. The malignancy of a lesion varies directly with its concentration of trophoblast and inversely with its concentration of somatic elements. The normal placenta, too, represents a composite tissue; for, here the trophoblast cell finds its normal canalization in the life-cycle. Just as the malignancy of a placenta, in a chorionepitheliomatous exhibition, varies directly with the concentration of trophoblast cells, so in the ectopic presentation of trophoblast that comprises cancer the malignancy of the lesion varies with its concentration of trophoblast. The only fundamental difference is that in the latter the trophoblast cells are morphologically masked by the resisting soma---except in the most malignant of extra-genital tumors: chorionepithelioma.

A tissue can be malignant only by being a composite one. Malignancy is an antithetic relationship between cells and finds being by virtue of a thetic benignancy. In its simplest terms, then, a malignant tumor comprises somatic tumefaction plus a malignant component. It is for this reason that the greatest tumefaction is usually associated with the least malignant exhibitions and the least tumefaction often with the most malignant exhibitions. Since trophoblast normally metastasizes, tumors of the highest malignancy and lowest tumefaction tend to be the most metastatic. Thus the increase or decrease in the malignancy of a given tumor is not the result of a continuing spontaneous generation of an infinite variety of cancer cells, *but merely the expression of the increase or decrease in the concentration of A CONSTANT MALIGNANT COMPONENT.* As the antithesis of this component determines the malignancy of the lesion so that the soma determines its benignancy.

LEUKEMIA

In the leukemias the constant malignant component (trophoblast) is present in the lymphopoietic or myelopoietic tissues. The reaction of such

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tissues to the malignant component results in the proliferation of *somatic* white blood cells of varying degrees of maturity. This is the counterpart of tumefaction in the sessile tumor. Thus the unitarian or trophoblastic thesis, different from the non-unitarian concept, finds no contradiction in the fact that often the most malignant phase of the leukemic process---the so-called aleukemic leukemia---actually involves a leukopenia. This phase is the most malignant because the somatic cells (leukopoietic tissue) have lost their ability to resist through virtue of the destruction of the leukopoietic tissue by ectopic trophoblast. For this reason the aleukemic or leukopenic stage is often terminal to a preceding highly leukemic or leukocytic phase.

TROPHOBLASTIC HORMONES

The routine utilization of the trophoblastic hormone, chorionic gonadotrophin, is, of course, a clinical commonplace as a means of diagnosis as an index to therapeutic response in the case of the most malignant exhibitions of cancer---the chorionepitheliomas and certain other exhibitions of cancer. The excretion of this hormone varies directly with the malignancy of the tumor which, in turn, varies directly with the concentration of trophoblast cells.

In 1944 Roffo[131] reported a similar gonadotrophin in all of 1,000 cancer patients examined, and none in the blood or urine of the control series---with the exception of pregnancy, of course. In 1946 Krebs and Gurchot[132] reported the identification of Roffo's gonadotrophin as trophoblastic. In 1947 Beard, Halperin and Liebert published a confirmation of the prior papers and suggested a practical utilization of the phenomenon.[133] Prior to these studies numerous scattered reports of chorionic gonadotrophin in cancer serum and urine appeared in the literature but without the context of any unified theory. Zondek reported the hormone in the urine of 82 per cent of females afflicted with cancers of the genital organs and in 36 per cent of female patients suffering from extra-genital tumors.[134,135] Five years later Zondek was able to duplicate and extend his original findings,[136] which had been confirmed by others.[137, 138, 139]

It is necessary to emphasize that the original work of Zondek as well as other workers was done on the erroneous assumption that the hormone was produced by the anterior pituitary gland. Even after tissue culture studies had proved the trophoblast-cell-origin of the hormone, its occasional identification in cancer urines, through the use of the Ascheim-Zondek or Friedman tests, was usually dismissed as an inexplicable datum of an inexplicable disease. Only within the context of the unitarian or trophoblastic thesis was sufficient theoretical justification found to concentrate and selectively extract the urines of the less malignant exhibitions of cancer specifically for the same hormones (chorionic gonadotrophin and syncytial steroids) always found by ordinary technics in the most malignant exhibitions.

Thus to the already established uniformities for 20 or more known

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factors among the various exhibitions of cancer, we now find an hormone (not only evidential of the unitarian thesis but of the specific trophoblastic nature of cancer as well) in the trophoblast cell-produced hormones. *Like all other uniformities found in the malignant lesion,* that for the trophoblastic hormones becomes increasingly apparent with the malignancy of the growth, so that frank chorionepitheliomas are found excreting as many as one million International Units of chorionic gonadotrophin every 24 hours, while the much less malignant exhibitions with no frank trophoblast cells excrete 50 or fewer units of the trophoblastic hormone.

DIAGNOSTIC IMPLICATIONS

There are only two fundamental kinds of cancer tests: (1) the indirect tests concerned with the detection of a substance produced *by the soma* as the result of the presence of cancer cells; and (2) the direct tests concerned with the detection of a substance produced by the cancer cells themselves. Though the incidence of a specific somatic change may bear a high correlation with the presence of an uniform stimulus, the correlation can never be a truly specific one, since obviously no *somatic* reaction is so specifically reserved for the presence of cancer or trophoblast cells that it can not be falsely elicited by other stimuli.

The limitations of the indirect tests have been well demonstrated in practice. The only reliable and generally accepted serum or urine tests for cancer are the direct ones, such as the Ascheim-Zondek test and its numerous modifications. Just as hundreds of indirect tests have been tried and discarded for pregnancy diagnosis, so have hundreds of indirect tests for cancer been tried and then discarded. The only tests for either pregnancy or cancer that have survived are those *direct* tests depending upon the identification of a substance unique to cancer and pregnancy: the hormone of the trophoblast cell. Since cancer is trophoblastic, its most malignant exhibition---chorionepithelioma---is highly amenable to the direct test. In fact, the possibility of either an indirect or direct general diagnostic test for cancer depends upon cancer being an unitarian phenomenon.

The efficient clinical implementation of the trophoblastic or unitarian thesis depends upon the development of a simple, reliable and highly accurate quantitative test for the specific products of the trophoblast cell.

While we have identified the presence of chorionic gonadotrophin in the urines of patients with all exhibitions of cancer, we have found the technological evolution of a quantitatively precise chorionic gonadotrophin test difficult for the less malignant exhibitions of cancer. When we consider that a chorionepitheliomatous exhibition of cancer in the male may yield over 1,000,000 I.U. of chorionic gonadotrophin while metastatic testicular cancers of a much lower malignancy---though biologically still more malignant than most extra-genital growths---may yield fewer than 50 I.U. for a like volume of urine, then the physical difficulties in the

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case of most of the extragenital tumors of still lower malignancy is obvious.

From the urines of patients with the common exhibitions of cancer, the authors have obtained highly active preparations of chorionic gonadotrophin, and are now engaged in the crystallization of chorionic gonadotrophin, by the method of Claeson, Hogberg and Westman (1948),[140] from pooled urines of various exhibitions of cancer. It is recognized that the

specific steroidal hormones of the syncytial trophoblast also comprise a most important avenue to the development of a satisfactory diagnostic technic. However, these steroidal hormones have not been studied as intensely as chorionic gonadotrophin which is now characterized as a glucoprotein containing 18 per cent acetylglucosaminedigalactose polysaccharide.

Several cancer tests relying on the detection of trophoblastic hormones are now under study for the purpose of achieving a sufficiently practical quantitative test for general use.

CLINICAL IMPLICATIONS

As a composite tissue, cancer in its somatic component represents many diseases; in its constant malignant component, one disease; and, in its totality, a local manifestation of a general disease. Since the perspective of the clinician is necessarily anthropomorphic, he sees cancer primarily in its somatic phase as a series of many diseases. On the other hand, as Oberling and Woglom have so aptly phrased it, "To the experimentalist cancer is one disease and one disease only."

Both clinician and experimentalist are generally agreed that the somatic or anatomical changes produced by the malignant process are largely irreversible. Surgical extirpation or the primarily non-selective cautery of radiant energy may destroy the composite tissue of a primary tumor. But the vague hope for an agent that will cause the "reversion" of an organized malignant tumor to normal tissue is scientifically indefensible. Aside from the physical destruction of the tumor itself, one primary factor can contribute to the amelioration of the effect of the tumor on the host. This is the growth inhibition or destruction of the constant malignant component of the tumor. Selective ablation of the malignant component will not alter the already existing somatic dysplasia nor histologically change the architectonics of the tumor, except in highly malignant anaplastic exhibitions. Here the histological as well as the gross changes take an expected course: an histological increase in connective tissue elements with a palpable increase in fibrosity.

In the advanced and well organized lesion, the possible changes are not, as a rule, dramatic. Were the malignant component ablated, the somatic component would tend to persist largely unchanged, or even show a slight increase in benign tumefaction. Since none of the cells in a malignant tumor is *per se* a "diseased" or pathological cell, but rather a cell normal to the life-cycle, cancer does not itself produce any "toxic effects." Its lethality is eminently a physical matter involving the normal behavior of normal trophoblast in a spatially abnormal relationship.

Above all, cancer is a natural phenomenon ultimately involving the soma in irreversible changes. To question the results expected from the selective ablation of the constant malignant component in a malignant lesion would be to suggest that, aside from actual tumor destruction, no malignant tumor has ever spontaneously regressed, that no highly anaplastic cancer has even spontaneously gone into a less malignant scirrhous exhibition, or that no patient has ever survived for five years or more after exhibiting an inoperable and highly malignant lesion. It is not necessary to review here an impressive literature on spontaneous regression. Much more important to a sound comprehension of the clinical implications of the

trophoblastic or unitarian thesis are the thousands of cases of cancer in which the host is able to resist and to live with the cancer cells for years.

What are the factors---cells, tissues, organs, and their secretions---contributing to such resistance? What causes trophoblast in the pregnant diabetic to overgrow, despite a normal insulin supplement? Why do the specific inhibitors to pancreatic chymotrypsin and trypsin rise with the increasing malignancy of a growth and decline following its amelioration? Why is the small intestine practically immune not only to primary tumors, but to direct invasion and metastases as well? Why does the growth of the invasive, erosive and metastatic trophoblast of normal gestation cease and degeneration commence concomitant with the commencing function of the fetal pancreas gland? Why does the urinary excretion of chorionic gonadotrophin fall concomitantly with the degeneration of the trophoblast? After more than 99 per cent of the trophoblast has been removed from the placenta, why does its size remain unaffected though its invasive and erosive properties are entirely lost? Why are pregnancy trophoblast cells often indistinguishable histologically from the somatic cells in the uterine wall of the pregnant host? Why is it that the removal of normal pregnancy trophoblast to tissue culture will result in a fiercely malignant exhibition of such trophoblast toward *all* nontrophoblast cells?*

Any attempt to implement clinically the trophoblastic or unitarian thesis should be made in the light of the answers to these questions.

RADIATION

Were malignant cells actually selectively susceptible to radiation, the most malignant exhibitions of cancer would be the most amenable to therapy, since they would, then, contain the highest concentration of radio-sensitive cells. Chorionepithelioma and malignant melanoma represent two of the most malignant exhibitions of cancer, yet they are radio-resistant. Glioblastoma multiforme and neurogenic sarcoma are also examples of highly malignant exhibitions of cancer that are radio-resistant.

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* The answers to these questions reflect the cogency of Oberling's prediction: "Some day, perhaps, it will turn out to be one of the ironies of nature that cancer, responsible for so many deaths, should be so indissolubly connected with life."[101]

We may generalize that the malignant component of a tumor is *slightly* less radio-resistant than the somatic connective tissue stroma but considerably more radio-resistant than the somatic parenchyma. This is why radiation often results in an increase in tumor fibrosity, which would be an excellent sign were this achieved at the cost of the radio-resistant malignant component (trophoblast) rather than at the cost of the somatic parenchyma. The so-called radio-sensitivity of a tumor is determined primarily by the radio-sensitivity of the somatic cells in which the constant malignant component happens to reside---not by the uniformly radio-resistant constant malignant component: the ectopic trophoblast.

RADIO-ACTIVE ELEMENTS

The most commonly used radio-active element is that of iodine in the therapy of cancer of the thyroid. Rhoads[141, 142] describes the limitations of this therapy as follows:

> "The more malignant and destructive forms tend to pick up (radio-active iodine) to a lesser and lesser degree as the invasiveness increases."

With an increase in the malignancy of the exhibition, there is necessarily an increase in the concentration of the definitively malignant cells (trophoblast) and a consequent decrease in somatic thyroid cells which are the only cells involved in the selective uptake of radio-active iodine. The decrease in tumefaction as a result of the uptake of radio-active iodine is an expression of the loss of functional somatic cells. This fact is further demonstrated in the successful use of this technic in toxic goiter.

SURGERY

The lower the concentration of trophoblast cells in a malignant lesion, the more amenable the lesion is to successful surgery. For this reason highly malignant growths like chorionepithelioma are generally inoperable.

PANCREATIC ENZYME THERAPY

The palliative use of the crystalline pancreatic enzymes in advanced human cancer rests *entirely* upon the validity of the unitarian or trophoblastic thesis of cancer.

CONCLUSION

Our own studies, too, appear to confirm the unitarian or trophoblastic thesis of cancer. The independently proved uniformities---which increase in degree of uniformity with the malignancy of the growth---of malignant lesions in the concentration of eight water-soluble vitamins; in vitamin C content; in water content; in cytochrome-c; in effect on liver catalase of the host; in Warburg's criteria of glycolysis; in lactic acid formation; in sugar content; in the respiratory response to added substrates; in a common means of induction; in antichymotryptic factors; in autonomy, invasiveness and erosiveness; in ability to metastasize; in amenability to universal therapeutic measures; in the general anticarcinogenic effect of

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caloric restriction on the incidence of mammary tumors and leukemia alike in experimental animals; in heterotransplantability; in loss of specialized function as malignancy increases (in all tumors except chorionepithelioma); in departure from the histology of the site of origin (except in primary uterine chorionepitheliomas);[*]; in numerous enzymes---all these uniformities, indeed, exclude any but an unitarian nature of cancer. Then as we examine the most malignant exhibition of cancer possible---chorionepithelioma---to find it comprised of trophoblast cells indistinguishable cytologically, endocrinologically or otherwise from those of normal pregnancy trophoblast, the fact becomes impelling that if cancer is, indeed, an unitarian phenomenon all of its properties must be exemplified in these most primitive of all cells in the life-cycle, the trophoblast cells. These cells in their normal canalization of pregnancy (as well as *in vitro*) exhibit *every known property of malignant cells*---though normally directed in pregnancy toward the physiological exploitation of the truly malignant process implicit in the embedding of the tissue of the conceptus into that of the mother.

Then, were all else evidential of the unitarian or trophoblastic nature of cancer set aside, and were there left for scrutiny but the single fact that primary exhibitions of trophoblast

(chorionepithelioma) are not infrequently seen that metastasize to an adenocarcinomatous or sarcomatous exhibition, and vice versa, then reason would admit of only one explanation: the trophoblastic or unitarian fact of cancer.

Were the cellular counterpart of cancer not an inextricable component of the life-cycle, represented in the most primitive cell of that cycle, the processes of natural selection themselves would have precluded the survival of the spontaneously generated cells that any alternative to the trophoblastic fact of cancer necessitates.

The unitarian thesis is not a dogma inflexibly held by its proponents; it is merely the only explanation that finds *total* congruence with *all* established facts on cancer. While the unitarian or trophoblastic thesis seemingly admits of no alternative, it warrants the most corrosive scrutiny. For cancer either is or is not an unitarian phenomenon, and thereby it is either trophoblastic or not trophoblastic in nature. The definitive cancer cell is either the most primitive cell in the life-cycle or it is not the most primitive. It is either the result of the *differentiation* or meiosis (however spatially or temporally anomalous) of a cell or it is not the result of cellular differentiation. It either has its normal cellular counterpart in

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* These are, indeed, instances in which the exception *proves* the rule; for, were cancer not trophoblastic, its most malignant exhibition---chorionepithelioma---would then show the greatest loss of function and the greatest deviation from the histology of the site of origin, instead of actually showing an accentuation in the normal function of trophoblast, as it does. Yet were one to attempt to ascribe to the malignant exhibition of trophoblast some *intrinsic* but subtle change from that of the non-malignantly exhibited trophoblast, such an attempt would be rendered nugatory by the fact that the most malignant exhibition of cancer possible in the male---- chorionepithelioma---comprises trophoblast cells indistinguishable from those of pregnancy or chorionepithelioma in the female; yet, in the male chorionepithelioma represents the widest possible deviation in histology and function from the site of origin. The latter fact corroborates the proof of a rule previously proved by its exception.

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the life-cycle, and thus is the result of cellular differentiation; or it has no cellular counterpart in the life-cycle, does not arise through cellular differentiation, and, therefore, is spontaneously created. The diploid totipotent cells within the soma, like their normally canalized daughter cells, can either undergo meiosis and subsequent trophoblast production, in response to sufficient organizer stimuli, or they can not. The occurrence of frank trophoblast cells within the soma (*invariably* as the most malignant exhibition of cancer) is either the result of the meiosis of a diploid totipotent cell or it is not; and, therefore, is the result of a spontaneous generation. The trophoblast or the cancer cell either produces specific inhibitors to pancreatic chymotrypsin and trypsin, or it does not (and the twenty or so independent workers how have so reported are all in error). A malignant tumor is either a composite tissue or it is not a composite tissue. The malignancy of a tumor is either determined by the concentration of a constant malignant component; or it is not so determined and depends, therefore, upon the successive spontaneous generation of a series of specific cells to account for the increasing malignant evolution of the tumor.

The trophoblastic or unitarian thesis holds the affirmative of all these propositions. It holds that *any* alternative to them will result in a *reductio ad absurdum*. The unitarian thesis recognizes the need for an orderly defined common ground of theory upon which all workers in cancer may at least meet, if not agree. It holds as reasonable the thesis that the more tenable of *two distinctly opposed hypotheses* should be given the greater credence in determining the

direction of future research. It holds that in the intensive study of the peculiar metabolism of trophoblast both in pure cultures and *in vivo*, with the goal of the selective lysis of the trophoblast cell or the occlusion of its metabolism, the cancer problem may find practical resolution. It holds that the cancer problem need not offer amnesty to unbridled empiricism and negation to the most basic tenets of the rational process.

Above all else, the trophoblastic or unitarian thesis urges that the alternative non-trophoblastic or non-unitarian thesis, which is at present overwhelmingly the dominant hypothesis, be scrutinized in the light of whatever experimental evidence might exist in its support.* Indeed, the evaluation of *any* alternative to the trophoblastic or unitarian thesis---within the context of experimental facts and scientific logic---by those who find the trophoblastic or unitarian thesis untenable or tenuous[143, 144] should prove most instructive. For in cancer, as in all else, facts do not speak for themselves but must be spoken for.

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*In reviewing over 17,000 papers on cancer and related biological subjects the senior author, in the course of his text on "The Biological Basis of Cancer," has not found a single valid contribution that fails to find congruence with, and illumination from the trophoblastic or unitarian thesis of cancer.

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