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# Ischemia and Tumor Pathogenesis as Strictly Characterized by Inflammatory Responsiveness of Cells and Tissues

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**Abstract:** Integral ischemic and inflammatory conditioning influences in determining responsiveness of cells and tissues in transforming pathology ranging from infection to neoplasia to tissue atrophy would in various ways perhaps help delineate pathways of pathologic progressiveness beyond simple etiologic considerations. Indeed, responsiveness of injured cells, tissues and organs as an inflammatory series of pathways in a conditioning setting induced by variable states of pre-existing or coincident ischemia might perhaps help account for the development of different patterns of pathologic progressiveness in cells and tissues. Indeed, a system of neoplastic transformation would be distinct from one of active infection, of progressive tissue atrophy, or of evolving frank infarction, simply in terms of the nature of the responsiveness pathways as developing in injured cells and tissues in the first instance. Ischemic effect would itself perhaps prove a prime mode of influence in determining the nature of such responsiveness of cells, tissues, and organs when injured in ultimately distinguishing between a pattern of active infection versus one of neoplasia or of atrophy in a progressive setting of disease evolution and transformation.

**Key words:** Ischemia, tumor, tissues, pathogenesis

## INTRODUCTION

## ESSENTIAL INTERFACE INTERACTIONS IN TRANSFORMING AND EVOLVING DISEASE AS PRIMARILY ISCHEMIC AND INFLAMMATORY IN NATURE

Fundamental interactions between essentially generic forms of pathologic involvement of various tissues ranging from ischemia to senile atrophy, to neoplasia and inflammation, might in a real sense constitute an essential characteristic component of progressiveness of disease. Indeed, the Prognostic Inflammatory Nutritional Index is a simple scoring system in evaluating prognosis in critically ill patients as those with advanced cancer[1]. Such a system involves the correlation of elevated Interleukin 6 levels with C-reactive protein values, albumin, pre-albumin and alpha 1-acid glycoprotein. In this regard, also, acute inflammatory reactions would appear an independent determinant of prognosis in some patients with acute ischemic syndromes[2]. In such terms, in particular, inflammation would appear a critical component of tumor progression, fostering proliferation, survival and migration of neoplastic cells[3].

Indeed, in terms particularly of essential interface interactions whereby various pathways both arise and evolve as forms of transformation in pathologic involvement as induced by ischemia, inflammation and infection, one might perhaps better understand the central characteristic properties of disorders ranging from Alzheimer's disease, to AIDS dementia to Primary Central Nervous System Lymphoma to a whole series of evolving attributes that are primarily pathologic. Also, for example, critical lower limb ischemia would appear particularly associated with Endothelin-1 binding to Endothelin (B) receptors in a manner specifically implicating endogenous vasoconstrictor peptides in chronically ischemic muscle[4]. On the other hand, tubulo-interstitial renal injury resulting from ischemia would appear to mediate salt-sensitive hypertension in a context particularly of microvascular disease[5].

It is perhaps in this strict sense of interface/interactive progressiveness in evolving pathologic transformation that one might better understand the essential nature of induction and of promotion in malignant transformation of tissues.

In a sense, indeed, inflammatory cascades of events in specific contextual evolution, ranging from possible forms of infectious complications to cytokine/chemokine effects, might not only help elucidate early malignant transformation events but also contribute to a better understanding of ischemia as fundamentally interface

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interactiveness. For example, Helicobacter pylori eradication from the stomach results in marked reduction in the severity and activity of chronic gastritis and resolution of intestinal metaplasia in the antrum. On the other hand, persistent Helicobacter pylori infection promotes progressive mucosal atrophy and intestinal metaplasia with a high incidence of gastric cancer in such patients[6]. Indeed, mucosa associated lymphoid tissue lymphoma appears to be related to long standing gastric inflammation due to the Helicobacter pylori infection [7].

Subjective evolution of disorders of apparently either genetic or sporadic origin might actually refer to systems of ischemia, of inflammation, and of infectious complications that would interact in multiple different modes of combination to constitute novel pathways of pathologic transformation in evolution.

In this connection, also, it would appear significant that the NF-kappa B system would appear involved for both tissue protection and for systemic inflammation as observed in cases of intestinal ischemia/reperfusion [8].

That Alzheimer brain atrophy would in various basic modes be related pathogenically to systems of pathologic evolution in transformation ranging from ischemia to inflammation to possible infectious agent participation might in strict terms help account particularly for syndromes of AIDS pathogenesis that so clearly evolve as inflammation and infection in a context of neoplastic development and progression.

In this sense, indeed, ischemia might actually reflect, in multiple ways and in both direct and indirect manner, a full evolutionary characterization of neoplastic tissue development that is transformed into systemic metastatic progression.

In such terms, indeed, the AIDS epidemic might indeed well characterize disease processes that evolve as different interactive pathways of ischemic, inflammatory and infectious nature towards true integrative transformation. Such integrative transformation, even in terms of the nature of evolving pathologic tissue involvement, might perhaps arise and progress largely as systems of interface evolution of generic forms of ischemia both as a cause and as a result of the inflammatory progressiveness.

In this regard, also, for example, myocardial contractile dysfunction as with septic shock or burns, or else in association with ischemia or direct inflammation of the heart, tends to activate the innate immune system as coordinated especially by the conserved Toll/IL-1 signal transduction pathway[9].

In simple terms, indeed, a basic formula of interactive progression in transformation arising from interface pathways between evolving ischemia and inflammation might perhaps help account for AIDS as an infectious series of complications that is inherently permissive towards immune deficiency, in the additional evolving context of malignant transformation ranging from CNS primary lymphoma to systemic Kaposi sarcoma spread as superimposed by the occurrence of multiple opportunistic infections.

Such a concept however has to be considered in a context of apparent stimulation of the innate immune system due to release of proinflammatory cytokines secondary to products of infection, ischemia and injury [10]. On the other hand, for example, Interleukin 12 (IL-12) appears a promising adjuvant for cancer vaccination as a very effective immunotherapeutic agent at low dose levels [11,12].

Beyond, however, considerations that would tend to distinguish infections as either primary causes of pathologic transformation of tissues, or else as essential complications induced by the infectious agent or agents, one might strictly recognize progressiveness of disease as an entity of significant clinical and pathologic attributes of interactions inherently arising from generic systems of an ischemic and inflammatory nature. In this regard, for example, DNA damage caused by oxidative stress in a characteristic damage and regeneration cycle might constitute a major contributor to colorectal cancer development in the ulcerative colitis patient as inflammation-driven carcinogenesis[13].

Even when one considers systems of evolving pathologic transformation developing as strict disease entity characterizations but particularly as pathways of interactive integration towards further pathologic transformation of tissues, one might perhaps recognize progressiveness as a direct attribute of mutual interdependence of ischemia with inflammation. In this regard, for example, the neuronal expression of interferon regulatory factor-1 would appear to play a role in ischemic neuronal death[14].

In simple terms, even neoplasia, as a fundamental attribute of carcinogenic processes, would evolve in terms of pathways of interactive transformation between systems closely analogous to ischemia and inflammatory progressiveness and in the added context of evolving complications ranging from possible infection to immune deficiency to atrophy of tissues. In particular, cytokine polymorphisms would appear to influence susceptibility to and even prognosis with regard to neoplasms ranging from malignant melanoma to prostatic carcinoma that would be affected also by diet. Indeed, dietary modulation of cytokine expression might prove genotype-dependent[15].

In this sense, perhaps, neoplasia might be better characterized as transformed tissue responses coupled with essential transformed tissue responsiveness in a context of evolving ischemic and inflammatory participation complicating infection and immune disorder of a progressive nature. In this regard, also, the presence of an inflammatory response identifies patients with more aggressive neoplastic disease that would, in addition, tend to compromise pharmacodynamics of anticancer drugs[16].

Alzheimer's disease would perhaps be an aspect of how tissue atrophy is itself an alternative form of evolving transformation that both develops and progresses as interactions especially between ischemia and neuroinflammation.

In this connection, inflammation and neutrophil-endothelial cell interactions in cerebral ischemia and reperfusion in particular, would appear to implicate selectin-ligand interaction in inducing subsequent microvascular plugging stasis and thrombosis[17].

In this essential context, the capillary vessel wall might actually participate as an essential anatomic system of constitutive progressiveness involving brain atrophy of Alzheimer type. An anatomical shift of variable degree implicating major disease processes ranging from neoplasia to infarction and/or infection or to immune deficiency, might categorically characterize etiologic evolution of the disease process in terms of pathogenetic progressiveness determining patterns of interaction especially between genotype and phenotype. For example, Helicobacter pylori-associated gastric cancer in INS-GAS mice is gender specific (males only)[18].

Even beyond such basic concepts of cellular pathology implicating especially also molecular systems of progression, one might characterize systemic pathologic transformation of tissues and organs as constitutive traits of interaction between genotype and phenotype evolving as pathologic attributes of involvement.

Also, for example, activation particularly of inflammatory pathways would appear to contribute to mortality and functionality decline in the development of the frailty phenotype in the elderly[19].

In this sense, indeed, molecular pathologic attributes might determine characterization of a disease process evolving as cellular, tissue and organ manifestations of progressive change and of nonviability in terms of ischemic and inflammatory mechanisms. Polymorphonuclear cell infiltration and subsequent protease production in particular appear to contribute significantly to tissue injury and to cell necrosis in ischemia/reperfusion injury in a context of variably modulated postischemic inflammation[20] and also of peroxynitrite cytotoxicity ranging from inhibition of lipid peroxidation to inhibition of mitochondrial and of membrane sodium channels and of Na(+)/K(+) ATPase activity[21].

## CELL LYSIS AS AN ACUTE TRANSFORMATIONAL EVENT IN RELATION TO THE INDIVIDUAL CELL ATROPHY PHENOMENON OF ISCHEMIC TYPE

Progressive individual cell atrophy as a necessarily chronic process leading to a critical point of individual cell lysis might influence a common disease sequence due to ischemic effect as induced by atheromatous vascular occlusion or stenosis of vessels.

In this regard, neointimal proliferation is itself associated with a role for inflammation in cases of clinical restenosis of vessels through early activation of leukocyte integrin mac-1[22].

Certainly, atherosclerotic narrowing of vessels might be associated with actual total occlusion of the vascular lumen as leading directly to cell death. Indeed, a very chronic state of ischemia and of ischemic hypoxia would culminate in cell death as a result of fundamental cascades of intracytoplasmic reactivity leading to cell lysis. Also, nitric oxide-derived oxidants such as nitrotyrosine might operate as inflammatory mediators in coronary artery disease, thus linking atherosclerosis with inflammatory oxidative injury[23].

Even the dramatic quality of the lytic event might itself attest to a long process of deprivation of the cell as systems of ischemic hypoxia involving patterns of evolving transformation in such progressiveness.

The actual events underlying many cases of cerebral ischemia would be a purely morphologic expression of the classic liquefactive necrosis of a primarily intracytoplasmic nature. Hence, neuronal and white matter involvement in cerebral ischemia would constitute ischemic hypoxia apparently evolving as critical thresholds of influence involving cascade series of events of cell membrane damage and of cell lysis.

## TIOLOGIC VERSUS PATHOGENIC DEFINITION OF DISEASE

Certainly, from a purely theoretical or conceptual point of view, a disease might be better characterized as a series of pathogenic processes leading to a disease state rather than simply in terms of the initiating etiologic agent. Certainly, an evolutionary pathway of lesion induction might implicate specific etiologic agents giving rise to essential evolutionary pathways of progression.

The patient's disease certainly might concern specific attributes of progression simply in terms of determination of specific etiologic characterization of pathways activated in self-promoting progressiveness of the transforming pathologic events, as for example, with regard to expression of cyclooxygenase in non-small cell carcinoma or adenocarcinoma of the lung[24]. Indeed, cyclooxygenase 2-derived prostaglandins appear to play an important role in tumor viability, growth and control of metastasis[25]. For example, aberrant cyclooxygenase 2 expression appears possibly involved in the development of colon cancer and of colon adenomas[26,25].

A single predominant etiologic agent in itself might not necessarily implicate essentially specific Disease States in different individuals.

Even the same infectious agent would result necessarily in the same disease state of pathologic transformation in different individuals in terms also of fundamental participation of several secondary systems of influence and of compounding/transforming nature.

Of course, possible parameters determining pathogenesis might include specific organ participation in a specific individual patient.

Indeed, mechanisms arising from specificity of the etiologic agent would characterize a disease activity in that individual patient. From the point of view of disease evolution, pathogenesis might in various ways perhaps be considered different modes of induced patient's involvement by that progressive disease process. In this sense, the increased risk for the development of malignant lymphoma in patients suffering from rheumatoid arthritis would appear to be a direct consequence of the inflammation or perhaps its treatment[27].

A picture of established pathologic progressiveness might primarily involve systems of manipulation of the various pathways in pathogenesis particularly in terms of compromised pathways of cell viability and of enhanced susceptibility to both progressiveness and to transforming influences in such progressiveness.

Moreover, essential characterization of disease would relate to a specific pathogenesis that allows etiological agents of induced influence towards the delineation of various syndrome complexes of variable specificity as with dementia and neurodegenerative diseases in general. In this regard, for example, activation of the P2X(7) nucleotide receptor, an extracellular ATP-gated ion channel expressed in astrocytes, would be involved in signaling pathways of astrocycte-mediated inflammation and would also be associated with neurodegenerative disease[28] through an essential phenomenon of reactive gliosis.

## SPECIFIC PATTERNS OF INVOLVEMENT BY SPECIFIC DISEASES

A highly characteristic series of patterned cellular, tissue and organ influences evolving as disease processes clinically and pathologically might often prove highly specific as characterized systems of progressiveness.

In this regard, infectious agents and even neoplasia might particularly evolve as direct attributes of pathobiologic change and of progression arising as inherent functions of biologic responsiveness of the cells, tissues and organs affected.

In particular, for example, chemokines (chemotactic cytokines) would appear to constitute pivotal determinants of angiogenesis in lesions such as non-small cell lung carcinoma[29]. Mast cells in particular appear closely related to cascades of angiogenic events [30].

Indeed, specific disease entities might establish themselves as specific patterns of expression and of progression simply within a single conceptual framework of disease specificity largely arising from patterned responsiveness of cells, tissues and organs. One might in fact speak of specific pattern unfolding in a manner that would be essentially invariable in nature but one that might be modified paradoxically by certain generic systems of influence implicating particularly ischemia. Indeed, homeostatic disturbances and active lesion infliction in tissues and cells would implicate patterned responsiveness and mechanisms of participation in determining characteristic pathologic transformation developing as reactions and defense mechanisms of origin. In this regard, for example, ischemia/reperfusion injury might constitute a form of host "innate" immunity in cases influencing graft survival after liver transplantation through the activation of toll-like receptors on Kupffer cells. Heme-oxygenase systems would appear to exert anti-oxidant and anti-inflammatory action and also modulate the cell cycle and maintain the micro-circulation[31].

Certainly, the occurrence of patterned disease involvement might directly implicate stereotyped pathways of progression integrating disease processes with stereotyped body responses as systems of transformation of cells, tissues and organs. In this connection, for example, downregulation of inflammatory prostaglandin synthesis by inhibition of cyclooxygenase-2 (COX-2) inhibition of the inducible nitric oxide synthase, and stimulation of phase II detoxication system, are presently being investigated experimentally and clinically [32].

The term mechanisms might itself constitute an appropriate reference to pathways of influence in disease responses. In a sense. a series of coordinated and programmed events might operate in stereotyped manner simply in terms of critical steps of evolving participation in transformation of cells, tissues and organs as induced by the pathogenic agent or agents involved. For example, inflammation might play a role in tumor cell entry and exit of the microvasculature since multicellular tumor clusters generally would traverse endothelial cell adhesion junctions in the development of tumor metastases. Indeed, intestinal bacteria might possibly significantly affect the behavior of colon carcinomas in terms of metastatic access within the circulatory system [33].

In particular, P selectin expressed on activated platelets and vascular endothelium would determine adhesive interactions with polymorphonuclear leukocytes or colon carcinomatous cells in inflammatory or blood-borne metastasis respectively[34].

## COINCIDENCE OF PATHOLOGIC EVENTS AND PROCESSES

The random or essentially not entirely random coincidence of pathologic lesions and pathways of progression might induce the genesis of disease entities as systems determining the nature of the disease process that progresses to specific endpoints of recognized or established endpoints of patterned transformation and stereotyped response.

Indeed, a particularly salient feature of pathologic lesions is that they might invariably result from essential transformation due to direct participation of coincident injury to cells and tissues as induced by two or more primary insults. Indeed, the very genesis of neoplastic transforming events would depend on essential coincidence of a number of insults or forms of injury that transform the cells to malignant types of progressiveness.

One might not simply attribute specific systems of neoplasia to the determined occurrence of independent pathologic processes without also implicating a series of cellular and tissue responses that themselves would result in integrative participation of progressiveness and of transformation of injury with such responsiveness.

In terms of neogenesis, a basic system of participation of the genome coupled to separate pathways of pathologic transformation of the mitotic cellular activity might help characterize neoplasia as simply a transformed form of cellular and tissue injury in terms of systems of responsiveness to such injury in transformation. Certainly, once such primary transforming influence in neogenesis develops, multiple patterns of progressiveness might mutually potentiate themselves as lesions of increasingly induced mitotic activity. The resulting genomic vulnerability to further potential genetic injury might implicate patterned DNA mutations, breaks, or recombination events that would specifically arise from the cell responsiveness to the injury as specifically characterizing such cellular and tissue injury.

What essentially controls the cellular mitotic machinery might especially implicate various pathways in combination with a sequential series of events developing towards further mitotic activity and further increased vulnerability to genetic damage.

In simple terms, it might perhaps be the essentially coincident occurrence of multiple primary, distinct pathologic insults or processes as themselves specifically characterized by the responses they themselves elicit in the affected cells and tissues that would lead to pathologic transformation that is specifically neoplastic in terms of such self-progressiveness. In this regard, for example, neoplastic transformation in AIDS patients would both arise and evolve as specific progression pathways that are distinct characterizations of the HIV infection process itself.

In more general terms, indeed, the tendency for essential coincident occurrence of physiologic and biochemical events would prove central to the set-up and maintenance of vital mechanisms determining the living state as a biologic system of progressiveness in its own right and subsequently also contributing to the progressiveness of pathological systems of transformation. In this regard, for example, a combined elevation of Interleukin-1beta and of Interleukin 6 as circulating inflammatory cytokines would appear to increase the risk for type 2 diabetes in a context of subclinical inflammatory pathogenesis[35]

## PATHOLOGY AS A MULTIFACETED ENTITY

Interpretation of pathologic events, in terms of the nature of transformation of cells, tissues and organs as a series of multi-faceted events, would characterize the nature of disease processes as a subsequent evolution of possible different forms of resolved or unresolved outcome events particularly as determined by essential attributes of states of disease progression. In this sense, for example, CD4+T cells might exert a protective effect against the development of intestinal cancer through their ability to reduce bacterially-induced inflammatory bowel disease[36].

Molecular biology would afford a mode of approach towards understanding the generation and progression of pathologic lesions arising as characterized effects of responsiveness on the part of the injured cells, tissues

and organs. It is in terms of a multi-disciplinary approach to the understanding of disease that one would perhaps better delineate pathophysiologic events and disease pathogenesis as simply modes of integrated responsiveness of damaged cells and tissues in terms of ischemia and inflammatory participation.

## ISCHEMIA AS A QUASI-ESSENTIAL SUBSTRATE UNDERLYING MANY OR MOST COMMON PRIMARY DISEASE PROCESSES

So widespread is the incidence of ischemia and of ischemic effects, not only in the general population but also within the same individual, that an important point arises regarding the common coincidental occurrence of ischemic effects and of numerous other primary disease processes in practically any organ or tissue of the body.

In this regard, also, lymphocyte activation and inflammation might develop prior to onset of acute myocardial ischemia in a context of atheromatous plaque rupture[37,38,39]. In renal ischemia/reperfusion injury, the enzymes s

Signal Transducers and Activators of Transcription (STAT) 4 and STAT 6 regulate Th1 (IFN-gamma producing) or the counterbalancing Th2 (IL-4) phenotype. STAT 6 in particular would tend to protect against renal ischemia/reperfusion injury through cytokine action, especially through IL4 expression[40].

Diseases such as multiple sclerosis and many specific etiologically specific forms of infection might prove intimately related to the circulatory system and hence probably also to ischemic effects resulting from vascular disease.

Indeed, an ischemic substratum as a generally associated background to many if not most primary diseases, would perhaps prove a particularly significant contributor in characterizing the responsiveness of the cells and tissues to injury. In this connection, for example, cyclooxygenase 2 would appear an important modulator in enhancing proliferation of neural progenitor cells after global ischemia[41] as seen in the dentate gyrus of the adult mouse hippocampus.

Even dementia syndromes and Alzheimer's disease might strictly participate as separate predetermined pathways of potential coincidental interaction of progressiveness as induced by ischemia and by various inflammatory responses to such ischemia. Acute renal failure after whole body ischemia would appear to influence also inflammation and T cell-mediated injury [42].

In fact, one might consider ischemic influence as simply a system of induced progressiveness of whole sets of pathologic transforming events ranging from infection to neoplasia to various increased states of susceptibility of cells and tissues in terms of variable enhancement of or selective vulnerability to progressive disease.

In particular, for example, reactive oxygen and nitrogen species produced during active infection and in inflammatory states would tend to damage DNA and thus induce mutations, and even activate oncogene products or inactivate tumor suppressor proteins[43].

Particularly significant would appear nitric oxide and p53 as a crucial pathway in inflammatory mediated carcinogenesis[44,45].

Furthermore, progressive background ischemia might prove an essential characterization of disease states leading to a determined distinction of infectious processes from infarction, neoplasia or from tissue atrophy as seen in the Alzheimer's brain.

Such phenomena of increased cellular, tissue and organ susceptibility, beyond even strict considerations of severity or of distribution of lesions, or even of specific biologic attributes of cells, tissues, or organs involved, might fully depend primarily on an essential responsiveness as typified primarily by inflammatory modes of consequent participation in the evolving pathologic events of transformation and progression.

In this regard, for example, neuroinflammation would primarily tend to target blood brain barrier integrity through the involvement of signaling systems in the tight and adherens junctions of the cerebral endothelium; resulting increased permeability would possibly constitute a dysregulation of mediators in stroke, multiple sclerosis, brain tumors and meningoencephalitis[46]. In this connection, the multi-drug transporter p-glycoprotein appears involved in the process of activated T lymphocyte-mediated blood-brain barrier dysfunction in later stages of inflammation[47].

Even such fundamental attributes of disease as pathologic progressiveness might primarily arise as biologic systems of ischemic origin towards further undefined potential endpoints of infection versus neoplasia versus tissue atrophy.

Ischemic effects might, in basic terms, help delineate a combination of concurrent events that would dynamically evolve as characterized patterns of influence primarily based on attributes of responsiveness of cells, tissues and organs and as conditioned primarily by generic pathways of integrative change as related to inflammatory response.

## CONCLUSIONS

Inflammatory responses might actually constitute reactive participation not only as far as infections are involved in a context of concurrent cellular and tissue

necrosis but especially in terms of evolving systems of ischemic injury. Indeed, neoplastic proliferation might in simple terms constitute aspects of operative interaction between inflammatory reactivity and systems of ischemic injury as far as such neoplastic progression would eventually evolve as both infiltrative and metastatic lesions of spread. Inflammatory responses would perhaps constitute a basic series of mechanistic pathways whereby the creation of desmoplastic stroma would subsequently participate in the evolving infiltrative pattern of spread of tumor cells especially targeting microvasculature. Indeed, the actual targeting of vessels in terms of infiltrating tumor cells that subsequently 1.02 metastasize via lymphatics and blood vessels might actually constitute the operative expression of a desmoplastic stromal reaction created in terms of an inflammatory reactivity that would participate together with other mechanistic pathways of influence such as ischemic injury to cells and tissues in a manner related somehow also to a phenomenon of angiogenesis.

Ischemic injury to cells and tissues might evolve as pathways of vascular luminal compromise as expressed subsequently in terms of inflammatory reactivity. Indeed, a dichotomy of evolving consequences of inflammatory reactivity and of ischemic injury would perhaps implicate especially a tendency towards subsequent persistence of cellular and tissue responsiveness beyond strict considerations of injury. In simple terms, an essentially aberrant series of consequences arising from inflammatory responsiveness might evolve as a persistence of ischemic injury and of subsequent possible creation of a neoplastic phenotype as expressed in terms of a whole series of changes ranging from angiogenesis to stromal desmoplasia to infiltrative spread leading directly to metastatic spread via lymphatics and blood vessels. It is perhaps in terms essentially of trophic influences evolving in a context of inflammatory responsiveness and of ischemic influence that one might better recognize neoplasia as a fundamental form of neogenesis of stromal and cellular elements in the subsequent development of aberrant pathways of cellular proliferation, of variable degrees of dedifferentiation and even of anomalous pathways of interactive cellular and tissue biology.

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