DENTAL CONDITIONS AND THEIR POTENTIAL FOR SYSTEMIC INTERACTIONS INDUCING CHRONIC DEGENERATIVE DISEASE

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SYSTEMIC DISEASE

PRIMARY SITE

Systemic Disease, by current understanding, constitutes the creation of a local condition which can exert a focal effect on the entire organism or on a remote site with increased susceptibility resulting in secondary local pathology at a *locus minoris resistentiae*, that is, an "area of least resistance". Basic to the understanding of systemic disease are two related factors: first, the status of immune function and second, the nature of the insult at the primary site. That injury must be differentiated as either being of an exogenous or of an endogenous exposure. This is the primary mechanism of systemic disease and proper diagnosis will, in essence, warrant opposing appropriate treatment regimens.

Exogenous exposure

Exogenous exposure may occur by either micro-organism or toxin, and will generally follow a classical model of exposure and pathological effect. Specific micro-organisms may exhibit the classical pathogen-host relationship, dictated by the postulates of Koch and Henle, wherein one organism will produce a particular pathology or disease state. This is evidenced when specific, highly virulent bacteria such as Mycobacterium tuberculosis, Corynebacterium diptheriae and Streptococcus pyogenes breach host defense mechanisms and proliferate selectively. The causative factor can be isolated from the clinical lesion, but is not found in healthy individuals. Further, these infections, in most cases, appear to possess a target tissue, as opposed to a susceptible tissue, whether it be the immune, lymphatic, respiratory or gastro-intestinal systems. Exogenous micro-biological exposure, then, as a rule follows the classical pattern of pathogen-host

response targeting specific tissue and gives rise to a particular disease pathology.

Exogenous toxic exposure, similarly, follows a familiar pathological relationship in that a particular toxin will target a specific tissue to produce a characteristic response. The reaction is far more complicated than microbiological exposure due to factors influencing toxicity and the types of potential responses. The three classical phases of toxicity involve exposure, toxicokinetics and toxicodynamics, each of which is influenced by numerous complex interactions. Exposure is influenced by bioavailability, frequency, time, dose, pathway, host factors and the physical and chemical form of the toxin. Toxicokinetics outlines the absorption, distribution, metabolism and excretion of the toxin once it enters local or systemic circulation. Absorption is influenced by bioavailability, ionization, functional groups and molecular variables. In an effort to rid the blood and lymph of the offending molecules, the body will distribute the offending molecules to the tissues to be metabolized. Distribution, however, is affected by the affinity of the tissues for the toxin, blood flow, protein binding, absorption variables and redistribution. Next, hepatic detoxification involving Phase I and II bioconversion, highly dependent upon metabolic and nutritional variables, affects whether the organism can excrete the toxin. Excretion proper may be facilitated or limited by renal, biliary, respiratory, integumentary and gastro-intestinal function. These contiguous mechanisms are further complicated by other interactions such as flora, hapten formation and toxicant interactions including additivity, antagonism, synergism and potentiation. Additive interactions of two similar toxins can increase toxicity, whereas antagonist action can reduce toxicity. These effects are frequently seen in pharmacological interaction. Potentiation, in which a normally labile chemical can become toxic by interaction with

another agent, represents another complication. Further, synergism, the interaction wherein one chemical causes a dramatic increase in the toxicity of another, along with potentiation, can result in sickness, disease and death to the organism. Toxicodynamics involving dose and response relationships adds another level of complex interactions. Simplifying toxicity to an "all-or-none" response, that is , a responder or non-responder, may be a deceptive oversimplification of the multiple levels of complex interactivity between toxin and host.

Endogenous Exposure

Another reaction of equal importance at the primary site is exposure to endogenous bacteria or toxins. Endogenous bacteria, that is, those micro-organisms pertaining to one's indigenous flora, function to limit growth of pathogenic species from exogenous and endogenous sources. The balance of flora can be disrupted by any assault to the immune system, such as malnutrition, toxic exposure, genetic defects, long-term antibiotic therapy, immunosuppressive modalities, surgery, trauma and other mechanisms placing stress on immune functions from which it cannot compensate. Tissue susceptibility may also play a role if the local lesion develops within areas such as the skin, oral cavity and GI systems, which are perhaps more vulnerable due to the trauma and stress these systems are subject to on a regular basis. As a result of decreased resistance, a dysbiosis results in which several species may proliferate. One such species may contain virulence factors which can cause a chronic inflammatory condition in the primary tissue initiating the primary lesion via connective tissue and/or bone destruction. Other virulence factors may allow metastasis into circulation causing systemic reactions and allowing such pathogens to reach remote *locus minoris resistentiae*. If the organism

possesses the ability to adhere to and colonize distant tissue, then a secondary pathology will develop. With regard to endogenous toxins, it is beyond the scope of this presentation to discuss dysfunction or pathology of the excretory organs, such as the kidneys, colon, skin and lungs, although accumulation of both exogenous and endogenous toxins and in these sites will indirectly affect a decrease in host resistance.

Focal Characterization

The primary site, or initial lesion, occurs as selective proliferation of resident flora which, under decreased immune resistance, organizes into a complex biofilm. As an example of an initial lesion, I will outline the mechanism of periodontitis as upwards of 90% of the population are inflicted and all forms of the infection, with the exception of Actionobacillus Actinomycetemcomitans (AA), are opportunistic in nature (Socransky and Haffajee 2002; Wolf et al 2005; Teles et al 2006). In the healthy periodontium, the initial lesion begins when biofilms release lipopolysaccharides (LPS), N-Formyl-Methionyl-Leucyl-Phenylalanine (FMLP) and fatty acid metabolites such as acetic, butyric and propionic acids which stimulate gingival crevicular junctional epithelial cells to release pro-inflammatory mediators. A local vascular reaction releases complement and activates macrophages creating a local acute inflammatory response. If the response is not interrupted by flossing or therapeutic dental prophylaxis, the inflammatory infiltrate, now dominated by T- cells, up-regulates the inflammatory reaction leading to detachment of the junctional epithelium and creation of the gingival pocket. Later, plasma cells dominate the chronic inflammatory lesion leading to collagen and bone destruction (Wolf et al 2005). The intensity of the inflammation in moderate to severe

chronic periodontitis is sufficient to produce metastasis and a systemic response (Gapski and Cobb 2006).

Metastasis

There are three metastatic mechanisms by which micro-organisms, bacterial antigens and local cytokines from the oral tissue gain access to circulation to produce systemic and secondary site effects (Van Velzen et al 1984). Metastatic infection is the result of bacteremia which, although transient, may find susceptible tissue. Those bacteria which have evolved or acquired mechanisms for cellular adherence and colonization have been demonstrated to cause such conditions as infective endocarditis, acute bacterial myocarditis, brain abscess, prosthetic joint infections and others (Rams and Slots 1992). Metastatic injury may occur from microbial toxins such as exotoxins and endotoxins (Van Velzen et al 1984). Gram-negative bacteria are constantly shedding endotoxins (LPS) which, in circulation, produce pathological effects. Even when gram-negative bacteria are killed by antimicrobials, large amounts of LPS are released which must be contained to prevent such reactions. Finally, metastatic inflammation is another mechanism whereby soluble antigen may react with a specific antibody giving rise to immune complex formation (Van Velzen et al 1984; Van Dyke et al 1986; Rams and Slots 1992).

SYSTEMIC REACTIONS

Immune System Reactions

Most systemic reactions induced by metastasis produce immune system and functional reactions. As a result of immunodysregulation at the primary site and the systemic dissemination of bacteria, endotoxins and cytokines, there will be an increased

production of liver-derived systemic inflammatory markers such as C-reactive protein (CRP), fibrinogen, haptoglobin and serum amyloid A (Gapski and Cobb 2006). High serum levels of CRP, fibrinogen, IL-6 and IL-8 are seen in patients with periodontitis, myocardial infarction and ischemic stroke with increasingly higher levels correlated to poor medical prognosis (Hansson 2005). Further, immunodysfunction with particular interest in autoimmune induction is currently focusing on bacterial heat shock protein 65 (Hsp65), which is strongly antigenic. Oral infections stimulate high levels of bacterial Hsp65 which, in turn, stimulates antibody production against these antigens. Human and bacterial heat shock proteins (Hsp) are strikingly similar suggesting a possible cross-reaction of bacterial directed antibodies with human Hsp in systemic and periodontal connective tissue and blood vessels (Loesche and Lopatin 1998).

Functional Reactions

Systemic reactions of a functional nature are evidenced by endothelial and platelet dysfunction. Endothelial dysfunction may be the key causative factor in coronary artery disease (Nitenberg 2006). Endothelial cells are the structural and functional cells of the entire circulatory system, lymphatic system and heart. A primary role of endothelial cells is to control blood flow and, hence pressure, by the release of nitric oxide which dilates and relaxes smooth muscle (Nitenberg 2006). Oxidative stress, caused by diabetes, hypertension, smoking, hypercholesterolemia and other reasons, inactivates nitric oxide (Cai and Hanison 2000). Once the endothelium's structural integrity is compromised, it can no longer protect itself from cholesterol, triglycerides and low-density lipoproteins creating a risk for atherosclerosis (Brocq et al 2008). A direct relationship has been established between the thickness of the tunica intima and tunica media of the coronary

artery with periodontal pathogens (Desranieux et al 2005). Further, systemic dissemination of oral gram- negative bacteria and LPS may induce endothelial inflammatory cell infiltration, vascular smooth muscle proliferation and vascular fatty degeneration (Mattila 1989; Marcus and Hajjar 1993). Platelet dysfunction may also occur as a result of bacteremia and LPS producing intravascular coagulation (Matilla 1989; Marcus and Hajjar 1993). Platelet dysfunction can also be induced by cytokines such as IL- 1ß which promotes coagulation and thrombosis (Li et al 2000; Herzberg and Meyer 1996). *Streptoccus sanguis* and *P. gingivalis* possess a platelet aggregation-associated protein on their surface which, in animal models, has been demonstrated to produce myocardial infarction- like events (Herzberg et al 1994).

LOCUS MINORIS RESISTENTIAE INTERACTIONS

Systemic focal infections from periodontal disease is perhaps one of the most researched subjects in current dental studies. Matilla and colleagues discovered an epidemiological relationship between gum infections, myocardial infarction, ischemia and atherosclerosis (Matilla et al 1989). The DeStefano study, the result of a 14 year follow-up of 9,760 individuals, further demonstrated the relationship of oral focal infections, strokes and coronary artery disease (DeStefano et al 1993). Relationships have thus far been demonstrated in myocardial infarction (Genco 1998; Matilla et al 1989), coronary artery disease (Xu et al 1991, 1992; Matilla et al 1993, 1995; Syrjänen 1990), diabetes (Genco et al 1998; Grossi et al 1997, 1998; Loe 1993), respiratory infections and complications (Scannapicco et all 1996, 1998; Donowitz and Manell 1990; Fiddian-Green and Baker 1991), obstetric complications such as pre-term birth and low birth

weight (Dasanayake 1998; Loe and Silness 1963; Offenbacher 1996, 1998, 1998) and other associations are currently under study.

DENTAL FOCAL INTERACTIONS

INFECTIONS AND ANTIGENS FROM MARGINAL PERIODONTITIS

Systemic implantation from periodontal disease is perhaps one of the most researched subjects in current dental studies. Matilla and colleagues discovered an epidemiological relationship between gum infections, myocardial infarction, ischemia and atherosclerosis (Matilla et al 1989). The DeStefano study, the result of a 14 year follow-up of 9,760 individuals, further demonstrated the relationship of oral focal infections, strokes and coronary artery disease (DeStefano et al 1993). Relationships have thus far been demonstrated in the following areas with other areas still under study:

- Myocardial infarction (Genco 1998; Matilla et al 1989)
- Coronary artery disease (Xu et al 1991, 1992; Matilla et al 1993, 1995; Syrjänen 1990)
- Diabetes (Genco et al 1998; Grossi et al 1997, 1998; Loe 1993)
- Respiratory infections and complications (Scannapicco et all 1996, 1998; Donowitz and Manell 1990; Fiddian-Green and Baker 1991)
-Obstetric complications such as pre-term birth and low birth rare (Dasanayake 1998; Loe and Silness 1963; Offenbacher 1996, 1998, 1998) .

The periodontal flora comprise as many as 300-500 species, serotypes and ribotypes of bacteria, all of which are considered non-pathogenic (Loesche 1994, 1997; Kilian 1982; Page 1998). When a patient possesses decreased immune function, virulence factors present in the oral flora may now initiate Chronic Inflammatory Periodontal Disease (CIPD). CIPD represents an opportunistic or endogenous infection and efforts in

controlling the systemic focal activity of such infections must be based in proper immune system nutrition, function and regulation. Once the pathogens predominate, a complex biofilm can evade the immune system and function to gain access to systemic circulation (Socranksy and Haffajee 2002).

There are three metastatic mechanisms by which micro-organisms, bacterial antigens and local cytokines from the oral tissue gain access to circulation to produce systemic and secondary site effects such as the gastrointestinal system (Van Velzen et al 1984). Metastatic infection is the result of bacteremia which, although transient, may find susceptible tissue. Those bacteria which have evolved or acquired mechanisms for cellular adherence and colonization have been demonstrated to cause such conditions as infective endocarditis, acute bacterial myocarditis, brain abscess, prosthetic joint infections and others (Rams and Slots 1992). Metastatic injury, another mechanism, may occur from microbial toxins such as exotoxins and endotoxins (Van Velzen et al 1984). Gram-negative bacteria are constantly shedding endotoxins or lipopolysaccharides (LPS) which, in circulation, produce systemic effects. Even when gram-negative bacteria are killed by antimicrobials, large amounts of LPS are released which still exert immunological reactions such as pyrexia and malaise. Finally, metastatic inflammation is another mechanism whereby soluble antigen may react with a specific antibody giving rise to immune complex formation (Van Velzen et al 1984; Van Dyke et al 1986; Rams and Slots 1992).

The risk of metastasis from the oral cavity must be considered in those conditions possibly involving an immunodysfunction mechanism. Regarding metastatic inflammation, it is believed this mechanism can cause immunological injury and promote

secondary inflammation in inflammatory bowel disease (IBD) (Walker 1975). Although circulating immune complexes have been found in IBD, their etiology is still unknown (Jewell and Machennan 1973).

Among the various systemic manifestations of IBD are its oral symptoms, particularly ulcerations, and moderate to advanced involvement of periodontal disease. The oral flora of those with IBD was studied and was found to be remarkably different from normals (Van Dyke 1986). Whereas the typical oral flora consist of aerobic, gram-positive cocci and rods, the IBD patients demonstrated motile, anaerobic, gram-negative rods found to be consistent with the *Wolinella* species. Further, the altered flora were similar in all IBD patients with and without periodontal disease, although those subjects with CIPD simply showed higher gingival sulcus bacterial levels. Regarding host resistance, the patients afflicted with IBD and CIPD were found to possess a serum-mediated neutrophil chemotaxis defect (Van Dyke 1986). A similar defect is found in localized juvenile periodontitis, although this form of CIPD is not particular to IBD patients.

The goal of an interdisciplinary and integrated periodontal treatment plan for those with immunodysfunction would follow the traditional Prevention-Monitor-Treatment Paradigm. CIPD patients with immune dysfunction do not respond well to conventional therapy such as root planning and periodontal surgery. Nonetheless, proper oral hygiene and a proper maintenance period to monitor signs of exacerbations are necessary to minimize disease activity. Further, inflammatory gingivitis and periodontitis must be closely controlled to minimize the risk of metastasis and the potential for secondary complications. Also, nutritional therapy should be instituted to consider whether the

patient presents with nutrient deficiencies, conditional nutrient requirements or if there are any offending food sensitivities or allergies.

INFECTIONS AND ANTIGENS FROM APICAL PERIODONTITIS

Another potential source of bacterial infection and antigens may reside in apical periodontitis (AP) or endodontal (root canal) lesions, that is, infections of tooth origin at the tip or 'apex' of the root. AP was studied in epidemiological studies in which those with chronic dental infections demonstrated associations between acute myocardial infarction (Matilla et al 1989) and coronary atherosclerosis (Matilla et al 1993). AP infections may possess 200 species of predominately anaerobic, gram-negative rods of which proximity to circulation can facilitate metastasis and systemic dissemination (Tronstad 1992). A recent study isolated Gram-positive anaerobic bacteria from patients undergoing treatment of AP and concluded, based on biochemical and antibiotic sensitivity testing, that recovered micro-organisms from the bloodstream originated from the teeth undergoing endodontic therapy (Debilian 1995). The primary cause of AP is untreated dental caries which infect the pulpal cavity of the tooth resulting in apical extension into the surrounding bone to produce a lesion. Treatment options include tooth extraction or endodontic therapy; the former being the current treatment of choice. According to a recent study, participants reporting two or more endodontic treatments were more likely to have coronary heart disease than those not having had endodontic therapy (Caplan et al 2009).

The goal of endodontic or root canal therapy is to sterilize the tooth and, by the use of bacterial sampling, to verify sterility before completion of the root canal. However, due to the inability to reach secondary canals and the dentinal microtubules, the

assumption these teeth are sterile and not capable of focal infections is currently being questioned (Wu et al 2006). Post-treatment AP, a condition characterized as an asymptomatic tooth with radiographic healing after root canal therapy may, in fact, still present as a chronic infection capable of activating immune cells (Wu et al 2006). Further, post-treatment AP may be associated with 50-90% of root canal treated teeth (De Moor et al 2000; Kirkenrang et al 2001; Dugas et al 2003) and may serve as a physiological attempt to prevent metastasis of bacteria and toxic metabolic by-products into systemic circulation (Wu et al 2006).

The standard of care in the determination of healing of the AP lesion is the absence of a radiographic translucency as an indication that no osseous lesion is present. However, several researchers have repeatedly documented the presence of Post-Treatment AP despite radiographic evidence to the contrary (Bender and Selzer 1961; Bender 1982; van der Stelt 1985; Huumonen and Orstavik 2002). Some have found that a lesion up to 8 mm may be present without any trace of radiographic evidence (Stabholz et al 1994; Ricucci and Bergenholtz 2003).

The treatment of AP has recently been redefined as the elimination of post-treatment AP at both the radiographic and the histologic level (Orstavik and Pitt Ford 1998; Friedman 2002; Trope 2003). The causes of post-treatment AP are well documented and are, for the most part, not treatable with current endodontics. Apical Micro-surgery, recently perfected by microscopy (Rubenstein and Kim 1999; Nari et al 2005) removes the causative infected apical portion of the root and surrounding bone resulting in clinical removal of the Post-treatment AP lesion. The early reported successes of Apical Micro-surgery are promising; ninety-seven percent of lesions greater

than 10mm were completely healed within one year after surgery (Rubenstein and Kim 1999). It is a concern, particularly in patients presenting with imunodysfunction, to rule out Apical Periodontitis and Chronic Inflammatory Periodontal Disease as sources of long-standing, low grade infections capable of activating immune cells which may then cause secondary immunologic injury to other normal cells and infiltrate the gut (Ridker et al 1997, 2000, 2001).

ANTIGENIC POTENTIAL OF DENTAL BIOMATERIALS

Another area of metastatic concern may involve dental restorative and implant materials or biomaterials proper. All materials are reactive and all biological interfaces are receptive; hence, there is no such phenomenon as a non-reactive or universal biocompatible material. When biomaterials are placed in the oral cavity, they undergo corrosion, degradation, separation and absorption (Clifford 1990; Wataha 2003). Once absorbed, each individual's immune system will independently react or not react to determine if the test material is compatible for the person. Sensitized biomaterial antigens, unlike environmental antigens, when placed into the mouth, present the possibility of chronic, 24 hour-365 days per year exposure. There are very few government or industry standards for biocompatibility testing and, until recently, such testing was not performed routinely (Wataha 2003). Recently, toxicological research in Europe has generated intense interest in dental biomaterial compatibility (Ahlgwist et al 1998; Richardon 1999; Berlin et al 1999; Lindh et al 2001; Siblerud 1990; Lindgvist et al 1996; Lichtenberg 1993; Berglund et al 1997; Halbach 1998) and protocols are currently being developed to ensure a new level of safety can be achieved (Wahaha 2003).

Adverse reactions from sensitized dental materials include toxicity, inflammation, allergenicity and mutagenicity (Wataha 2003). Allergenicity in the oral cavity may occur by nickel, palladium or acrylic, which may result in a contact dermatitis (Wataha 2003). Thirty-eight percent of women demonstrate nickel allergies whereas up to three percent of men may be affected (Ragsdale 1998; Hindsen et al 1999). Nickel is utilized in adult crowns, pediatric stainless steel crowns, partial denture frameworks and orthodontic brackets and wires (Wataha 2003). Metal ions such as mercury (Hg^{2+}) and palladium (Pd^{2+}), components of restorative materials and crowns, both deplete glutathione levels in monocytes at subtoxic concentrations. Hydroxyethylmethacrylate (HEMA), a component of dental bonding systems, has also been demonstrated to reduce TNF-α secretion by monocytes at subtoxic levels (Wataha 2003). Bonded composites and sealants contain bis-phenol A (BPA), an estrogenic substance, although the physiological impact is unknown (Wataha 2003). Titanium, a component of implants, can negatively impact the immune system by causing hypersensitivity (Stejskal et al 1999; Ahlgren et al 2002; Ahnlinde et al 2000). Further, titanium has been found to corrode in the body, particularly when exposed to fluoride (Strietzel et al 1998; Reclaro et al 1998). IL-1 and complement were also found to be upregulated by titanium implants (Perala et al 1991). Nickel, copper, beryllium, some components of root canal sealers and dental resins have demonstrated mutagenic potential (Wataha 2003). The carcinogenicity of arsenic, hexavalent chromium (Cr^{6+}) and nickel (Ni^{2+}) has been established, whereas antimony and cobalt may be human carcinogens (Hayes 1996). Clinical biomaterials can corrode to produce systemic and remote site concentrations sufficient to predict an adverse reaction could occur, particularly with immune responses, metal overload and accumulation

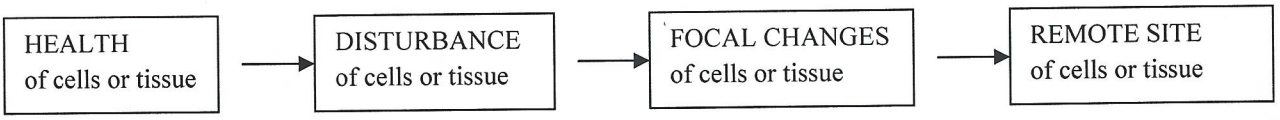
conditions (Black 1984). Epidemiological studies on a large scale are necessary to assess the systemic effects of biomaterials whether oral, knee or hip (Black 1984). Further, the release of metals in the mouth is of sufficient quantity to elicit an immunological reaction in sensitive individuals (Lindh et al 2002).

The management of a biomaterial-sensitized individual must focus on prevention and monitoring. The mechanism of toxicity, both individual and quantal, must be considered in terms of what these biomaterials can exert on the whole individual in terms of exposure, toxicokinetics, toxicodynamics and toxic interactions. Treatment, if necessary, must consider the immunological record of the patient. All known allergens and mutagens, regardless of amount, concentration or bio-availability, should not be implanted or placed in the oral cavity. If a sensitive or allergic material must be placed for lack of a biocompatible equivalent, steps should be taken, if possible, to desensitize the individual. A dental and orthopedic material reactivity screening test is now available to screen individuals for potential sensitization (Clifford Consulting and Research). There are at least 89 known reactive groups in over 6000 dental materials, and these can be analyzed to determine IgG or IgM sensitivity (Clifford 1990). A positive or adverse immunological reaction would preclude the use of any material containing a proven reactant to that patient. Such precautions would prevent dental reactive products from corrosion, chemical compounds and haptens from contributing to systemic and gastroenterological adverse events.

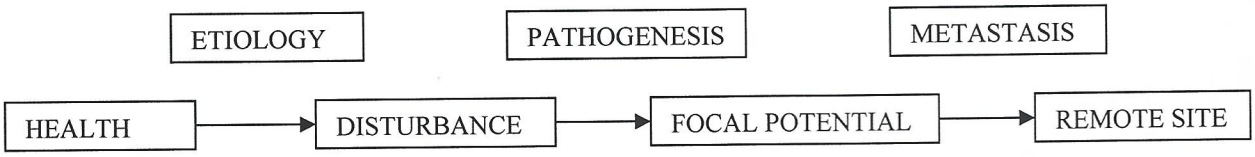
THE ALGORITHM AND DISEASE MATRIX

As one can appreciate, the scope and extent of interactions a the level of oral tissue alone is complex and, therefore, a methodology for the organization of data would

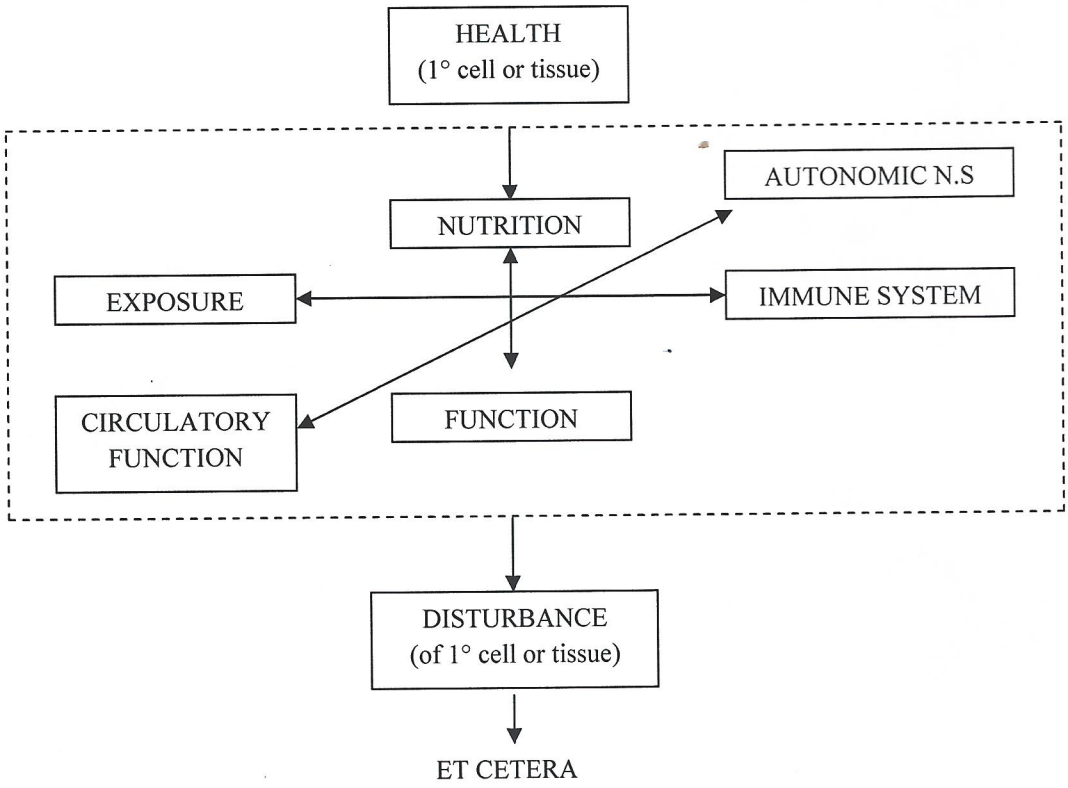
be useful. In order to study a "real-life" analysis of a patient or for a particular disease process, one would, in essence, need a 5-dimensional (5-D) complex analysis capability or an algorithm (Memoli 2007). In the 2-D framework, the mind's eye view of the disease process should be evident; for the subjects we are studying:



These represent actual states of health or disease; the processes represent those interactions responsible for homeostasis and breakdown:



In order to understand how this model can be studied in 3-D, we will represent it in a vertical column and define those interactions we can identify at each process:



The 3-D study of the etiological process would involve, here defined, the interactions between nutrition and function, exposure and immune system, autonomic nervous systems and circulatory function as represented on the x, y and z-axes to create a 3-D structure. Each category can be broken down into detail relevant to the subject or disease being studied. Further, each category should contain all pertinent research and clinical data to allow a coordinated and detailed study. Further, 'inter-process' interactions such as between nutrition and the immune system can be represented. The algorithm would be further constructed to include the processes of pathogenesis and metastasis to provide an overall "picture" or disease matrix of the pathology being studied.

The 4-D study would represent a Time-Line. In essence, the 3-D processes would be placed on a Time-Line at those significant moments in time or cellular events identifying milestones of the disease process. The 5-D MESA (Mental- Emotional Stress Analysis) would be an attempt to place the influence of consciousness and emotion on disease into the equation.

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