Materials Reactivity Testing

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Background, Basis And Procedures For The Immunological Evaluation Of Systemic Sensitization To Components Which Emanate From Biomaterials

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By
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To one and all, thank you.

About The Author

Born in 1944, Walter Jess Clifford is a native of Southeastern Arizona. Early schooling was provided in the public schools in Safford, Arizona, graduating from Safford High School in 1962. College experience began at Eastern Arizona College In Thatcher, and was completed at The University Of Arizona in Tucson where the Bachelor of Science ('68) and Master of Science ('75) degrees in microbiology and immunology were received. College attendance was punctuated by a two year break for full-time religious service and by a four year break for commissioned service in the United States Army.

Career service has been divided between clinical, teaching and research settings. Specialized areas of work, research, study and professional certification include general clinical microbiology, clinical and industrial anaerobic microbiology, clinical immunology, hematology, microscopy and food, dairy and sanitation microbiology. Cross-literacy in computer science and programming has enabled the automation and analysis of various aspects of work in the biological and clinical sciences. Publications include three papers, two monographs and an invited review. Mr. Clifford has taught microbiology, immunology and chemistry in the community college setting for nursing, biological science and pre-professional students. He has also worked in educational television and radio.

Professional affiliations include the American Society For Microbiology, The National Registry Of Microbiologists, the American Chemical Society, the American Association for the Advancement of Science, the American Association for Clinical Chemistry, the New York Academy of Science, and the International Academy of Oral Medicine and Toxicology.

Mr. Clifford was married to Laura Bigler in 1967, and they are the parents of eight children (four boys and four girls). The Cliffords make their home in Colorado Springs, Colorado, where they are active in various church and community affairs. Mr. Clifford has actively served as a church organist and choir director, holds a commercial pilot's license and is avocationally involved in photography and gardening.

SYNOPSIS

This monograph was written to provide information on the basis, background, protocol and procedures used in Materials Reactivity Testing. It is intended to document and demonstrate that when biomaterials (with special emphasis on dental restoratives) deteriorate, separate or break down in-vivo, chemical groups and entities are released as corrosion byproducts. These byproducts are absorbed via various routes of entry into the body of the patient and may be extremely toxic. The effects of absorbing such toxic chemical entities include a stimulation of the systemic immune mechanisms which produce immunoglobulins of the IgG, IgM, and IgA classes. They are quite specific against the offending chemical groups. The resultant immune record resident in the blood serum offers a detectable and reliable basis for determining substances which have been toxic for the given patient. Matching reactivity data from the immune record against known formularies and corrosion analysis patterns from biomaterials being considered for use can assist in selecting materials for the patient which are least likely to be offensive to the genetic and biochemical nature of the individual.

The immune record does not discriminate between those toxic exposures from biomaterials breakdown versus those exposures which may result from substances taken in from environment, workplace, food or water, etc. For this reason, examination of the immune record for evidence of toxic exposures of all varieties can assist in selecting biomaterials which are least likely to exacerbate any pre-existing problems originating from outside sources as well as from prior restorations and treatments.

Materials Reactivity Testing is a relatively simple procedure for both patient and professional. It can be a useful adjunct to a thourough program of good professional practices and careful selection of restoratives for each individual patient.

INTRODUCTION

Progress and accomplishment for the human family as chronicled in its history have often been accompanied, along with the conquests and discoveries, by a substantial litany of suffering and pain. Life, and more especially the prized quality of life, seem to come with a price. The sick and the crippled share a common desire just to have themselves repaired or restored to some semblance of normal function. Moreover where possible, they also seek for some restoration of esthetic appearance so as not to remain a spectacle or curiosity amongst their fellows.

The need to find appropriate repair or replacement materials for body tissues destroyed through disease or injury has been a goal of those who practice the healing arts for centuries. Medical and dental researchers have tried various combinations of materials and transplanted tissues in an attempt to find the right combination of strength, function, tolerance and esthetics. These efforts have necessarily led to a most unusual mixing of chemistry, physics, biology, physiology, pathology, immunology, engineering, pharmacology, psychology, toxicology and other scientific disciplines. Some of these efforts in biomaterials have given rise to entirely new disciplines. However, other areas have not fully kept pace with available knowledge and thus are now somewhat antiquated.

The biocompatibility and suitability of dental and medical restorative materials with other body tissue has been an area of considerable concern and controversy. Most of the materials currently in use in dentistry today have been developed and selected on the basis of a set of certain physical, chemical and mechanical criteria which lend themselves to repeatable testing and evaluation (142). These criteria have been fairly well standardized within the materials industry and are well understood. While this approach has led to improvements in the physical and esthetic quality of materials and to validation of manufacturer's claims, it has not uniformly brought complete success in clinical dentistal practice. The existence of a standard of biological testing and evaluation has neen sighted as completely lacking within the materials promulgated by the American Dental Association, and certain amalgam formulations have been speeded to market even before any studies could be published on their effects on pulp (351).

Although product design and the manufacturer's formulation for a dental restorative material can be carefully controlled, the ultimate application of the product comes to rest squarely on the shoulders of the dentist. His/her knowledge and ability to apply a mix of materials in locations for which they were recommended and in a manner which permits all of the properties of the combined materials to have the intended optimum expression is the critical variable. Improper placement technique, mixed material modalities and lack of adequate technical background on the part of those placing new and changing products is often a problem. But even under the most ideal conditions, with flawless placement technique and component matchups, there are still major differences with respect to clinical success. These deficiencies are often ignored or inadvertently mishandled by well-intentioned but uninformed professionals. Most blatant is the area of human material reactivity resulting from the individual patient biochemistry and physiology. Chemical and electrical factors which vary from patient to patient and even from day to day within the same patient can contribute to materials breakdown and the production of

byproducts which may not be well handled by the patient (74, 146, 179). No two patients are completely identical. One individual's nourishment may be another's poison, and all things seem to be a matter of degree (9).

It is not the purpose of this monograph to explore all of the toxicologic, pharmacologic nor metabolic activities of corrosion byproducts. Rather, it will concentrate on the immunologic detection of evidence that is generated by an adverse exposure from whatever source. The toxicology and pharmacology of dental restorative materials demands long-term concern not so much in the matter of acute poisonings and dysfunctions with rapid onset, but rather in the lower-grade chronic exposures to various substances which slowly exit the materials as corrosion and degradation byproducts (74). These moieties may accumulate in certain target tissues in amounts which can produce a number of poorly understood and often apparently unassociated effects. These target accumulations may eventually become sufficient to result in non-specific symptoms. Sometimes actual clinical disease can result.

Two key questions must be investigated: First, how long will it take during slow administration of a toxic substance for a dysfunction or disease to manifest in the patient (see 9, 43, 116)? Second, how do we identify those individuals which are immunologically sensitized or toxicologically sensitive to the material?

THE DEVELOPMENT OF DENTAL MATERIALS SCIENCE

The criteria for choosing dental materials has shown a spasmotic progression, with most development oriented solely towards expedience and durability. Developments addressing many aspects of biocompatible materials have definitely lagged behind. Historically, the first tooth replacements or tooth repairs were borrowed or recarved from animal or human teeth. The Phoenicians, Etruscans, Greeks and Romans are amongst those known to have attempted to employ gold metal in the oral cavity. The Phoenicians are credited as originating use of gold appliances at least 2500 years ago (142, 158, 159, 306, 490). These appliances were often held in place with fine gold wires. Early evidence of artificial teeth and crowns made of gold or gold alloy, soldered to small gold rings which held them in place, are found in Roman ruins dating from about 700 BC.

The filling or repairing of carious teeth was originally accomplished with lead and other substances, not for permanent repair purposes, but solely to give support to the tooth against breakage during the extraction process. The use of ground mastic, alum, honey, oil of cloves, ivory, bone, waxes, gums, ground pearl and ground coral have all been noted at one time or another as filling materials (142, 158, 159, 306, 422, 490, 529, 530). At the same time as these early excursions in dental materials science were being made, Hippocrates is reported to have used gold wire and linen threads to mend broken bones with the hope of obtaining performance similar to that of the dental practitioners. Little changed after these early experiments and exploratory techniques for a number of centuries.

The use of gold leaf to fill tooth cavities appeared during the 15th century in Italy. Of greater importance was the procedure of carious matter removal prior to placing the gold leaf. Progress in the development of restorative materials accelerated, and porcelain, tin, gold, copper, bronze, silver, vulcanite, and even wood were all employed in restorative efforts.

The 18th century saw the introduction of a Chinese invention of mercury and silver to France as a means of making a quick, inexpensive plastic amalgam paste. Amalgam alloy formulation was controlled by the individual dentist and might include tin, zinc, copper and other metals along with the silver. Common to all amalgam is mercury, for amalgam is defined as an alloy, mixture or blend of various metals with mercury (526). Many of the common amalgam formulations used even today had been introduced by the year 1900. Progress since the turn of this century has largely been a matter of refining the ratio of metals in the amalgam mix to enhance the physical characteristics, improving the testing procedures which evaluate and standardize the other dental materials. New dental material developments have also come from the application of space-age materials developed in other disciplines and then applied to dentistry. There is a notable interest in making materials inexpensive and giving them qualities which emphasize ease of placement and workability for the dentist. There is also continuing interest in the strength, elasticity and durability of dental restoratives.

It is unfortunate that some of the very finest and most durable dental materials in-vitro often do not lend themselves well for in-vivo use in the mouths of some patients. Although many of these materials have superb wear and retentional characteristics, the leaching of various combinations of corrosion and degradation byproducts from the materials renders them relatively biologically unsuitable for those persons who possess systemic

immune sensitivities. These sensitized individuals may already be laboring with substantial chemical body burdens from sources outside of dentistry. The simple criteria of what is least costly for the dentist to procure and what is quickest and easiest to place into the mouth of a patient can no longer be the primary critera of the modern dental practice. Increasingly, the practice of dental medicine must consider the long range total systemic health effects of any treatment being applied to the mouth. Virtually every organ system in the body may be affected by dental treatment and by the presence of inappropriate dental materials. While longevity of the tooth or filling is an important consideration, the quality of systemic health is of greater importance.

Thus, the choice of any restorative material must include consideration of how the patient will handle the material's byproducts when the mass begins to deteriorate or break down. No restorative material, including the ceramics, gold and stainless steels will last forever. In the breakdown sequences, some tissues can be adversely affected and their function impaired. Still other tissues may not tolerate the presence of abnormal galvanically generated electrical interference or the adverse effects of electrically and chemically stimulated aberrant metabolites on cellular DNA and mitochondrial sites when the restorative material byproducts become involved in various metabolic activities and pathways.

THE SCIENCE AND DEVELOPMENT OF IMMUNOLOGIC PROCEDURES

The capacity to distinguish that which is useful or benign as opposed to that which harms the body is primarily a surveillance function of the immune system. The human body's defenses against the "invasion" of unwanted substances makes it possible to neutralize, isolate or kill the offender and prepare it for voiding from the body. This is partly accomplished by the generation of antibodies which specifically react with the offending substance. It is from these residual antibodies that Materials Reactivity Testing finds its basis.

Immune challengers often leave behind additional evidence of their encounters with the body by sensitizing the immune system so that future encounters with the same challenge can be more easily handled. However, continual challenge of the system with the offending substances can backfire and produce undesireable results. In matters of systemic sensitization, it does not matter whether the challenge originated from external environmental sources or from internal sources such as dental materials. Any further presentation of the challenge may lead to the formation of in-vivo immune complexes, cytotoxic reactions which damage tissues, autoimmune processes and in certain cases to tolerance of toxic materials with no attempt to protect the body further. If an offending material from any source or combination of sources has led to a systemic response by the immune system with the generation of immune globulins and memory lymphocytes, then it is seldom appropriate to use anything containing or generating that substance within that person's body again (22, 23, 24, 25, 260, 261, 447, 494, 528). Consideration of this fact must be as important when selecting a dental material as are the mechanical and esthetic considerations. To do less is to commit a purposeful pollution of the body, inasmuch as such pollution has been defined as the release of substances which have a measureable adverse effect on the living organism (62).

Research published in 1933 indicated an awareness of potential for tissue damage and intolerance due to the byproducts of dental materials breakdown (155). There is implication in the findings that immune processes may have played a role in the problem with adverse substances. To properly understand the workings of the immune system and the testing protocols for assessing prior immune exposure to adverse substances, let us take a brief overview of the historical and technical background of immunology and serology.

Using a large variety of structural, chemical, electrical and oscillatory data, the white blood cells and possibly other structures can usually detect materials which are not intended to be within the body (26, 27, 175, 211, 262, 410). The sequence of events following the detection of foreign matter leads to the production of specific processes which can help to protect the body from the adverse material, by binding and immobilizing the material so that it can be removed. They help to neutralize certain of its noxious effects of both animate and inanimate materials (147).

As early as the 16th century, physicians and scientists such as Giralamo Fracostoro began to suspect that disease might be caused by the presence of foreign materials gaining entrance into the body (70, 83, 258). Late in the 18th century, Edward Jenner made his famous observations that milkmaids who developed the relatively mild cowpox fever after handling cattle with the disease seemed to be immune to deadly smallpox (70, 84, 258, 286, 214). In a rather daring experiment, Jenner obtained fluid from

the sores of cowpox victims and inoculated it into otherwise healthy individuals. He then waited until these test subjects developed and ran the course of cowpox. When they recovered, he took fluid from the sores of smallpox victims and injected the same test subjects. Not only did they fail to develop smallpox, but they seemed immune to it even in later years.

Other notable historical developments followed at the hands of researchers with names such as Bassi, Henle, Semmelweis, Pasteur, Lister, and Koch (70, 84, 178, 286). Each, in turn, found ever greater evidence that disease and destruction of body function could be associated with the invasion of foreign entities into the internal systems of the body. Different foreign agents produced different disease symptoms, but all had the peculiar similarity of disruption of the normal state of good health.

In the latter 19th century, Eli Metchnikoff published his findings of strange cells which seemed to "eat" anything that got into the body which was foreign (70, 83, 214, 258, 286). First observing these strange ameboid cells in starfish larva and water fleas, he later found phagocytic cells in various other animals and within the blood of humans. Emil von Behring and Shibasaburo Kitasato were able to show that serum from the blood of those who had survived diphtheria had a factor which was lacking in the serum of those who had not been infected with the disease (70, 286). They had seen the effects of special proteins which are now called antibodies, which are produced by the immune system as a protective and neutralizing resource against outside matter or lifeforms.

By the early years of the 20th century, serologic techniques were applied to make or confirm diagnosis of exposure to infectious or foreign materials (214, 256). Work carried out by notables such as von Behring, Kitasato, Pasteur, Pfeiffer, Isaef, Bordet, Ehrlich, Landsteiner, Kraus and others demonstrated that the reactivity of the proteins within the serum was quite specific, which is to say that a protein (antibody) which reacted with one kind of foreign entity (antigen) was not reactive with most other antigens (214, 280). This notion of specificity gave rise to the ability to determine the nature of the offending foreign material and to routine methods for in-vitro testing of the patient's responses to these materials (211). While methods, equipment and sophistication of testing have all increased, the concepts and principles of immunology have remained remarkably intact from these early periods.

The early observations of certain blood cells which had the ability to engulf and "eat" foreign material led to the formation of the cellular theories of immunity (343). These white blood cells were capable first of recognizing that which was foreign, and then of attacking it directly. The term which was applied to the process was phagocytosis. However, there were certain problems and observations which could not be directly accounted for by the phagocytic mechanism. The observations of Fodor, von Behring and Kitasato suggested that immune sera carried something which could act in the protective role without the presence of cells (466), and a conflicting theory of immune activity referred to as the humoral theory arose. Fortunately, the conflict was resolved by demonstrating that both cellular and humoral immunity play an interactive role in overall body defense, and that the observations of both sides were correct as far as they had been carried out.

Currently, immunological techniques are carried out at the molecular level. The structures and systems of the white cells have been microscopically observed in their functional roles. The proteins which comprise the antibody population are being mapped by molecular biologists. The interrelationship of the immune cells and their formed products show

tremendous intricacy and a high success rate in protecting the body. The residual antibodies left by these interactions permits one to accurately determine the nature of the offending agent. These are the antibodies upon which Materials Reactivity Testing for dental materials depends. Please note that the principal immunoglobulins which create the trail of evidence are IgG, IgM and IgA, or the systemic immunoglobulins as opposed to IgE which is associated with allergic reactions and hypersensitivities.

Use of immune system products as a detector for adverse exposure to chemicals and chemical complexes is neither new nor novel. Molecular biologists and physiologists have found that receptor sites on white blood cells are capable of the recognition of inorganic as well as organic stimulants, and are very electrically sensitive to the ionic nature of most chemical complexes (19, 203, 213, 229, 234, 249, 251, 271, 317, 345, 369, 385, 476, 516, 534). It is notable from some of the aforementioned references that very small concentrations of the offending antigen are sufficient to induce tremendous immune responses. Even very minor exposures can be shown to set up conditions which may deliver massive responses upon subsequent exposure with substantial damage to tissues in various parts of the body (272).

ADVERSE IMMUNE ACTIONS FROM DENTAL RESTORATIVE MATERIALS

Susceptibility factors to toxicity from either metals or organic moieties found in dental materials vary with the individual nature peculiar to each patient. Individual host reactivity will strongly influence both dose-effect and dose-response relationships (272), and the issue of biological thresholds which differ from patient to patient will be examined below. The general immune responses which may interfere with normal functions of body tissue or which may be destructive to the organization and structure of tissue have been classified into four major groups by Coombs and Gell (135). These are as follows: (a) anaphylactic or immediate hypersensitivity, (b) cytotoxic sensitization, (c) immune complexing agents sensitization and (d) cell-mediated actions by sensitized white cells. Of these, the cytotoxic and immune complexing agents are of primary concern with biomaterials. They are mainly of general systemic nature. Cell-mediated actions and immediate hypersensitivities are of lesser importance in most patients, but may still play a role in health problems.

All of these systems of sensitization and hypersensitization are dependent upon an initial contact with an offending substance, followed at a later time by secondary and tertiary exposures. It is also readily acknowledged that most original systemic immune sensitization contacts are from sources other that dental or medical. Most are the result of contaminants and dissolved or suspended materials in food, water, air, chemicals which are used in the home and workplace, personal care materials and other environmental exposures (81, 223). However, the mechanism by which dental or medical materials enter the problem as part of secondary and tertiary exposures and exacerbate existing immune reactions is quite well demonstrated. Occasionally the dental and medical products can also be the primary source of the problem. There is sufficient problem of direct skin absorption of mercury with subsequent toxic reactions that dentists and ancillary operatory personnel are advised to stop and immediately wash hands or other sites of direct skin contact with soap and water (1, 275, 472). Protocols to reduce exposure to vapor, increase ventilation in the operatory and provide for tightly closed storage of new and scrap mercury have also been promolgated (1, 472). Storage of waste napkins and used tools is also noted to be a source of risk to dental office personnel. Eating and drinking where mercury has been used is expressly forbidden.

For most chemicals and many drugs, it is not the native molecule that is toxic to the body. Studies have shown that the native molecule needs to be broken down and/or have remaining unreacted components and/or be bound with tissue component sites to reach maximum interference or toxicity (102, 153, 224, 393, 495, 533). This is demonstrated by the nature of the antibodies which form against the byproducts (148, 200, 534). In the case of either prosthetic or dental materials, the antigen which stimulates the immune system begins as a chemically bound constituent (organic or inorganic) of the restorative material. Some of the material may simply be physically broken off from the mass in either micro or macro proportions and swallowed during placement, mastication or phonation (74, 76, 236, 431, 507, 510, 511). Some antigens may be converted to organically active form by the metabolic actions of certain indigenous oral flora (151, 230, 241, 391, 394, 426, 458). Some of the restorative mass is expected to be removed and swallowed during brushing, professional polishing or the prophylactic care or alteration of amalgam fillings (74, 134, 291, 348, 400). Vapors produced during such prophylaxis may even constitute a hazard to operatory

personnel as well as to the patient (145). Other products may enter the body by direct osmotic migratory penetration of the dermal surroundings or gingiva by ionized forms of the components (459). This may lead to local conditions such as inflammation, hyperkeratinization, desquamation and general oral lesions (12, 38, 51, 79, 170, 179, 172, 195, 227, 264, 359, 448, 507). It is obvious that neither oral and muscle tissues nor bone and cartilage are impermeable to the breakdown products of materials placed in the mouth or other areas of the body. When the byproducts of these materials are brought into the tissues, they may react producing either a local immunologic challenge or systemically as part of a general challenge (38, 51, 75, 112, 172, 195, 470, 507, 554).

In the case of mercury from the common silver mercury filling, conventional wisdom has assumed that a passivation layer forms over the filling and that the mercury in the filling essentially remains intact (427). However, it is increasingly apparent that such wisdom is faulty. The mercury may exit the amalgam mass as a vapor at physiological temperature, pH and osmotic conditions by free kinetic action and surface tension property as described by physical law. It may also be vaporized by local stress and mechanical vectoring acting on surface tensions during mastication, phonation and routine oral movement without the need for any complex chemistry to take place whatsoever (3, 61, 64, 65, 76, 79, 107, 122, 126, 141, 174, 195, 201, 228, 236, 400, 481, 482, 483, 501, 510, 511, 512, 513, 514). Brushing and other prophylactic care remove any passivated layers of corrosion and bring the new mercury underneath to fresh exposures from all sources mentioned above on a cyclic basis (79, 126, 348). Contrary to accepted tradition, the surface layer on a silver-mercury amalgam does not completely repair and recover its passivated layer for several hours after stress has been applied (126). If additional stress is placed on the surface in the interim, the passivated layer may not completely heal at all during daytime and evening hours. Bruxing and other oral movements may maintain the condition through the night for some patients. It has been estimated that for patients with an average number of amalgam filling surfaces, the offloading of mercury by these simple mechanisms approximates 3ug per square centimeter of surface or more. The total mercury released into the body from the fillings each day may equal or even exceed the daily sum received from all food and drink sources combined (3, 79, 81, 126, 201, 400, 510, 511, 512, 513). Mercury is not the only corrosion byproduct which follows certain of these pathways.

Various body fluids including saliva, blood, mucosal secretions, sweat, pancreatic fluid, bile, gastrointestinal contents and interstitial liquids, by virtue of their dissolved solids, pH, oxidation-reduction potential, organic components and the temperature of the body environment, induce and/or complete a variety of biologically closed electrical circuits. These circuits promote the ionization, dissolution and migration of the components of virtually any restorative material or prosthetic devices in contact with those fluids, whether in the mouth as intact masses or elsewhere in the body as broken bits or abrasions from the original oral mass (3, 5, 8, 13, 16, 30, 38, 61, 70, 71, 72, 73, 74, 76, 78, 79, 103, 106, 116, 117, 118, 124, 137, 138, 142, 143, 146, 151, 156, 162, 171, 177, 179, 183, 184, 185, 186, 190, 191, 202, 217, 219, 235, 237, 238, 239, 241, 244, 248, 253, 255, 263, 290, 294, 297, 307, 308, 312, 313, 319, 323, 324, 336, 345, 349, 356, 357, 358, 359, 362, 379, 388, 395, 407, 413, 415, 420, 425, 428, 438, 439, 440, 458, 460, 461, 462, 463, 470, 471, 475, 479, 480, 492, 493, 498, 502, 507, 519, 537, 538, 542, 546, 547, 550, 552, 553). The resulting corrosion of the intact masses leads to pitting, loss of

strength and discoloration of the restorative material. This further releases the corrosion byproduct components from the masses as metallic salts, organometallic complexes or organic molecules to join with the bits already broken physically from the restorations. Many of the released substances will evidence strong electrical mobility. Their presence may lead to further deterioration of the surrounding restorative substrates as is seen in the case of mercury, nickel, chromium, copper, tin, composite resins and fluoride compounds coming into contact with gold, silver and palladium structures in the mouth (38, 79, 196, 204, 240, 284, 330, 406, 519). Gold surfaces may discolor and dirty residue may become evident on the amalgam surfaces. Such changes observed in artificial saliva in the laboratory show grossly observable changes within an hour or so (330). The corrosion mentioned has been reported to occur acrossed the entire surface of any metallic mass involved in the process, and is not confined to any special site nor to a minimal area (241). Thus, the rate of breakdown is substantially affected by total surface area of all metallic or conducting masses which have continuity of contact either physically or via fluid conducting bridge within the oral cavity. The electroactivity is not restricted to the metallic components, either (252).

The potentially harmful effects of corrosion or release of unreacted or imtermediary byproducts relate immediately to the cytotoxicity and immunogenicity of the byproducts released. These effects may portend a greater hazard in the latter roles than to the actual slow loss of strength of the restorative mass (61, 74, 94, 102, 111, 118, 187, 224, 247, 288, 365, 470, 489, 495, 499, 506, 524). The formation of protective metallothioneins and the rapid influx of competitive essential trace metals to the tissues invaded by corrosion forms attests to the powerful stimulus they present (111, 122, 252, 489). Studies have shown that chemical constituents similar to those found in the corrosion process proceed to disrupt microtubules from which mitotic spindles are formed, distort cellular organelles and instigate powerful cytolytic/cytotoxic influences on various types of mammalian cells (247). Inhibition of proper growth was also noted, and complete cellular distruction could be observed with some forms.

Typically, these byproducts of corrosion may take the form of acetates, acrylamides, carbonates, chlorides, chromates, iodides, malates, methylates, nitrates, nitrites, oxides, oxylates, phosphates, silicates, sulphates, sulfides, tartrates, and metallic ions complexed into binding sites on various proteins, amino acids, peptides, carbohydrates, lipids, unpolymerized organic precursors and various monomers (8, 13, 16, 50, 53, 56, 61, 72, 74, 75, 78, 79, 102, 103, 104, 116, 117, 119, 122, 142, 143, 146, 151, 156, 176, 177, 179, 180, 184, 186, 194, 195, 202, 217, 224, 231, 232, 239, 241, 253, 281, 283, 290, 295, 310, 313, 318, 319, 325, 326, 335, 342, 347, 356, 359, 363, 375, 376, 388, 391, 394, 395, 396, 397, 409, 412, 425, 429, 430, 431, 432, 433, 434, 439, 458, 470, 471, 484, 495, 499, 500, 507, 517, 518, 519, 525, 539, 549, 550, 554).

The chemistry and energy exchange by which these reactions take place have been studied or reviewed by several researchers (17, 61, 74, 79, 125, 142, 240, 252, 379, 498). A reaction set showing the expected electrical exchanges has been worked out and published by Dr. Krister Nilner (377) and is approximated as follows in Figure 1.

Figure 1. ORAL GALVANIC CHEMISTRY

A summary of the primary electrochemistry involved in oral galvanism and the degradation of restorative materials (after Dr. Nilner).

Anodic Reaction:

$Me \rightarrow Me^{n+} + ne^-$ (Metal Dissolution)

Cathodic Reactions:

$2H^+ + 2e^- \longrightarrow H_2$ (Hydrogen Evolution)

$O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$ (Oxygen Reduction)

$O_2 + 2H^+ + 4e^- \rightarrow H_2O_2$ (Oxygen Reduction)

$O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$ (Oxygen Reduction)

$Me^{n+} + ze^- \longrightarrow Me^{(n-z)}$ (Metal Ion Reduction)

$Me^{n+} + ne^- \longrightarrow Me$ (Metal Deposition)

The vapors, salts and complexes which exit the restorative or prosthetic mass enter the blood, cells and interstitial spaces by a diversity of means. As noted above, some complexes will simply be swallowed as part of the dissolved solids in the saliva or as part of a food bolus. Action by hydrochloric acid and other components of the stomach may accelerate the dissolving and conversion of these solids to bioavailable forms (173, 415). Dietary intake and plaque found on the teeth can enter into the breakdown process (517, 518). Absorption into the body may occur from various locations along the alimentary canal with special emphasis on the mucosal surfaces of the digestive tract (76, 157, 289, 378, 449). These surfaces are rich in both complex chemistries and bindable moieties as well as many broken nutrients which are also being prepared for absorption. The salts and corrosion products may easily attach to some of these nutrients and gain accelerated entry. The microbial flora and even the sterile humic content of the bowel also contribute significantly to facilitating bioconversion and absorption. These organisms and substances have been demonstrated to have the capability to transform virtually all of the metals and many of the organics used in biomaterials into forms with very high biological availability and marked assimilation characteristics (166, 173, 252).

Other vapors, salts or complexes may be inhaled into the lungs, with absorption occuring through the mucosae of the trachea, bronchial tree and the alveoli of the lungs (61, 86, 100, 122, 165, 206, 215, 328, 331, 349, 367, 374, 399, 418, 491, 510, 511, 512). Such actions may leave partial residues behind at mucosal surfaces which are radiopaque, and actual depositions of elements such as mercury, nickel, and chromium may accumulate in the lungs to levels which are grossly manifest either at surgery, autopsy or upon radiological examination (100, 165, 254, 276, 356). Some further suggest that mercury which first entered the blood can

also deposit as metallic mercury in the lung or be exhaled as mercury vapor after lung conversion (10, 105, 120, 276). Mercury which embolizes in the body may have concomitant sterile abcesses, necrotizing bronchitis or perfusion abnormalities associated with it (90, 91, 100, 133, 278, 282, 441, 505). Inhaled mercury vapor has been reported to lead to pneumonitis in acute exposure, with concomitant tachypnea, cough, fever, gastrointestinal disturbance and central nervous system manifestations (331). Accumulation of white blood cells to the source of the irritation, the induction of fever and their subsequent activities is an important immunological means of protection from further insult and in preparing the irritant for removal.

Some moieties are absorbed directly into adjacent hard and soft tissues via migration and electroosmosis (8, 14, 15, 38, 40, 47, 50, 51, 52, 68, 69, 99, 101, 122, 124, 143, 164, 179, 191, 202, 220, 222, 225, 257, 264, 279, 296, 316, 329, 332, 334, 339, 352, 356, 361, 372, 377, 408, 425, 448, 453, 460, 461, 465, 468, 469, 470, 484, 485, 499, 507, 525, 555, 556). Discolorations, polypous hyperplasias, loss of tissue strength and integrity, impairment of blood, release of histamines with allergic indications, nutrient and waste flow as well as altered pH and redox conditions may result, with concomitant changes in surrounding microflora and dissolved solids. Localized edema and erythema may occur as these moieties infiltrate the tissue with pain sensations which may be nondescript and difficult to identify with a single focus. Tremor and motor interference may also be a factor. Small brownish-black irregularities may be seen in affected connective tissue in the oral region, sometimes accompanied by granulomatous and chronic inflammatory lesions as well as influxes of macrocytic cells (80, 82, 101). Collagen, elastic fiber, vascular walls, epithelium, basement membranes, nerve sheaths and the sarcolemma of muscle bundles have shown these same effects. The immunological stimuli and responses are classical. Human studies have shown the characteristic inflammations and drawing of phagocytic and immune cells (82). In animal model, it has been shown that potassium and albumin levels increase markedly with concomitant elevation of general serum osmolality as these ionized and bound products enter surrounding tissues (68, 194). Ligand binding and accumulation with direct bearing on albumin levels is expected (252). Some of these effects may also be directly attributed to the adverse action of metals such as mercury on various binding sites in hemoglobin and the destruction of both form and function of the heme unit (41, 68, 110, 122, 157, 181, 199, 221, 378, 488).

Though route of entry may differ, the corrosion chemical groups are electroactive, migratory in varied degrees and highly antigenic (53, 132, 138, 146, 179, 187, 200, 218, 229, 250, 272, 289, 307, 317, 340, 362, 363, 372, 373, 428, 470, 496, 499, 506, 534, 535, 539). Their activity and reactivity is believed to be due in part to the following group of interactive factors. These include (a) the intermolecular forces which develop at the interface between tissue and these chemicals, (b) the presence of various hydrogen and sulphur bonds, (c) certain dipole-dipole interactions which are known to occur with some of the reactants, (d) electrostatic forces and energy field orientations found especially in the organometallic complexes and amino acid bound metals, (e) donor-acceptor bonds, (f) acid-base relationships, (g) physical morphology and (h) actual tertiary structure (131, 445). The greatest level of activity is associated with a high surface free energy on the surfaces of the tooth or bone and the surfaces of restorative masses which may also be tied to galvanic activity in the region. The application of certain surfactants such as

aminfluoride reduces both the electrical activity and the adhesion rate of pellicle and proteins to tooth surfaces, perhaps through the formation of an electrically polarized or insulated layer of calcium fluorapatite (87).

The chemical entities that become attached to macromolecular proteins, nucleoproteins, metallothioneins or other organic structures are considered to be the most antigenic and most toxic (21, 44, 45, 46, 49, 53, 58, 59, 72, 74, 83, 116, 108, 117, 122, 136, 143, 146, 169, 179, 188, 195, 200, 203, 208, 211, 230, 252, 266, 267, 292, 299, 341, 347, 359, 363, 397, 470, 489, 496, 499, 523, 539, 548). The noble metals and those of the so-called transition bridge region of the periodic table seem especially prone to congregate with available protein and to become incorporated with it as organically active entities (252, 435). Other metals such as cobalt and chromium show a 30 to 40 times greater corrosion rate in the presence of protein and saline, with intense binding of the metallic ion to the protein to form organometallic structures (118). Copper has been implicated for interference in mitichondrial and nuclear structures (169) and may have adverse impact on the general immune response and tissue division activities (51). Zinc and copper acting together have been implicated in the induction of multiple polypous hyperplasias (51). Silver and mercury acting together were implicated in eliciting various low grade foriegn body responses from oral tissues adjacent to their placement (309). Nickel has been shown to be involved in the customary contact dermatitis familiar to allergists as well as inducing precipitating antibodies which are systemic in nature and which are associated with widespread erythema and possible internal and external vesicular eruptions following oral challenge with nickel (187, 506). Gold and mercury have also been demonstrated to induce IgG and IgM antibodies which may combine with the antigenic metals and deposit in layers in various tissues (200, 272, 274, 287, 298, 315, 451, 478).

Aluminum found in some ceramics, porcelains and composites exits many of these restorative masses at accelerated rates of 30 times greater than normal or more in the presence of fluoride ions. It also has special affinity for the proteins and structures found in brain and nervous tissue (436). Aluminum ion entering the blood is expected to interact with silicic acid to form aluminosilicate species solublized by citrates, which in turn have been associated with core materials in senile plaques found in Alzheimer's patients (56, 92, 93). Aluminum ion deposition has also been found in neurofibrillary tangles within the neurons in many of these same patients as well as some with certain forms of Parkinson's disease (56, 403, 402). The metabolic eitiology and biology of aluminum may suggest other pathways in which this ion has an adverse impact in many disease processes including renal failure, osteomalacia, interference with membranes and DNA, alteration of ATP actions and various types of dementia (150, 268, 327, 333, 497, 508, 535, 541, 545).

With mercury, the suggested impact is not limited to structural cellular proteins in the membranes and organelles, but the capacity of virtually any protein to participate as a mercury ligand opens a broad avenue of involvement with bound, mobile or soluble protein (52, 66, 195, 363, 499). The qualities of the bound mercury assume those of the host to which it binds much more closely than of native mercury itself (446). Severe damage to the gastrointestinal tract, proximal tubules of the kidney, cortical and cerebral tissue, nerve structures in the sensory system, cardiovascular homeostasis and to certain structures in the liver has been seen (52, 55, 88, 97, 108, 121, 124, 125, 172, 198, 226, 267, 272, 311, 346, 387, 404, 559). Patients who have ingested organically-bound

mercury over a long period have shown symptoms resembling amyotrophic lateral sclerosis and muscular dystrophy, with gingival swelling and a bluish line at the gum margins or erythematous rash in some (267). Other patients who have had exposure to mercury vapor have had similar ALS symptoms, some of which remeliorated after three months in a mercury-free environment (4, 39). This suggests great affinity for a wide variety of binding sites. One other exceptionally disturbing aspect of this broad spectrum protein association and mobility lies in the concentrations of mercury which may show up in mammary glands, lactational secretions and in the fetus (85, 220, 514, 557, 558). One group of researchers has shown substantial interference in various placential enzyme activities and fetal development patterns by mercury and its compounds at very low exposure levels in human and animal model (269, 270). Another team has shown that transfer of radio-labeled dental mercury from mother's teeth to fetus in sheep model can accumulate fetal mercury to very substantial levels within 29 days or less from time of dental placement (220).

The organic moieties may have affinity for binding which is at least equal to the metallic byproducts. Ligands characterized by low polarizability, high electronegativity, fairly large electric charge, small physical size with inaccessable empty orbitals of high energy (carboxylic groups, hydroxlic, phosphate, and amino groups [oxygen and nitrogen]) preferentially complex small, highly electropositive metal ions that have a large positive charge/oxidation state and low polarizability with few outer electrons. Such metallic ions are not easily excited with ionic and electrostatic bonds. Examples of the metals include magnesium, calcium, manganese, aluminum, selenium, galium, indium, lanthanum, chromium, cobalt, iron, titanium, zinc, tin, and arsenic. Ligands of high polarizability, relatively low electronegativity, small negative charge, and large physical size, with accessable, low-lying empty orbitals such as sulfhydryl groups, preferentially form covalent and covalent-type bonds with large metal ions. These metallic ions are characterized by low electropositivity and high polarizability, small positive charge, and low oxidation number, with several easily excited outer electrons. Such metals are copper, silver, gold, thallium, mercury, palladium, platinum, tellurium, lead, bismuth, antimony, and vanadium (252). Both anodic and cathodic constituents mentioned in the lists above are found in biomaterials breakdown products as well as in various tissues and secretions. The ability to affiliate is contributory to materials breakdown, tissue binding and various transport mechanisms.

Both organic and metallic products accumulate in fatty tissue to substantial levels (446). They interfere with general lipid metabolism. When the body is placed under stress and fatty deposits are mobilized to meet metabolic and energy needs, these entities are freshly released in substantial quantities to circulate in the blood stream. The mechanism by which these actions take place is quite similar to that which is encountered with the lipid binding of pesticides, herbicides, antifungal agents and various environmental pollutants which enter the body. Some of the agents will find new deposition sites to attach to around the body which are non-fatty in nature. Others will actually enter back into adipose tissue after the crisis to repeat the mass release at a later stress point (192, 412, 421). This phenomenon must be considered with patients who do not exhibit a high response rate in symptom aleviation after the sources of toxic substances have been removed. Failure to ameliorate observed clinical problems may continue for a period into postintervention treatment modalities. The stress factors which can initiate the release of fatty

substances from storage (along with any bound toxic products therein) are not only the physical stimuli of exercise, but also include heat exposure, emotional and mental stress, illness, food deprivation and even the overnight fast during sleep (127, 437, 540, 544).

The stress of the overnight fast has been suggested as a possible reason for the exacerbation and intensification of toxic symptoms experienced by some patients when they first arise in the morning from sleep (412). Nocturnal release of fat-bound toxic moieties may be involved in some patients who have difficulty sleeping or have irregular sleep patterns. It may also explain why urine concentrations of mercury and other toxic materials are concentrated in first morning urine when there has been no noticeable increase in current system intake. Another consideration in symptomology is the sweating which often occurs at night during sleep when there is no particular temperature load to account for the activity. Sweating is an excellent means of voiding metallic and some organic toxics which may be present in increased levels during lipid mobilization. Some health professionals have used this mechanism as a means of reducing body burden by purposely placing patients in a modest ventilated heat environment for controlled periods (130, 144, 412, 520). For some patients, toxicity and pathology may result as much from failure to excrete toxic materials such as mercury as from the gross exposure to the material (206).

Perhaps most disturbing of all recent research delving into the consequences of toxic distribution to body sites is an animal study using pregnant sheep model (220, 514). While it has been previously known that mercury from various sources can cross placental barrier (108, 109, 123), the current study raises immediate alarm as to the contribution of dental amalgam to in-utero exposures. Using radiolabeled mercury in twelve fresh occulusal amalgam fillings per ewe, the study was able to demonstrate a direct passage of mercury from those fillings to both maternal and fetal blood, amniotic fluid and various body tissues of each. Placental concentration of radiolabeled mercury over passage of gestation was recorded. After partum, radiolabeled mercury concentration from the fillings began to show in mammary secretions with great potential to provide a high risk exposure to mercury for the suckling newborn. Methods used in this important research virtually assure that mercury under study had to originate from the dental fillings and from no other source, indigenous or exogenous. Questions regarding possible impeded tissue and system development in endocrine, nervous and immune systems must be raised in light of demonstrated exposure to mercury from mother's dental placements during embryonic development and early developmental stages postpartum.

Continuing chronic exposure to low-dose mercury levels manifests with changes in agglutinin titers, alteration of the overall leucocyte count, specific alterations of phagocytic cells and changes in complement levels in the peripheral blood (496). When the ingested corrosion products remain primarily intact or their ions attach to certain prominent binding sites of circulating serum proteins other that the immunoglobulins, the first form of contact with the immune system will probably be a direct physical encounter with a phagocyte from the polymorphonuclear neutrophils, or PMN's (34, 320, 457, 476, 535). These cells are relatively short-lived, highly specialized and frequently last no more than 3 or 4 weeks after origination in the bone marrow (34, 35). At maturation, the PMN contains azural granules with peroxidase and other enzymes, and secondary or specific granules which do not contain readily stained materials (32, 33, 536). The PMN activates several systems in the presence of antigenic surfaces or in

the presence of certain immune complexes composed of reacted antigen and antibody (34) and prepares to attack the offending material (5, 28, 443). Engulfment by phagocytosis brings the material or complex into the interior of the PMN with a membrane partially wrapped around it, forming a small packet called a phagosome (36, 515). Special reactive oxygen metabolites are produced for action against the ingested products within the phagosome (19, 20, 29, 242, 249, 423, 527). Lysosomal granules resident within the cytoplasm of the PMN move to the phagosome and discharge their contents into the capsule with the ingested material, usually just before the phagosome seals itself off from general contact with the balance of the PMN's cytoplasmic contents (36, 205, 234, 442, 532). Unfortunately, some of the corrosion product material may actually be able to diffuse out into the cytoplasm of the PMN along with some of the lysozymes prior to phagosome sealing, and may set the stage for inactivating and killing the PMN. The gross appearance of increased ghost or smudge cells in a stained blood smear or at detected levels greater than 50 per microliter actual count in whole blood may be a strong indication of such activity. The observation is in keeping with depressions in total available phagocyte counts mentioned above (496).

When the digestive and catabolic activities within the phagosome have been completed as far as they can proceed, most of the residue will be encapsuled and voided (31) or excreted as a soluble system (152) with eventual exit through the lymphatic system, the kidney and the bowel (476). Some of the generated loose molecules from the phagosomal residue may adhere to the surface of the phagocyte and can cause various problems with the further function or integrity of the PMN's membrane and detection system (34). This will render the PMN useless for further action and ready for discard by the body. It may create a depletion condition and place stress on the immune mechanism and hemopoietic tissue to generate additional replacement granulocytic cells.

However, if the phagosomal residue is complexed into an organic form and elaborated by the intact PMN, or if it induces inactivation or killing of the phagocyte and the uncontrolled residue escapes into the body fluids, both the bound fragments of the PMN and the residue may become very active antigens (314, 337, 405). The residue may also become very active as a spoiler by substituting onto various tissue binding sites throughout the body in place of normally occuring enzymes, metabolites or substructures which have related identity (125). This latter action can effectively stop or severely impair body function in sites quite remote from the oral cavity and seldom, if ever, related to dentistry. If the combined moieties enter the bowel, they may be further complexed within the gut by normally occuring fecal flora or by fecal materials themselves. These new complexes can be processed as an organically active antigen by other immune cells resident in or around the intestinal mucosa with autoimmune implications (53, 54, 113, 161, 181, 205, 233, 293, 528).

When the phagocytic cell actions are complete or have been impaired past the point of recovery, the resulting antigenic structures present to the second line of immune defense. This process is responsible for the generation of immune globulins and the humoral aspect of protective factors. Most of the antigens will pass through a multiphasic process with several cells becoming involved in an afferent entry limb of analyzing and preparatory actions. After processing, this is followed by an efferent limb of productive and defensive actions as specific proteins are synthesized against the antigen.

The first site of contact in the afferent limb of routine antigen

processing is expected to be the mononuclear phagocyte, usually in the form of a macrophage (83, 208, 251, 503). Approximately 60% of the monocytic cell population resides in the marginal blood pool (imterstitial spaces) under normal circumstances (504) where they may have ready contact with antigenic substances which have infiltrated the tissue. First attraction of the macrophage to the antigenic matter is thought to be a combination of both electrical and chemotactic cascaded steps which follow a logical progression (5, 37, 113, 114, 385, 370, 535). The ability of the macrophage to respond to these stimuli is believed to reside in the minute regional variations of geometry, charge, polarity and spatial energy fields along the surface structures of its outer membrane, although the predominant expected electrical charge overall on all white blood cells is negative. The metallic cations which have been introduced as corrosion byproducts from restorative materials, which can readily be phagocitized or pinocytized by the macrophage (504), as well as those cations which have become actively bound up with large organic molecules during an absorption process or in a phagosome are expected to exert a relatively positive charge in the region of the molecule where they have become bound. This helps to create electrical as well as spatial alterations in the surfaces of these organometallic complexes. The macrophage assimilates the offending materials into itself by process of phagocytosis, rhopheocytosis or pinocytosis, depending on the nature, size and type of any macromolecules involved. If the phagocytized material is sufficiently toxic unto itself or if it is organically modified to a configuration which will bind in certain sites within the substructures of the macrophage or to certain secreted factors which control mononuclear cell proliferation, it may at this early stage shut down some macrophage function and elicit a compensatory reaction by other immune cells in response to a detected deficiency or immune crisis (60, 168, 300, 302, 322, 335, 467). Otherwise, the macrophage processes the antigenic material into a suitable binding configuration and then displays the processed surface structure of the ingested substance out on its own membrane surface (147, 208, 251, 317, 457, 551). Simultaneous with this membrane surface display comes the active secretion of various lymphokines of the interlukin group by the macrophage. They serve in turn to attract various programmed helper T-cells (2, 155, 197, 369, 389, 474). The T-cells actively bind to the macrophage in the region of the display and undergo changes to activate and initiate the reading and replication of the surface template of the displayed antigenic substance (210, 212). Certain additional lymphokines secreted by the lymphocytes, in turn, further activate new steps in the macrophage's response in a coordinated exchange between macrophage and lymphocyte (364, 370).

Some of the activated T-cells (also referred to as T4 cells) will secrete a lymphokine called B-cell Growth Factor (BCGF) which is intended to stimulate the hemopoietic tissues into new B-lymphoid cell production. BCGF calls certain lymphocyte maturation sites into activity in the maturation sequences of B-cells capable of manufacturing immune globulins (11, 182, 350, 390, 516). At some point another lymphokine known as B-cell Differentiation Factor (BCDF) is released by the helper T-cells which actually instructs the B-cells to begin production of globulins specifically keyed to the template and pattern of the offending chemical moieties. These globulins are also referred to as the systemic antibodies (95, 140, 160, 197, 243, 419, 474, 521).

Some of the lymphocytes may not have the capacity to respond to the secreted lymphokines or may respond in an aberrant manner under stimulation due to the chemical and electrical nature of some of the antigenic

metallo-groups which are present. These metallo-groups are toxic, pharmacologically and physiologically active, and are found in the various secretions of the lymphocytes from earlier steps in the antigen processing. Some of the metallo products may have been picked up directly by the lymphocyte from the blood plasma and interstitial fluids after absorption through the tissues or escape from the PMN's or macrophages (98, 161, 163, 245, 285, 383, 380). The actual impairment of response within these lymphocytes may be due to interference with DNA activity and strand breakage, genetic alteration, mitochondrial interactions or membrane interference (42, 79, 94, 115, 161, 167, 193, 345, 368, 380, 381, 382, 384, 386, 401, 424, 452, 454, 455, 496). In any case, immune competence is compromised, some viability of existing cells is lost and compensation mechanisms for more lymphocyte production may be activated. It is for this reason that clinical personnel are advised to perform lymphocyte function and viability testing even when actual lymphocyte numbers appear to be adequate. Some of the lymphocytes present may not be capable of full function, and some may be completely nullified. This also points to another method of approaching reactivity testing. When lymphocytes are exposed to challenge materials such as expected corrosion byproducts and they lose viability in vitro, adverse impact against proper function might well be expected if these same products are encountered by this patient in vivo. The author has examined this phenomenon in the laboratory using both corrosion byproducts and various local anesthetics as the challenge materials. Viability loss is predictable and replicateable (unpublished data).

Reactivity testing relies on the immune globulins produced by the B-lymphocytes. The overall function of these glycoproteins (a) is to inactivate soluble toxic products, (b) facilitate phagocytosis of offending materials, (c) interact with serum complement in certain binding actions and (d) help to reduce proliferation of some etiological agents (47, 129). Attention in testing is primarily focused on those globulins which result from systemic reactions rather than those which are commonly associated with hypersensitive and allergic-type phenomena.

Some of these systemic globulins, or antibodies, will appear early in the sensitization process and are referred to as IgM antibodies (212, 466). Comprising approximately 10% of the immune globulin present in the body, IgM is associated with increased complement fixation and implementation of the complement cascade. The IgM level rapidly gives way to IgG as the dominant immunoglobulin. IgG comprises approximately 75% of the immune globulin present in the adult. It is recognized that IgG is itself actually comprised of a number of subspecies, and that the expected levels of each are under both genetic and challenge control (212, 266, 466). A third type of immune globulin is IgA, which may be found in secretions such as saliva, tears, bronchial secretions, nasal fluids, prostatic fluid, vaginal fluids and intestinal mucosa fluids. Its purpose is centered in local prevention of infection and possibly in preventing access of massive amounts of exogenous antigen to the general immunologic system (147, 273, 466).

Once an antigen has been introduced, processed and an antibody produced against it, a small body of memory lymphocytes with proper coding and imprinting for that antigen are also produced (371). These memory lymphs provide anamnesis, or make it possible for the body to recall and initiate mainline immunoglobulin production on a much quicker and more intense basis if the antigen is found in the body a second time. These memory lymphs have been suggested to have a lifespan lasting for years and are thought to reside in the tissue interstitial spaces rather than in general

circulation.

Antibody is produced and contributed into blood plasma for circulation throughout the body's vascular and interstitial spaces. Some of this antibody will bind to various cellular sites among the blood and other cells or may continue to circulate until it either chemically reacts with the antigen for which it has been programmed or until it is lost from the body gradually through bowel, nephric and lymphatic activity (96, 129, 147, 212, 466). If there is little or no further contact or challenge with the antigen, then the immunoglobulin levels of the specific antibody may drop to undetectable levels over a period of time ranging from weeks to months (83, 216, 259). If additional antigen is presented in the future, however, the memory lymphs can quickly elevate titers to levels well above the initial response (216).

LONG-TERM CONSEQUENCES FROM CONTINUING IMMUNE CHALLENGE

Long-term consequences from repeated immune challenge will be dependent upon the type and amount of globulins produced and ready availability of the stimulating antigens to interact. In the case of globulins formed against the corrosion byproducts of restorative materials or prosthetic devices and appliances, some antigens may elicit only IgM, IgA and IgG forms without the presence of IgE globulin as expected in a classical Type I allergy (216, 507). In other cases, IgE will be present along with the other systemic globulin types (175, 187, 272, 506, 509, 534). Thus, an allergic-type reaction may or may not be associated with an immune sensitization and response. The absence of the allergic symptoms does not rule out an ongoing immune challenge and does not constitute a particularly desirable means of demonstrating the safety of a restorative material for a particular patient.

It was noted in at least one study that when amalgam materials were implanted into the subcutaneous muscles of rats, a necrotic process could be demonstrated in the tissue just adjacent to the foreign bodies by the 16th day after implanting. Strong hyperemia and infiltration were evident in only some of the sites examined. By the 25th day, the formation of poorly defined fibrous walls had begun to appear around the sites with concomitant fibroblasts pointing into the foriegn bodies and a few giant cells. Most of the gross pathological signs began to remeliorate into subsequent weeks. Examination at day 75 showed well-defined fibrous walls surrounding the bodies which varied in thickness and blended into surrounding tissues. Of special note, lymphocytes could be found resident in the tissues adjacent to these walled areas. Continuing necrotic zones adjacent to the foreign bodies but inside the walls continued to progress throughout the test period (63). There is good suggestion of antigenicity and immune action within these tissue sites. progressed.

Some of the antibodies produced by the various actions may react with the offending antigenic materials which are the corrosion byproducts from restorative masses. This reaction results in the formation of an immune complex of antigen and antibody in-vivo. This is especially true when the antigen has bound with or become associated with normal body tissue. Such complexes are often recognized as a key part of autoimmune disease, or those diseases in which the immune system has begun a fight against the body itself (209, 213, 477, 494). Once formed, these complexes attract certain immune cells, complement and cytolytic factors to the sites where they may be bound. Resultant tissue destruction, lesions and dysfunction are seen in a variety of diseases, including systemic lupus erythematosis, collagen disease, scleroderma, polymyositis, rheumatoid arthritis, pemphius, asthma, primary billiary cirrhosis, Goodpasture's syndrome, Grave's disease, idiopathic neutropenia, idiopathic thrombocytopenia purpura, nephrotic syndrome, ulcerative colitis, chronic active hepatitis, autoimmune hemolytic anemia, pernicious anemia and several diseases of the pancreatic and cardiac tissues (272, 274, 287, 298, 315, 451, 478, 494, 543). When the autoimmune reaction involves key binding sites which are cell surface receptors, diseases such as myasthenia gravis and insulin-related problems such as the acanthosis nigricans syndrome and ataxia-telangiectasia result.

It is useful to note the symptoms and conditions which often accompany these diseases. They might include weakness, fatigue of voluntary muscles, depression, neurologic impairment and transmission disorders, decreased

outputs of endocrines (adrenalin, pituitary secretions, sex hormones, insulin and thyroid), anemias and hemoglobin dysfunction, skin irritation, internal ulcerations, digestive disruption, interference with the clotting mechanism, irritation of border membranes in the kidneys and creation of fibrous formations therein, irritation and inflammation of the bladder and related structures, defective nutrient uptake, dysfunction in vitamin and mineral mediations, aches in the joints and connective tissue, impairment of lymphatic operation and voiding, inflammation and fluid accumulation in various tissues, interference in oxygen/carbon-dioxide exchange, impairment of exchanges at the blood-brain barrier, triggering of cardiac disease, possible malignant development, and accumulation of macromolecules at various sites which simply stop the supply of nutrients to cells and the outflow of wastes (44, 45, 46, 88, 108, 246, 344, 417, 444, 487, 494, 523). Many symptoms continue in some patients for weeks and months even after the offending antigens have been removed from the body. This portends long-term immunogenic effects and antigens bound to key target sites in tissue (53, 88, 274, 298, 315). There is little wonder that many of these patients experience loss of energy, appetite and vigor. Many will present with persistent headaches, insomnia, depression, suicidal behavior, anger, fear, paranoia, clouded thinking and judgement, detachment and inability to cope with even gentle stresses. It is noted that these very symptoms have all been reported as occuring with increased frequency among dentists and their operatory personnel who have second-handed exposure to toxics from materials they are working with on a daily basis (360, 444). The conditions in patients and professionals are closely related to those expected with general toxicity from various sources (18, 246, 301, 344, 355, 353, 360, 414, 417, 450, 531). The cross-correlation between continuing toxicity and immune-based reactions has been made (18, 246, 301, 353, 360, 450).

Because the appearance of such symptoms can be subtle and interlaced with other problems, a broad analysis of clinical questionnaires and histories was undertaken by the author while serving as Director of Research at the Toxic Element Research Foundation. The results were published as part of a seminar presented to dentists, physicians and other health care professionals by TERF in 1986. This sampling of patient responses was drawn from a database of 1320 patients for which clinical, laboratory and historical data had been obtained as part of their ongoing treatment regimes in connection with toxic conditions of various types. Patients were qualified for inclusion by having high levels of toxic metals in keratinized tissue, blood cell counts and hemoglobin levels in compensatory ranges, and by blood serum chemistry values and urine excretion values deemed to reflect toxic conditions by the treating professionals. These data are synopsized in Figure 2. The percentages of patients with symptoms related to those listed in the preceding paragraph is of at least casual interest.

FIGURE 2. SUMMARY OF SYMPTOM FREQUENCY

(Data based on 1320 respondents indicating presence of symptom)

EXPERIENCED BY 70% OF PATIENTS OR MORE:
Unexplained irritability
Constant or very frequent periods of depression

EXPERIENCED BY 60% OF PATIENTS OR MORE:
Numbness and tingling in extremities
Frequent urination during the night
Urgent urination onset
Unexplained chronic fatigue
Cold hands and feet, even in moderate/warm weather
Bloated feeling most of the time

EXPERIENCED BY 50% OF PATIENTS OR MORE:
Difficulty remembering or use of memory
Sudden, unexplained or unsolicited anger
Constipation on a regular basis
Uncontrolled twitching of facial and other muscles
Difficulty in making even simple decisions

EXPERIENCED BY 40% OF PATIENTS OR MORE:
Experience frequent leg cramps
Constant or frequent ringing or noise in ears
Get out of breath easily
Frequent or recurring heartburn
Excessive itching
Otherwise unexplained rashes, skin irritations

EXPERIENCED BY 30% OF PATIENTS OR MORE:
Constant or frequent metallic taste in mouth
Jumpy, jittery, nervous
Constant death wish or suicidal intent
Frequent insomnia
Unexplained chest pains
Constant or frequent pain in joints
Tachycardia
Tremors or shakes of hands, feet, head, etc.

EXPERIENCED BY 20% OF PATIENTS OR MORE:
Unexplained fluid retention
Burning sensation on the tongue
Get headaches just after eating
Frequent diarrhea or alternating diarrhea and constipation

(This table is synopsized from data developed and published by the author at the Toxic Element Research Foundation, Colorado Springs, CO.

Symptoms such are listed in Figure 2 can result from conditions other than immunologic challenges. Also, immune sensitizations and complex formations can result from a wide variety of stimuli in food, water, air, personal care products, chemicals used in the home and workplace, general environment, and in the personal lifestyle of the individual. Health care professionals will recognize that not all of the problems listed can be laid at the feet of dental restoratives and medical devices. Additional research is certainly indicated. However, restorative materials, prosthetic appliances and implantation devices have a unique opportunity to input challenge to the immune system in a very close proximity to body reactive sites (220, 514). Further, these placements are subjected to numerous fluids and environments which create corrosion products that are extremely immunoactive. The very nature of these fluids and environments encourages the formation of organically bound metals and the rapid conversion of inorganic ions to organic in intermediary steps (8, 43, 71, 75, 76, 115, 118, 125, 162, 170, 181, 183, 203, 227, 230, 250, 264, 300, 317, 338, 339, 341, 345, 383, 384, 396, 398, 413, 424, 428, 432, 433, 448, 452, 456, 464, 465, 475, 479, 480, 546, 537, 538, 548, 549). From the information in Table 1 and an examination of the symptoms found in diseases which are caused by or are related to the formation of immune complexes, it may be suggested that the problem of patient tolerance of their environment and especially some of the restorative materials placed in their bodies may not be quite as good as has been assumed by the various elements of the professional community. Although great concern is placed upon physical strength of the restorative or prosthetic material and upon its longevity, professional attitudes towards biological tolerance of materials extends little further than answering complaints when a filling or joint replacement causes rapid and extreme irritation of the immediate region about the placement. Even with irritation to the pulp, gingiva, tongue or buccal tissue, the prevailing professional attitude is generally to encourage the patient to sit out the irritation in the hopes that tolerance can be induced with time. Should the immune system be coaxed into tolerance, the issue of long-term effects of immune complexes in other areas of the body is largely ignored. For the patient who did present with regional irritation, few if any professionals will bother to check on the patient for other systemic symptoms which might be related to restorative materials in three, six or twelve months. Ironically, at least 75% of the 1320 analyzed patients who were seen in consultation were able to correlate the onset of their symptoms within a timeframe ranging from several days to a month or so from the time they had had dental intervention and restorative treatments.

An understanding of the timing of immune responses, both primary and secondary, and of the concept of individual biological thresholds may be helpful. When an antigenic stimulus is presented to the immune mechanism for the first time, the production of antibody and the differentiation of specialized cells is not immediate. Phagocytosis by the PMN population may proceed as soon as contact between the white cell and the antigenic material takes place. Macrophages may enter the process upon first contact. However, the first completion of the immune activation cascade and programming of B-lymphocytes to secrete globulin requires between 4 and 5 days for the appearance of IgM antibodies and 5 to 7 days from initial presentation of antigen for the appearance of IgG antibodies (83, 89, 128, 259, 371). This suggests that the first significant formation of immune complexes may not be seen for a week or more after the initial presentation of new antigenic corrosion products. More rapid response will be seen only if the patient has had prior sensitization with the development of memory

lymphocytes. In many cases, levels of corrosion products may not rise to significant levels for several weeks. Thus, first onset of symptoms of a given pathology related to immune complexes could be delayed for as long as 4 to 8 weeks after initial placement of restorative materials. If there has been no patient education as to the potential for a problem, and if the professional does not actively enquire after the welfare of the patient within a month or two, who will expect that dentistry or medicine has been involved with new problems just beginning to manifest in the patient?

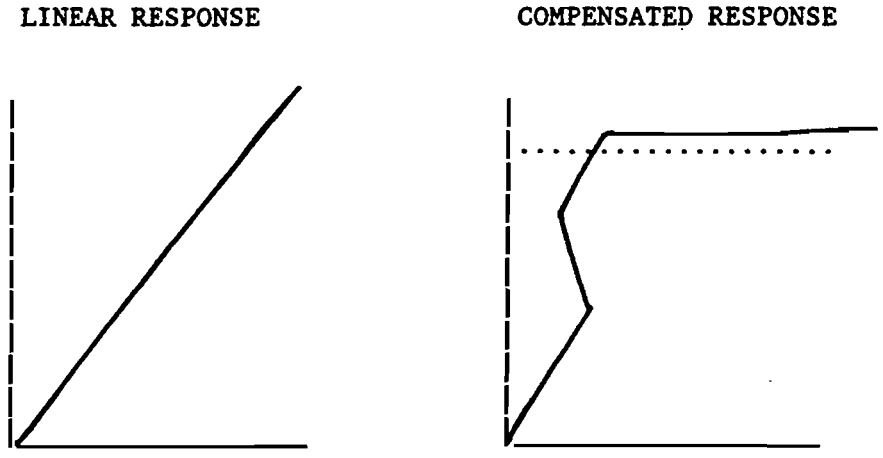
The professional handling the patient may wish, in addition to taking some time to advise the patient of symptoms and conditions to watch for, to schedule a brief check up for the patient in-office in 3 to 4 weeks for the purpose of verifying physical tolerance of materials and completion of a brief questionnaire which inquires into changes noted in factors mentioned in Figure 2. Office auxiliaries can be very helpful with this activity, and the patient might be provided with the questionnaire in advance so as to minimize the time factor with staff members for those patients who are doing well with their materials. It may even be possible to handle this requirement via phone if the patient-professional relationship is sufficiently developed, especially after several professional sessions in the office.

THE NATURE AND PROBLEMS OF THRESHOLD PHENOMENA

Patients are unique in that each person has various thresholds set within the body that will vary from one individual to the next. An accurate model of biological thresholds in relation to functional performance and sense of well-being has been well reviewed in a recent presentation by Aldridge (9). Conceptually, no two patients will react in the same manner as each other to the presentation of the same antigenic stimulus due to differing compensation and tolerance abilities in their physiological makeup. The condition or occupancy of crucial binding sites within the structure or spatial orientation of a macromolecule and the total number of such binding sites available within the given tissue becomes the criteria for whether or not a clinical or other response will take place. This has been shown in connection with inhaled pollutants as well as in several active enzyme studies involving acetylcholine and organophosphorus compounds in various settings (6, 7, 67, 277, 411). If capacity exists during a stress or crisis for a toxin or competitive foreign chemical agent to inactivate, occupy or cover a binding site, the body may be able to adjust and either produce more substrate/binding sites, or alternatively redirect the appropriate chemistry along an alternate pathway. In some cases, the alternate pathway may completely bypass the expected chemical metabolites routinely used.

A common misunderstanding of toxic interference, reactivity and impairment suggests the existence of a linear response relationship between loss of physiologic function, sense of health and well being decreasing in direct proportion to the degree of stress or challenge levied against a system. This misunderstanding is graphically portrayed to the left in Figure 3, and reflects an inaccurate correlation. A more accurate graphic model portraying actual degradation of physiologic function and sense of well-being is shown to the right in Figure 3.

FIGURE 3.



Increasing Metabolic Stress (vertical)
VS.
Complete System Dysfunction / Loss Of Sense Of Well Being (horizontal)

On the right, the upper horizontal line represents the actual threshold level of the patient at which loss of function or of well being is rapidly and dramatically lost. At this point, the body has no further mechanism by which to increase ability to counter a toxic effect nor any further alternate metabolic pathways which can be substituted for a poisoned function. As the stress against function increases below the challenge level of the threshold limit, the body is able to increase capacity or select alternate pathways in such a manner that performance is compensated. The patient may not even be aware that there has been any difficulty whatsoever by the criteria of general sense of well-being. When the challenge or toxic phenomenon reaches the threshold level, the patient may suddenly and unexpectedly present with onset of symptoms or pathologies which are a complete surprise to himself and to attending professionals. No two patients present in an identical manner, and no two patients have threshold limits which are at the same concentration or degree. It has been suggested that such great variability exists in humans in their response to mercury alone that an entire new investigation may be required to analyze host factors and their entire role in patient variability (207).

Although variations of symptoms and pathologies are substantial, the progression towards threshold aquisition can be broken into four prime phases, with acute and chronic toxicities or challenges differing only in timespan and duration (9). These four phases might be defines as follows.

FOUR PHASES OF THRESHOLD LEVEL ACQUISITION
[After Aldridge (9)]

a. DELIVERY OF CHALLENGE - This phase involves the acquisition, absorption, physical movement and chemical binding or modification of the challenge. It may also be interlinked with certain secretory and excretionary functions such as has been previously mentioned with the PMN's and macrophages.

b. FIRST REACTIONS WITH TARGETS - This phase is the setting for either covalent or dissociable interactions with macromolecules, membranes, biosynthetic machinery and feedback binding sites. It may also involve the generation of aberrant chemical substrates and moieties.

c. BIOCHEMICAL AND PHYSIOLOGICAL CHANGES - At this phase, there may be generation of additional substrates, capacity, and binding sites, as well as secondary changes in composition, function and morphology. Most toxicities are not readily apparent externally at this juncture, and the patient is seldom aware of the altered activity.

d. CONSEQUENCE TO THE INDIVIDUAL - When the fourth phase is reached, either a complete shift is made into alternate pathways which avoid the targets affected in 2nd phase, or the individual reaches threshold and has immediate and severe manifestation of pathology, clinical signs, symptoms or syndromes. Please note that symptoms and syndromes may cover several body systems so that confusion may result as to the exact causative etiology.

The question of patient response can be summarized by asking whether a challenge load leads to a reaction with target tissue in a manner that further leads to clinical signs or whether the loading simply induces chemical and physiological changes which compensate for that level. At some point, the chemical and physiological changes may also lead to a variety of secondary clinical signs. Unfortunately, some symptoms may abate with suggestion of clinical improvement only to be replaced in the long term with other symptoms which are slow to appear. This has been acutely observed with various neurotoxic materials (303, 304, 305). An interesting early study of sensitization with mercury was reported in which the patient did not show overt symptoms with silver amalgam fillings in the mouth for a number of years, but suddenly had adverse immune activity with urticaria after a new filling was placed (321). This leaves the suggestion that challenges to any of the body systems may proceed through a variety of functional variations and stages which cloud the issue of causation and effect with the issues of secondary effects and side effects resulting from the alteration of primary physiological chemistry. It may not be appropriate to set absolute exposure standards for any given foreign substance based solely on appearance or cessation of the primary effect expected, but rather on the additive and cumulative burden of all effects and contributions to loss or compromise of functions placed upon the body as well.

Medicine and dentistry cannot formulate exposure standards for the body based solely upon the contribution of corrosion products from restorative and prosthetic materials. The body burden of adverse compounds and foreign challenges from age, dietary, environmental and lifestyle sources must also be taken into factor. Genetic and teratologic predisposition based upon geographic, anthropologic and ancestoral background must also be factored (9, 67, 412). Finally, a system of individual challenge assessment must be available for each person who is to be subjected to restorative or reconstructive work prior to any application of materials. Threshold for the individual is the ultimate problem to be addressed. General qualification of restoratives cannot be made for an entire populace when some of the corrosion products shown to be generated in references previously cited in this monograph have the potential for inducing massive destruction of health and well being in systemically sensitized individuals. Lifelong exposure to adverse materials from restoratives and prosthetics may not preclude physiologic function at an acceptable level if total body burden of similar acting materials is held in check. Complete loss of function and compensation may result from even minute temporary exposure if body burden and environmental wounding are already at or near threshold. This means that even a nanogram of adverse materials exposure may be excessive and unsafe for many patients.

Complication of the issue results from the understanding that clinical circumstances are seldom, if ever, mediated solely by a single threshold or compensatory pathway. Multiple thresholds, interactions, interwoven pathways and metabolite concentrations are the rule (9). The unfortunate aspect of thresholds is that physical function may appear normal in both man and animals while memory, problem solving and any cognitive resources may be diminished (189, 416, 425, 486, 522). The tragic aspect is that such losses may be slow to appear and may be judged to be associated with subsequent events or even with unrelated stimuli. Gradual loss or impairment of thinking or rationality are generally postulated to be the result of advancing age or genetic makeup of the individual. If, on some days, the patient has lucidity and on others seems lost, it must be considered that such cyclic presentation may represent an effort to cope with multiple

interactive thresholds. When deficiencies in vitamins and trace minerals are borderline and the patient is already coping with marginal buffer zone in physiologic, psychologic and pharmacologic factors, even a simple change in eating habits or schedule can be enough to push the individual through a critical threshold with resulting impairment of judgement, rationality or lucidity. Gradual increases in severity of impairment may also be seen as compensation routes become inundated, saturated and less resurgent.

It would be unfair not to mention at this point that chemistry and chemicals are not the only factors to be considered. Osmotic tension in the lungs varies as barometric pressure changes, with oxygen-carbon dioxide exchange rates and volumes being affected accordingly. Electrical generation via galvanic action within the oral cavity, the gut and certain other tissues dramatically alters ionizations throughout the body and hence, the availability of binding sites, catalysts, trace minerals in useable form, metabolic substrates and membrane viability. These must also be considered as part of the regulation and activation of threshold phenomena and the ultimate control of body physiology, function and form.

Control of thresholds and the buffer zone between the threshold levels of the individual and current challenge levels can be mediated by several mechanisms. These include the reduction of total body burden of challenge, and fortification or optimization of body systems and compensations. If reduction can be made in certain heavy metals contributed from the environment or lifestyle, this action may make it possible to accept and tolerate a certain level of input from restorative and prosthetic materials without achieving threshold and loss of function. If body systems can be brought to high potential and the supply of nutrients and trace minerals can be brought to optimum levels, this will reduce the total number of thresholds likely to interact with the restorative materials problem. Compromised systems have numerous thresholds ready to acquire.

A brief revisit to the periodic table of elements studied during high school and college chemistry days may be helpful. (A copy of the table may be found in Appendix A of this monograph). You may recall that the elements have been organized into the periodic table in certain columns and rows for a purpose. The elements differ from each other basically by virtue of the number of protons, neutrons and electrons which their atoms contain. The elements which share a common column in the table have the same number of electrons expected to be found in the outermost level of the electron cloud where chemical reactivity is usually determined. The elements which share a row in the table have a common quality in that their outermost electrons all occupy a common region in the swarm levels. There is a major segment of elements, however, which bend the rules somewhat. These are referred to as the transition elements, and they occupy a special area which lies somewhat centered in the periodic table. They have some compliance with the column and row concepts of the table, but differ from other elements in that they do not continue to add electrons in sequence like building blocks from the lowest level up to the outermost levels. They have in common a similar number of electrons in their outermost regions and add electrons by skipping around in the levels down in the inner regions of the swarm. Thus, these transition elements, with similar complements of electrons in their outermost levels, have some remarkable similarities in their chemical and electrical behavior.

This makes for an interesting academic study, but also makes for a disaster in health considerations. Because of the similarities in chemical behavior, these elements can and do cause many physiologic problems in common. For the patient, this means that there is not one set of problems

resulting due to lead contamination in the body, and another set of problems resulting from arsenic, and still another from cadmium and mercury. Rather, the adverse presence of these metals results in additive effects in which the problems caused by lead are exacerbated further by arsenic, and still further from cadmium and further by mercury. If the patient has a sensitivity to mercury and judiciously avoids contact with the metal, but has a lead exposure or a heavy cadmium intake, the amount of mercury needed to acquire the threshold for mercury may often be only a fraction of what is normally required because some of the systems which mercury poisons or interferes with have already been impaired by the lead and cadmium. Rather than needing an exposure of 50 micrograms of mercury to achieve threshold, it may only take 5 micrograms as long as the lead and cadmium are present. And this sample combination of three elements is certainly not the only potential collection for additive effects.

Herein lies the great struggle in establishing health limits of exposure to adverse materials. Not only do we deal with genetic and hereditary differences between individuals, but we must also examine total body burden of adverse elemental neighbors from the transition group as found in the environment, food, water and lifestyle occupied and practiced by each individual. Setting a practical limit for exposure must be ultra-conservative and must be interlinked with other elements that have similar reactivities and health impingements. Animal studies which examine only one toxic parameter at a time must be modified to consider multiple toxic impacts before they can be effectively extrapolated to the needs of humankind. When medicine and dentistry fail to take these factors into consideration, but simply set individual limits of exposure for each element which might cause offense to the body, the risk to patient mounts geometrically in real world terms. Patients may be left to suffer a substantial spectrum of maladies because the causative agent of their threshold acquisition may not be one of the primary focal factors usually suspected or examined in subsequent health-care diagnostic efforts by the attending professional. In the allopathic approach usually followed by orthodox western medicine, great effort will be expended to treat the symptoms and evidence of threshold acquisition, but seldom the root cause. Additive effects of heavy metals and various organic compounds are ignored because the patient has not exceeded the exposure limit values derived from studies for any single element involved. Laboratory test findings for levels of individual toxic materials in blood, urine and keratinized tissue samples may never show sufficient elevation to account for clinical observation of malfunction or deficiency.

In this regard, there is an urgent need for collaborative team examination and diagnosis of patients by practitioners from various clinical disciplines. Terf war barriers between physicians, dentists, allopaths, osteopaths, etc., serve only to cloud and impede good patient care by all involved. The current artificial barriers between professional groups brings a philosophical reflection of the group of blind men who were trying to describe an elephant. Upon feeling the trunk of the elephant, one became convinced that elephants must be very much like snakes. Feeling the large round leg of the animal, another blind man became convinced that the elephant was undoubtedly like a tree. And so the story goes. Patients suffer. Tragically, the only benefit to come from the current political separation of territories is to the practitioners, insurance companies and pharmaceutical houses.

It is inappropriate not to mention the effects which may also accrue to healthcare practitioners and ancillaries in the operatory environment.

Aquisition of thresholds may be a significant occupational hazard for them from the slow but continuous exposures they receive from handling materials for patients. Murray and Butler noted in a remarkable recent study conducted with 51 operatory personnel that considerable dysfunction and impairment was present after a battery of psychological and performance tests were administered (360). The following is quoted from their findings.

"....a significant percentage of dental office personnel including dentists are exposed to chemicals common to the dental office (nitrous oxide, methyl mercury, formaldehyde, phenol, and acrylic) and this exposure may well contribute to the psychoneurological cognitive dysfunctioning found in a surprisingly high percentage (above 90%) of dental office workers.

"It was concluded that these individuals probably suffer adverse reactions to the chemicals in their work environment. These areas included perceptual motor difficulty (eg., 90 percent showed tremor), deficits in cognitive functioning, concern with bodily function, and despondency, as well as interpersonal problems.

"Assuming that this sample population was greater than 1 standard deviation above the normal population prior to exposure, the deficit seems even greater and the urgency of a solution to the problem of existence in the contaminated environment seems more pressing.

"Chemicals that alter psychopharmacology, psychoimmunology, and neurochemistry are becoming more suspect concerning their role in altering human behavior...." (Ref 360, pps. 64-65)

THE TESTING METHODS

To detect and differentiate antibodies against offensive materials, including the corrosion byproducts and components which are of interest herein, several methods are commonly recognized among immunologists. Some are rather costly and require considerable investment in time and equipment. Others, especially those which were developed decades ago for differentiation of microbial infectious agents, are elegantly simple and have well-substantiated track records.

In the introduction chapter to the 3rd edition of Manual Of Clinical Laboratory Immunology, Robert Ritchie wrote, "The fixation of the laboratory and industry on the speed of analysis is often unwarranted. Manufacturers will at times exert tremendous efforts toward reducing the time for completion of an assay by a factor of 2 or shaving 5 to 10 minutes off the turnaround time, with the primary goal being to upstage the competition or at least satisfy the marketing department's distorted perception of user needs. The time required to complete an assay, particularly when automated devices are used, is of little consequence when most assays can be completed in an hour or less, with the remaining assays best managed by overnight processing" (421).

The methods examined experimentally by the author for detection of systemic antibodies included precipitin, Oucterlony diffusion, latex agglutination and hemaaglutination inhibition. All methods offered approximately similar results in preliminary trials. The precipitin and Oucterlony diffusion methods were as valid as the other two and were more easily set up and handled at the bench. The latex agglutination method gave comparable results for most parameters when conducted in microtiter wells but could not easily make distinction between immunological reactions and certain interfering non-specific protein aggregations which can sometimes be seen with challenges such as copper, mercury and nickel. The hemagglutination inhibition test, which utilizes sensitized sheep red cells, gave comparable results to the other methods but was deemed to be too expensive, cumbersome and time consuming at the bench without providing any real advantage over the simpler methods. For interested parties, the agglutination and hemagglutination inhibition methods have been well discussed and defined elsewhere (366, 473). The methods to be discussed here are the precipitin and Oucterlony diffusion procedures. These have been reported to have approximately equal limits of detection when compared with each other (149).

Precipitin reactions in liquid base were part of the process which gave birth to modern microbiology and immunology as we know them (27, 214, 256, 280). Early researchers previously alluded to used the technique to detect antigenic components from infectious agents to identify the nature of a disease. Technically, precipitin reactions are considered to be serological procedures rather than advanced immunological methods. The process is described as both a means for qualitative detection and for quantitation by end-point titration (27, 265, 366). In theory, when antigen and specific antibody are mixed in a tube, precipitation of a grossly observable immune complex will occur if they are in approximately equal quantities. If the reactants are not equally proportioned, precipitation may be poor or non-existant. This condition is referred to as the prozone/postzone phenomenon (27, 366). In actual practice, the precipitin method is either set up on a serial dilution basis for quantitation purposes or with an optimized dilution for qualitative screening.

For serial dilution application, it is possible to titrate either

antigen or antibody. The agent to be titered will be diluted through a standard scheme while the other agent will be used at fixed concentration in all tests. The following description would apply if the antibody were to be titered. For this example, the antigen will be a solution of 0.0001 molar HgCl in distilled water.

Ten glass culture tubes (10x75mm, borosilicate glass, CMS 339-267 or equivalent) are arranged in a support rack and numbered 1 through 10 with an appropriate glass marker common to most laboratory benches. Tubes 2 through 10 will each receive 0.5 ml distilled water. Tube 1 will receive 1.0 ml fresh patient serum. Using a precision pipettor set to receive and dispense 0.5 ml volumes, 0.5 ml of the serum is withdrawn from Tube 1 and placed into Tube 2. After thourough mixing, 0.5 ml of the diluted serum in Tube 2 is withdrawn and placd into Tube 3. The steps of removing 0.5 ml of the diluted serum and introducing it into the next tube in line is repeated through Tube 10, when the final 0.5 ml is discarded. The tubes now represent 2-fold serial dilutions beginning with undilute serum, represented as 1:1, and proceding through a dilution of 1:512 in Tube 10.

To each tube is now added 0.5 ml of the mercury antigen solution. Tubes are mixed gently and observed for the formation of a cloudy precipitate. The last tube in the series showing precipitation is determined to be the end point. Depending on the dilution factor in that tube, results might be reported as a titer of 1:32 or 1:64, etc. The higher the titer, the greater the quantity of antibody present in the original serum specimen. If the quantity of either mercury antigen or serum antibody was too far out of proportion when compared to the other, the first tube or two might not have had any precipitate, but precipitate might have been observed through several of the central tubes in the series. This would be an illustration of the prozone/postzone phenomenon (27, 366), and corrections in beginning concentrations could be made for a second run if deemed critical. Diluting the mercury solution rather than the serum would have permitted titering the mercury in reference to a standard serum.

Evaluation of test results in liquid precipitin reactions can be time sensitive and require attentive action on the part of the immunologist. Certain soluble combinations may precipitate out within a minute or so of mixing components and then dissolve past any point of observability. Other precipitating reactions require a longer period to form and are relatively stable. Caution is required in that substantially increasing either antigen or antibody after first reaction products form can cause reversal of immune complex formation. Continuous observation following mixing of reactants is recommended. Sensitivity for this method has been quoted as low as 0.1 ug of antibody per milliliter of serum (366).

It is not always necessary to reach an endpoint titer. The precipitin reaction can be used as a single tube qualitative screen for the large majority of serologies employing this method. In such cases, it may only be necessary to know whether or not an antibody is present or not. This simple "yes-no" determination permits an easy and reliable method to determine exposure to toxic materials. Antibody titers are typically high with recent spot exposure, and low after the passage of time without recurrent exposure. Thus, the simple determination of antibody presence suggests that an adverse contact has occurred with immune response and sufficient sensitization to induce protective systemic antibodies. It is only necessary to experimentally determine an approximate or optimized concentration of the antigen to be able to conduct effective screening.

The Ouchterlony diffusion method is a modification of simple immunoprecipitation technology (27, 366, 392, 473). Melted agar (Difco Bacto

Agar Purified 0560-01-1 or equivalent, pH 7.1-7.2) cooled to approximately 40 degrees C is poured into Petri dishes to a depth of approximately 3 millimeters and allowed to solidify into a gel. Small holes, or wells, are then punched into the agar several millimeters apart. Approximately 50 lambda of patient serum is placed into one well and 50 lambda of antigen challenge is placed into an adjoining well. The principle of the test is that the serum containing antibodies and the challenge containing antigen will diffuse through the gel towards each other and form bands of stable antigen-antibody complexes which can be grossly observed and evaluated. The bands can occur anywhere between the two wells, and are believed to correlate with diffusion rate characteristics of the soubles and to the zone of equivalence where the quantities of antigen and antibody are approximately equal. If more than one antibody type is present or there are more than one component in the antigen callenge, two or more distinct bands may appear in the gel. When antigen and antibody are of similar molecular weights, the band formed at their conjunction is linear in nature. If the reactants are of differing weight, the band will form a concavity in the direction of the lower weight component (27). Sensitivity for this method has been quoted as low as 0.1 - 0.3 ug antibody per milliliter of serum (366).

The gel diffusion method permits testing with greater economy of test materials. Required volumes are 10% of those needed for liquids in tubes. However, the procedure requires approximately 18-24 hours for reactions to move to completion. Results are usually reported as positive or negative in detecting a reaction band, although scoring of the test can also be semiquantified according to the size of the bands formed and in certain cases by the number of bands formed. Where needed for additional study, the bands of immune complexes can be physically cut and removed from the Petri dish and stored in a moist chamber.

Of the two preferred methods (liquid precipitin and Ouchterlony diffusion) discussed above, the liquid precipitin method is perhaps easiest and simplest to carry out. Results of testing are quickly available and simple to read without the need for expensive and complex equipment. The method readily adapts to use in the field away from the normal laboratory bench. Some economy of reagents and serum can be obtained by utilizing microtiter assay trays (Falcon 3912 Microtset III Assay Plate or equivalent) rather than glass tubes.

TEST DATA AND OBSERVATIONS

Several examinations were made at the outset to determine whether or not reactions might be observed using either plasma or serum with challenges. These early tests were also used to define concentration parameters and dilution factors for the work which followed. The results of these first trials are not of sufficient importance to report herein, but were useful in setting guidelines for subsequent controlled studies. It was apparent from this phase of work that plasma could be used successfully. However, serum was deemed to be the ideal specimen due to familiarity in specimen collection by most laboratories and in its known working qualities in various other immunological testing. The antibody specimen was standardized to be separated serum taken from venous blood drawn with evacuated clot tubes. Bloods were centrifuged within 15 minutes of collection and serum removed from the formed elements and clot. Physiological saline (0.067N) and distilled water (resistivity 2.5+ mega-ohm) were compared as a diluent and showed no observable difference or influence in the outcome of testing. Distilled water was made the standard diluent of choice.

In initial controlled testing, donated specimens were examined from 24 subjects comprised of 10 males and 14 females. No special selection nor screening with regards to sex, age nor clinical history was made. Serum was tested fresh within 2 hours of collection. Agar plates for diffusion and serial dilution tube series with antigen being the variable were prepared as previously mentioned.

Initial antigen challenges used included mercury, copper, zinc, tin and aluminum. These challenges were formed using various salts and combined forms of the elements concerned in proprietary mixtures. Each was adjusted to a final concentration of 0.0001 to 0.0005 molar concentration, depending on the cation involved. All tests were conducted in triplicate, and numbers reported are the average derived from triplicate tests.

The results observed are shown in Figures 4 and 5.

FIGURE 4. PRECIPITIN REACTION TITERS
Number of specimens out of 24 showing indicated titer

Test Material	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256
Mercury	17	18	19	19	14	6	0	0
Copper	17	17	16	16	8	2	0	0
Tin	17	17	17	17	4	0	0	0
Zinc	13	14	14	13	6	2	0	0
Aluminum	21	20	20	19	19	11	0	0

FIGURE 5. IMMUNODIFFUSION REACTIONS
Number of specimens out of 24 showing band formation

Test Material	1 band	2 bands	3 bands
Mercury	19	2	0
Copper	17	0	0
Tin	17	3	0
Zinc	14	0	0
Aluminum	21	7	2

As shown in these tables, correlation between liquid precipitin and diffusion methods was comparable, especially when qualitative detection was sufficient. There is some evidence in mercury and zinc reactions at the 1:2 and 1:4 levels of possible prozone phenomena. The aluminum reactions in diffusion testing presented with multiple banding in some patients, suggesting that more than one haptenic binding site or stereochemistry might be involved.

Flocculation of immunoglobulins on a non-specific basis by certain chemicals is familiar to most immunologiosts. By using a solution of ammonium sulfate, immunoglobulin may be taken out of solution non-specifically with no implication of immune sensitivity nor specificity (27). The question which immediately arises from the above data has to do with whether or not the observed reactions are truly specific for the metallic challenge component or whether they might simply be non-specific flocculations or agglutinations of serum protein by metals. To answer this question, 10 reactive samples from the above group of 24 which had shown reactivity with copper, aluminum and mercury were selected and further tested as follows.

Samples of each serum specimen were placed into clean borosilicate glass test tubes and mixed with the indicated mercury challenge. After being permitted to react for 5 minutes, the specimens were centrifuged and the supernatant fluid removed into separate tubes. A small part of the supernatant fluid was set aside for other purposes, while the bulk of supernatant fluid received an additional challenge of mercury solution. This new mixture was allowed to form any additional precipitate possible for 5 minutes. Each tube was again centrifuged and the clear supernatant fluid removed to a clean tube. These steps were taken to permit the mercury challenge to precipitate whatever protein it could. All precipitates were saved for further analysis. No precipitates were observed to have formed from the second exposure to mercury challege.

The supernatant fluids from the above procedure were then mixed with the requisite amount of copper challenge for 5 minutes. Precipitates were observed in all tubes. The specimens were centrifuged as before and precipitates were separated from supernatant fluids and set aside. The harvested supernatant fluids were exposed to a second copper challenge in the same manner as with mercury. No precipitates were observed with second exposure. All tubes were centrifuged and clear supernatant fluids set aside.

A similar procedure was then carried out using aluminum challenge on the supernatants previously exposed to mercury and copper challenges. Precipitation was seen in all tubes. Precipitates were set aside for analysis and the supernatant fluids were held for repeat exposures to mercury, copper and aluminum challenges for a third time. No precipitates

occured at any stage on this last passage.

This procedure was further applied by reversing the order of challenges on fresh serum alloquots. Each stage of the testing showed precipitation with each challenge in succession. This would suggest that the precipitation observed was specific to the challenge being presented, and that reaction with one challenge did not affect the ability of the serum to react wih a different challenge second-handedly. The precipitation was specific to the challenge used in each case.

To further investigate the nature of each harvested precipitate taken from the experiments above, the residues were prepared for analysis by atomic absorption to determine the amount of each cation present in the precipitate. The quantitations were compared with the supernatant samples separated out at the time of residue harvest. A comparison of metals is as follows in Figure 6.

FIGURE 6. COMPARISON OF METAL CONTENTS BETWEEN RESIDUES AND SUPERNATANTS
Expressed as a ratio of residue content / supernatant content
(Rounded to nearest tenth)

Sequence #1 (Hg-Cu-Al)	Hg	Cu	Al
Mercury Added	3.9/1	0/0	0/0
Copper Added	1/1	2.8/1	0/0
Aluminum Added	1.1/1	0.9/1	5.1/1

Sequence #2 (Al-Cu-Hg)			
Aluminum Added	0/0	0/0	5.3/1
Copper Added	0/0	2.6/1	1.2/1
Mercury Added	4.0/1	2.5/1	1.1/1

These results suggest that the precipitated residues were binding the metals quite specifically and that the supernatants were uniformly losing the specified cation as it was being picked up in the precipitate.

To further examine the nature of the precipitates formed, each was observed in its native suspension prior to centrifugation. The nature of the precipitates showed a very fine granular appearance. When observed in transmitted light, each had a slight opalescence with small red, yellow and blue refractions showing. Conversely, when serum samples were mixed with ammonium sulfate solution, the residue which formed was grossly flocculant, had no refracions whatsoever when viewed in transmitted light, and showed no qualities of granularity.

In the next phase of investigation, fresh serum samples were treated with ammonium sulfate solution and permitted to flocculate. The flocculated residue was separated by centrifugation from each of the test serum samples, and each serum was then exposed to challenges with the mercury, copper and aluminum soultions mentioned previously. No precipitation was found with any challenge after the ammonium sulfate treatment took place. In that ammonium

sulfate is expected to bring down only immune globulin and not other serum proteins (27), this suggests that the missing activity for mercury, copper and aluminum was present only in immune globulin and had been tied up or bound and removed in the ammonium sulfate flocculation.

At the next stage of development, serum samples from 300 donors were examined in both precipitin and gel diffusion methods for a broader spectrum of challenges. The 300 subjects studied were either drawn voluntarily for the project or were persons who had been drawn for other clinical laboratory testing and had unused excess serum remaining after primary work had been completed. All were coded by number without any indication of donor identity. Serum specimens were accepted randomly without regard to sex, age or specific clinical history. No preselection nor screening was performed to bias results for those thought to be presenting with any symptoms of toxicity, sensitivity or evidence of pathology. The results showed good correlation between liquid precipitin and gel diffusion detection of antibody. Only the liquid precipitin results are presented here in Figure 7.

FIGURE 7. PRECIPITIN REACTION TITERS
Number of specimens out of 300 showing indicated titer
(Last column shows % positive for challenge on qualitative basis)

Test Material	1:2	1:4	1:8	1:16	1:32	1:64	1:128	% Positive
Aluminum	240	242	259	258	125	29	0	86%
Antimony	48	48	19	2	0	0	0	16%
Barium	1	1	0	0	0	0	0	<1%
Beryllium	116	117	116	19	0	0	0	39%
Bismuth	72	72	72	64	38	1	0	24%
Chromium	111	106	101	23	0	0	0	37%
Cobalt	108	97	37	36	18	1	0	36%
Copper	167	187	169	144	119	43	2	62%
Gallium	60	54	18	2	0	0	0	20%
Gold	9	4	4	1	0	0	0	3%
Indium	164	167	168	82	9	0	0	56%
Iridium	57	56	31	29	9	0	0	19%
Mercury	200	204	193	118	87	11	0	68%
Nickel	139	133	138	79	64	17	1	46%
Palladium	48	49	7	1	0	0	0	16%
Platinum	2	2	0	0	0	0	0	<1%
Silver	25	24	25	3	0	0	0	8%
Strontium	1	1	0	0	0	0	0	<1%
Tin	183	183	99	16	1	0	0	61%
Titanium	2	1	1	0	0	0	0	<1%
Vanadium	12	9	2	0	0	0	0	4%
Zinc	148	157	156	112	14	1	0	52%

For the next phase of test development and evaluation, a variety of organic materials were examined in 187 subjects by liquid precipitin method. It may be noted from the following table that precentages of reactors are substantially lower in most challenges with the exception of entities such as the polyethimines, tannins and toluenes. Titers were never observed to exceed 1:32 in any challenge and most did not exceed 1:8. This may relate to the quality of haptenic structures and to the adjuvant effect of metallic cations which have been avoided as much as possible in composing challenge

formulations. When metallic salts were absolutely required to form the challenge, sodium, potassium or calcium salts were chosen.

FIGURE 8. PRECIPITIN REACTION TITERS
Number of specimens out of 187 showing indicated titer
(Last column shows % positive for challenge on qualitative basis)

Test Material	1:2	1:4	1:8	1:16	1:32	% Positive
Acrylates	4	3	1	0	0	2%
Butyrates	2	1	0	0	0	1%
Carboxylates	7	4	3	0	0	4%
Cellulose	11	8	0	0	0	6%
Hexanes	5	5	2	0	0	3%
Polyethimines	63	65	31	10	4	35%
Polyvinyls	6	2	1	0	0	3%
Styrenes	2	1	0	0	0	1%
Tannins	91	91	84	19	11	49%
Toluenes	33	33	7	1	0	18%
Urethanes	1	1	0	0	0	<1%
Xylenes	13	2	1	0	0	7%

While the organic moieties do not demonstrate the intensity of action seen with some metallic components, it is likely that some of those reacting have done so due to association with metallics bound to them when initially presented to the immune survelience mechanism. Current assessments of the data, however, have not shown any set pattern of association between any one organic reactant and any one metallic reactant in patient specimens.

To assess both precision and accuracy in detection by liquid precipitin method, specimens available in quantity were divided into aliquots and groups for multiple evaluations. Measurements were performed on serums from 10 selected donors found to be reactive to mercury and tin by precipitin and gel diffusion methods. Each donor's specimen was further divided into 20 aliquots for use in end-point titration determinations for mercury and for tin challenges. Challenge materials were prepared in the usual and customary manner for the author's laboratory bench and dispensed into microtiter trays. A two-fold dilution scheme was used for testing, with serum being the variable. The following tables show the endpoints determined for mercury and tin challenges.

FIGURE 9. Mercury Endpoint Determinations
(Number out of 20 determinations ending at indicated titer)

Donor	1:2	1:4	1:8	1:16	1:32	1:64	1:128	Variance
1	20	20	18	2	0	0	0	9.000E-2
2	20	20	20	19	1	0	0	4.749E-2
3	20	20	20	20	0	0	0	0
4	19	20	20	20	19	1	0	4.749E-2
5	20	20	18	2	0	0	0	9.000E-2
6	20	20	19	1	0	0	0	4.750E-2
7	20	20	0	0	0	0	0	0
8	20	20	17	3	0	0	0	0.127
9	20	20	20	20	0	0	0	0
10	20	20	20	20	19	0	0	4.750E-2

FIGURE 10. Tin Endpoint Determinations
(Number out of 20 determinations ending at indicated titer)

Donor	1:2	1:4	1:8	1:16	1:32	1:64	1:128	Variance
1	20	20	0	0	0	0	0	0
2	20	19	19	0	0	0	0	0.189
3	20	20	18	1	0	0	0	0.100
4	19	20	19	0	0	0	0	4.749E-2
5	20	20	19	1	0	0	0	4.750E-2
6	20	20	0	0	0	0	0	0
7	20	20	20	20	0	0	0	0
8	20	1	0	0	0	0	0	4.750E-2
9	20	20	20	0	0	0	0	0
10	20	20	19	0	0	0	0	4.749E-2

As may be seen, data are tightly packed for quantitative endpoint titration purposes. If data are taken at optimal dilution for qualitative determinations only, antibody determination would score 100%. For purposes of determining variance, dilution positions were assigned increasing values in increments of 1, ie., 1:2 scored as 1, 1:4 scored as 2, 1:8 scored as 3, 1:16 scored as 4, etc.

It may be noted that donor #3 in the mercury table had one test which did not precipitate at 1:2 dilution factor. It is suspected that this may be due to a prozone effect, as precipitation of the remaining 19 trials for that donor at 1:2 dilution factor were weak and poorly characterized.

One other problem should be addressed in this writing, and that is the appearance of non-descript hazing or light clouding which periodically appears in test channels containing gold, silver, titanium, nickel, platinum and palladium, among others. The nature of this clouding does not meet the criteria set forth above in detecting a true antigen-antibody precipitate. To determine whether this clouding has to do with immune globulins, samples of patient serum which evidenced this peculiar type of reaction were briefly treated with a dilute solution of ammonium sulfate, previously cited as a means of removing globulins from serum but not other proteins (27). Products formed upon reacting samples in this manner were removed via centrifugation. Samples were then tested with the appropriate metal challenge. The clouding continued to form, and was deemed to represent a non-specific agglutination of general serum proteins having no relationship to antibodies.

Serum specimens which showed the characteristic precipitation believed to be associated with antigen-antibody precipitates (finely granular, slightly opalescelent and refractive) were also exposed to similar ammonium sulfate treatments. Upon challenge with the appropriate metals, no activity of any kind could be detected in the serum. It is expected that the ammonium sulfate solution removed the immune globulins from the serum upon which antigen-antibody reactivity was dependent. This suggests that the non-descript hazing sometimes seen is essentially a "noise" and should not be considered when assessing reactivity results. In my hands, there is not much difficulty distinguishing between the noise and a true immune reaction when the test plate is read in transmitted light by trained eye.

The data presented herein suggest that there is a specificity of reactants when challenges are tested in very dilute ranges commensurate with serologic and immunologic testing. They also suggest that testing can be reproduced with good reliability. If quantitation were needed, it could be done using the methods defined. In acknowledgement of titer variations due to currency of exposure, etc., qualitative determination of reactivity is more than adequate to detect prior adverse exposure with sufficient sensitization to elicit systemic antibody production. No attempt to define threshold acquisition nor defined pathology correlation has been attempted, nor is it likely that such determinations could be made from this kind of testing. What can be inferred from these data is that (a) patients have had adverse contact with toxic materials, (b) that they have had sufficient body burden to induce immune activity, and (c) probably retain memory cell-based immunity against the offending immunogen. In light of known problems due to invivo formed immune prducts, antigen-antibody complexes, etc., it would seem unwise to make any further challenge to the patient from any contributing source once reactivity has been detected.

REPORTING AND USE OF TEST FINDINGS

When laboratory testing has been concluded, a reporting system with three sections is generated. these sections include (a) a report of basic observations in terms of chemical groups and families, (b) a categorical section in which results are correlated to product tradenames of related appliction such as composites, cements, impression materials, etc., and (c) an alphabetical listing of all product tradenames with simple suited/not-suited indications for rapid reference in the operatory environment.

Basic reactivity results for each chemical group or family are reported with characterization as weakly, moderately, strongly or non-reactive. These determinations are made by correlation of opacity in the test well with a MacFarlane opacity standard. A reaction corresponding to a Mac-1 standard opacity is reported as weak, a Mac-2 standard as moderate, and Mac-3 or greater opacity as strong. Caution must be taken that intensity of opacity does not indicate degree of sensitization in the patient. Rather, indications as weak, moderate or strong are reported to suggest something about currency of exposure to the chemical group being tested, quality of antigenic stimulation or presentation and possible indication of antigenic tolerance when testing is examined in light of various other immune system function tests. Antibody titers may be reduced in the patient when exposure has not occurred within a period of time, even though memory lymphocytes with quick secondary response capability are present in interstitial spaces.

To assist practitioners, most of whom seem to know little or nothing about what is contained in the materials which they use, results are tied to product trade names. Correlation with product tradenames is performed by assembling a computer database containing expected and known chemical group and family information for each product to be reported. Data as to ingredients, breakdown byproducts and corrosion forms have been obtained by (a) physical testing of the product, (b) examination of the technical literature for reports of such testing, (c) manufacturer's Material Safety Data Sheets for the product, and (d) product insert sheets and contraindication lists from the manufacturers. If the appropriate chemical groups or families are tested in the serology tray, then correlation to any dental product can be made which contains or is expected to generate the tested forms.

Any single component, chemical group or family can cause a tradename product to be placed into a 'not well-suited' category. In a theortical consideration, let us say that a patient was tested for reactivity with gold, silver, indium and tin groups. The patient may show reactivity with the tin group and no reactivity with any other components tested. If a certain alloy product contained gold, silver, indium and tin, the patient's report would show this alloy by tradename as not well-suited for this patient solely due to the tin reactivity. If the patient had shown no reactivity with any of the four chemical groups under consideration, the tradename would have reported as a product which "may" be suited for his or her use. The word "may" is purposely used in that some reactivities with extremely low titers might not have been adequate to detect, etc. There is always the potential for developing new reactivities, although the author has noted in logitudinal testing that most persons who have passed out of their pubescent years seem to have relatively stable reactivity patterns (personal data which is not yet sufficient for statistical reliability).

The categorical section of the reporting system groups tradename

products together by common application or intended use, such as composites, cements, etc. Each category contains the names of products which may not be well-suited for this patient and those for which there have been no contraindications and which may be suited for use. Selection of components which work well together, such as the proper composite, cement, liner and base must be made by the practitioner. The categorical listings provide choices and the dentist determines from the lists the products which meet strength, durability, esthetic and intra-product compatability requirements. A listing of presently reported categories may be found in Appendix B.

Finally, the alphabetical section permits rapid checking of suitability within test constraints for the tradename products. This eliminates time consuming searches through the categorical pages when the dentist knows the products intended for use and needs quick tradename verification in the operatory environment. If any contraindication is noted, reference to the categorical section might suggest an alternative product.

A sample page from each of the three sections of the report may be found in Appendix B, C and D. A complete report runs to approximately 35 pages.

CONCLUSIONS AND RECOMMENDATIONS

The primary purpose for testing is to assist in the selection of dental materials for new application which will be least offensive for the patient. Occasionally, for purposes of esthetics, physical properties or serviceability, the dentist may need to choose a contraindicated material. This does not guarantee problems, but the professional and patient are both alerted in advance that special following and periodic checkups may be needed to insure that there are no adverse problems resulting from the selections made.

Attempts to determine degree of toxicity or specific pathologies which might result from an adverse exposure to something found reactive in this kind of testing should not be made. Information presented earlier dealing with threshold phenomena and individual variances from patient to patient underscore this precaution. For some patients which show adverse reactivity with material components, the only observable symptoms with product use may be low-key and may not ever exceed threshold limit to become grossly manifest. Nevertheless, when use of a contraindicated product is combined with various potential burdens from the environment, food, water, etc., thresholds may be exceeded at some point in the future. The intent of the testing is to assist in overall body burden reduction and not to lay blame on any certain product, manufacturer or practitioner.

Further, the testing cannot of itself indicate that existing biomaterials and restoratives should be removed and replaced by the dentist. By presenting a list of products by tradename which may cause problems for the patient, and by listing those chemical groups and families with which the patient reacts, it may be possible for the dentist or physician to review clinical history, physical data and results of other ancillary clinical testing to arrive at a diagnosis which recommends replacement of existing materials. Test results can be very beneficial in counseling patients regarding lifestyle changes and things to avoid which might also contribute to total body burden of toxic materials.

Patients who have presented with titers too low to detect by the methods employed in testing may need further assistance and subsequent retesting. Conscientious monitoring and patient followup for several months after dental intervention should help to isolate such needs in a timely manner. Special attention may need to be extended to pediatric and youth patients whose immune exposures and reactions may not have reached maximum levels. There is no guarantee that new sensitizations cannot occur.

Since it may be impossible to track the exact responsible sources which induced sensitizations in the patient, test results should not be considered to be an overt indictment of the profession for materials previously selected. Once informed about individual patient burdens and needs, responsible professionals will make the necessary alterations in materials and techniques to insure the least level of adverse challenge to that patient.

Finally, the testing is not intended to supplant good clinical judgement, and should not be used without professional evaluation and diagnosis. In the atmosphere of professional liability and due diligence which exists today, as well as in the consideration of doing all that can be done to improve the lot of the patient in life, materials reactivity testing can be a helpful adjunct to any thorough program of dental treatment and care.

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PERIODIC CHART OF THE ELEMENTS

Orbital	IA	IIA	IIIB	IVB	VB	VIB	VIIB	VIIIB	IB	IIB	IIIA	IVA	VA	VIA	VIIA	VIIIA
	±1 1 H 1.0079 1															0 2 He 4.00260 2
	+1 3 Li 6.941 2-1	+2 4 Be 9.01218 2-2									+3 5 B 10.81 2-3	±2 ±4 6 C 12.011 2-4	±3 ±5 7 N 14.0067 2-5	-2 8 O 15.9994 2-6	-1 9 F 18.998403 2-7	0 10 Ne 20.179 2-8
	+1 11 Na 22.98977 2-8-1	+2 12 Mg 24.305 2-8-2						Transition Elements			+3 13 Al 26.98154 2-8-3	±2 ±4 14 Si 28.0855 2-8-4	±3 ±5 15 P 30.97376 2-8-5	±4 16 S 32.06 2-8-6	±1 ±3 ±5 ±7 17 Cl 35.453 2-8-7	0 18 Ar 39.948 2-8-8
2	+1 19 K 39.0983 -8-8-1	+2 20 Ca 40.08 -8-8-2	+3 21 Sc 44.9559 -8-9-2	±2 ±3 ±4 22 Ti 47.88 -8-10-2	±2 ±3 ±4 ±5 23 V 50.9415 -8-11-2	±2 ±3 ±4 ±5 ±6 24 Cr 51.996 -8-13-1	±2 ±3 ±4 ±6 ±7 25 Mn 54.9380 -8-13-2	±2 ±3 26 Fe 55.847 -8-14-2	±2 ±3 27 Co 58.9332 -8-15-2	±2 ±3 28 Ni 58.69 -8-16-2	+1 +2 29 Cu 63.546 -8-18-1	+2 30 Zn 65.38 -8-18-2	+3 31 Ga 69.72 -8-18-3	±2 ±4 32 Ge 72.59 -8-18-4	±3 ±5 33 As 74.9216 -8-18-5	±2 ±4 ±6 34 Se 78.96 -8-18-6	±1 ±3 ±5 ±7 35 Br 79.904 -8-18-7	0 36 Kr 83.80 -8-18-8
2-8	+1 37 Rb 85.4678 -18-8-1	+2 38 Sr 87.62 -18-8-2	+3 39 Y 88.9059 -18-9-2	+4 40 Zr 91.22 -18-10-2	±2 ±3 ±4 ±5 41 Nb 92.9064 -18-12-1	+6 42 Mo 95.94 -18-13-1	±2 ±3 ±4 ±7 43 Tc (98) -18-13-2	+3 44 Ru 101.07 -18-15-1	+3 45 Rh 102.9055 -18-16-1	±2 ±4 46 Pd 106.42 -18-18-0	+1 47 Ag 107.868 -18-18-1	+2 48 Cd 112.41 -18-18-2	+3 49 In 114.82 -18-18-3	±2 ±4 50 Sn 118.69 -18-18-4	±3 ±5 51 Sb 121.75 -18-18-5	±2 ±4 ±6 52 Te 127.60 -18-18-6	±1 ±3 ±5 ±7 53 I 126.9045 -18-18-7	0 54 Xe 131.29 -18-18-8
2-8-18	+1 55 Cs 132.9054 -18-8-1	+2 56 Ba 137.33 -18-8-2	57-71 See Lantha-nides	+4 72 Hf 178.49 -32-10-2	+5 73 Ta 180.9479 -32-11-2	+6 74 W 183.85 -32-12-2	±4 ±7 75 Re 186.207 -32-13-2	±2 ±3 ±4 76 Os 190.2 -32-14-2	±2 ±3 ±4 77 Ir 192.22 -32-15-2	±2 ±4 78 Pt 195.08 -32-16-2	+1 +3 79 Au 196.9665 -32-18-1	+1 +2 80 Hg 200.59 -32-18-2	±1 ±3 81 Tl 204.383 -32-18-3	±2 ±4 82 Pb 207.2 -32-18-4	±3 ±5 83 Bi 208.9804 -32-18-5	±2 ±4 84 Po (209) -32-18-6	±1 ±3 ±5 ±7 85 At (210) -32-18-7	0 86 Rn (222) -32-18-8
2-8-18-32	+1 87 Fr (223) -18-8-1	+2 88 Ra 226.0254 -18-8-2	89-103 See Acti-nides	+4 104 (261) -32-10-2	105 (262) -32-11-2	106 (263) -32-12-2										Noble Gases

KEY: Oxidation States → ±1 ±3 | 79 ← Atomic Number | Au ← Atomic Symbol | Atomic Weight → 196.9665 | Electron Configuration → -32-18-1

Lanthanides	+3 57 La 138.9055 -18-9-2	±3 ±4 58 Ce 140.12 -20-8-2	+3 59 Pr 140.9077 -21-8-2	+3 60 Nd 144.24 -22-8-2	+3 61 Pm (145) -23-8-2	±3 62 Sm 150.36 -24-8-2	±2 ±3 63 Eu 151.96 -25-8-2	+3 64 Gd 157.25 -25-9-2	+3 65 Tb 158.9254 -27-8-2	+3 66 Dy 162.50 -28-8-2	+3 67 Ho 164.9304 -29-8-2	+3 68 Er 167.26 -30-8-2	+3 69 Tm 168.9342 -31-8-2	±2 ±3 70 Yb 173.04 -32-8-2	+3 71 Lu 174.967 -32-9-2
Actinides	+3 89 Ac 227.0278 -18-9-2	+4 90 Th 232.0381 -18-10-2	±3 ±4 ±5 91 Pa 231.0359 -20-9-2	±3 ±4 ±5 ±6 92 U 238.0289 -21-9-2	±3 ±4 ±5 ±6 ±7 93 Np 237.0482 -22-9-2	±3 ±4 ±5 ±6 94 Pu (244) -24-8-2	±3 ±4 ±5 ±6 95 Am (243) -25-8-2	+3 96 Cm (247) -25-9-2	±3 ±4 97 Bk (247) -27-8-2	+3 98 Cf (251) -28-8-2	+3 99 Es (252) -29-8-2	+3 100 Fm (257) -30-8-2	±2 ±3 101 Md (258) -31-8-2	±2 ±3 102 No (259) -32-8-2	+3 103 Lr (260) -32-9-2

Note: Atomic weights are those of the most commonly available long-lived isotopes based on the 1979 IUPAC Atomic Weights of the Elements. A value given in parentheses denotes the mass number of the longest-lived isotope.

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