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Oral inflammatory process and general health

Part 1: The focal infection and the oral inflammatory lesion

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Abstract. – A focal infection is a localized or generalized infection caused by the dissemination of microorganisms or toxic products from a focus of infection in various organic districts, including the oral district. In the Part 1 of this two-part review article, after historical signs, the Authors describe the current pathogenic concepts like the "immuno-allergic theory" and the formation of auto-antibodies in human body, contributing to the genesis of autoimmune illnesses sustained by individual reactivity linked to eredo-constitutionality. Some theories suppose a focal origin even for general pathology such as cancer, sarcoidosis, multiple sclerosis, amyotrophic lateral sclerosis, autism, Guillain-Barré syndrome, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS), Tourette's syndrome, myasthenia gravis, polycystic kidney disease, obesity, Alzheimer's disease and diabetes mellitus. Laboratory analyses (leucocytic formula, protein electrophoresis, C-reactive protein, REUMA test VES, TAS, etc.) are suggestive of the presence of an inflammatory process or of the presence of an aspecific answer to an inflammatory situation. The DNA-Polymerase Chain Reaction method (PCR) is fundamental for the diagnosis of bacterial and viral infections, particularly for those that have non-culturable microorganisms or in cases where are present but in extremely small number in the sample to be analyzed. A positive result confirms the diagnosis, but negative result is not indicator of the absence of illness. Even for oral inflammatory lesions, different basic mechanisms concerning the possible association with systemic diseases exist. They concern local spread, metastatic spread or immunologic cross-reactivity. In this case we assume that most of the ailments come from dental or periodontal foci, as in the bacterial endocarditis, but instead of considering them as possible pathogenetic mechanism of an immune nature, we consider them as originated by the body's response to the presence of bacterial antigens through the formation of specific antibodies. Much researche, sometimes contrasting, has evaluated periodontal pathogens in atheromatous plaques isolated from patients with chronic periodontitis. Oral inflammatory lesions have been shown unequivocally to contribute to elevated systemic inflammatory responses. In some researches intensive periodontal therapy showed a significant reduction of lymphocyte formula, of CRP levels, of interleukin-6 (IL-6) and of LDL cholesterol after two months.

Key Words:

Bacteremia, Endocarditis, Focal infection.

Introduction

In accordance with Easlick[1], a focus of infection is a confined area that: (1) contains pathogenic microorganisms, (2) can occur anywhere in the body and (3) usually causes no clinical manifestations. A focal infection is a localized or generalized infection caused by the dissemination of microorganisms or toxic products from a focus of infection.

Historical Signs

The first "report" of focal infection has been ascribed to Hippocrates who attributed the cure of a case of arthritis to a tooth extraction. In the early 1800s, Benjamin Rush, an American physician and signer of the Declaration of Independence, also related arthritis cure to tooth extraction[2].

In 1890, the dentist and physician, WD Miller, published his treatise: "*The Micro-Organisms of the Human Mouth: The Local and General Dis-*

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eases Which are Caused By Them" and a year later in Dental Cosmos first used the term: "focal infection".

In 1900, the English physician, William Hunter, reported in the British Medical Journal on "Sepsis as a Cause of Disease" listing poor oral health and the expanding use of 'conservative dentistry' (the preservation of the dentition by dental treatment) as a cause of the multitude of diseases attributed to focal infection: he theorized that the microorganisms presented in the oral cavity were able to diffuse throughout the whole organism, with consequent possible systemic illness.

From 1910 to 1940, the medical and dental literature contained several references to researcher's focal infections of dental origin and of the idea that efforts were instrumental in gaining the medical profession's broad acceptance a localized, low grade chronic infection could produce disease elsewhere in the body.

Other published articles[3,4] claimed a clearly defined link between infective rheumatoid arthritis and foci of infection, with oral sepsis cited as a main contributing origin. Billings[4] declared "when the focal infection, wheresoever it may be located, seems to be related to the systemic disease, radical measures should be instituted to remove it".

Mayo[5] concluded that "root abscesses and pus pockets connecting with them are often the source of acute and chronic rheumatism".

Afterwards, other researches[6-8] supported the hypothesis that systemic diffusion of microorganisms and their toxins from a focus infection in a determinate tissue, was able to originate or to increase a general illness and/or damage a distant tissue.

Initially, only a few scientists expressed some doubts[9].

Several Authors[10,11] regarded all pulpless teeth as probable foci of infection and conciuded that the extraction of teeth in several individuals improved their various medical conditions or pathologies as rheumatoid arthritis.

According to this point of view, a research of Shandalow[12] revealed that the primary infective agent in rheumatoid sufferers was apparently the *Streptococcus* organism which was prevalent in the oral tissues. Rhein et al[13] suggested that the extraction of healthy teeth was justifiable in the prevention of focal infection.

These early papers promoted the ritual of wholesale dental extractions and tonsillectomies as the complete cure for many systemic ailments, and consequently, the theory of focal infection was vigorously taught, citing infected teeth or their surrounding structures as being responsible for a wide range of diseases[14].

Since 1930 researchers began to question the evidence supporting the focal infection theory, despite review articles upholding its claims[15].

Some Authors[16,17] started to closely analyze heart disease, considerate the only apparent identifiable form of a focal infection and elective localization from dental origin.

Reimann and Havens[18] concluded that "the removal of local infections in the hope of influencing remote or general symptoms and disease must still be regarded as an experimental procedure not devoid of hazard".

Similarly while Slocumb et al[19], even if they continued to support the concept of focal infection, particularly in relation to specific clinical entities including heart disease, chronic infectious arthritis and glomerulonephritis, they thought accepted that a more logical and scientific approach to focal infection should be adopted.

Lazansky et al[20] recorde large variations in the frequency of bacteremia following dental extractions, ranging from 34 to 100%, depending on the different techniques employed at the time of extraction.

In a critical appraisal reviewing the relationship between focal infection and rheumatoid disease, Freyberg[21] postulated that removal of foci of infection should only be part of a broad spectrum of treatment and in chronic cases removal of these foci would be of little benefit.

In the sixties, the critical review of focal infection continued thanks to Easlick[1] and Mitchell and Helman[22] who brought into question the precise connection between dental foci and systemic diseases.

All this scientific diatribes created doubts among researchers and motivated them to improve the quality of the research about this issue, centralizing the attention on the relationship between bacteremia and endodontic procedures. Kennedy et al[23] showed that bacteremia could occur in monkeys after the introduction of *Streptococcus haemolyticus* into the root canal. Other oral activities were also demonstrated to produce a bacteremia, including chewing[24], periodontal scaling[25,26], tooth brushing[27], oral prophylaxis[28], dental flossing[29] and the removal of osteosynthesis plates[30]. In reguard to possible problems with the laboratory methodologies technics used in scientific study Rogosa et al[31] pointed out the

sole use of aerobic culturing techniques was an inadequate environment for the growth of all microorganisms originating within the oral cavity and that in order to detect a broader range of microorganisms, better anaerobic techniques would have to be employed.

More recently there has been a renewed interest on the influence that the focus of infection has on the general health. A current thesis suggests a possible relationship between dental health and cardiovascular illness, while many published case reports have pointed to an individual's dental sources as the causes of many systemic illnesses[32].

According to the recent WHO Oral Health Report[33], caries, despite of all efforts and measures undertaken to control the disease, is still identifiable as a continuing global health care problem. The consequence of caries are not limited to the destruction of tooth substance that results in needs for dental restoratives, crown and bridgeworks as well as implants in case of tooth loss. Caries, if left untreated, also causes inflammatory conditions and infectious processes of the dental pulp and the tissues surrounding the involved tooth. The sequel to infectious pulpitis, namely apical periodontitis, must be regarded the more severe disease condition from a general health care perspective[34].

Pathogenesis

In accordance with traditionalist medicine, an organ is able to develop a focal role when it is afflicted with an inflammatory chronic process on infectious base.

Previous Pathogenetic Conceptions

The "toxic-infective theory" of Rosenow, the "allergic theory" of Berger and the "neurotrophic theory" of Speransky have to be mentioned among several formulated theories.

"Toxic-infective theory" of Rosenow: focal pathology is due to the passage of germs and toxins from the focus to the blood stream and to their elective localization in some organs (articulation, eyes, kidneys, heart, skin) through an organotropism process or an "anacoresis" phenomenon for which septic inactive foci can capture circulating germs from the blood and so become acute or active.

"Allergic theory" of Berger: bacterial toxins, coming from chronic inflammated areas, such as apical granuloma, tonsillar and periodontal disease, sensitize the predisposed organism and provoke allergic-hiperergic reactions in secondary organs during successive insertion in the blood stream.

"Neurotrophic theory" of Speransky: dental foci are starting point of neurotoxic stimuli which irritate the neurovegetative system and provoke neurodystrofic alterations of organs far from dental apparatus. When secondary dystrofic stimulus is activated, it becomes independent from the initial provoking stimulus and does not regress when the original focus is removed.

The above-mentioned theories can coexist and complete among themselves: a toxic-infective genesis indeed can integrate with allergic awareness that can have an impact on an altered excitability of the neurovegetative system.

The focal disease is due to an immune pathogenic mechanism according to a new theory formulated during recent decades.

Current Pathogenic Concepts

The immuno-allergic theory supporting focus explains auto antibodies formation in human body, contributing to the genesis of autoimmune illnesses sustained by individual reactivity linked to eredo-constitutionality (biological substratum genetically predisposed). A series of antigens that are unrecognized by the orgamism as it's own are released in the affected zone wich leads to the formation of antibodies. The antibodies react with the antigens, and form a series of antigen-antibody complexes; the complexes precipitate in some target organs determining the activation of the complement and an inflammatory chronic process and the consequent damage to those organs.

The focal disease can therefore been considered as a pathological autoimmune process, that causes the alteration of an organ that is defined the "target". The alteration is caused by the unbalance of another organ that is defined as the "focal organ". The most common centers of focus of infection have been considered to be tonsils, adenoids, sinuses and oral cavity, with the less common foci have been considered to be prostate, appendix, gallbladder and kidney[35].

The most important chronic infective dental and periodontal foci are apical granuloma, periodontal affections (pockets and deep bone lesions), chronic apical osteitis, pulpal necrosis and gangrene, incomplete canal therapy on devitalized teeth and radicular cysts.

The systems and the organic apparatuses involved as target organs are manifold: we remember the locomotor system (rheumatoid arthritis, myositis, myalgia), the nervous system (neuralgias, neuritides), the cardiovascular system (myocarditis, endocarditis, pericarditis, thrombophlebitis), the excretory system (nephritis, urethritis, cystitis), the ocular system (uveitis, conjunctivitis, keratitis, ulcer of the cornea, optic iritis, choroiditis, neuritis), the dermatologic system (knotty erythema), the hematic system (primitive and secondary anaemias) and the digestive system (subacute and chronic gastritis, peptic gastric ulcer, duodenal ulcer, appendicitis and gallbladder). A focal origin is hypothesized even for general pathology as cancer[36,37], sarcoidosis, multiple sclerosis, amyotrophic lateral sclerosis, autism, the Guillain-Barré syndrome, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS), the Tourette's syndrome, myasthenia gravis, polycystic kidney disease, obesity, Alzheimer's disease and mellitus diabetes[38]. In clinical medicine these disorders are often found to occur contemporaneously with septic focuses of the oral cavity such as chronic infections of the pulp and the periodontium, chronic osteitis and osteomyelitis of the maxillary, cysts and granulomas understood as pathogenic noxae.

Diagnosis

The issue of metafocal pathology is controversial, because the clinic observations indicate long oral infections are accompanied rarely by secondary diseases of other distant organs and because in several secondary infections with suspect focal origin, the careful removal of all potential foci is not followed by the healing of the infection.

The diagnostic criteria are all based on elements of presumption, which may be of clinical nature, bacteriological or immunological. Typically, the clinician is suspicious when recognized tipical features, such as a tendency to become chronic, easy to relapse, insensitivity to specific therapies, a secondary aggravation of the disease in distant organs during an inflammatory re-ignition of outbreaks of oro-dental (*ex nocentibus criterion*) as well as the disappearance or improvement of focal disease after the removal of the targeted or accidental focus (*ex adiuvantibus criterion*) and, finally, high titers of Ig blood. The diagnosis of suspicious pathology from focal stimuluses make use of a series of clinical examinations. It is essential to do inspections of specific lesions in the oral cavity such as gengivitis, periodontitis, alveolar abscess and fistulas. Thermal tests are performed for the evaluation of the pulpal vitality of the teeth and percussion and mastication tests can be indicative of the passage of pathogenic germs and bacterial toxins from the periapical region to the systemic circulation, causing the exacerbations of the secondary clinical manifestations (*diagnosis ex adiuvantibus*). Moreover radiological investigations (ortopantomography and endoral periapical radiography) are used for the evaluation of endo-perio-apical anatomical lesions and for previous endodontic therapies (incomplete therapies, fragments of tools or diffusion over apex of materials of closing).

Laboratory Examinations

Laboratory examinations have a fundamental role in diagnosis.

The hemochrome examination is usefull in order to appraise the leucocytic formula. The absolute number and the percentage of all of five types of specific cells: neutrophils, eosinophils, basophils, lymphocytes and monocytes are a parameters of specific interest. Neutrophils that defend the organism from the infection caused by bacteria, contain different chemical proteins and substances that irreversibly damage the membranes of the pathogenic microorganisms. Eosinophils have the principal function of defending the organism to several kind of parasites and their number also increases in the allergic illnesses and they are accountable for some typical symptoms of these illnesses. The function of the basophils is not well known, although their number increase in the allergies. They contain histamine that, when released in excess in the blood and in tissues, provokes itching or the appearance of cutaneous rash. Lymphocytes are appraised generically to be one class, but include different subtypes, mainly B and T lymphocytes. The B lymphocytes are responsible for humoral immunity and they produce immunoglobulins (antibodies), while the T lymphocytes are responsible for the immune cellular-mediated overall response against viral infections. Lymphocytes are basically able to recognize extraneous or not-self cells as in case of rejection of the transplants. Fi-

nally, monocytes (M), are phagocytary cells. They are important in the defence of the organism against many types of bacteria and they help the neutrophils.

Protein electrophoresis evaluate the proteins content in the serum. The liver produces the greatest part of these proteins, which are released in the blood to cells of the immune system. Their presence constitutes a sure index in an elevated number of pathology and during electrophoresis they are categorized by per cent age and divided in to their subtypes: albumins, α1-globulins, α2-globulins, β-globulins and γ-globulins. During the acute phase, aptoglobulin (n.v. 30-160 mg/100 ml) (α2-globulin), ceruloplasmin (n.v. 30-40 mg/100 ml) (α2-globulin) and C factor (β2-globulin) have been found. During inflammation their counts increase.

The separation of plasmatic proteins in to the counts of immunoglobulins, idendifies the proteins that possess antibody activity. These are separated in to antigenic subgroups, indicated as immunoglobulins of types G, A, M, D and E. IgG are usually present in the plasma and they direct their antibody activity mainly toward soluble antigens as bacterial toxins. IgA are present primarily in the secretions of apparatuses and act against the infectious agents of respiratory apparatus. IgM are present primarily in the plasma and inactivate extraneous substances to the organism and corpuscular antigens. IgD are represented in small number and we don't know their functions. IgE act in all allergic manifestations.

The C-reactive protein is a glycoprotein. Its count increases in all cases of inflammatory problems. It is not modified by the state of pregnancy, by anemia or altered eritrocitary values (hyperglobulinemias). It is more sensitive than the erythrosedimentation rate (ESR), but above all it is more specific. It is found in autoimmune pathology, bacterial and infections, tissutal necrosis and neoplasias.

All these data are undoubtedly useful, but have limits because some conditions cause an increase in the levels of the proteins of the acute phase (false positiveness). The ESR increases in the infectious illnesses. The antistreptolysinic titre (AST) indicates antistreptolysin presence in circle. It usually constitutes a consequence of a *β-haemolytic streptococcus* of A group infection: its presence is an indicator of an antigenic stimulus and of a persistence of bacterial focality. The antistreptokinasic titer (ASKT) indicates the presence of substances during the infections from *β-haemolytic streptococcus* of the A, C and G group. The antistaphylolysinic titer (ASTAT) indicates the staphylococcic lysines, soluble substances produced by pathogenic logs (the most important are the lysines a and b). The antistreptohyaluronidasic title (AH) indicates the titer hyaluronidase, an enzyme secreted by any types of *β-haemolytic streptococcus* of A, B, C, G group and that is important to the diffusion of the microorganism in the tissues. The gammaglutamiltranspeptidase (Gamma-GT) are enzymes localized in many organs such as kidney, pancreas, spleen, heart and, above all, liver and learned bilious. Although in renal tubular cells they are contained twelve times more than in the liver, the clinical application of their dosing is almost exclusively limited to the liver, bilious tree and cardiac illnesses. It has usually been considered a very important indicator of cholestasis (with the alkaline phosphatase) to control hepatopathy (acute hepatitis), or the heart attack (in the 50% of the cases the increase of its value begins on the four or fifth day).

During particular therapies (such as barbiturates), or after alcohol use or abuse, lactic-dehydrogenase (LDH) catalyzes the oxidation of the lactic acid to pyruvic acid. Its anomalous presence does not discriminate pathology of a specific tissue, being representative of a class of five isoenzymes, but constitutes a marker of cellular suffering. The reuma test or factor rheumatism (FR) indicates the presence in the serum of M type immunoglobulins versus human G type immunoglobulins. It is not a specific test for the diagnosis of rheumatoid arthritis and is often in association with the Waleer Rose, a reaction of emoagglutination to indicate the rheumatoid factors. The system of complement consist of proteins of the immune system, it is activated after bacterial infections or inflammations. Its fundamental is to protect the organism purpose by removing of pathogenic agents (bacteria and virus), facilitating their elimination or their control trough biological systems like serum or the cellular system. The C3 fraction of complement is activated when the organism recognizes the presence of bacterial cells or immunocomplex. The pharyngeal tampon and the cultivation examination of the urines for the confirmation or the exclusion of other active sites complete the aforementioned tests.

The DNA-Polymerase Chain Reaction (PCR) is a process through which a specific sequence of nucleic acid can be amplified exponentially *in vitro*. This amplification pratically replaces the biological one obtained with traditional culture methods. There are several applications of this technique such as the clinical diagnosis of diseases caused by mutations, the determination of chromosomal translocations associated with onset of cancer and the study of resistance. It is fundamental for the diagnosis of bacterial and viral infections, particularly for those associated with non-culturable microorganisms or in case where the microorganism are present, but in extremely small numbers, in the sample to be analized. With PCR method is possible amplify the nucleic acid to produce a sufficient quantity to detect and identify the type of organism present. Much researches, sometimes contrasting, have evaluated periodontal pathogens in atheromatous plaques isolated from patients with chronic periodontitis. Dental plaque was taken from pockets, bacteria were isolated, placed in culture and analyzed by the PCR method and the same procedure was done for carotid atheromatous[39,40].

Laboratory analyses are suggestive of the presence of an inflammatory process or of the presence of aspecific response to an inflammatory situation. A positive result confirms the diagnosis, but a negative result is not indicator of the absence of the illness.

According to Idikó et al[34] there are different basic mechanisms that can account for a possible association between oral inflammatory lesions and systemic diseases.

Local Spread of Oral Inflammatory Lesions

The acute infection of the oral cavity, including periapical lesions, may result in complications characterized by *per continuitatem* extension of the local infection towards adjacent tissues and organs. Purulent discharge may penetrate the oral mucous membranes and the skin resulting in sinus tract or fistula formation. The progression of bacterial infection may take a more generalized form involving the paranasal sinuses, the bones of the skull, the eye, the brain, the preformed soft tissue planes and spaces around the pharynx and the mediastinum. Severe, even life-threatening diseases, such as orofacial abscesses, cellulitis, deep cervical infections, mediastinitis[41], cavernous sinus thrombosis, acute osteomyelitis, requiring immediate surgical interventions and antibiotic therapy may develop.

Metastatic Spread

One of the facets of microbial metastasis that is often unappreciated is that microorganisms expend much of their time and energy locating, developing and defending biological niches in which they can prosper. Microbes require very specific growth nutrients, favorable local environments (i.e. pH) and safety from their enemies: other bacteria and viruses and natural host defenses. This is the reason for biofilms. To survive and thrive, microbes have learned to avoid hostile regions of the body.

Even the most ubiquitous of human pathogens (streptococci and staphylococci) may only be such because they possess elaborate adhesive properties that allow them to attach to the body surface (skin and mucosa). *Streptococcus pneumoniae* is abundant in the pharynx, sinuses and lower respiratory tract but has never been isolated from an oral cavity only inches away. For some reason the oral environment is very inhospitable to the pneumococcus.

The periodontal pathogens, *Prevotella* and *Porphyromonas*, are only located in the oral cavity and the genitourinary tract.

Actinobacillus actinomycetemcomitans has only one biological niche: the oral cavity.

It is also imperative to distinguish between metastatic infections that merely reflect the typical pathology produced by the microorganism but in a different place (a streptococcal-induced liver abscess) and non-typical pathology as seen with cancer and various autoimmune disorders resulting from antigenic mimicry: microbical antigens similar to the host antigens induces an immune reaction, that damages the same host tissue[42].

Metastatic Infection I

Hematogenous spread of oral microbes to tissue surfaces of remote organs.

Transient bacteremia is a well-known consequence of invasive professional dental treatments, including endodontic instrumentation approaching beyond the tooth apex and periapical surgery[43,44], but there is a wide variation in reported frequencies of bacteremia in patients resulting from dental procedures: tooth extraction (10-100%), periodontal surgery (36-88%), scaling and root planing (8-80%), teeth cleaning (up to 40%), rubber dam matrix/wedge placement (9-32%) and endodontic procedures (up to 20%)[45]. Transient bacteremia also occurs frequently during routine daily activities unrelated to a dental

procedure: tooth brushing and flossing (20-68%), use of wooden toothpicks (20-40%), use of water irrigation devices (7-50%) and chewing food (7-51%)[46].

The extent and the duration of bacteremia are related to the aggressivity and duration of the intervention, as well as to the number of bacteria inhabiting the area of the procedure.

In particular the magnitude of bacteremia resulting from a dental procedure is relatively low, is similar to that resulting from routine daily activities[47,48] and is less then that used to cause experimental (i.e. in animals) effects. Although the infective dose required to cause i.e. in humans is unknown, the number of microorganisms in blood after a dental procedure or associated with daily activities is low.

The role of duration of bacteremia on the risk of acquisition of focal infection is uncertain. More recent studies support these data, but report a small percentage of positive blood cultures from 30 to 60 minutes after tooth extraction[48-50]. Intuitively, it seems logical to assume that the longer the duration of bacteremia, the greater the risk of focal infection, but no published studies support this assumption. Few results exist that show the incidence or magnitude of "spontaneous bacteremias" from infected root canals with chronic periradicular lesions or with acute periodontal abscesses[46] and of "provokes bacteremias". In their studies Baumgartner et al[51,52] demonstrated that nonsurgical root canal treatment resulted in a much lower bacteraemia incidence (3.3%: as a result of over-instrumentation), than surgical flap reflection (83.3%), periradicular curettage (33.3%) or tooth extraction (100%). Bender et al[53] have developed a study to measure bacteraemia subsequent root canal treatment. The Authors found a misure of 0% (if the instrumentation remained within the canal) and 15% incidence of bacteremia (if it extended beyond the apex). The postoperative bacteraemia following endodontic procedures was shown to last no longer than 10 min[54], the microorganisms within the circulation being cleared by phagocytes initially and then by the reticuloendothelial system. Debelian et al[43] in 1992 published further evidence that a bacteraemia occurred if root canal instrumentation was carried beyond the apex, and the most likely bacteria involved were anaerobic types. In other following works same Authors, besides, showed that (1) a bacteraemia could occur even if instrumentation was maintained within the root canal and that the most common organisms present within the associated bacteraemia were anaerobes[55], (2) using SDS-PAGE electrophoresis they established that the organisms in an endodontic-related bacteraemia were identical to those arising from within the root canal[44], (3) the same results were repeated with ribotyping using a DNA hybridization method[56] and then using both phenotype and genetic methods[57]. An other paper, where there was an intentional instrumentation through the apex, reports that bacteremias occurred with an incidence of 31 to 54% and biochemical tests and antibiograms revealed that the bacterials isolated from the root canal and from blood had identical profiles within the patients, strongly suggesting that the microorganisms isolated from the blood had the root canal as their source[58].

In conclusion all these studies, although they were based on a small sample group, showed far greater bacteraemias resulting from root canal treatment procedures then data produced in the past, as a result of the more sensitive culturing and identification techniques applied. Since it may not be technically determined if instrumentation has occurred beyond the apex, an antibiotic prophylaxis for the prevention of the endocarditis is recommended, especially for patients at risk[59].

However, the colonization of the endocardial layer and destruction of heart tissues, such as valves, by oral bacteria is a rare complication that occurs only in a selected group of patients at risk, carriers of previous cardiac valvular lesions, congenital or acquired. These lesions make possible the settlement and colonization by bacteria in circulation, thus giving rise to a process of bacterial or infective endocarditis. Other categories of people at risk of this serious disease that is still characterized by a high mortality rate despite the remarkable success of antibiotic therapy, are patients with immunodifensive cellular and humoral mechanisms, those being treated with steroids, cytostatics or immunosuppressive drugs, as well as those who have undergone recent cardiac surgery.

Metastatic infection II

Intracellular invasion. Repeated identification of *Chlamydia pneumoniae*, *Helicobacter pylori* and human *Cytomegalovirus* (CMV) in atheromatous lesions, as well as demonstration of elevated antibody titers to these microorganisms suggest that a direct infection of endothelial cells may be responsible for the genesis of ather-

osclerotic lesions in some patients[60]. Moreover, DNA of periodontopathic/endodontopathic bacteria were repeatedly recovered from atherosclerotic lesions[61].

Metastatic Infection III

Airways may be inoculated by pathogenic bacteria originating from the oral cavity. Bacteria recovered from patients with aspiration pneumonia were shown to be either part of the indigenous oral microflora or nosocomially acquired pathogens[62]. DNA genomic analysis demonstrated that an identical microbial strain was isolated from oropharyngeal or gastric samples and bronchial samples of the majority of patients[63].

Immunity

Molecular Mimicry

Immunologic cross-reactivity. Pathological immunoreactions and inflammatory processes play a fundamental role in the pathogenesis of metafocal diseases. In this case, we assume most of the ailments do not have a direct dependence from dental or periodontal foci, but rather are pathogenetic mechanisms of an immune nature. They originate as a lively body's response to the presence of bacterial antigens through the formation of specific antibodies. The continued production of antigens by the chronic outbreak leads to the synthesis of immune complexes, i.e. antigen-antibody complexes, both locally and within the general circulation. These immune complexes can settle anywhere in the organs with vascular structures in the filter, such as, for example, the synovial joint, the choroid of the eye, the kidney glomerulus, the skin tissues, etc. We do not excluded, as part of this mechanism, a massive cell-mediated immunity, i.e. immunoreactions delayed hypersensitivity of type IV, these are considered responsible for the direct cytotoxic effects (cytotoxic T lymphocytes), the release of a series of numbers of lymphokines, and finally the attraction and activation of mononuclear cells (macrophages). T cell-mediated injury of cardiac myocytes in *Chlamydia* infections was proven to be initiated through antigenic mimicry between the bacterial 60 kDa cystein-rich outer membrane protein and M7Aα, the dominant autoaggressive epitope of the cardiac-specific α myosin heavy chain molecule[64]. Experimental observations suggested that a similar mechanism may explain host tissue damage or an inflammatory type of response in remote organs induced by oral infections. In the context of molecular mimicry, we also consider the case of bacterial proteins molecules with sequence homology of human regulatory molecules. A heptamer amino acid sequence of an outer membrane-associated protein of the oral pathogen *Streptococcus sanguis* was shown to be identical to the platelet-interactive domain of type I and III collagens equipping the microbe with a potential for inducing platelet aggregation, an event that has been shown to contribute to vascular plaque development[65].

Soluble Immune-Inflammatory Mediators

Soluble immune-inflammatory mediators may elicit systemic effects.

Oral inflammatory lesions, elicited by pathogenic microorganisms, are connected with the production and release of soluble regulatory compounds amplifying the consequences of local cell-to-cell interactions, and mediating inflammatory reactions to remote tissues and organs. Detection of biochemical markers of a chronic low-grade inflammation has repeatedly been reported in patients with cardiovascular diseases[66]. Moreover, C-reactive protein (CRP), as a sensitive marker of inflammation has been shown to predict future risk of cardiovascular diseases in initially healthy individuals[67]. Oral inflammatory lesions have been shown unequivocally to contribute to elevated systemic inflammatory responses[68]. D'Aiuto et al[69] reported data on the effect of periodontal standard therapy vs aggressive therapy after six months. The intensive therapy group showed a significant reduction of lymphocyte count, of CRP levels, of interleukin-6 (IL-6) and of LDL cholesterol after two months.

Soluble Mediators I

Bacterial toxins. The anaerobic Gram-negative bacteria constitute the majority of the microflora present in polymicrobial oral infections, especially in the contents of septic necrotic root canals and periodontal pockets. They contain bacterial endotoxins, which are chemically defined as lipopolysaccharide (LPS). Among the soluble factors, these are probably the most powerful and most studied components involved in the systemic inflammatory response. The LPS, present in dental plaque and infected root canal, can penetrate the gingiva and the periapical area in high concentration[70]. These par-

ticular toxic substances are considered to be responsible for systemic diseases, trigeminal neuralgia and atypical facial neuralgia. They are a potent vasodilator and also possess an action detrimental to the PMN, preventing chemotactic activity and phagocytosis. Biological activity is explained by the production of an array of proinflammatory and chemotactic cytokines including granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, interleukin (IL)-1α and -β, IL-6, -8, monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor (TNF)-α[71].

The proinflammatory and procoagulant state, as well as the endothelial dysfunction elicited by LPS may contribute to atherogenesis. CMV and Epstein–Barr virus (EBV) infections, which have recently been implicated in the development of root canal and periapical lesions, also can induce inflammatory and chemotactic cytokines[72]. The deleterious effects of CMV and EBV on the vascular endothelium adds to that produced from the LPS[73,74].

Soluble Mediators II

Host compounds. The most studied chain of events is represented by the oral inflammatory lesion → (LPS) → IL-1/IL-6/TNF-α → liver positive acute phase proteins/coagulation factors target organ axis. Positive acute phase proteins, including certain coagulation factors, such as fibrinogen, are synthesized by hepatocytes in response to IL-1, -6, and TNF-α[75].

Common Etiopathogenic Factors

There are well-defined patient-related and environmental risk factors, such as age, smoking, diabetes, socio-economic status and lifestyle that are common in certain oral inflammatory diseases and systemic diseases.

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