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# Focal Infection

Hubert N. Newman

Ideas tend to be many, good ideas few. Ideas also tend to become entrenched, and the protagonists adopt glowering stances on opposite hills, like David and Saul of old, although, as with them, the real glowering is usually somewhat one-sided.

The real problem is the good idea, or, in scientific terms, the sound hypothesis. These take many years to establish, and computers don't seem to help. Fashions come and go. Many seek fame and fortune by betting on the prevailing fashion. Often they achieve. Arguably this can prove regrettable, since few scientific hypotheses stand the test of time.

What can be even more frustrating is the perennial re-invention of the wheel. Scientists seem to be at least as prone to this malady as any other group. The result is a waste of time, effort, and resources which would have been more profitably directed in the pursuit of human welfare. This is particularly relevant in matters of health and disease. Most news bulletins carry items—usually lurid, misinformed, exaggerated, and scare-mongering, not to say somewhat misleading—about diseases and their treatment or prevention.

Therefore, before we contact the wider media, let me preface this review by saying that this is about a re-discovery, not a discovery. I wonder why it has taken so long to be accepted—and then not unanimously, I would guess—that oral health is so important in relation to systemic health that the dentist has a responsibility for general health. That comment came from a great parent with no scientific training.

About a century ago, William Hunter first synthesized the notion that oral micro-organisms and their products were involved in a range of systemic diseases not always of obvious infectious origin, such as arthritis (Hunter, 1900, 1921). Arguably, as in so many other spheres of dentistry, perhaps the first actually to draw attention to the relationship between oral and systemic infections was W.D. Miller (1890), especially with his study of the human mouth as a focus of infection (1891). The orgy of extraction that ensued, without clear positive results, resulted in the notion of "focal infection" or "focal sepsis" falling into disrepute. By relegating this notion to the professional back burner, we compromise our role as oral physicians—physicians whose area of specialization is the mouth.

The problem about the original discovery was the tenuous nature of the link between putative oral foci of infection and related disease. And that is the warning to us:

that for the hypothesis not to fall into disrepute for a second time, there must be no unsubstantiated attributions, no theories without evidence. Many original publications were anecdotal. Direct cause-and-effect evidence was lacking. Apart from the association between oral bacteria and endocarditis in patients with congenital heart disease or after rheumatic fever, the subject lay dormant for decades. Yet now there is a resurgence of interest, and it may be salutary to observe the extent of current evidence for and the farsightedness of our predecessors in recognizing the relationship between oral foci of infection and a wide range of diseases. Some are clearly infectious, some inflammatory without direct evidence of microbial infection, and some one would never have thought of as attributable in any clear way to micro-organisms. [What about toxic shock syndrome in a patient with Down's syndrome (Navazesh *et al.*, 1994)?]

## Direct infection

Focal infection of oral origin may derive from closed or open sites. Open foci include caries lesions, periodontal pockets, and extraction sockets; closed foci, infection around root apices, unerupted but infected teeth, and infected pulps (Newman, 1968). Focal infection leading to infective endocarditis can even occur *via a dens in dente* (Whyman and MacFadyen, 1994). From the oral foci, micro-organisms—bacterial, viral, or other—or their products may gain entry to the deeper tissues directly, by spreading along fascial planes, through bony cavities, or even along blood or lymph vessels or nerves, or *via* salivary gland mucous surfaces. Can one die of such simple chronic infection? One may cite the coroner's court, but there is also extensive literature evidence.

## The susceptible patient

In this context, it is also important to recognize the relevance of lowered resistance. Patients who are more susceptible seem more subject (Thoden van Velzen *et al.*, 1984; Goldberg, 1987), even the older age groups, without apparent underlying systemic cause (Navazesh and Mulligan, 1995). Fevers of unknown origin but with a dental infection link have been recorded without other systemic disease (Naschitz and Yeshurun, 1985; Shinoda *et al.*, 1987) and in patients with leukemia (Chapman *et al.*, 1976), cancer (Peterson and Sonis, 1982), joint replacement (Little, 1983;

Lindqvist and Slätis, 1985), diabetes mellitus (Harrison *et al.*, 1983), rheumatoid arthritis (Iida and Yamaguchi, 1985), and liver transplants (Svirsky and Saravia, 1989). Immune suppression resulting from treatment of malignant neoplasias may be a cause of focal infection. Vertebral osteomyelitis and pneumonia due to systemic candidiasis followed treatment of an oral carcinoma (Hashimoto and Tanioka, 1991). Arguably the best-known focal infection, infective endocarditis, has been a sequel in a patient with Hodgkin's lymphoma (Meehan *et al.*, 1994). Further, oral infection has been shown to be a principal cause of febrile episodes in lymphoma patients receiving cytostatic drugs (Laine *et al.*, 1992).

Infection of dental or periodontal origin is a major problem in cancer patients, likely to be enhanced by chemo- or radiation therapy. Immunosuppression as in HIV-related conditions plainly has a similar effect, although many of the resulting infections tend not to be attributable to the usual oral commensals. Optimal oral hygiene may be considered a prerequisite in patients due to receive chemo- or radiation therapy (Wright, 1990; Blaha and Reeve, 1994; Mealey *et al.*, 1994; Semba *et al.*, 1994). Secondary or opportunistic infection—candidiasis, for example—may be controlled by conventional oral hygiene with antimicrobials (Ferretti *et al.*, 1988, 1990; Ellegaard *et al.*, 1989; Bergmann *et al.*, 1992; Rutkauskas and David, 1993). Nor should one overlook the link between chronic inflammatory periodontal disease and osteoradionecrosis of the jaws (Galler *et al.*, 1992; Carl, 1993), or the consequences of extraction in this regard (Mealey *et al.*, 1994). Bone marrow suppression is also likely to predispose to increased systemic risk from oral infections (Peterson *et al.*, 1987; Peterson, 1990; Glick and Garfunkel, 1992; Barrett and Schifter, 1994).

## Localization of infection

It is fascinating to observe, so many years since the suggestion of a link between chronic focal infection and chronic arthritis (Miller, 1890, 1891; Hunter, 1900, 1921; Billings, 1912, 1913), the advances in supporting evidence over the years (Davidson *et al.*, 1949; Ebringer *et al.*, 1989; Dixon, 1990). And yet earlier workers had considered that different organisms selectively colonized specific loci—the theory of elective localization (Rosenow, 1919, 1921, 1923). By this hypothesis, bacteria would localize from the source focus to the distant, systemic focus, and Rosenow demonstrated a targeting process in a series of experiments, reviewed by Hughes (1994). This should not surprise us. Micro-organisms cause infections of tissues, organs, or systems, clearly depending on an ability to survive and grow better in those loci—a clear extension of the principles of microbial ecology in general.

It may be noted that Hughes (1994) reviewed the topic from the rheumatologist's standpoint. He cites perhaps the earliest relevant reference, none other than Hippocrates, whom he quotes as reporting a patient whose arthritis was cured by extraction of an infected tooth (see also Mayo, 1922). Further, while we may think it a modern discovery that bacterial products rather than the whole cells are the

source of focal infection, the same point was made many years ago (Swift *et al.*, 1928), with further proof through the years (Schwab and Cromartie, 1957; Ebringer *et al.*, 1989). Lens and Beertsen (1988) showed that injection of an antigen into the gingiva produced (mouse) knee joint inflammation. Focal infection has been cited in arthritis of the knee (Morer, 1975) and infected joint prostheses (Rubin *et al.*, 1976; Schurman *et al.*, 1976; Jacobsen and Murray, 1980; Lindqvist *et al.*, 1989). There has even been a suggestion that dental infectious foci may be involved in other obscure inflammatory disorders, such as erythema nodosum (Kirch and Duhrsen, 1992).

The mechanisms of spread are direct, through the local tissues and along fascial planes, along mucous surfaces, including ducts such as the salivary, and by inhalation and ingestion along respiratory and gastrointestinal mucosal surfaces, respectively, *via* the bloodstream, the lymphatics, and even, possibly, along nerves (Newman, 1968). Debelian *et al.* (1994) identify three pathways: metastatic infection from the oral cavity due to transient bacteremia, metastatic injury due to oral microbial toxins, and metastatic inflammation due to immunologic injury caused by oral micro-organisms.

The development of labeled stabilized liposomes may be expected to extend our ability to localize infection foci (Goins *et al.*, 1993; Boerman *et al.*, 1995), as may the use of labeled chemotactic peptides (Babich *et al.*, 1993; Hovi *et al.*, 1993; Fischman *et al.*, 1995). As well as being used to identify sites of focal infection, liposomes and analogous carriers may also serve to target antimicrobial treatment to such sites (O'Connell *et al.*, 1992).

## The target tissues

### Head and neck

Direct infection has clearly been shown to spread from defined oral foci to various locations in the head and neck, and from thence to the mediastinum. Many such conditions are fatal but fortunately are comparatively rare. Most are common, such as maxillary sinusitis (Dayal *et al.*, 1976; Smith *et al.*, 1979) and infections of the deep and superficial tissues of the face (Mitchell and Nelson, 1993). Implants may become infected due to recurrent dental pathology (Williams, 1994), as with prosthetic joints (Lindqvist and Slätis, 1985), and even cardiac pacemakers (van Winkelhoff *et al.*, 1993).

Infection may involve the ethmoid (Helidonis *et al.*, 1979) or spread to surrounding soft tissues, as in masticatory muscle space cellulitis (Bird and Smith, 1973), and the floor of the mouth (Ludwig's angina—Whitley, 1986), or cause cavernous sinus thrombosis (Goteiner *et al.*, 1982; Ogundiya *et al.*, 1989).

### Fascial planes

A major path of spread is through the fascial planes nearest to the teeth and may lead to parapharyngeal cellulitis (English and Kaiser, 1979), retropharyngeal space infection

(Peterson, 1993), infected neck cysts (Smyth and Ward-Booth, 1993; Janicke *et al.*, 1994), descending cervical cellulitis (Cogan, 1973), and mediastinitis, of which there are many reports (McCurdy *et al.*, 1977; Moncada *et al.*, 1978; Hendler and Quinn, 1978; Levine *et al.*, 1986; Garatea-Crelgo and Gay-Escoda, 1991; Esgaib *et al.*, 1992; Petrone, 1992; Zeitoun and Dhanarajani, 1995). Necrotizing mediastinitis may (Steiner *et al.*, 1982; Rubin and Cozzi, 1987) or may not (Economopoulos *et al.*, 1983) be fatal. Mediastinitis, thoracic empyema and pericarditis or other cardiac problems have been reported as sequels of dental abscesses (Zachariades *et al.*, 1986; Musgrove and Malden, 1989; Bonapart *et al.*, 1995).

Even without spreading so deeply, necrotizing fasciitis is another dangerous consequence of focal infection (Mruthyunjaya, 1981; McAndrew *et al.*, 1987; Steel, 1987; Kubo *et al.*, 1989; Ogiso *et al.*, 1992; Reed and Anand, 1992; Stoykewych *et al.*, 1992; Mizuno *et al.*, 1993). One may note how recent are some of these references. It is now possible to consider that we are approaching a sufficient evidence base for focal infection.

### The eye

Apart from the antra, other bony spaces of the head are also at risk. Orbital space infections have been cited as relatively rare sequels of dento-alveolar infections, with cases of acute infection that originated as dental abscesses (Gans *et al.*, 1974; Yates and Monks, 1978; Pellegrino, 1980; Bullock and Fleishman, 1985; Hovinga and Christiaans, 1987; Henry *et al.*, 1992; Mitchell and Nelson, 1993; Miller and Kasselbaum, 1995). Superior orbital fissure syndrome (peri-orbital edema, proptosis, subconjunctival ecchymosis, ptosis, ophthalmoplegia, pupil dilation, interference with light reflexes) has presented as a complication of an infected dentigerous cyst (Falcone *et al.*, 1994). Other inflammatory eye conditions in which focal infection may be involved include uveitis (Sela and Sharav, 1975; Kaban and McGill, 1980; Knox, 1981; Dernouchamps, 1992) and endophthalmitis (May *et al.*, 1978; Lass *et al.*, 1984; Donzis and Rappazzo, 1984; Ishak *et al.*, 1986).

### Intracranial sequelae

Intracranial infections constitute another serious sequel of oral focal infection. Brain abscesses are recorded (Churton and Greer, 1976; Gallagher *et al.*, 1981; Goteiner *et al.*, 1982; Aldous *et al.*, 1987; Marks *et al.*, 1988; Andrews and Franham, 1990) and may be more localized, e.g., to frontal (Ingham *et al.*, 1978), parietal (Andersen and Horton, 1990), or frontoparietal lobes (Saal *et al.*, 1988), with occasionally fatal consequences, often being resistant to antibiotics (Gallagher *et al.*, 1981; Schuman and Turner, 1994). The role of focal infection in relation to brain abscess in particular draws attention to the need for care in the assessment of evidence, referred to at the outset. As Schuman and Turner (1994) observe, dental infection or treatment was frequently incriminated in the articles they reviewed "solely because an infection or treatment occurred within several months of brain abscess, when non-dental bacteria were cultured from

the brain abscess and without culturing both the dental infection and the brain abscess to ascertain flora match." It is a caution one might invariably apply to all focal infection. In relation to brain abscess, however, it would be misleading to conclude that all the reports were vague, since for this as for a range of focal infections oral organisms have been directly associated with the condition (Navazesh and Mulligan, 1995).

Meningitis has also occurred as a focal infection (Hedström *et al.*, 1980; Zachariades *et al.*, 1986; Fernando and Phipps, 1988), as has acute hemiplegia following a dental abscess (Hamlyn, 1978). Larkin and Scott (1994) reported a case of metastatic paraspinal abscess and paraplegia secondary to dental extraction. Nerves themselves may be affected, including such problems as actinomycosis of the gasserian ganglion (Perna *et al.*, 1981) and trigeminal nerve anesthesia (Barrett and Buckley, 1986).

### Respiratory system

Concerning focal infection involvement of the respiratory tract, it has been observed that solitary lung abscesses are rare in the absence of teeth (Newman, 1968) and have been noted secondary to dental infection (Latronica and Shukes, 1973; Terezhalmay and Bottomley, 1978; Rams and Slots, 1992). A particular problem in the susceptible elderly group is aspiration pneumonia of oral microbial origin (Loesche *et al.*, 1995).

### Cardiovascular system

Infective endocarditis remains the most clear instance of focal infection (Eggleston, 1975; Strauss, 1975; Spaulding and Friedman, 1975; Kraut and Hicks, 1976; Kaplan, 1977; Oakley, 1979; Whittington, 1979; Thornton and Alves, 1981; Bayliss *et al.*, 1983; Siegman-Igra *et al.*, 1984; Lieberman, 1992). As mentioned previously, some malignancies may lead to nonbacterial thrombotic endocarditis, which in turn may predispose to infectious endocarditis (Meehan *et al.*, 1994). It may also be observed that the causative oral organisms of infective endocarditis include anaerobes as well as aerobes (Asikainen and Alaluusua, 1993). It is also clear that bacteremia is more frequent after extraction due to inflammatory dental diseases (Okabe *et al.*, 1995). Of the 132 cases of bacteremia the latter examined, nearly 80% yielded anaerobes, mostly eubacteria, peptostreptococci, and propionibacteria. It is pertinent to note that significant bacteremia may follow routine dental procedures apart from extractions, including toothbrushing, intraligamental injection, rubber dam or matrix placement, and polishing of teeth (Roberts *et al.*, 1996). Baseline bacteremia was also evident in a minority of subjects in this study.

With regard to other cardiovascular problems, septicemia secondary to oral infection has been a sequel of internal jugular thrombophlebitis (Mitre and Rothran, 1974), and an oral isolate, *E. corrodens*, has been associated with septicemia and pleural effusion (Stiegler, 1979). A fatality has been reported as a result of acute dento-alveolar abscess and the subsequent development of septicemia with disseminated intravascular coagulation (Carter *et al.*, 1992;



Currie and Ho, 1993).

One of the most intriguing developments in focal infection research is the recent association of dental infections and myocardial infarction, apart from the more direct link between dento-alveolar abscess and acute bacterial myocarditis (Palank *et al.*, 1979). A series of case control studies has been reported (Mattila *et al.*, 1989; Mattila, 1993) indicating an association between dental infections and acute myocardial infarction and chronic coronary artery disease. An epidemiological survey indicated a possible association between missing teeth and coronary heart disease (CHD), and a 14-year follow-up study associated periodontitis with an increased risk of CHD (DeStefano *et al.*, 1993). As a possible mechanism, it was suggested that bacterial aggregation of platelets could relate to the pathogenesis of atherosclerosis and arterial thrombosis. A caution: Although the association between dental infection and severe coronary atheromatosis in males remained significant after adjustment for the effects of age, blood lipids, body mass index, hypertension, smoking, and social class, no such association was observed in the (small) number of females studied (Mattila, 1990; Mattila *et al.*, 1993). Mattila (1990) based his research concerning a possible oral link on observations of connections between bacterial and viral infections and atherosclerosis or myocardial infarction. In a recent study, Beck *et al.* (1996) demonstrated that inflammatory periodontal disease was a significant risk factor for the development, morbidity, and mortality of cardiovascular disease, the odds of fatal CHD and stroke being 1.6- to 2.1-fold higher in such cases after adjustment for the usual risk factors. Syrjänen *et al.* (1989) had previously noted an association between chronic inflammatory periodontal diseases (CIPD) level and stroke.

### Gastrointestinal tract

In view of the possible association between *H. pylori* and gastritis and gastric and duodenal ulcers, and its occasional detection in the mouth (Mapstone *et al.*, 1993; Nguyen *et al.*, 1993), one may consider this another possible instance for focal infection research. Liver infections have also on occasion been cited as attributable to dental infections (Crippin and Wong, 1992). Micro-organisms from periodontal lesions have also been implicated in the pathogenesis of inflammatory bowel disease (Van Dyke *et al.*, 1986).

### Fertilization, pregnancy, and birth weight

At the outset, it was mentioned that many interesting areas now involve the possibility of focal infection. There are now reports of a high level of potential dental foci of infection in relation to bacteriospermia, with "the bacterial spectrum of the intraoral samples being almost identical with the spermograms", with improvement in spermatological parameters following appropriate dental treatment (Bieniek and Riedel, 1993). It has also been observed (in animals) that infection with Gram-negative periodontitis-associated organisms may adversely affect pregnancy outcome (Collins *et al.*, 1994), and that severity of maternal inflammatory periodontal disease is associated with a risk for low birth weight in humans (Gibbs *et al.*, 1992; Offenbacher *et al.*, 1993,

1996), this development deriving from the concept of an association between subclinical infections and premature birth.

### Conclusions

New knowledge this may not be, but we certainly now have the means of evaluating these rejected and now re-awakened theories of focal infection. These may lead to a time when we will be true oral physicians, less pre-occupied with the commonest of human diseases, and with more concern and time for their systemic implications. We certainly need to realize that there are links between oral and systemic health and oral and systemic disease. For some, the evidence is strong, for others tenuous, and for many indirect but intriguing. Only our research, in collaboration with other medical colleagues in their specialties, will enlighten. Let us prepare to broaden our minds.

### References

- Aldous JA, Powell GL, Stensaas SS (1987). Brain abscess of odontogenic origin: A case report. *J Am Dent Assoc* 115:861-863.
- Andersen WC, Horton HL (1990). Parietal lobe abscess after routine periodontal recall therapy. Report of a case. *J Periodont* 61:243-247.
- Andrews M, Farnham S (1990). Brain abscess secondary to dental infection. *Gen Dent* 38:224-225.
- Asikainen S, Alaluusua S (1993). Bacteriology of dental infections. *Eur Heart J* 14(Suppl K):43-50.
- Babich JW, Solomon H, Pike MC, Kroon D, Graham W, Abrams MJ, *et al.* (1993). Technetium-99m-labeled hydrazine nicotinamide derivatized chemotactic peptide analogs for imaging focal sites of bacterial infection. *J Nucl Med* 34:1964-1974.
- Barrett AP, Buckley DJ (1986). Selective anaesthetics of peripheral branches of the trigeminal nerve due to odontogenic infection. *Oral Surg* 62:226-228.
- Barrett AP, Schifter M (1994). Antibiotic strategy in orofacial/head and neck infections in severe neutropenia. *Oral Surg* 77:350-355.
- Bayliss R, Clarke C, Oakley C, Sommerville W, Whitfield AG (1983). The teeth and infective endocarditis. *Br Heart J* 50:506-512.
- Beck JD, Garcia R, Heiss G, Vokonas PS, Offenbacher S (1996). Periodontal disease and cardiovascular disease. *J Periodont* (in press).
- Bergmann OJ, Ellegaard B, Dahl M, Ellegaard J (1992). Gingival status during chemical plaque control with or without prior plaque removal in patients with acute myeloid leukaemia. *J Clin Periodont* 19:169-173.
- Bieniek KW, Riedel HH (1993). Bacterial foci in the teeth, oral cavity, and jaw—secondary effects (remote action) of bacterial colonies with respect to bacteriospermia and subfertility in males. *Andrologia* 25:159-162.
- Billings F (1912). Chronic focal infections and their etiological relations to arthritis and nephritis. *Arch Int Med* 9:484-498.
- Billings F (1913). Chronic focal infection as a causative factor in chronic arthritis. *J Am Med Assoc* 61:819-822.
- Bird JS, Smith RL (1973). Auditory canal drainage from a masticator space cellulitis. *J Oral Surg* 31:854-857.
- Blaha PJ, Reeve CM (1994). Periodontal treatment for patients with cancer. *Curr Opin Periodont* 64-70.
- Boerman OC, Storm G, Oyen WJ, van Bloois L, van der Meer JW, Claessens RA, *et al.* (1995). Sterically stabilized liposomes labeled with indium-111 to image focal infection. *J Nucl Med* 36:1639-1644.
- Bonapart IE, Stevens HP, Kerver AJ, Rietveld AP (1995). Rare complications of an odontogenic abscess: mediastinitis, thoracic empyema and cardiac tamponade. *J Oral Maxillofac*

- Surg* 53:610-613.
- Bullock JD, Fleishman JA (1985). The spread of odontogenic infections to the orbit: diagnosis and management. *J Oral Maxillofac Surg* 43:749-755.
- Carl W (1993). Local radiation and systemic chemotherapy: preventing and managing the oral complications. *J Am Dent Assoc* 124:119-123.
- Carter TB, Blankstein KC, White RP Jr (1992). Severe odontogenic infection associated with disseminated intravascular coagulation. *Gen Dent* 40:428-431.
- Chapman RM, Crosby WH (1976). Elective dental extraction in leukemia (letter). *New Engl J Med* 295:114.
- Churton MC, Greer ND (1980). Intracranial abscess secondary to dental infection. *New Zeal Dent J* 76:58-60.
- Cogan IC (1973). Necrotizing mediastinitis secondary to descending cervical cellulitis. *Oral Surg* 36:307-320.
- Collins JG, Windley HW 3rd, Arnold R, Offenbacher S (1994). Effects of a *Porphyromonas gingivalis* infection on inflammatory mediator response and pregnancy outcome in hamsters. *Infect Immun* 62:4356-4361.
- Crippin JS, Wang KK (1992). An unrecognized etiology for pyogenic hepatic abscesses in normal hosts: dental disease. *Am J Gastroenterol* 7:1740-1743.
- Currie WJ, Ho V (1993). An unexpected death associated with an acute dentoalveolar abscess—report of a case. *Br J Oral Maxillofac Surg* 31:296-298.
- Davidson LSP, Duthie JJR, Sugar M (1949). Focal infection in rheumatoid arthritis. *Ann Rheum Dis* 8:205-209.
- Dayal VS, Jones J, Noyek AM (1976). Management of odontogenic maxillary sinus disease. *Otolaryngol Clin N Am* 9:213-222.
- Debelian GJ, Olsen I, Tronstad L (1994). Systemic diseases caused by oral microorganisms. *Endod Dent Traumatol* 10:57-65.
- Dernouchamps JP (1992). Intermediate uveitis and focal infection. *Dev Ophthalmol* 23:118-119.
- DeStefano F, Anda RF, Kahn S, Williamson DF, Russell CM (1993). Dental disease and risk of coronary heart disease and mortality. *Br Med J* 306:688-691.
- Dixon B (1990). Bacteria and arthritis. *Br Med J* 301:1043.
- Donzis PB, Rappazzo A (1984). *Endogenous Actinobacillus actinomycetemcomitans* enophthalmitis. *Ann Ophthalmol* 16:858-860.
- Ebringer A, Khalafpour S, Wilson C (1989). Rheumatoid arthritis and proteus: a possible aetiological association. *Rheumatol Int* 9:223-228.
- Economopoulos GC, Scherzer HH, Gryboski WA (1983). Successful management of mediastinitis, pleural emphysema and aortopulmonary fistula from odontogenic infection. *Clin Thorax Surg* 35:184-187.
- Eggleston DJ (1975). Teeth and infective endocarditis. *Aust Dent J* 20:375-377.
- Ellegaard B, Bergmann OJ, Ellegaard J (1989). Effect of plaque removal on patients with leukemia. *J Oral Pathol Med* 18:54-58.
- English WJ 2nd, Kaiser AB (1979). Lethal toothache: parapharyngeal cellulitis complicating dental infection. *Southern Med J* 72:687-689.
- Esgaib AS, Ghefter MC, Lira RdeM, Guidugli RB, Trajano AL, Ferreira SM (1992). Mediastinitis after cervical suppuration. *Rev Paul de Medicina* 110:227-236.
- Falcone F Jr, Lazow SK, Berger JR, Gold BD (1994). Superior orbital fissure syndrome: secondary to infected dentigerous cyst of the maxillary sinus. *NY State Dent J* 60:62-64.
- Fernando IN, Phipps JSK (1988). Dangers of an uncomplicated tooth extraction. A case of *Streptococcus sanguis* meningitis. *Br Dent J* 165:220.
- Ferretti GA, Ash RC, Brown AT, Parr MD, Romond EM, Lillich TT (1988). Control of oral mucositis and candidiasis in marrow transplantation: a prospective, double-blind trial of chlorhexidine digluconate oral rinse. *Bone Marrow Transpl* 3:483-493.
- Ferretti GA, Raybould TP, Brown AT, MacDonald JS, Greenwood M, Maruyama Y, et al. (1990). Chlorhexidine prophylaxis for chemotherapy and radiotherapy-induced stomatitis: a randomized double-blind trial. *Oral Surg* 69:331-338.
- Fischman AJ, Babich JW, Barrow SA, Graham W, Carter E, Tompkins RG, et al. (1995). Detection of acute bacterial infection within soft tissue injuries using a <sup>99m</sup>Tc-labeled chemotactic peptide. *J Trauma* 223-227.
- Gallagher DM, Erickson K, Hollin SA (1981). Fatal brain abscess following periodontal therapy: a case report. *Mt Sinai J Med NY* 48:158-160.
- Galler C, Epstein JB, Guze KA, Buckles D, Stevenson-Moore P (1992). The development of osteoradionecrosis from sites of periodontal disease activity. Report of 3 cases. *J Periodont* 63:310-316.
- Gans H, Sekula J, Wlodyka J (1974). Treatment of acute orbital complications. *Arch Otolaryngol* 100:329-332.
- Garatea-Crelgo J, Gay-Escoda C (1991). Mediastinitis from odontogenic infection. Report of three cases and review of the literature. *Int J Oral Maxillofac Surg* 20:65-68.
- Gibbs RS, Romero R, Hillier SL, Eschenbach DA, Sweet RL (1992). A review of premature birth and subclinical infection. *Am J Obstet Gynecol* 166:1515-1528.
- Glick M, Garfunkel AA (1992). Common oral findings in two different diseases—leukemia and AIDS: Part 1. *Compend Contin Educ Dent* 13:432-447.
- Goins B, Klipper R, Rudolph AS, Cliff RO, Blumhardt R, Phillips WT (1993). Biodistribution and imaging studies of technetium-99m-labeled liposomes in rats with focal infection. *J Nucl Med* 34:2160-2168.
- Goldberg MH (1987). Infection in the compromised host (the fatal periodontal pocket). *J CT Dent Assoc* 61:76-77.
- Goteiner D, Sonis ST, Fasciano R (1982). Cavernous sinus thrombosis and brain abscess initiated and maintained by periodontally involved teeth. *J Oral Med* 37:80-83.
- Hamlyn JF (1978). Acute hemiplegia in childhood following a dental abscess. *Br J Oral Surg* 16:151-155.
- Harrison GA, Schultz TA, Schaberg SJ (1983). Deep neck infection complicated by diabetes mellitus. Report of a case. *Oral Surg* 55:133-137.
- Hashimoto Y, Tanioka H (1991). Vertebral osteomyelitis associated with disseminated candidiasis in an oral cancer patient. *J Oral Maxillofac Surg* 49:901-903.
- Hedström SA, Nord C-E, Ursing B (1980). Chronic meningitis in patients with dental infections. *Scand J Infect Dis* 12:117-121.
- Helidonis E, Bosinakou M, Pantazopoulos P (1979). Odontogenic ethmoiditis. *Rhinology* 17:271-274.
- Hendler BH, Quinn PD (1978). Fatal mediastinitis secondary to odontogenic infection. *J Oral Surg* 36:308-310.
- Henry CH, Hughes CV, Larned DC (1992). Odontogenic infection of the orbit: report of a case. *J Oral Maxillofac Surg* 50:172-178.
- Hovi I, Taavitsainen M, Lantto T, Vorne M, Paul R, Remes K (1993). Technetium-99m-HMPAO-labeled leukocytes and technetium-99m-labeled human polyclonal immunoglobulin G in diagnosis of focal purulent disease. *J Nucl Med* 34:1428-1434.
- Hovinga J, Christiaans B-J (1987). Odontogenic infection leading to orbital cellulitis as a complication of fracture of the zygomatic bone. *J Craniomaxillofac Surg* 15:254-257.
- Hughes RA (1994). Focal infection revisited. *Br J Rheumatol* 33:370-377.
- Hunter W (1900). Oral sepsis as a cause of disease. *Lancet* i:215-216.
- Hunter W (1921). The coming of age of oral sepsis. *Br Med J* i:859-861.
- Iida M, Yamaguchi Y (1985). Remission of rheumatoid arthritis

- following periodontal treatment. A case report. *Nippon Shishubyo Gakkai Kaishi* 27:234-238.
- Ingham HR, Hood FJC, Bradnum P, Tharagounet D, Selkon JB (1977). Metronidazole compared with penicillin in the treatment of acute dental infections. *Br J Oral Surg* 14:264-269.
- Ishak MA, Zablit KV, Dumas J (1986). Endogenous endophthalmitis caused by *Actinobacillus actinomycetemcomitans*. *Can J Ophthalmol* 21:284-286.
- Jacobsen PL, Murray W (1980). Prophylactic coverage of dental patients with artificial joints: a retrospective analysis of thirty-three infections in hip prostheses. *Oral Surg* 50:130-133.
- Janicke S, Kettner R, Kuffner HD (1994). A possible inflammatory reaction in a lateral neck cyst (branchial cyst) because of odontogenic infection. *Int J Oral Maxillofac Surg* 23:369-371.
- Kaban LB, McGill T (1980). Orbital cellulitis of dental origin: differential diagnosis and the use of computed tomography as a diagnostic aid. *J Oral Surg* 38:682-685.
- Kaplan EL (1977). Prevention of bacterial endocarditis. *Circulation* 56:139a-143a.
- Kaplan DM, Fliss DM, Shulman H, Leiberman A (1995). Computed tomographic detection of necrotizing soft tissue infection of dental origin. *Ann Otol Rhinol Laryngol* 104:164-166.
- Kirch W, Dührsen U (1992). Erythema nodosum of dental origin. *Clin Invest* 70:1073-1078.
- Knox DL (1981). Uveitis syndromes and foci of infection. *Trans Ophthalmol Soc New Zealand* 33:155-156.
- Kraut RA, Hicks JL (1976). Bacterial endocarditis of dental origin: report of a case. *J Oral Surg* 34:1031-1034.
- Kubo S, Abe K, Oka M (1989). Necrotizing fasciitis of the middle third of the face. A case report. *J Craniomaxillofac Surg* 17:92-95.
- Laine PO, Lindqvist JC, Pyrhonen SO, Strand-Pettinen IM, Teerenhovi LM, Meurman JH (1992). Oral infection as a reason for febrile episodes in lymphoma patients receiving cytostatic drugs. *Eur J Cancer Part B Oral Oncol* 28(B):103-107.
- Larkin EB, Scott SD (1994). Metastatic paraspinal abscess and paraplegia secondary to dental extraction. *Br Dent J* 177:340-342.
- Lass JH, Varley MP, Frank KE (1984). *Actinobacillus actinomycetemcomitans* endophthalmitis with subacute endocarditis. *Ann Ophthalmol* 16:54-61.
- Latronica RJ, Shukes R (1973). Septic emboli and pulmonary abscess secondary to odontogenic infection. *J Oral Surg* 31:844-847.
- Lens JW, Beertsen W (1988). Injection of an antigen into the gingiva and its effect on an experimentally induced inflammation in the knee joint of the mouse. *J Periodont Res* 23:1-6.
- Levine TM, Wurster CF, Krespi YP (1986). Mediastinitis occurring as a complication of odontogenic infections. *Laryngoscope* 96:747-750.
- Lieberman MB (1992). A life-threatening, spontaneous, periodontitis-induced infective endocarditis. *J CA Dent Assoc* 20:37-39.
- Lindqvist C, Slätis P (1985). Dental bacteremia—a neglected cause of arthroplasty infections? Three hip cases. *Acta Orthop Scand* 56:506-508.
- Lindqvist C, Söderholm A-L, Slätis P (1989). Dental x-ray status of patients admitted for total hip replacement. *Proc Finn Dent Soc* 85:211-215.
- Little JW (1983). The need for antibiotic coverage for dental treatment of patients with joint replacements. *Oral Surg* 55:20-23.
- Loesche WJ, Terpenning MS, Bromberg JL, Dominguez BL, Kinder-Kerr C, Langmore SE (1995). A possible role for salivary bacteria in aspiration pneumonia (abstract). *J Dent Res* 74:127.
- Mapstone NP, Lynch DAF, Lewis FA, Axon ATR, Tompkins DS, Dixon MF, et al. (1993). Identification of *Helicobacter pylori* DNA in the mouth and stomachs of patients with gastritis using PCR. *J Clin Pathol* 46:540-543.
- Marks PV, Patel KS, Mee EW (1988). Multiple brain abscesses secondary to dental caries and severe periodontal disease. *Br J Oral Maxillofac Surg* 26:244-247.
- Mattila K (1990). Infections and coronary heart disease (dissertation). Helsinki, Finland: Helsinki University.
- Mattila KJ (1993). Dental infections as a risk factor for acute myocardial infarction. *Eur Heart J* 14(Suppl K):51-53.
- Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesäniemi YA, Syrjäälä SL, et al. (1989). Association between dental health and acute myocardial infarction. *Br Med J* 298:779-781.
- Mattila KJ, Valle MS, Nieminen MS, Valtonen VV, Hietaniemi KL (1993). Dental infections and coronary atherosclerosis. *Atherosclerosis* 103:205-211.
- May DR, Peyman GA, Raichand M, Friedman E (1978). Metastatic *Peptostreptococcus intermedius* endophthalmitis after a dental procedure. *Am J Ophthalmol* 85:662-665.
- Mayo CH (1922). Focal infection of dental origin. *Dent Cosmos* 64:1206-1208.
- McAndrew PG, Davies SJ, Griffiths RW (1987). Necrotising fasciitis caused by dental infection. *Br J Oral Maxillofac Surg* 25:314-322.
- McCurdy JA Jr, MacInnis EL, Hays LL (1977). Fatal mediastinitis after a dental infection. *J Oral Surg* 35:726-729.
- Mealey BL, Semba SE, Hallmon WW (1994). The head and neck radiotherapy patient: Part 2—management of oral complications. *Compend Contin Educ Dent* 15:442-458.
- Meehan S, Schmidt MC, Mitchell PF (1994). Infective endocarditis in a patient with Hodgkin's lymphoma: a case report. *Special Care Dent* 14:57-60.
- Miller EH, Kasselbaum DK (1995). Managing periorbital space abscess. Secondary to dentoalveolar abscess. *J Am Dent Assoc* 126:469-472.
- Miller WD (1890). The microorganisms of the human mouth. The local and general diseases which are caused by them. Philadelphia: S.S. White, pp. 274-341.
- Miller WD (1891). The human mouth as a focus of infection. *Dent Cosmos* 33:689-695.
- Mitchell CS, Nelson MD Jr (1993). Orofacial abscesses of odontogenic origin in the pediatric patient. Report of two cases. *Pediatr Radiol* 23:432-434.
- Mitre RJ, Rothran EB Jr (1974). Anaerobic septicaemia from thrombophlebitis of the internal jugular vein. Successful treatment with metronidazole. *J Am Med Assoc* 230:1168-1169.
- Mizuno I, Mizutani H, Ueda M, Kaneda T (1993). Temporal necrotizing infection of dental origin. *J Oral Maxillofac Surg* 51:79-81.
- Moncada R, Warpeha R, Pickleman J, Spak M, Cardoso M, Berkow A, et al. (1978). Mediastinitis from odontogenic and deep corneal infection. Anatomic pathways of propagation. *Chest* 73:497-500.
- Morer G (1975). Arthritis of the knee healed after dental avulsion (letter). *Nouv Presse Med* 4:2338.
- Mruthyunjaya B (1981). Necrotizing fasciitis: report of a case. *J Oral Surg* 39:60-62.
- Musgrove BT, Malden NJ (1989). Mediastinitis and pericoronitis caused by dental infection. *Br J Oral Maxillofac Surg* 27:423-428.
- Naschitz JE, Yeshurun D (1985). Occult infection in the facial area presenting as fever of unknown origin. *Israel J Med Sci* 21:995-998.
- Navazesh M, Mulligan R (1995). Systemic dissemination as a result of oral infection in individuals 50 years of age and older. *Special Care Dent* 15:11-19.
- Navazesh M, Mulligan R, Sobel S (1994). Toxic shock and Down Syndromes in a dental patient: a case report and review of the literature. *Special Care Dent* 14:246-251.
- Newman HN (1968). Focal sepsis—modern concepts. *J Irish Dent Assoc* 14:53-63.



- Nguyen AM, Engstrand L, Genta RM, Graham DY, El-Zaatari FA (1993). Detection of *Helicobacter pylori* in dental plaque by reverse transcription-polymerase chain reaction. *J Clin Microbiol* 31:783-787.
- Oakley CM (1979). Prevention of infective endocarditis. *Thorax* 34:711-712.
- O'Connell B, Crotty G, Cafferkey MT, Stephens R, McDonald GS, McCann SR (1992). Successful treatment of focal hepatic candidiasis with liposomal amphotericin B. *Irish J Med Sci* 161:664-665.
- Offenbacher S, Lin Y-Y, Boyd DL, Arnold RR (1993). *Actinobacillus actinomycetemcomitans* infection associated with low birth weight (abstract). *J Dent Res* 72:2157.
- Offenbacher S, Katz VL, Fertik GS, et al. (1996). Periodontal infection as a risk factor for preterm low birth weight. *J Periodont* (in press).
- Ogiso A, Tamura M, Minemura T, Kurashima K, Kotani A (1992). Mediastinitis caused by odontogenic infection associated with adult respiratory distress syndrome. *Oral Surg* 74:15-18.
- Ogundiya DA, Keith DA, Mirowski J (1989). Cavernous sinus thrombosis and blindness as complications of an odontogenic infection: report of a case and review of literature. *J Oral Maxillofac Surg* 47:1317-1321.
- Okabe K, Nakagawa K, Yamamoto E (1995). Factors affecting the occurrence of bacteremia associated with tooth extraction. *Int J Oral Maxillofac Surg* 24:239-242.
- Palank EA, Janardhana ML, Utell M (1979). Fatal acute bacterial myocarditis after dentoalveolar abscess. *Am J Cardiol* 43:1238-1241.
- Pellegrino SV (1980). Extension of dental abscess to the orbit. *J Am Dent Assoc* 100:873-875.
- Perna E, Liquori R, Petrone G, Mannarino E (1981). Actinomycotic granuloma of the gasserian ganglion with primary site in a dental root. A case report. *J Neurosurg* 54:553-555.
- Peterson DE (1990). Pretreatment strategies for infection prevention in chemotherapy patients. *NCI Monogr* 9:61-71.
- Peterson DE, Sonis ST (1982). Oral complications of cancer chemotherapy: present status and future studies. *Cancer Treat Rep* 66:1251-1256.
- Peterson DE, Minah GE, Overholser CD, Suzuki JB, DePaola LG, Stansbury DM, et al. (1987). Microbiology of acute periodontal infection in myelosuppressed cancer patients. *J Clin Oncol* 5:1461-1468.
- Peterson LJ (1993). Contemporary management of deep infections of the neck. *J Oral Maxillofac Surg* 51: 226-231.
- Petrone JA (1992). Mediastinal abscess and pneumonia of dental origin. *J NJ Dent Assoc* 63:19-23.
- Rams TE, Slots J (1992). Systemic manifestations of oral infections. In: Contemporary oral microbiology and immunology. Slots J, Taubman MA, editors. St. Louis: Mosby, pp. 500-510.
- Reed JM, Anand VK (1992). Odontogenic cervical necrotizing fasciitis with intrathoracic extension. *Otolaryngol Head Neck Surg* 107:596-600.
- Roberts GJ, Holzel HS, Sury MRJ, Simmons NA, Gardner P, Longhurst P (1996). Dental bacteraemia in children. *Pediatr Cardiol* (in press).
- Rosenow EC (1919). Studies on elective localization. *J Dent Res* 1:205-249.
- Rosenow EC (1921). Focal infection and elective localization of bacteria in appendicitis, ulcer of the stomach, cholecystitis and pancreatitis. *Surg Gynecol Obstet* 33:19-26.
- Rosenow EC (1923). Production of spasms of the diaphragm in animals by living cultures, filtrates and the dead streptococcus from epidemic hiccup. *J Infect Dis* 32:72-94.
- Rubin MM, Cozzi GM (1987). Fatal necrotizing mediastinitis as a complication of an odontogenic infection. *J Oral Maxillofac Surg* 45:529-533.
- Rubin R, Salvati EA, Lewis R (1976). Infected total hip replacement after dental procedures. *Oral Surg* 41:18-23.
- Rutkauskas JS, Davis JW (1993). Effects of chlorhexidine during immunosuppressive chemotherapy. A preliminary report. *Oral Surg* 76:441-448.
- Saal CJ, Mason JC, Cheuk SL, Hill MK (1988). Brain abscess from chronic odontogenic cause: report of a case. *J Am Dent Assoc* 117:453-455.
- Schuman NJ, Turner JE (1994). Brain abscess and dentistry: a review of the literature. *Quintessence Int* 25:411-413.
- Schurman DJ, Aptekar RG, Burton DS (1976). Infection in total knee joint replacement, secondary to tooth abscess. *West J Med* 125:226-227.
- Schwab JH, Cromartie WJ (1957). Studies on a toxic cellular component of Group A streptococci. *J Bacteriol* 74:673-679.
- Sela M, Sharav Y (1975). The dental focal infection as an origin for uveitis. *Israel J Dent Med* 24:31-35.
- Semba SE, Mealey BL, Hallmon WW (1994). Dentistry and the cancer patient: Part 2—oral health management of the chemotherapy patient. *Compend Contin Educ Dent* 15:1378-1387.
- Shinoda T, Mizuani H, Kaneda T, Suzuki M (1987). Fever of unknown origin caused by dental infection: report of a case. *Oral Surg* 64:175-178.
- Siegan-Igra Y, Schwartz D, Ophir O, Konforti N (1984). Endocarditis caused by *Actinobacillus actinomycetemcomitans*. *Eur J Clin Microbiol* 3:556-559.
- Smith D, Goycoolea M, Meyerhoff WL (1979). Fulminant odontogenic sinusitis. *Ear Nose Throat J* 58:411-412.
- Smyth AG, Ward-Booth RP (1993). Lympho-epithelial cysts: a maxillofacial surgeon's perspective. *Br J Oral Maxillofac Surg* 31:120-123.
- Spaulding CR, Friedman JM (1975). Subacute bacterial endocarditis secondary to dental infection. A case report. *NY J Med* 41:292-294.
- Steel A (1987). An unusual case of necrotizing fasciitis. *Br J Oral Maxillofac Surg* 25:328-333.
- Steiner M, Grau MJ, Wilson DL, Snow NJ (1982). Odontogenic infection leading to cervical emphysema and fatal mediastinitis. *J Oral Maxillofac Surg* 40:600-604.
- Stiegler P (1979). Septicaemia and pleural effusion from *Eikenella corrodens*, a normal inhabitant. *MN Med* 62:635-636.
- Stoykewych AA, Beecroft WA, Cogan AG (1992). Fatal necrotizing fasciitis of dental origin. *J Can Dent Assoc* 58:59-62.
- Strauss SI (1975). Bacterial endocarditis in dentistry. *FL Dent J* 46:17.
- Svirsky JA, Saravia ME (1989). Dental management of patients after liver transplantation. *Oral Surg* 67:541-546.
- Swift HF, Derick CL, Hitchcock CH (1928). Bacterial allergy (hypergy) to non-hemolytic streptococci. *J Am Med Assoc* 90:906-908.
- Syrjänen J, Peltola J, Valtonen V, Ilvanainen M, Kaste M, Huttunen JK (1989). Dental infections in association with cerebral infarction in young and middle-aged men. *J Intern Med* 225:179-184.
- Terezhalmay GT, Bottomley WK (1978). Pulmonary nocardiosis associated with primary nocardial infection of the oral cavity. *Oral Surg* 45:200-206.
- Thoden van Velzen SK, Abraham-Inpijn L, Moorer WR (1984). Plaque and systemic disease. A reappraisal of the focal infection concept. *J Clin Periodont* 11:209-220.
- Thornton JB, Alves JC (1981). Bacterial endocarditis. A retrospective study of cases to the University of Alabama Hospitals from 1969 to 1979. *Oral Surg* 52:379-383.
- Van Dyke TE, Dowell VR Jr, Offenbacher S, Snyder W, Hersh T (1986). Potential role of microorganisms isolated from periodontal lesions in the pathogenesis of inflammatory bowel disease. *Infect Immun* 53:671-677.



- Van Winkelhoff AJ, Overbeek BP, Pavicic MP, van den Bergh JP, Ernst JP, de Graaff J (1993). Long-standing bacteremia caused by oral *Actinobacillus actinomycetemcomitans* in a patient with a pacemaker. *Clin Infect Dis* 16:216-218.
- Whitley BD (1986). Ludwig's angina: a rare case of dental origin. *New Zealand Dent J* 82:48-50.
- Whittington BR (1979). Bacterial endocarditis: a clinical report. *New Zealand Dent J* 75:39-43.
- Whyman RA, MacFadyen EE (1994). Dens in dente associated with infective endocarditis. *Oral Surg* 78:47-50.
- Williams CW (1994). Malar implant infections resulting from recurrent infections of adjacent dental pathology. *Plast Reconstr Surg* 93:1533-1534.
- Wright WE (1990). Pretreatment oral health care interventions for radiation patients. *NCI Monogr* 9:57-59.
- Yates C, Monks A (1978). Orbital cellulitis complicating the extraction of infected teeth. *J Dent* 6:229-232.
- Zachariades N, Vairaktaris E, Mezitis M, Triantafyllou D, Papavassiliou D (1986). Cerebral abscess and meningitis complicated by residual mandibular ankylosis. A study of the routes that spread the infection. *J Oral Med* 41:14-20.
- Zeitoun IM, Dhanarajani PJ (1995). Cervical cellulitis and mediastinitis caused by odontogenic infections: report of two cases and review of literature. *J Oral Maxillofac Surg* 53:203-208.
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