

NICO Historical Review

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From: LadyLollipop (LadyLollipop_at_insightbb.com)

Date: 03/17/05

Date: Thu, 17 Mar 2005 05:52:51 GMT

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The History of Maxillofacial Osteonecrosis (NICO)

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Painful osteonecrosis/osteomyelitis, or "phossy jaw," of upper and lower jaws sloughed out when dentist tried to extract several teeth because of "toothache." Source: American Journal of Dental Science, 1859.

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History of Maxillofacial Osteonecrosis (NICO)

First described in 1794 in a case of septic necrosis of the femoral head, this enigmatic disease is as old as the dinosaurs but has been poorly understood and has such subtle radiographic changes that until recently it was seldom diagnosed prior to end-stage damage.[11-13] Contemporary research has so enhanced our understanding of its basic pathophysiology that

it now bears little resemblance to the entity once known as "aseptic osteomyelitis."

Heightened awareness and improved imaging techniques have confirmed this once rare disorder to be one of the most common of bone disorders. In certain diseases, such as lupus erythematosus, almost a third of patients may be affected.[9] IO is able to affect any bone of the human skeleton and is represented by a large number of orthopedic diseases now seen as simple anatomic- and age-related variations of intramedullary ischemia and infarction.[1-5,9,14,15]

The old, overly-simplified histopathologic definition of IO as massive loss of osteocytes without pus is now substantially expanded to include specific and often subtle signs of ischemic marrow damage which may not even include obviously dead tissues.[2-9,14-16] Histopathologically less severe or nascent involvement has begun to be consolidated under a common diagnostic term, bone marrow edema (Table 1), and the disease is now known primarily as a vascular disorder readily influenced by a variety of risk factors or trigger events ("hits") which promote thrombosis.[7,9,17-21] Persons with multifocal IO are more likely to suffer from systemic risk factors than those with single site involvement and the great majority of patients have inherited or acquired a systemic tendency toward fibrin generation (Table 2) which predisposes them to microinfarction and ischemic marrow damage.[8,9,15-22]

Usually associated with pain, IO can nevertheless show a surprising capacity to remain painless until great destruction has occurred, even to the point of joint collapse for hip lesions -- there is little correlation between the degree of bone involvement and the intensity of associated pain.[5,9] The pain can take on a neuralgic character but its etiology is primarily a function of intraosseous fluid dynamics and inflammatory mediators rather than damaged nerves, as discussed later.[4,5,9,11,14-16]

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The Pre-Antibiotic Era: 1850-1930.

IO of the maxillofacial region is not new to dentistry. During the pre-antibiotic era "phossy jaw" and other forms of "chemical osteomyelitis" resulted from environmental pollutants, such as lead and the phosphorus used in safety matches, as well as from popular medications containing mercury, arsenic or bismuth.[23-29] This disease was well established by 1867, did not often occur in individuals with good gingival health, and appeared to "attack" the mandible first.[25] It was associated with localized or generalized deep ache or pain, often of multiple jawbone sites. The teeth often appeared sound and suppuration was not present. Even so, the dentist often began extracting one tooth after another in the region of pain, often with temporary relief but usually to no real effect.[24] Occasionally, large fragments of necrotic bone would come out with the tooth, sometimes

involving much of an entire quadrant, as depicted in the figure at the top of this page. Apparently, Lorinser of Vienna in 1845 was the first to call attention to the problem.[25]

Less severe cases of maxillofacial osteonecrosis were discussed in the classic 1898 oral pathology text by Barrett,[28] wherein he described "caries" and "necrosis" of bone with cellular "devitalization" and "inhibition of nutrient currents," characterized by a slowly progressive "breaking down" of the "territory" of marrow tissues receiving those nutrients and resulting in little or no production of granulation tissue. He had no suggested etiology for his cases. Thirty years earlier and more than a century ahead of his time, Noel[27] separated bone caries into two distinct categories: "bone death" and the less intense "reduced vitality." Even earlier, the 1848 text by Thomas Bond[23], which appears to be the first true oral pathology text, was the first book to discuss bone necrosis as such, emphasizing that this disease did not require abscessed teeth or gums, could result in the complete death of bone. Bond mentioned that "necrosis may be caused by any means which destroys the nutrition of the bone or any part of it"—usually from "constitutional vitiations, or defects of nutrition consequent upon general pravity." His recommended treatment: "when necrosis has taken place, the bone must be removed."

G. V. Black,[29] the father of modern dentistry, described in 1915 an osteomyelitis look-alike disease which he called "chronic osteitis." He described slow bone death "cell by cell" with the creation of alveolar intramedullary "cavities" up to 5 cm. in size and wondered about its unique ability to produce extensive bone destruction without pus, without redness and swelling of the overlying tissues, without an increase in the patient's body temperature, and often without pain. His suggestion to curette diseased bone reiterated the treatment proposed by Ferguson[24] in 1868 and by Bond[23] in 1848. Around the same time period osteonecrosis of the hip in children was being recognized by the author's whose names would eventually be affixed to that disease, i.e. the Legg–Calvé–Perthes disease.[31–33]

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The Forgotten Decades: 1930–1970.

For most of the twentieth century this disease was largely forgotten by the dental profession, although a few investigators made significant contributions to the advancement of our understanding. Wilensky[24] and Hankey[25] suggested that persistent regional necrosis in osteomyelitis of the jaws was secondary to vascular insufficiency, while Brosch[26] described the potential for hollow medullary spaces to enlarge and coalesce one with another. Thoma[37,38] was likely the first to specifically correlate this "residual infection" or "osteitis" with old extraction sites, many of which demonstrated focal "necrotic exudates," fibrosis and "osteoclastic resorption" of surrounding bone. His observations were affirmed in 1955 by Box,[34] who reported a very large series of limited intraosseous

cavitations or "vacuolations" in old extraction sites with no production of pus or bony sequestra. Box was especially intrigued by the radiographic subtlety of the disease, by its multifocal nature, its localized tenderness without inflammatory signs, and the neuralgia-like nature of accompanying pain.

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The Over-Emphasis of Pain: 1970-1990.

The 1970s and 1980s saw a strong emphasis placed on the neuralgia-like pains often accompanying osteonecrosis of the maxillofacial region, an influence embodied in the currently popular diagnostic name NICO (neuralgia-inducing cavitation osteonecrosis).[40-48] Significant or complete pain reduction was achieved in chronic "idiopathic" facial pain by the simple expedient of decortication and curettage of damaged alveolar bone (Table 3), supporting the contention by neural researchers that persistent odontogenic and osseous disease can be important contributing factors for such neuralgias.44-49 None of these investigations included a control group, nor has any facial neuralgia follow-up study. Ethical considerations and the ever-present potential for silent or subclinical disease will likely prevent valid control groups from being identified, but a 1995 NICO follow-up investigation confirming earlier surgical successes went so far as to guarantee patient anonymity, to use a well-established pain evaluation instrument instead of surgeon records to determine outcomes, and to use a third party to collect and analyze data in order to reduce potential biases.[50]

Unfortunately, the major emphasis on the association with neuralgic pain initiated significant controversy among professionals treating "idiopathic" facial pain and kept involved researchers from focusing on other features of the disease process, such as more appropriate diagnoses and diagnostic techniques, and better understanding of the pathophysiology and pathoetiology of the disease. Early lesions were diagnosed by a number of independent pathologists as chronic osteomyelitis, and microorganisms cultured from many NICO lesions, combined with occasional facial pain relief with antibiotic therapy, assured that these cases would be diagnosed and treated as chronic osteomyelitis. And yet, a significant number of patients did not respond in a fashion appropriate to that diagnosis. This led some investigators to seek alternative interpretations for the biological behavior and histopathology. A critical shift in perspective (return to the original concepts?) occurred in 1989 when this odd alveolar disease began to be viewed primarily as a problem of compromised medullary blood flow driven by progressive thrombosis, rather than as a unique infection unknown to other bones.[56,57]

This new perspective as a maxillofacial manifestation of IO provided, for the first time, a logical explanation for the curiously multifocal nature of the disease; its frequent intermingling of ischemically damaged and normal

marrow (also influenced by the perfusion irregularities of fatty marrow[58]), its frequent lack of inflammatory cells, its remarkably chronic and recurring character, its deep bone pain and varied pain syndromes, its relatively high failure rate with local interventions, and its primary localization at the ends of the arterial inflow (retromolar and subcrestal alveolar regions) where weak, irregular blood flow favors the formation of intravascular thrombi.[5,7,9,14,15,59]

This is not to say that intraosseous microorganisms do not represent a significant risk factor or triggering mechanism for thrombosis in these stagnant zones of cancellous bone. Affected bone is ideal fodder for periodontal and periapical bacteria chronically stimulating inflammatory and immune responses.[60–62] Impaired medullary circulation prevents proper healing in these instances and the chronic infection, in turn, enhances local and systemic clotting. This further exacerbates the medullary ischemia and initiates a slow, ever-increasing spiral of thrombosis and microinfarction with progressively elevating intramedullary pressures, additional thrombosis, and frequent propagation of spontaneous pain. Prothrombotic factors, especially fibrinogen, also allow increased adherence of bacteria to thrombin-activated endothelial cells.[63]

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Decade of Major Advances: 1990–2000.

Once it became clear that this disease of the jaws resembled avascular necrosis of other bones, investigators used newly available laboratory tests, including allele-specific polymerase chain reaction, to identify in NICO patients heritable disorders predisposing to adverse thrombotic events. At least 72% proved to be afflicted with a variety of such disorders, as compared to 70–87% for patients with IO of the hip and knee.[9,19–21,64–67] This was seen as a major breakthrough, eventuating in the use of anticoagulants (without surgery or antibiotics) in persons with NICO and hip osteonecrosis.[68–71] Although not all affected individuals benefited, the significant pain relief experienced by a large proportion of treated patients confirms an association in those persons between the symptoms of IO and the hypercoagulable disorders.[69,71]

Viewing NICO as the oral manifestation of a systemic disease also allowed application of the clinicopathologic qualities of long bone disease to maxillofacial cases, especially the use of diagnostic imaging techniques such as 99technetium-MDP (99mTc-MDP) scintigraphy and Single Photon Emission Computed Tomography (SPECT) scans, instead of the indium and gallium scans typically used for bone infections.[64,72–74] The small number of chronic inflammatory cells found in NICO lesions makes radioisotopes which attach to leukocytes much less useful than those which attach to new or exposed bone matrix. There is usually a small amount of ongoing healing in IO lesions and so they present as "hot spots" of increased radioisotope uptake, with "cold spots" of extremely reduced uptake in the occasional severely desiccated

lesion. Newly developed ^{99m}Tc isotopes directed at fibrin "–chain peptide may prove useful for patients actively forming microclots.[75]

A substantial proportion (25–35%) of scans will be falsely negative because the disease has long periods during which no bone is destroyed or regenerated, even as symptoms and marrow damage progress. This holds true regardless of the affected bone, but maxillofacial involvement suffers from an unexpected false–negative phenomenon: radiologists not attuned to jawbone ischemia often interpret a hot spot of alveolar bone as "normal," presuming it to relate to ubiquitous dental and periodontal disease. We recommend, therefore, that the surgeon review all films interpreted as negative. Thin–sliced spiral CT scans and ultrasonic scans have also proven effective in localizing NICO, although they require very careful evaluation.[76] MRI scans are valuable for the rounded ends of bones but in our experience are of little benefit in alveolar cases.[77,78]

In a similar fashion the more contemporary histopathologic features of ischemic osteonecrosis and bone marrow edema (its less severe counterpart) often overlooked by or unfamiliar to oral pathologists, could be applied to maxillofacial examples with the notable caveat that there are no features of cortical collapse in jaw lesions and odontogenic infections are often superimposed.[1–9,57] Additionally, microscopic evaluation of maxillofacial biopsy samples is made much more difficult by the small number and size of available curettage fragments, especially when an intramedullary cavitation exists, in contradistinction to the large specimens available for study after resection and core biopsies of long bone cases. Recent analyses have, significantly, reported that almost 3/4 of jawbone biopsy samples of ischemic osteonecrosis and NICO can be classified as the histologically more subtle variants called bone marrow edema or regional ischemic osteoporosis.[81,82] This has helped to explain why some oral pathologists, certainly not the majority, have difficulty distinguishing the classic features from "normal" bone and bone marrow.

The first microscopic review of a large series of biopsied cases of NICO was reported during the 1990s, as was the first necropsy example.[57,82] These papers strongly emphasized the multifocal nature of the disease, while others reinforced the strong association between chronic facial pain and inflammatory or ischemic marrow disease.[55,83] In this light, one of the most important advances was the refinement of the old anesthesia/hyperesthesia and microanesthesia diagnostic tests to more successfully localize areas of medullary disease in facial pain patients.[84–86]

During the 1990s sophisticated assays were also applied, for the first time, to maxillofacial osteonecrosis. Haley and Pendergras[87] used a well–established neurotoxicity assay on a very large number of tissue samples, finding almost all to be extremely toxic — often more toxic than hydrogen sulfide, the chemical normally used to establish maximum level of neurotoxicity. The exact nature of the toxin is not yet known, but the discovery of the neurotoxicity led some to question whether or not this process damaged the peripheral nerve myelin of the alveolar nerves. This

idea was further stimulated by the finding in a small number of NICO biopsy samples of an unusual form of nonwallerian degeneration in the majority of visible nerves.[55] To this end the blood of another small sample of NICO patients was evaluated by a newly-established assay which, for the first time, allowed the determination of circulating antibodies against peripheral nerve myelin.[88] The sera of healthy humans normally show none of these antibodies, as was true for a few of the NICO patients, but other NICO patients had antibody levels as high as or higher than those found in the classic demyelination disease, the Guillain-Barré syndrome.[89,90] This suggests chronic exposure of the peripheral myelin to the immune system, either as a primary attack (autoimmune) or secondary to myelin exposed or partially destroyed by a local inflammatory/ischemic phenomenon.

While some patients had no such antibodies, others demonstrated Elevated levels of circulating anti-peripheral nerve myelin (anti-PNM) antibodies have been found in NICO patients, suggesting .120-122 Chronic nerve damage is likely enhanced by the very high levels of neurotoxicity found by bioassay in virtually all tissue samples of maxillofacial osteonecrosis, although the responsible neurotoxins have not yet been identified.123

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References

1. Burwell RG, Harrison MHM (eds). Symposium: Perthes' disease. Clin Orthop 1986; 209:2-161,234.
2. Milgram JW. Radiologic and histologic pathology of nontumorous diseases of bones and joints. Northbrook, Illinois, Northbrook Publishing, 1990, vol 2, p 868.
3. Ono K, ed. Symposium: recent advances in avascular necrosis. Clin Orthop 1992; 277:2.
4. Schoutens A, Arlet J, Gardeniers JWM, Hughes SPF. Bone circulation and vascularization in normal and pathological conditions. New York, Plenum Press, 1993.
5. Steinberg ME, Steinberg DR. Osteonecrosis. In: Kelly WN, Harris ED Jr, Ruddy S, Sledge CB. Textbook of rheumatology (4th ed). Philadelphia, W.B. Saunders; 1993, p 1628.
6. Mazieres B. Osteonecrosis. In: Klippel JH, Dieppe PA (eds). Rheumatology. St. Louis, Mosby; 1994, 41.1.
7. Bullough, PG. Orthopaedic pathology (3rd ed). Baltimore, Mosby-Wolfe, 1997.

8. Jones JP Jr. Osteonecrosis. In: Koopman WJ (ed). Arthritis and allied conditions; a textbook of Rheumatology (13th ed). Baltimore, Williams & Wilkins, 1997,1923
9. Urbaniak JR, Jones, JP Jr (eds). Osteonecrosis --- etiology, diagnosis, and treatment. American Academy of Orthopaedic Surgeons; Chicago, Illinois, 1997.
10. Phemister, DB. Repair of bone in the presence of aseptic necrosis resulting from fractures, transplantations, and vascular obstruction. *J Bone Joint Surg* 1930; 12:769.
11. Russell J. A practical essay on a certain disease of bones termed necrosis. Edinburgh, Neill and Co, 1794.
12. Martin LD, Rothschild BM. Paleopathology and diving monasaurs. *Amer Scientist* 1989; 77:460.
13. Norgard MJ, Carpenter JT, Conrad ME. Bone marrow necrosis and degeneration. *Arch Intern Med* 1979; 139:905.
14. Arlet J, Mazieres B (eds). Bone circulation and bone necrosis. Heidelberg, Springer-Verlag, 1990.
15. Ficat RP. Idiopathic bone necrosis of the femoral head: early diagnosis and treatment. *J Bone Joint Surg* 1985; 67B:3.
16. Arnoldi CC. Intraosseous engorgement-pain syndromes. The pathomechanism of pain. In: Arlet J, Mazieres B (eds). Bone circulation and bone necrosis. Proceedings of the IVth International Symposium on Bone Circulation, Toulouse (France), 17th-19th September, 1987. New York, Springer-Verlag, 1990.
17. Jones JP Jr. Intravascular coagulation and osteonecrosis. *Clin Orthop* 1992; 277:41.
18. Van Veldhuizen PJ, Neff J, Murphey MD, et al. Decreased fibrinolytic potential in patients with idiopathic avascular necrosis and transient osteoporosis of the hip. *Am J Hematol* 1993; 44:243.
19. Glueck CJ, Freiberg R, Glueck HI, et al. Hypofibrinolysis; a common, major cause of osteonecrosis. *Am J Hematol* 1994; 45:156.
20. Glueck CJ, Crawford A, Roy D, Freiberg R, et al. Association of antithrombotic factor deficiencies and hypofibrinolysis with Legg-Perthes Disease. *J Bone Joint Surg* 1996; 78A:3.
21. Glueck CJ, Freiberg R, Gruppo R, Crawford A, et al. Thrombophilia and hypofibrinolysis: reversible pathogenetic etiologies of osteonecrosis. In: Urbaniak Jr, Jones, JP Jr (eds). Osteonecrosis: etiology, diagnosis, and treatment. Chicago, Illinois, American Academy of Orthopaedic Surgeons, 1997

p 105.

22. Mont MA, Jones LC, La Porte DM, et al. Symptomatic multifocal osteonecrosis: a multicenter study. *Clin Orthop* 1999; 369:312.

23. Bond TE Jr. *A practical treatise on dental medicine*. Philadelphia: Lindsay & Blakiston, 1848.

24. *Am J Dent Sc* 1859 [phossy jaw photo]

25. Anonymous. Necrosis of the lower jaw in makers of Lucifer matches. *Am J Dent Science* 1867; 1 (series 3):96–97.

26. Ferguson W. New treatment of necrosis. *Am J Dent Science* 1868; 1 (series 3):189.

27. Noel HR. A lecture on caries and necrosis of bone. *Am J Dent Science* 1868; 1 (series 3):425, 482.

28. Barrett WC. *Oral pathology and practice*. Philadelphia, S.S. White Dental Mfg Co, 1898.

29. Black GV. *A work on special dental pathology* (2nd ed). Chicago, Medico_Dental Publ Co, 1915.

30. [old: discolored nerve]

31. Calve J Sur une forme particuliere de pseudo-coxalgie greffee sur des formations caracteristiques de l'extremite superieure du femur. *Rev Chir* 1910; 42:54–84.

32. Legg AT. An obscure affection of the hip joint. *Boston Med Surg J* 1910; 162:202–204.

33. Perthes G. Uber Osteochondritis Deformans Juvenalis. *Arch Klin Chir* 1913; 101:779–807.

34. Wilensky AO. Osteomyelitis of the jaw. *Arch Surg* 1932; 25:215.

35. Hankey GT. Osteomyelitis (necrosis) of the jaws: it pathology and treatment. *Brit Dent J* 1938; 63:552.

36. Brosch F. Die histopathologische Grundlage der Symptome bei Keifer-osteomyelitis. *Deutsch Zahnartz Zeit* 1958; 13:426.

37. Thoma KH. *Clinical pathology of the jaws, with a histologic and roentgen study of practical cases*. Baltimore, Charles C. Thomas, 1934, p 94.

38. Thoma KH. *Oral surgery* (vol 1). St. Louis, C V Mosby; 1948, p 773.

39. Box RM. Post-extraction oral sepsis. *Ontario Dent J* 1955: Oct/Nov:1.

40. Ratner EJ, Person P, Kleinman DJ, et al. Jawbone cavities and trigeminal and atypical facial neuralgias. *Oral Surg Oral Med Oral Pathol* 1979; 48:3.
41. Roberts AM, Person P. Etiology and treatment of idiopathic trigeminal and atypical facial neuralgias. *Oral Surg Oral Med Oral Pathol* 1979; 48:298.
42. Shaber EP, Krol AJ. Trigeminal neuralgia __ a new treatment concept. *Oral Surg Oral Med Oral Pathol* 1980; 49:286.
43. Mathis BJ, Oatis GW, Grisius RJ. Jaw bone cavities associated with facial pain syndromes: case reports. *Milit Med* 1981; 146:719.
44. Demerath RR, Sist T. Treatment of osteocavitation lesions in facial pain patients: preliminary results. *J Dent Res* 1982; 61:218.
45. Wang M, Xiwei J, Qingrong I, Sanyou Z. [A study of the relation between the various trigger zones of idiopathic trigeminal neuralgia and jaw bone cavities.] *Acta Acad Med Sichuan* 1982; 13:233.
46. Grechko VE, Puzin MN. [Odontogenic trigeminal neuralgia] *Zh Nevropathol Psikhiatr* 1984; 84:1655.
47. Roberts AM, Person P, Chandran NB, et al. Further observations on dental parameters of trigeminal and atypical facial neuralgias. *Oral Surg Oral Med Oral Pathol* 1984; 58:121.
48. Ratner EJ, Langer B, Evins ML. Alveolar cavitation osteopathosis -- manifestations of an infectious process and its implication in the causation of chronic pain. *J Periodontol* 1986; 57:593.
49. Harris W: Forward. In: Wartenberg R: *Neuritis, sensory neuritis, neuralgia, a clinical study with review of the literature*. New York, Oxford University Press, 1958, p vii.
50. Mumford JM. Role of the dentist in trigeminal neuralgia. *Pain* 1978; 5:83.
51. Sisk AL. Management of chronic orofacial pain: surgical treatment of chronic facial pain. *Anesth Prog* 1983; 30:180.
52. Fromm GH, Terrence CF, Maroon JCL: Trigeminal neuralgia; current concepts regarding etiology and pathogenesis. *Arch Neurol* 1984; 41:1204.
53. Sessle BJ. Neurobiology of orofacial pain. *Dent Clin North Am* 1987; 31:595.
54. Raskin NH. *Headache*, 2nd ed. New York, New York, Churchill Livingstone, 1988.

55. Bouquot JE, Christian J. Long-term effects of jawbone curettage on the pain of facial neuralgia; treatment results in neuralgia-inducing cavitation osteonecrosis. *J Oral Maxillofac Surg* 1995; 53:387.

56. Bouquot JE, Roberts AM, Person, P, Christian J. The histopathology of neuralgia-inducing cavitation osteonecrosis (NICO). *J Dent Res* 1989; 68:952.

57. Bouquot JE, Roberts AM, Person P, et al. NICO (neuralgia inducing cavitation osteonecrosis): osteomyelitis in 224 jawbone samples from patients with facial neuralgias. *Oral Surg Oral Med Oral Pathol* 1992; 73:307.

Byron MA. A clinicopathologic review of 2278 NICO cases (neuralgia-inducing cavitation osteonecrosis). Master's Thesis (Endodontics). Morgantown, WV: West Virginia University, 1994.

Bouquot J, McMahon R. Ischemic osteonecrosis of the jaws in 2,023 patients with facial pain. *J Oral Pathol Med* 1996; 25:271.

Bouquot JE, McMahon RE. Ischemic alveolar osteonecrosis in 2,023 patients with chronic facial pain. *J Orofacial Pain* 1997; 11:180.

Odell EW, Morgan PR. Biopsy pathology of the oral tissues. London: Chapman & Hall, 1998: 268–270.

58. Kiaer T. Bone perfusion and oxygenation. Animal experiments and clinical observations. *Acta Orthop Scand* 1994; 65 (Suppl 257):1.

59. Hiroshi I, Matsuno T, Kaneda K. Prognosis of early stage avascular necrosis of the femoral head. *Clin Orthop* 1999; 358:149.

60. Lerner UH. Regulation of bone metabolism by the kallikrein-kinin system, the coagulation cascade, and the acute-phase reactants. *Oral Surg Oral Med Oral Pathol* 1994; 78:481.

61. Stashenko P, Want C-Y, Tani-Ishii N, Yu SM. Pathogenesis of induced rat periapical lesions. *Oral Surg Oral Med Oral Pathol* 1994; 78:494.

62. Torabinejad M. Mediators of acute and chronic periradicular lesions. *Oral Surg Oral Med Oral Pathol* 1994; 78:511.

63. Shenkman B, Runinstein E, Tamarin I, et al. Staphylococcus aureus adherence to thrombin-treated endothelial cells is mediated by fibrinogen but not by platelets. *J Lab Clin Med* 2000; 135:43.

64. Neville B, Damm D, Allen C, Bouquot JE. Oral & maxillofacial pathology. Philadelphia: W. B. Saunders, 1995, p 631.

65. Glueck CJ, McMahon RE, Bouquot JE, et al. Thrombophilia, hypofibrinolysis and osteonecrosis of the jaws. *Oral Surg Oral Med Oral*

Pathol 1996; 81:557.

66. Gruppo R, Glueck CJ, McMahon RE, et al. The pathophysiology of osteonecrosis of the jaw: anticardiolipin antibodies, thrombophilia, and hypofibrinolysis. *J Lab Clin Med* 1996; 127: 481.

67. Glueck CJ, McMahon RE, Bouquot JE, Tripplet D, et al. Heterozygosity for the Leiden mutation V gene, a common pathoetiology for osteonecrosis of the jaw with thrombophilia augmented by exogenous estrogens. *J Lab Clin Med* 1997; 130:540.

68. Glueck CJ, Freiberg R, Glueck HI, et al. Idiopathic osteonecrosis, hypofibrinolysis, high plasminogen activator inhibitor, high lipoprotein (a), and therapy with stanozolol. *Am J Hematol* 1995; 48:213.

69. Glueck CJ, McMahon RE, Bouquot JE, Tracy T, et al.. Preliminary pilot study of the treatment of thrombophilia and hypofibrinolysis and the amelioration of the pain of osteonecrosis of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 85:64.

70. Hammerschmidt DE. Thrombophilic osteonecrosis: another chapter. *J Lab Clin Med* 1997; 130:451.

71. Glueck CJ. NICO and anticoagulation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86:5.

72. Langlais RP, Langland OE, Nortje CJ. Diagnostic imaging of the jaws. Baltimore: Williams & Wilkins; 1994:393.

73. Boudreau RJ, Griffiths HJ. Bone infarcts and osteonecrosis. In: Collier BD Jr, Fogelman I, Rosenthal L. *Skeletal nuclear medicine*. St. Louis: Mosby, 1996;293.

74. Bouquot JE, LaMarche MG. Ischemic osteonecrosis under fixed partial denture pontics: radiographic and microscopic features in 38 patients with chronic pain. *J Pros Dent* 1999; 81:148.

75. Thakur ML, Pallela VR, Consigny PM, et al. Imaging vascular thrombosis with ^{99m}Tc-labeled fibrin "–chain peptide. *J Nucl Med* 2000; 41:161.

76. Nicol K, Klingman J, Holt J, et al. Ultrasonic gum/jaw bone detection instrument. Thesis. Socorro, New Mexico, New Mexico Institute of Mining & Technology, 1996.

77. Larheim TA, Westesson P–L, Hicks D, Eriksson L, et al. Osteonecrosis of the temporomandibular joint: correlation of magnetic resonance imaging and histology. *J Oral Maxillofac Surg* 1999; 57:888.

78. Sano T, Westesson P–L, Larheim TA, Rubin SJ, et al. Osteoarthritis and abnormal bone marrow of the mandibular condyle. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 87:243.

80. Bouquot J, McMahon R. Bone marrow edema syndrome: new disease or early presentation of ischemic osteonecrosis? J Oral Pathol Med 1998; 27:346.

81. Bouquot J, McMahon R. Bone marrow edema syndrome, independent disease or early presentation of ischemic osteonecrosis? Proceedings, Annual Meeting, American Academy of Oral & Maxillofacial Pathology; Williamsburg, Virginia; April, 2000.

82. Adams WR, Spolnick KJ, Bouquot JE. Maxillofacial osteonecrosis in a patient with multiple facial pains. J Oral Pathol Med 1999; 28:423–432.

83. McMahon RE, Griep J, Marfurt CP, et al. Local anesthetic effects in the presence of chronic osteomyelitis/necrosis of the mandible: implications for localizing the etiologic sites of referred trigeminal pain. J Craniomand Pract 1995; 13:212–226.

84. Brown RS, Hinderstein B, Reynolds DC, et al. Using anesthetic localization to diagnose oral and dental pain. J Amer Dent Assoc 1995; 126: 633–641.

85. McMahon RE, Adams W, Spolnik K. Diagnostic anesthesia for referred trigeminal pain, Part I. Compendium Cont Educ Dent 1992; 11:870–881.

86. McMahon RE, Adams W, Spolnik K. Diagnostic anesthesia for referred trigeminal pain, Part II. Compendium Cont Educ Dent 1992; 11:980–997.

87. Haley BE, Pendergrass JC. <http://www.altcorp.com>. [Affinity Labeling Technologies; University of Kentucky]

88. Koski CL. Humoral mechanisms in immune neuropathies. Neurol Clin 1992, 10:629.

89. McMahon R, Bouquot J, Mahan P, Gremillion H. Elevated serum peripheral nerve anti–myelin antibody titers in atypical facial pain patients with NICO. J Orofacial Pain 1994; 8:104.

90. McMahon R, Bouquot J, Mahan P, Saxen M. Elevated anti–myelin antibodies in patients with maxillofacial osteonecrosis (NICO). J Oral Pathol Med 1998; 27:345–346.

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Table 1: Alternative diagnostic names used for bone marrow edema and ischemic osteonecrosis. 1–9, 14–16

Bone Marrow Edema
Ischemic Osteonecrosis

Arlet Type I osteonecrosis
Bone compartment disease
Bone marrow edema syndrome
Chronic traumatic edema
Medullary engorgement–pain syndrome
Migratory osteolysis
Migratory osteoporosis
NICO *
Post–traumatic painful osteoporosis
Post–traumatic reflex dystrophy
Primary algodystrophy
Regional ischemic osteoporosis
Regional osteoporosis
Roentgenologic transient osteoporosis
Sudeck's disease (RSD) **
Transient bone marrow edema syndrome
Transient demineralization
Transient ischemic osteoporosis
Transient marrow edema
Transient osteoporosis
Transitory demineralization in pregnancy
Aseptic necrosis
Aseptic osteomyelitis
Aseptic osteonecrosis
Avascular necrosis
Bone infarction
Coronary disease of bone
Ischemic necrosis
NICO *
Osteochondrosis desiccans
Perthe's disease

* NICO: neuralgia–inducing cavitational osteonecrosis

** RSD: reflex sympathetic dystrophy

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Table 2: Coagulation disorders found in patients with ischemic osteonecrosis of the hips, knees and jaws. These are compared to the proportions found in patients with deep vein thrombosis of soft tissues and with the normal population. Resulting proportions do not total 100% because some patients had multiple disorders. Modified from Bouquot JE, LaMarche MG. *J Pros Dent* 1999; 81:148–158.

Normal Population
Deep Vein Thrombosis
Osteonecrosis

Thrombophilia

Hereditary types*

2–5%
5–9%
50–70%

Acquired types

3–7%
20–50%
33%

Hypofibrinolysis:

Hereditary types *

<1%
5–15%
18–22%

Acquired types

<1%
20–25%
50%

Total (includes multiple coagulopathies):

5–9%
20–50%
65–87%

* usually autosomal dominant

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Table 2: Results of surgical curettage of jawbone NICO (Neuralgia–Induced Cavitational Osteonecrosis) lesions, an average of 4.5 years after last surgery, in 103 patients with "idiopathic" chronic facial pain for an average of 6 years (range: 2–18 years) prior to NICO surgery.

Reference: Bouquot JE, Christian J. Long–term effects of jawbone curettage on the pain of facial neuralgia. J Oral Maxillofac Surg 1995; 53:387–397.

Follow–up Rating Reduction % Pain Present Status of Pain % of Total Cases

0 0–10 % No improvement 8.8% *
1 11–33 Minimal improvement 2.9
2 34–75 Moderate improvement 15.5
3 76–99 Considerable improvement ** 13.6
4 100 No pain 59.2
Total:
100.0 %

MO47VQY&(0JQ(R2/2J4;31M)^7G+*A'2I4; 7I7B2V.\@8P,\FJ]Q<?9+</
M.I+&DI&O7%1V5JMSASD[WW\$YXJEK%U</.#: !%.PMZFNPS\H6Z\I8C#&OS
M,]ZN07]O,["S=\$*G;CU&*QKR&2=_D?]XB9VYZ@5#IUB+DY"O&P)(8>E+J,
M[,W,,:1*Q.?4#DU6@U>WN+G[.-RR\$9&1UJ#;N@16<#!'XXIB2PR2%(_ED' ?'
M2AP0C:Y]*HP/-L5EF\WCOWJ59I=^/D8XR4S@BL^5@32.(DW'Z >IJK+^CAI
M+L]1P 2,"FSS^:PX7;SC/4UG7%RD: 3SYC ^;UJU'0^O+M]BQVZ8D; 0=AZ
MFH83>22)8JHE1?`62@?\?G0UM)J+1260*1XPTC>E;MH(H-MM".%7)842?8"C
M8VC6CS[NB'AN]6[9FA>02#*,V0XZ417!N+RX@.% "KC'<^]1Q!P[1<,J+|WKG
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M1(%C+N&1QQGKS6;\$?:8J>65&1SUS_.M8;")5"J&:(C!-)'&YD7=U/H>M(G[
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MQ0@&3,\$5>=N.0??TIC[7WG>N#P<BG2(7>.,<AFP% ^Z6> ;#\$J@\$]#VH' @F\$
M<;1HA"R\$<E1R!ZU"]DD@1,EY6)RXXP/?*D4.C229#W ^3@<'9JY:6YYW\$>:
MXSGT%)@+Y8M\$1T.U(UP%]3[USX@F<#SFRGF<1CI70W195\HE0#W8<'LN6:<
MDC*P?.TK_6E8!BM")TG+JA"\$,]*5;A90HMW*ECT`ZCUJ6060SE\$8D] .:+2
M6WWR2>64=4VX(Z'F!(L1E@!<9QGBGV:\$SQJ ,YY^E.CO5:1HHU897AL<9JQ8
M\$E]\NT.I(&/2F]@*44TEG?R6Z\$VSM@'N#[5<\$UE'L@2Y=SWX)(J:^6*:6\$R
M+TR_%1QO%'7CA5BQP2!R,U"ON!5>P6X"/"DTROSN+;0*F31+.,E[I>%&0N[
M.:M&>2!\$,8#@+TZ5';HMS+Y]TKB7. F>`*33`5)I;DI:1^5`JC(8=16FJ*G
MW0!Q52YOEM;A8O)9MPZJ*CU*=S!%'668@?+U4=ZAW8#;5W:,SE=KLQRWJ
M:G#?-(BK\#)-,CB*6B(I+;3CGJ:<I,1`Y*_G6@#(9U:42*#G.QSV-7^]4E
MC\JQ?C!SG/XU<0?2HD`M%%0,2BBB@!14JU\$*E6I8T#5&:D:HS0@84444Q!
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MJ>WMQ+:*6!3/3ZCTZ,O!+YD@8LPYK1Q@ #H*RE)I@5+F!6C"LQXZ\$52A\$QM
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MAZCIZU.JT M8G#.LT;87^/!JT#(BCRH_G;NWI4S3*B_*#(\$\$?+4-[+(9XX
M.&_B;T!2NWI8"2[N(X/FV[YL8"CDU% ",&;B4C)]LU"!;QI*9=I#L<&L[6;
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MBB@`JG?@RF.+%)RP]:N51O&\$=U\$S="IQ50W\$1W\$RQJ4&!D=*R/[0,5Q`I&

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M_P#+.#[FKE0QA1112 **** "BBB@ %2BHA4HJ6-`U1FI&J,T(&%)GG%+13\$
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M3<<XZT^L7\$GF)9@KQ'AUX#_`%K4ANDE.PG;Z'O2<; 34445(P\$P&.M% % %

M`"TTJ", \$4ZDH`3;R2&/—_> KT([T^BBX#0YW;2I'O1YJ\].M.HP/04: `P
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MGD9R:S<=+@7D=7&48&EK)GN&CNU:UC !"[S/^%2IJ;[U1X=S-V2DX/H!HT5#
M% =1R/LPROZ,,9J;(P)^E0TT,**/K10`M)110`4444` .1Q11]**`"BC%%
M!11BJVH78LK5I2 3T H`LTR26.(9D=4`N:I&[N\$M/M&U77;DXZBL2Y!N-1L9

MY7,UN^XMGAIUJN4#HS?6H(!F7)]*9?ZC!86OGR'<#]T#O7/:C;/V[K=6@0K'
M(K)CAJBOM'U2[43Y"1E<B(-P*&D@-JTNVU.U\$QN1`&Z*G4?C6'<:LUEJR@W+
MW42==QSBG6FEI+!LEDC8';*H8]:W3H&GM:K"TR!)\=?SIO0#%;79]3G\$-E
M9@MV?."OO5VY\3W8%Q/>-]I5<`<5JZ?IMMIR;;=">K'J:LS.(XF8G%3=O
M0#CK&Q#7\$4,S*0I_>HI[UV\$(C2)5B4*@X %<9?*MCJ3N)3O;]X^_C73VMT)
M+57QG(#+5M7 O2*KQLC_'2"#6?H5O';612/G+\$DU-<W2^5\N?F'/M5?3'-O
M:JKDD?R-+E=A&A/*(XV)ZD8%<_J^I3;XM.M6*R"FN.U-U+7"FH+;)L.!R3T
M!I=/\$4<<E])("<D,S=#ZTTEL,N:5=BW\$EO<W'94Y1F/.*UXY8YDWQ.'7U%8E
MII]FUH;V\4/O)8;CP!VJQH2""..#"@AMP"G(P:EKJ!JT445(!1110 444=J
M'5**B%2K4L:!!8:>U1FA`PHHHIB"D(R,'O2TE '):FKGS8VW8!R"IZ5DB0V\
MT 'AKC?/N3ZUTVJQF.YD'02ID\$5@7"-)Q88CWX&!SQ6SUU W-5E6.6*55#9
M!ZT^VG6TLXFN' #NP!)Z'YQ444GVW1CM4%PG?U'6LUIXI-!(E;\$\;*>M-NP
MCH00BI+G_9^HK"U*W1=1E4@@@7\$?SU-&K7\$JV^GWD+,8E W = :KZG[39S[
MB%V ^\^N)NXS-LKDV=XD?))5P:T+_5[<0")2"[N#QVYJO*MMOCCD#JYY8^C5
MF3P"*Z*N&PS?NV/UI7<58#L(FWJ-X #I6!;6Z6.NK'(2V02A/:M>\$K"B>?J
MJ\$ZL>M5(9HK_`%21XC^CCP#CK5RL["-`0())&D;H<^E8MW8D7L3@DP<NI]^
MN/SK2U:X\$-CDLP_NE:9)= V5N+=A([D?+W]33E9Z'1LUXKQI;(#&HW\$GWJQJ
M-S);6>]74,<^WTJ=,A@R]&[>E9OB-!+-C@..2GJ*'HF!;T0S2:<9I6+O(V
M3FG-J2:=(CO&7<G!'(%2V2!-*MU4[6"##:JZC;F:"2>\$XEQ\P]0*60*!=2Y
MCUEXY@7BBC; QQNJ]<I&BB./(?KG-9^EH%TR\$8^8?^M6Y26/F9)-"6P#K2)
M99IBQ;/<TS[7>)++!"!&!&1AF!.15FUPD,DI&.OZ5GV<CS(TLN<R,3SZ9XI;
MR: M^??X.3;KZ9SS^M(])<01I+-\$CQ[S]VJ+#AY"QR",I[8J;4YXX-,?=PI
M3M4N*0#3J9E.+5 VX90M_%38+V_==\MHJ(#@G/-9UF_D:5:.@W' Q^-.!GD*
M+\$N";]*KE0%V"Z661HR"LB\X/<5DZKJ'FWL=C'/Y(S\Y_2K^H3QV:K,1\Z
M*0/?TKFXX%+F0RW6?GY'M4J-J4,VKBXL["\$-<.S`]FW;JCU#Q%':VD;+&RS
MR=\$<8Q[UG:5:];M4< QQMD9[FMG7]:"6SWO&ID4C8Q[<TF@(K.%I+9KB^O22
MW/# !16-K%XKQQI9W+W.TD\$9HNHFFV"!B2Q'P.F:Z73]+MK& 1I&"3R2>N:
M<M .:CU&^&G"171\$4F/!7ZU+9:->WEH0;H)"PR !WJ1ML.M75F0IBD!90>Q
MK>L2L5M'#G&U?SH>UT!C3:>FG_9Q< O\$C#Y@..O>ND!!08Z\$<51U-HI=/E#-
MP!GBJHU9\$M@KGY@F>.N*5G(12LV\$=]?(#N99BWX9K8^W,&4!-P/4]Q7*6UP)
M[F\N\$RBMCK]175+#;S1QNTA!P#G/M5Z-:@61<0EMN\ ^AJI<W(FW1 84'K5>
M^"6R!E;>6(&?J)S)%!"\SMC`V\]S3C%+4#+UF8S2+(\$#0P);@.IJ[HVH+=Q
M%<HCQGY5SU%4[30'ND9OM+):DY.X=:+;0;0F)KF3S >66HYFG<9NNO&_*#
MUW=169<W;1HMI9R":5N&E'*KFLZ:XLf=8K:>68@?\M3A14T%DUK(45U:23D@
M]OI5<S>PBQ;ZO((G>YVRR@Y9L]_2F:@C3-9VSR(B[P9\$!P',)#5K2]/FDN)3
M),YRP_NFJLEO&VKSC?^]523CIITL,T;RXBG?[.\$8"N!M[>]06^GQZ9/9RI=
MN7D?:REOO"J=A>#S& !<YVJ0*W);*+?9F0;IE?*^P[TG:PC6/6DI3UI*Q&%%
M%%,`HHHH'!UJ45*\$E%2QH&J,U(W2HZ\$#"BD_E2TQ"4444 4M51C:&1!EX^?P
M[UA7*?ZQ6P?,4.@[9KJB`V01D'K7++:M,9X9#C8VU<]JU@[JPB31HW1IHV>,
M!0200:LN_1'NV?ROE+#:_8D4IL+U5F#;8]O *G[X]*CW7LR)"',DL\$VD9P1Q
MFFWIJ,M-(`+VR7 BBDYV-TS[5'-=/=61LI,2-&P'D'3BM:/PSYD:/=SM)*J
M#L#5""V"V]P"FO6P0G!4BDM=@(<.UO+H(H\$L)#1[OXQ46H0>=%#,A(#*,^@
M.:=*T*VV^3S""WR\$]1[5;@PKJQ :V8AL?W:JU] ,EX%0HSR&4GY7/H?*"O:-
M\$Z:LT;+L!C. 3U%1S('O51CA93SCH/05<TJ,R:E'(WWD5DY/)Z5*6H\$&N\$MY
M%LC\$<\$[?6LW0RT6JQG."N00:U=.;IO/,M]CB/Y#ZJU5 UM!/#)@M>>8%=?2A
MZRN!NR1[9'EC8[AP:K36D%S;M<7!VO",EO6K5V9%?:B_ZP<"J5XKWT4EE9R
M>4/WIQU/I6DMA%BS8SZ;;RQONVBJVK7+1:??+&-K<#KFI="1[6 VLH7<IW#
M!SD&CQ#&IT>; ^?</YBE=H=2>R=HHK9L?*4P3]:L"?<'3G?Z5'8*LEC!&^?
MG4?A4DD+E%:+`F%'4@)W<&QCAWX:4X7W[TWA3M7D*2..W-17=PD,RP#F6\$##
MXS@FEM@^TEOF9B23@CO4Q[@2,K,P4<8.0?456\1C% @L2'[QPWL*M99H@%^^N
M<5FRS)?Z@ 9"\$7Y3D?*:& L*0VEK! TP96Y6KL;D3AE PA_*LO4+9;AXGB^[

M\$^T@5K(H4.A'WEP#5>0&7J@NKO4E60,L"C@CHQI;I-E@BHQV!A@CK]*BBU&=
MIV2=@8E^Z".1VJY\$)(0K-GG.*F*TT @TL*]W(X8N\$'/XU8U^9W@2)2"7(V^
MW>G6MLMB-J@AFY;/<55N)\$N=2*C/EQC@]LT6^EL[\$1-%D8((Y)*Z(<5CL1LY
M(*M@9!Z5/>:B+6P9U!>0K\H'J9KL!Q^IW\$C:_<2Q#)C<XKH;;4H[A8"&&[&&
M'H:Q!:236Z3A`#(V7)-:PL+554*"K-R<'FB":&R#4;X2RM9VAW.ZG<1VJC.L
MT**]R#A6^]G@CTJ;[3:6VO((T(39M=O6KFOO#]A54&XRMA0.33O>[H:?:- 9
MY,AHPRY" ,.,5L)*GV9?./RMC`K#U+3KRUMK:YE(>, +@#! J:VU:V>WRYVF+
MHI[T1ET8&AK\$<-I\$Q;#!OW8]?JND:;>)A[G4G80J<JF>#3=/L[C5KT7-T"
MML#H(ZUNRR+(HAB4B-#@TOB8B.:[3!]GA^2#@<>E8KZ5;O*1Y>'IP..OK6
MQ+((8S@=?2D,(50^?FQR:TY4!CC3X8[@1B/EOF!(]*;96=U?:P92X58F^]ZU
MLB/++*W&W/7M5JUABLH!,3U)S[DU\$HI!<DD6"SGFGW_/LR5'3ZUS]IDVLM^#
ME[HN,D?>ZXX4U:1\$<LKB8D+- .NU%/7%9T/EIX?C1VRJGHHZG-2MQECOPMIIS
M&/D8Y/<U)I\U_KC2\$@P0*54#MFJBP709I)IE2\$K^Z"]]:V=#T\?:9X/,DAR
MQ/6B5D@-&BBBLP"BBB@`I*6B@ %2K40J45+&@:HS4C5&:\$#\$I:*3O3\$&1G&>
M:6DQSFEI@%8NI6WEWXG4D*RY/U'_.NMJJ6J0R2VO[KEE.<>H]*<79@8-NTV
MKD1Q.8R'+;E*CWK?T^P2RB(SOD8Y9R.IJ:V@2WA540*<<XJ:G*38!61>VHM
M;@W49Q&_#B]L^M:]17\$"W,#PO]UQ@THNS YN^M ;=VCQUSS1I4'EHUK*.<9)
MSGKTJ22QU"S@E)*RQ*!>Y7UI([NW0#<VUI\$SN/MVK9-/410DMIFN&B ""^7\
MV>Y]*BU'=;213*[1W##EIT-:BWBR*\Z88)A7]ZAUJ-9X5G0^A1CZ&DUIH!12
M)H2GF+AI(R&&>I]:IPS\$7;3+MD+JK#:M:YQ=:?(IV;2"&/TK(F22YG\R-
M&! !WGV%3+389TFKW+6=N9 <RR_]#[#UI=%-M;6TJY(E4_O"W4Y[U1MA+J,`
MD%T//C4@';D'59TRVBVN6G\$C-U8CJ:K=B)(XGM;Z9MR/"Q'S=ZFFC%R]L;8
M&!(/.[TJ1X,RQJZ;T)R-I^!4QMB%+(Q5LYSGM5:("G")(_CD4JQSQZ<5?@
M7:[7\$AP\$4]C1%\$5LV,K;I%R=QI]ZRII^T\$?A1GO4MZ6 PHC+JIN)(H60D_
MZP?Q<5IV[3*6BFZQC ^E3P,ENH@MDYZA5["HIK:X6Y\$R9?=G>,_E0GW'9=S
MB"(\$#2?*_#_) [U4M(E:SDB@/FRHN&P.IJ2RCGGFS=+M#'=M/8 _6K8C"1G
M\$;A0?2ANP&-8P7\$0"RQ,"1DD],U+<.4B=&<(6R%)K7E8)&68@ =:R-2D28 0
M@NS+A2!P.>M\$97 J) OFL,5\Q\$78R@?K5A<#)Z<Y]*=-")K- ?EFX!4<;L4
MVVP\$;"X/3::M':<KQ-;NSXWJF2?2N:M+Q([7RB"!)9LCU.:T]0D-NB02@,T
MYV_ABH#8O:LLC(C[4QM!J\$K/0" _H40;3%69<DL20U8U]<7/VJXJ(RQ+P!VQ
M6Q:7HC1BPV C.#45NQ*1*Y56F8D8]*+68&";YX-P7!4!A(X6I+K4)Y6BC2#
MRHY!MW \U)J<ZR:A<1QVX80L<D=>M3:-"UU%->N2?*RL<?OTS4WZ##]XGDW
M2VT\$8,SJ &M[UNZ9H\$MO<1W%W<="EZ# J6RT@RS"\OA^^*X4#^\$SEMxBN;
M.>X@>)75#M7!Z4F!U<J1R)B10R^AKG)O#MK)K? 'E,F\QCUKG9M3OIXUS*R@
M< #O71>)&)(A+YD>Z=?F)Y"CTJ0-B"!HK5HPNU "\$6AUA\$4);?,ZGGO3]0O\$
MM(@7))8X"CJ:IK@LTQR&^TK2-WJ(9L=I4CQP>2WI5F6(JH7'7M2V*:>:[.2
M<]*MR"-6WMUQQ3E*SL!7%NH1?,(/7-5;J9)'>1^+6VY^`M-1-<M=W!2)U
M6*/EW/\#]5SFH:C+>LMG91G[*K\GNY]:EON`]O/U>_ \$K[@,9 '10>U:LEJ%
MCCM4^51\ST`J6&#"#3+)Y6.2HRX[DU7\$]S+;*SIMENG 51V7_P#55*R M6%D
M;F^U2G]Q'Q\$OK[UM4R&(0PI&O11BGUDW=C"BBBD`4444 %%%)O`HJ5:B%2K
M4L:!]C)Q4C5&10@8@)]BEHI <U0A:**2D M%%(1D=<4^+2=Z6B@`HHHH`2L^
MXT.PN-Q:;!0Q[CUK1I*8";7.BW#*[(T,AQ@_P^0]*GNV\JPF9,"4Y4]:UM
M>TMM3MD\$3!9\$;)]*KZEIXM[:!P2PC7RW&>Q[UI%] ,72Y0YCM0IP1T[9JO=
MMY4TMJS\$8?_`&I;2*2'6([%4X)QP:V+[38KJ?S<#>>.>)]M6 KV=C E
MM"BR-\$"WE_B/O2RVPBEA%N"L2 G./O=*6!7M!";W";@#\O(%: GC^7:IXXQ
MC.*M(O:?(QBQ)&59C[8%2(\@O)%>,B(+)]>FNT4VU6?#;MP7%":(Y9"R,
MK,-H!2D!,TI"NH7:2,X)ZU#J#(IM4<XVG=C"!J:<;I(Y0H+J,'Z51G\$TQ"
M_(@4A=PYSZBA*X%]5WDR`;*YR#S26UQ-(2&4J,_*<]JI(\9\MF4;?OJ33
MFG9?+0IM63@,#WH: N^;ND*F0%F.,>E336_FM&Q;0YP.]4+.W\NYDDD`+N>
MN:O^;ENOR^E2T^@!-MDC*COR/>J#SR0S>7:VQ9 /FQBIY0QG#9R%Z8XQ5"PF
M<7\$TTK\$B1B\$QUII:~/DXG1KM@C=(U4YJ2RMU:^6;R%P?>DOD9P&B2-F5@0

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MW4U-8GS'+C(VYR*;V8%#59E^W*2@<QG !]34L1WNSNH+=,CZ51\XS7BY565G
M)#@=:T6*00.[-M"Y-.(&>F^*:0-\YB0L\$^\`\$>U:=M&R6\<DL:JX4_\`::;H
M=JSVPN)QN9R2"?3/%7=4/EZ7<%1R\$.*AR Y:RU".-)51\$WSS\$AB1UJII>HOIL
MLV\$+Y!"KG[O-/TX?+;R2P!8MVWS#TS5Q=-B>9S;VTTQ9C\V<"EOJ,?)XAO+Q
MQ#!B`%?OGKFJ,EE;[%FEN2)3]Y3U)J^=(U)02MO&\$4\$*@89^M03::KJ9`ID8
M\YL;30E?8"L8[17\$<2L<_,'<UIZ+?KIFCRW\$_>1MBCK67!O9P!OV'J#TJ
MWI%A%JTC+\RV\9W\$9YSZ4F!<TB276+B2^N4^5/EC'85JG G1#T;BK,<,5K&L
M4"A4'&T5#*8!(#AL@=JJ+\$36\V8R9(VG[OTK-OYYKRY2WM..C%_[M2ZA?;
MVJE8MSYP!GM6)YU[]'+-;E4,G!_O+GC%%NKW`NZN0EJ=.TW#7\$A_>!1U^M)I
M>G1V4.+I3* <9&./K6U86B6UO&2@\XJ-SXY)^M664,/F/U%0G9C,AK1;Y)(
MX#L3=\TA'WL5H1VBK*DLC;W087C %6 H484`#T%%#DV(#1114C"BC-% "8YS
M2T4G>@!:*2@!14JU\$*E6I8T#5&:D:HS0@88]Z.U%':F(0#%+2 Y-&*8"T4G
M2@FD`M%)VHZ4`+1110`4444`%,FB6>