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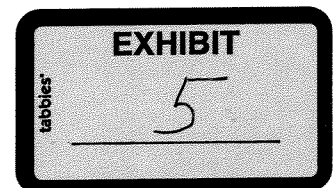
James C. Crumlish, III  
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RE: Cavitat Medical Technologies, Inc. vs Aetna, Inc.

Dear Mr. Crumlish:

I have asked to offer an opinion in the above referenced case. My opinion will be offered in four specific categories with a summary opinion at the end of each category. The categories will include (I) The historical background concerning the entity known as NICO, and comments as to whether NICO (neuralgia-inducing cavitation osteonecrosis) actually exist?; (II) Is there an effective management modality for NICO lesions?; (III) Is Cavitat ultrasonographic technology an effective management aide in diagnosing NICO lesions, and is there scientific evidence to support its use; and, finally, (IV) A summary of my conclusions related to the above referenced case follows. I understand that discovery is on-going and I reserve the right to supplement this report as additional facts are made available. I have been provided materials for my review which are detailed in the enclosed attachment.

I. Historical Background and Opinions on the Existence of the Disease Described as NICO (neuralgia-inducing cavitation osteonecrosis)



Neuralgia-inducing cavitation osteonecrosis (NICO) is a term that has most recently been brought to the forefront of dentistry and medicine by Bouquot and others<sup>(1-6)</sup> via a series of research abstracts and articles. This entity has been defined as a disease related to the degeneration of, and death of bone marrow related to a compromised vascular supply to the jaw bones. Clinically, NICO lesions are defined by its proponents as radiolucent cavitations within the bone that are associated with clinical symptoms of facial pain, headaches, neuralgia, and phantom tooth pain. Bouquot<sup>(1)</sup> has defined NICO histopathologically as a zone of ischemic osteonecrosis of the jaws with a distinct pathology. Long before Bouquot's studies, NICO-like symptoms or entities had been variously referred to in the literature under a host of names, including most prominently, Ratners bone cavity<sup>(7)</sup>, a term that has been discarded by clinicians and pathologists, and a term that was coined on the basis of very limited, if any, investigational effort.

There are a host of conditions and diseases that can induce pain in the maxilla and mandible, and such pain can be associated with altered radiographic findings upon radiographic examination of the patient. Nonspecific pain that might be related to a patient's complaint that would cause a clinician to consider a diagnosis of NICO could in fact include pain caused by a host of diseases ranging from metastatic cancer to the very well studied and scientifically adjudicated entity known as osteoradionecrosis. Thus, the proposed entity known as NICO, that is described by Bouquot as a non-infected cavity within the jaw bone, could quite possibly represent as many as ten different pathologic entities, and NICO could be an exclusionary diagnosis of last resort.

Marx and Stern<sup>(8)</sup> have done a masterful job of discussing NICO in what I consider to be the most complete clinico-pathologic based textbook on surgery and

pathology currently published. In this book, Marx states that the proponents of NICO in early studies, disproportionately aggregated post-menopausal females in their studies; and these individuals may have a myriad of reasons for having jaw pain, including alterations in the cyclic expression of estrogen, possible metabolic associated thinning and porosity of the bone, and unattributable ischemia. Marx further states that the facial pain reported in other non-postmenopausal patient's with a diagnosis of NICO may be seen in concert with a host of other diseases that are unrelated to the finding of a solitary radiolucency in their jaw. Thus, the generalized facial pain reported to occur in NICO may be nothing more than pain from some other disease that has an associated large hollow marrow space in concert with it.

Physicians and dentists have tried to wrap their arms around the issue of NICO for years and the condition has opponents and proponents. It is my opinion that the vast majority of the nearly three hundred board certified oral pathologists in the world regard NICO as a not fully scientifically defined entity.

Marx<sup>(8)</sup> reports that in a series of eleven NICO diagnosed patients he evaluated, all of whom were females, he was able to identify seven individuals with a bona fide source of pain that initiated from pulpitis, abscessed teeth or infections around a foreign object and even from a non-union fracture. This seems to reinforce the premise that the condition known as NICO can easily be confused with a myriad of conditions.

As a board certified oral and maxillofacial pathologist, my position on the issue of NICO relates more to its presentation as a histopathologic entity than its presentation as a clinical process. I have practiced oral and maxillofacial pathology for over thirty-two years and I consider myself to be a reasonably astute pathologist. I have examined in

excess of a hundred thousand surgical specimens from the oral and maxillofacial region during that time, and have had no opportunity in that time to render a microscopic diagnosis of the condition known as NICO. I have read what I believe to be most of the articles that describe the histopathologic parameters that must be seen in order to render a *diagnosis* of NICO. In those instances where I have been called upon to examine tissue from a patient with a possible diagnosis of NICO, I have not been able to identify in any objectivity scientific manner the specific histopathologic criteria that would match those that are necessary to render that diagnosis.

It is my impression that most qualified pathologists would have a difficult time diagnosing this entity. I would certainly not argue that ischemic changes don't occur in the jaw bone, they do; or that infections do not occur in the jaw bone, they do; or that neoplasms and the oral manifestations of syndromes of the head and neck and genetic diseases don't occur in the jaw bones, for in fact, they do. Ultimately, I am of the opinion that these and many other disorders manifesting as radiolucent lesions in the jaws are at times claimed to be NICO.

Finally, if we may return to the studies of Marx<sup>(8)</sup>, I would note that in his histologic review of NICO slides that were reported to have dead bone associated with empty lacunae, a feature that is reported as a common and necessary finding in NICO, Marx comments correctly that adult bone biopsies will show 15-40% empty lacunae due to the fact that the osteocytes within lacunae may simply be missed during random sectioning of the tissue, resulting in false positive result and a diagnosis that supports bone death, a necessary histologic component of NICO. In order to prevent this error, the person evaluating the slides must "bread loaf" or cut enough sections through the tissue

block to be able to identify the fact that lacunae actually may be absent. Since part of the proposed definition of NICO histopathologically rests on the finding of the lacunae that are devoid of osteocytes, the possibility of rendering a misdiagnosis is as high as 15-40% according to Marx.<sup>(8)</sup>

#### CONCLUSION (1):

It is my expert opinion that neuralgia-inducing cavitation osteonecrosis is a not fully described, and often disputed entity that is very likely is confused or co-mingled with other conditions in the jaws including inflammatory disease, facial neuralgias, simple enlarged marrow spaces, periapical dental disease, and other medical or dental conditions, and that the entity, described as NICO as it has been reported in the literature, as a separate and distinct disease entity, has yet to be fully defined clinico-pathologically and with scientific validity.

#### II) Is there an effective management modality for NICO lesions?

The management of NICO in the past has ranged from “watchful waiting” to “round house” root canal therapies on all the teeth to extraction of a full dentition. This broad range of therapies has largely occurred because, in part, the disease has been so ill-defined. Costly, painful and sometimes risky full mouth extractions seem to be a treatment modality in current vogue by some clinicians. I could find nothing in the scientific literature that would suggest that a well controlled study evaluating patients with NICO and pairing them in a three arm study with individuals who received (1)

surgical management for their condition, (2) management of their condition with antibiotics or some neuralgia inhibiting drug, or (3) no treatment at all, has ever been done. It appears that proponents of the condition have erroneously concluded anecdotally that the disorder can not be treated with antibiotics or other medications and have used surgical intervention as the most convenient treatment modality. Anecdotal findings have no place in the community of evident-based science and in my reading of the literature concerning NICO, surgical management ensues too often on that basis.

I had the opportunity in the course of my evaluation of this case to review radiographs on eight patients who were managed clinically and surgically for the condition known as NICO. In five instances I was unable to identify radiographic evidence of pathology that would necessitate such aggressive management of the disease (extraction of the teeth). It has been reported that drugs including antibiotics, the antineuralgic drugs Neurotin and Tegretol can be used to decrease the pain in ischemic bone conditions in the body, including the jaws, but I could find few instances in which drugs were used, and in most instances, in the end, the management modality of choice for NICO patients was surgery. Since one of the first rules of medicine is to first do no harm, it would seem to me that aggressive surgical interventions tends to fly over the top of managing patients in a humanistic and ethical manner.

CONCLUSION 2: There seems to be no effective standard management modality for the disease known as NICO that I can recognize. Doctors who employ wholesale surgical intervention and extractions in patients who have “phantom bone pain” without appropriate diagnostic work-ups or employ work-ups that risk practicing below the

medically accepted standard of care should work to fully understand the condition. It is my conclusion that the myriad of treatments that have been offered to patients with NICO appear to be largely ineffective and without scientific merit.

III. Is Cavitat ultrasonographic technology an effective management aide in diagnosing NICO lesions and is there scientific evidence to support its use?

The Cavitat ultrasonographic device is described as a bone densitometer that has the ability to identify NICO lesions in the jawbones. The machine is described as being invaluable, reliable, and accurate by its proponents in defining NICO lesions in the jaws by identifying diagnostic pulse-echo ultrasonic signals that emanate from the lesion.<sup>(9)</sup> It has been defined by its proponents at various times as being more effective than panoramic radiology, CT scans or computed tomography, or MRI imaging. These claims are clearly debatable, at the least and hyperbolic at worst. Certainly, it is possible to define so-called "hot spots" in the jaws as NICO proponents suggest, using technetium 99, MDP radioisotopic bone scans for instance, and MRI or CT scans. There is not much dispute about that. But to assume that an apparatus that is investigational with little scientific evidence to support its use can do the same thing is quite a leap of faith, especially since even radioisotope scanning has a downside, missing as many as a third of lesions that are evident, resulting in a false negative finding. To suggest that an experimental ultrasonic machine that displays a cluster of simple column-like images can define an unique form of bone pathology several degrees better than the tools we

currently have including MRI's and CT scans is uniformly, if not certainly, open to debate.

The Cavitat machine itself produces a block-like three dimensional image that reports to define bone ischemia, producing a color image read out. Red displayed images suggest that there is significant bone necrosis, yellow suggests moderate bone necrosis, and green, no bone necrosis. The brochure outlining the use of the Cavitat system clearly indicates that the Cavitat images have not been evaluated by the FDA as defining whether or not a patient has normal or specific osseous pathology. This disclaimer alone, seems to me, should make anyone concerned about whether or not the machine has any value in identifying bone disease, including NICO, quite wary.

The Cavitat machine does indeed have marketing clearance via the FDA, 510 (k) application process, but his process does not require the manufacturer to demonstrate efficacy at the level of what the FDA mandates in its more rigorous premarket approval application. I could find no scientifically valid peer-reviewed articles to support the effectiveness of the Cavitat machine and although there are several abstracts that support its usefulness<sup>(10-12)</sup> and a lengthy, unpublished paper by Bouquot<sup>(13)</sup> supporting the efficacy of the technology, I am not aware of any one who is a radiologist or ultrasound expert who has validated these studies.

None of the papers I reviewed related to the machine's use showed a comparison with any other device or technique except radiographic plane films. In cases where there was "positive" NICO histology, the histopathology was not fully defined.

In none of the studies that I reviewed, was there any blinding of the investigators and no studies that resulted in any additional or competing studies that compared the



outcome of the Cavitat machine with other imaging methods that might be appropriate including MRI and CT scans. The FDA in its evaluation of the Cavitat ultrasonic device for use has mandated that manufacturer in fact state that the device has not been deemed to be effective for identifying any specific bone pathology. It is indeed dichotomous that a device that has labeling with this disclaimer would not at least by now have had more rigorous scientific evaluation to prove its efficacy.

Finally, the Cavitat machine scan appears to be open to manipulation by the practitioner since the cubed 3D image it produces can be rotated, zoomed and tilted by the operator. It also seems to me that since positive ischemia is defined only by a simple colometric scale, the device can be easily be operator manipulated. This is exceedingly worrisome when it comes to establishing baseline data on patients.

It has been well documented that the bone structure of the jaws is quite different from that of other weight bearing bones in the body. There seems to be no data available on the Cavitat device that suggests that there has been a comparison between the findings in the jaw bones and other osseous sites such as the hip, which has frequently been compared with the jaw bone by Cavitat proponents as an equivalent site. Thus, use of this device without going through a rigorous routine of establishing scientifically valid norming data which would allow for comparisons with other bony sites in the body seems to be premature.

In reviewing the nine patient records and radiographic films that I had an opportunity to review, there was a surprising sense of duplication of Cavitat results, in almost every instance. Most patients were deemed to have, on the basis of examination with the Cavitat machine alone, significant bone porosity, and, by inference, marked

ischemic disease consistent with NICO. All patients were subjected to extensive surgical intervention. It is surprising to me that every patient treated by the practitioner using the device had, almost exactly, the same diagnostic findings.

### CONCLUSION 3:

In summary, the Cavitat machine which purports to detect areas of ischemic bone change, and bone porosis does not have an FDA approval for diagnosing definitive bone pathology. It is a machine that only correlates a clinical finding with purported loss of bone density and, in my judgment, it appears open to manipulation by the practitioner. It is not standardized or normed against other methodologies and, in my judgment, as a scientist, it is at best an investigational stage tool.

### ADDITIONAL CONCLUSIONS:

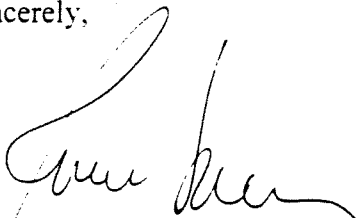
My final comment relates to the findings by Goldstein and Epstein,<sup>(14,15)</sup> reported in a series of five articles commenting on so-called unconventional dentistry. These articles which appeared in the *Journal of the Canadian Dental Association* report that although papers supporting the concept of NICO have been published in peer-reviewed journals, the publications are largely anecdotal case reports that do not effectively address the etiology of the disease, its biochemistry, its histopathology, or its neuropathology. Use of an experimental device to detect such a controversial entity seems to put the cart before the horse.

It is my position that AETNA acted in a reasonable and prudent manner by

issuing a clinical policy bulletin to define its position on NICO and the use of Cavitat ultrasonography, expressing its concern that the management of NICO is experimental and investigational, and that the use of the Cavitat ultrasonograph is correlatively an investigational tool with an insufficient scientific base to warrant its use in the clinical diagnosis of maxillary or mandibular osseous disease.

I hope that this information is helpful in your assessment in this case. My CV is enclosed along with a list of references.

Sincerely,

A handwritten signature in cursive script, appearing to read "Robert O. Greer, Jr.", written in dark ink.

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1. Complaint (first amended)
2. Aetna Answer and Counterclaims
3. Plaintiffs Rule 26 Disclosures (As Supplemented)
4. Confidentiality Agreement
5. CPB 642 (as revised)
6. Source materials cited by CPB 642
7. Deposition of Dr. McDonough
8. Deposition of Dr. Koumaras
9. Cavitat "Important News" (CAVGLAROS00032)
10. TMJ & Facial Pain Center form letter (CAV-Jones 00309-00311)
11. TMJ & Facial Pain Center – Oral Surgery Patient Authorization Form
12. 510 (k), FDA correspondence
13. Ada production materials (ADA 1-994) including Cavitat Owners Manual (ADA 1-35)
14. Sales Correspondence from Cavitat re: efficacy of Cavitat
15. Cavitat Seminars (transcripts and DVDs)
16. Bouquot documents relied upon by Aetna and subsequently published articles
17. Preliminary Report of Dr. Michael Rohrer
18. Preliminary Report of Dr. Susan L. Zundt
19. Preliminary Report of William P. Glaros
20. Preliminary Report of Wesley Shankland
21. Shankland Patient Charts (Bates Nos. 2639 – 2790; 1745 – 1856; 2448 – 2546; 1857 – 1970; 3225 – 3302; 3303 – 3424; 3069 – 3224; 0899 – 1007)

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## REFERENCES

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12. Bouquot JE, Shankland WE II, Margolis M, Glaros W. Through-transmission alveolar ultrasonography (TAU) – new technology for detection of low bone density of the jaws. Comparison with radiology for 92 osteoporotic alveolar sites with histopathologic confirmation. Proceedings, annual meeting, American Academy of Oral & Maxillofacial Pathology, New Orleans, LA, April 2002.
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