

## Stroke Revisited: The "Chinatown" Syndrome

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Now that the Lana Lewis inquest has ended with a verdict of "accident," all you have to do is review the 17 recommendations in the official *Verdict of the Coroner's Jury* to realize how self-incriminating that document truly is. For example, when you read about such matters as the handling of tissue specimens; the requirement that the coroner's office examine all relevant tissues and information prior to offering an opinion; the need to "keep the family from feeling out of the loop"; the need to avoid any reflection of impropriety on the part of the coroners' office, by keeping the family aware of meetings with parties with vested interests; and keeping the seal of the coroner's office for "government business and not as personal business, *curriculum vitae*,"<sup>1</sup> the penny drops and you immediately realize that it perhaps was no accident that the jury elected to throw the matter up in the air by handing down "accident" as the proposed means of death. Indeed, there is plenty of "accident" to go around.

This is so reminiscent of the chaotic ending to the film classic, "Chinatown" in which gumshoe Jake Gittes [Jack Nicholson] tries to decipher the cause of the deliberate and fatal shooting of Evelyn Mulwray [Faye Dunaway] in her car. Above the din of the crowd, Lawrence Walsh [Joe Mantell] can be heard screaming, "Forget it, Jake, it's Chinatown!"<sup>2</sup>

And so it is with so much of the evidence concerning the association of strokes and spinal manipulation. Elsewhere (and at great length), I and others have discussed the relative risks of medical procedures, NSAIDs, and lifestyle activities that dwarf the risks of serious cerebrovascular accidents attributed to chiropractors by usually several orders of magnitude.<sup>3-13</sup> But what needs to be teased out here are a couple highlights that should immediately give the reader pause as to where the rancor lies, or worse, where the accusations have been made.

To begin, some of the most compelling information that needs to be brought forward to bring the debate about cervical manipulations to a level playing field has to do with the fact that a significant number (most likely the majority) of vertebral artery dissections (VADs) happen to be spontaneous [sCADs]. The fact that numerous reports have addressed both the frequency of occurrence of VADs and their association with virtually any activity associated with turning the head should reduce the utility of attributing strokes to cervical manipulations to virtually an academic exercise.

It has been shown, for example, that the estimate annual incidence of spontaneous VADs in hospital settings is 1.0-1.5 per 100,000 patients.<sup>14</sup> The corresponding VAD incidence rate in community settings has been reported to be twice as high.<sup>15,16</sup> Using an estimated value of 10 from the literature to represent an average number of manipulations per patient per episode,<sup>17</sup> it becomes apparent that the proposed exposure rate for CVAs attributed to spinal manipulation is no greater than equivalent to the spontaneous rates for cervical arterial dissections as reported.<sup>14-16</sup> If the threat of stroke or stroke-like symptoms is to be properly assessed, therefore, at least half our attention needs to be directed toward the spontaneous events, instead of primarily or solely upon spinal manipulation.

Furthermore, a large number of common lifestyle activities, ranging from swimming to stargazing to *tai chi*, have all been associated with cerebral ischemia<sup>11</sup> or CVAs themselves.<sup>18</sup> All are decidedly nonmanipulative. Beauty parlor stroke syndrome and salon sink radiculopathy are but two of the many examples described in the literature, but not receiving enough public attention.<sup>19</sup> However, a real key to understanding spontaneous arterial dissections may be at hand from the amino acid homocysteine, long implicated in cardiovascular disease.<sup>20,21</sup> More direct observations point directly toward its central role in the disruption of collagen and elastin in the arterial wall:

1. In the majority of skin biopsies taken from patients with cervical arterial dissections, irregular collagen fibrils and elastic fiber fragmentations have been found.<sup>22</sup>
2. Homocysteine activates metallo-proteinases<sup>22</sup> and serine elastases,<sup>23</sup> directly or indirectly leading to the decrease *in vitro* of the elastin content of the arterial wall. The opening and/or enlargement of fenestrae in the medial elastic laminae would be expected to lead to the premature fragmentation of the arterial elastic fibers and degradation of the extracellular matrix.<sup>22,23</sup>
3. Homocysteine has been shown to block aldehydic groups in elastin, inhibiting the cross-linking needed to stabilize elastin.<sup>24</sup>
4. The cross-linking of collagen may also be impaired by homocysteine.<sup>25</sup>
5. Experimentally elevated levels of homocysteine produce patchy desquamation of 10 percent of the aortic surface in baboons.<sup>26</sup>
6. Endothelium-dependent and flow-mediated vascular dilation is impaired in individuals with elevated levels of homocysteine.<sup>27</sup>
7. In cell culture experiments, addition of homocysteine into the medium induces cell detachment from the endothelial cell monolayer.<sup>28</sup>

An even tighter coupling between sCADs and increased amounts of homocysteine is suggested by the following observations:

1. Patients undergoing sCADs are more than three times as likely as asymptomatic patients to yield plasma homocysteine levels exceeding 12 micromoles/L. They are also more than twice as likely to have elevated homocysteine as patients experiencing ischemic strokes without arterial dissection.<sup>29</sup>
2. CAD patients yield average homocysteine levels of 17.9 micromoles/L, while asymptomatic patients report an average of 6.0 micromoles/L.<sup>30</sup>
3. Homocysteine levels exceeding 10.2 micromoles/L are associated with a doubling of vascular risk.<sup>31</sup>
4. A genetic defect in humans involving tetrahydrofolate reductase, the enzyme that produces the methyl-donating cofactor required to convert homocysteine to methionine, is associated with elevations in the rates of sCADs.<sup>29</sup> This metabolic block would be expected to cause homocysteine to accumulate intracellularly.<sup>32</sup>

What are the practical implications here? Simply put, rapid and inexpensive automated immunoassay techniques for determining homocysteine in the blood serum are readily available, requiring only microliter portions of reagent and sample.<sup>33-35</sup> This essentially means that homocysteine levels can be determined in any number of clinical reference laboratories already established to measure blood analytes. Considering that other premanipulative tests have not fared well,<sup>36</sup> the homocysteine determination would seem to be an outstanding candidate for consideration at this time.

Not only has the spontaneity question been conveniently swept under the rug, but so has a common everyday item found in most modern households with women of childbearing age: the oral

contraceptive. The dirty little secret here emerged some four years ago in a systematic review of some 804 studies retrieved from the literature and reduced to 16 relevant studies for a meta-analysis. In this review, the stroke risk ratio for low-estrogen preparations of oral contraceptives translated to an additional 4.1 ischemic strokes per 100,000 women using low-estrogen oral contraceptives, or 1 in 24,000.<sup>37</sup> That is 66 times the rate of stroke attributed in the most recent literature to chiropractic cervical spinal manipulation.<sup>3</sup>

Wait - it gets worse. From a newsletter from the University of California, San Francisco, come the following quotes from S. Claiborne Johnson, MD, MPH:

"The risk [of oral contraceptives] is so low to begin with that even when the risk doubles, it remains low."<sup>38</sup>

Hmmm - when was the last time you heard a palliative like that applied to chiropractors performing manipulation of the cervical spine? (Seems to be some strange variation of the immortal line, "even when the heat is on, it's never too hot," from the Loesser and Burrows classic musical, "Guys and Dolls.")

Then, we have this gem:

"If we were to remove oral contraceptives from the market in the United States and replace them with condoms, we would expect about 400 fewer strokes each year, but the cost would be 690,000 additional unintended pregnancies."<sup>38</sup>

Roger, copy that. Am I missing something, or do we have some bizarre, frightening, dictatorial value system being imposed here? And can anyone here spell "Hippocratic oath?"

In the interests of the patient, I can only hope that we can recuperate from what appears to be a rampant "Chinatown" syndrome in future appeals. Once again, it is only with the knowledge achieved with the research base FCER has provided for 60 years that the chiropractic profession can hope to secure anything resembling an equitable basis in health care delivery.

## References

1. Verdict of coroner's jury, Office of the Chief Coroner, Ontario, Canada, Jan. 16, 2004.
2. Towne, R. Screenplay for Chinatown, Paramount Studios, 1974.
3. Haldeman S, Carey P, Townsend M, Papadopoulos C. Arterial dissections following cervical manipulation: the chiropractic experience. *Canadian Medical Association Journal* 2001;165(7):905-906.
4. Deyo RA, Cherkin DC, Loesser JD, et al. Morbidity and mortality in association with operations on the lumbar spine: The influence of age, diagnosis, and procedure. *Journal of Bone and Joint Surgery Am* 1992;74(4):536-543.
5. Seagroatt V, Tan HS, Goldacre M. et al. Effective total hip replacement: Incidence, emergency, readmission rate, and post-operative mortality. *British Medical Journal* 1991;330:1431-1435.
6. Stremple JS, Boss DS, Davis CH, McDonald GO. Comparison of post-operative mortality and morbidity in Veterans Affairs and nonfederal hospitals. *Journal of Surgical Research* 1994;S6:405-416.
7. Roebuck DJ. Diagnostic imaging: Reversing the focus [letter]. *Medical Journal of Australia* 1995;162:175.
8. Horowitz SH. Peripheral nerve injury and causalgia secondary to routine venipuncture. *Neurology* 1994;44:962-964.

9. Dabbs V, Lauretti W. A risk assessment of cervical manipulation vs NSAIDs for the treatment of neck pain. *Journal of Manipulative and Physiological Therapeutics* 1995;18(8):530-536.
10. Dinman BD. The reality and acceptance of risk. *Journal of the American Medical Association* 1980;244(11):1226-1228.
11. Rome PL. Perspectives: An overview of comparative considerations of cerebrovascular accidents. *Chiropractic Journal of Australia* 1999;29(3):87-102.
12. Rosner A. Chiropractic manipulation and stroke [Letter to the Editor]. *Stroke* 2001;32(9):2207-2208.
13. Rosner A. Spontaneous cervical artery dissections: Another perspective. *Journal of Manipulative and Physiological Therapeutics* 2004;27(2): In press.
14. Shievink WT, Mokri B, O'Fallon WM. Recurrent spontaneous cervical-artery dissection. *The New England Journal of Medicine* 1994;330(6):393-397.
15. Shievink WT, Mokri B, Whisnant JP. Internal carotid artery dissection in a community: Rochester, Minnesota, 1987-1992. *Stroke* 1993;24(11):1678-1680.
16. Giroud M, Fayolle H, Andre N, et al. Incidence of internal carotid artery dissection in the community of Dijon [Letter]. *Journal of Neurology and Neurosurgical Psychiatry* 1994;57(11):1443.
17. Carey TS, Garrett J, Jackman A, et al. The North Carolina Back Pain Project. The outcomes and costs of care for acute low back pain among patients seen by primary care practitioners, chiropractors, and orthopedic surgeons. *The New England Journal of Medicine* 1995;333(14):913-917.
18. Terrett, AGJ. Malpractice avoidance for chiropractors. 1. Vertebrobasilar stroke following manipulation. Des Moines, IA. National Chiropractic Mutual Insurance Company, 1996.
19. Foye PM, Najjar MP, Camme A Jr, et al. Prospective study of pain, dizziness, and central nervous system blood flow in cervical extension: Vascular correlations to beauty parlor stroke syndrome and salon sink radiculopathy. *American Journal of Physical Medicine and Rehabilitation* 2002;81(6):395-399.
20. Graham IM, Daley LE, Refsum HM, et al. Plasma homocysteine as a risk factor for vascular disease: The European Concerted Action Project. *Journal of the American Medical Association* 1997;277: 1775-1781.
21. Selhub J, Jacques PF, Bostom AG, et al. Association between plasma homocysteine concentrations and extracranial carotid artery stenosis. *The New England Journal of Medicine* 1995;332(5): 286-291.
22. Charplot P, Bescond A, Augler T, et al. Hyperhomocysteinemia induces elastolysis in minipig arteries: Structural consequences, arterial site specificity and effect of captoprilhydrochlorothiazide. *Matrix Biology* 1998;17:559-574.
23. Rahmani DJ, Rolland PH, Rosset E, et al. Homocysteine induces synthesis of a serine elastase in arterial smooth muscle cells from multi-organ donors. *Cardiovascular Research* 1997; 34(3): 597-602.
24. Jackson SH. The reaction of homocysteine with aldehyde: An explanation of the collagen defects in homocystinuria. *Clinica Chimica Acta* 1973;45(3) :215-217.
25. Kang AH, Trelstad RL. A collagen defect in homocystinuria. *Journal of Clinical Investigation* 1973;52(10):2571-2578.
26. Harker LA, Slichter J, Scott CR, Russell R. Homocysteinemia: Vascular injury and arterial thrombosis. *The New England Journal of Medicine* 1974;291:537-543.
27. Woo KS, Chook P, Lolin YI, et al. Hyperhomocysteinemia is a risk factor for endothelial dysfunction in humans. *Circulation* 1997;96:2542-2544.
28. Wall RT, Harlan JM, Harker LA, Striker GF. Homocysteine-induced endothelial cell injury in vitro: A model for the study of vascular injury. *Thrombolytic Research* 1980;18:113-121.
29. Pezzini A, Del Zotto E, Archetti S, et al. Plasma homocysteine concentration, C677T MTHFR genotype, and 844-ins68bp genotype in young adults with spontaneous cervical artery dissection and atherothrombotic stroke. *Stroke* 2002;33 (3):664-669.
30. Gallai V, Caso V, Paciaroni M, et al. Mild hyperhomocyst(e)inemia: a possible risk factor for

- cervical artery dissection. *Stroke* 2001;32:714-718.
31. Graham IM, Daley LE, Refsum HM, et al. Plasma homocysteine as a risk factor for vascular disease: The European Concerted Action Project. *Journal of the American Medical Association* 1997;277: 1775-1781.
  32. Lehninger AL, Nelson, DL, Cox MM. *Principles of Biochemistry*, 2nd edition. New York, NY: Worth, 1993, pp.524-526.
  33. Frantzen F, Faaren AL, Alfheim I, Nordhei AK. Enzyme conversion immunoassay for determining total homocysteine in plasma or serum. *Clinical Chemistry* 1998;344:311-316.
  34. Shipchandler MT, Moore EG. Rapid, fully automated measurement of plasma homocyst(e)ine with the Abbott IMx analyzer. *Clinical Chemistry* 1995;41:991-994.
  35. Quillard M, Berthe M-C, Sauger F, Lavoine A. Dosage plasmatique de l'homocysteine sur l'Immulite 2000 DPC: comparaison avec le dosage sur l'IMX Abbott. *Annals de Biologie Clinique* 2003;61:699-704.
  36. Bolton PS, Stick PE, Lord RSA. Failure of clinical tests to predict cerebral ischemia before neck manipulation. *Journal of Manipulative and Physiological Therapeutics* 1989;12(4):304-307.
  37. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives. *Journal of the American Medical Association* 2000;284(1):72-78.
  38. The pill increases stroke risk, but risk generally miniscule. UCSF Daybreak News. [www.ucsf.edu/daybreak/2000/07/.06\\_pill.html](http://www.ucsf.edu/daybreak/2000/07/.06_pill.html).

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