The Foundation for Chiropractic Education and Research

Response to Vertebral Artery Dissection Study: Paper by Smith *et al.* Published in May 13, 2003 Issue Of *Neurology*

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The recent publication by Smith et al. in *Neurology* addressing vertebral artery dissection[1] represents another episode of regrettable studies which, despite serious flaws which raise substantial questions as to their internal validity, go at great lengths to selectively disparage the advisability of performing cervical manipulations as a means of patient care while obscuring the larger picture.[2-6] By this I refer both to the failure to fully present the well-documented *benefits* of this procedure as well as the equally well-chronicled risks of *alternatives* to cervical manipulation—including the use of medications which is so deeply entrenched in our society as to be obviously far more prevalent than any applications of manipulation. The fact that Smith's study has been so extensively and immediately propagated in the printed and televised media (in contrast to the many investigations which have supported cervical manipulations with no reports of substantial side-effects[7-30]) represents a major disservice to the American public and threatens their access to the best available options in healthcare.

This critique will be discussed from two vantage points, in terms of both internal flaws and its analysis in the larger context.

INTERNAL FLAWS:

1. Sampling and time frame issues:

To begin, there is no indication that the 151 *dissection* cases were randomly identified; only the control patients were so chosen. The fact that some demographic features of the two groups (such as age or dimensions of the arteries involved) differ implies a more basic and global characteristic pertaining to arterial dissections that lies outside cervical adjustments (a point to be discussed in detail below regarding spontaneous arterial dissections). This would seem to be particularly true since the number of patients in which spinal manipulative therapy (SMT) has

been reported to occur within 30 days is just 7, compared to 3 in the control group. The differential of just 4 individuals between the two groups is a paltry number indeed upon which to base association—let alone any hint of causality over the extended period of 30 days. The fact that two patients actually experienced a stroke or transient ischemic attack (TIA) immediately following SMT is clearly more compelling—but even here the authors fail to make a distinction between stroke and TIA (far more benign). The fact that strokes could happen at the time of SMT but not necessarily reflect it as a risk factor will be discussed below.

2. Exclusion of iatrogenic cases:

To one's amazement, the authors excluded a larger number of patients (8) due to "iatrogenic dissection with or without stroke" than actually were listed as having a dissection within 30 days of spinal manipulative therapy (7). In addition to making the low number of dissection cases within 30 days of SMT appear even more absurd, the authors raise the more serious question as to exactly *what had caused* the "iatrogenic dissections" in the first place. By most common definitions, "iatrogenic" is thought to have been brought on by *medical* interventions, a point to be discussed in more detail below.

3. Lack of a control population:

This study bases its conclusions only upon the association of a single observation (presence of vertebral artery dissection) with previous events recalled by the patient. There are no baseline (control) readings to accompany this. One could argue that without a *control hospital* laboratory finding (e.g., elevated blood urine creatinine or presence of an arterial artery occlusion), the frequencies of possible precipitating events prior to the primary finding (presence of arterial artery dissection) are meaningless. By the reasoning put forth in this study, we would be forced to the rather strange conclusion that patients who recall cervical manipulation prior to their yielding elevated urine creatinine (for example) could be used as evidence that this form of intervention is necessarily *associated* with the aberrant blood chemistry levels obtained.

4. Incorrect identification of precipitating factors to vertebral artery (VA) dissection:

Other than "SMT," the authors have produced no indication that *cervical* manipulations were administered to every patient listed, so that their attempts to link VA dissections and manipulation

become that much more problematic. Until an actual relationship is struck between the location, actual number of adjustments, and vertebral dissections is given, and until some light can be shed on the mechanisms which could produce this result, any speculation of causality of manipulation and arterial dissection gleaned from the data in this study must be greeted with only the most extreme skepticism.

Furthermore, the authors appear to have given little consideration to the fact that cerebrovascular accidents appear to be a *cumulative* rather than traumatic events. This fact is emphatically driven home by the fact that no less than 68 everyday activities have been implicated in disrupting cerebral circulation.[31-33] Among the activities listed, 18 (childbirth, interventions by surgeon or anesthetist during surgery, calisthenics, yoga, overhead work, neck extension during radiography, neck extension for a bleeding nose, turning the head while driving a vehicle, archery, wrestling, emergency resuscitation, star gazing, sleeping position, swimming, rap dancing, fitness exercise, beauty parlor events, and Tai Chi) have actually been associated with vascular accidents but are decidedly non-manipulative [**Attachment 1**].[33]

The risk of fatal stroke following cervical manipulation has been assessed in an exhaustive systematic literature review of many sources to be 3 per 10 million manipulations,[34] or about 0.00025%.[35] The mortality rate from stroke in the general population in 1992-93 was 0.00057%, which raises the possibility that the death rate from stroke in the general population could conceivably be *higher* than that amongst chiropractic patients.[36]

Given the frequency of significant consequences from cervical manipulations (6 per 10 million manipulations, or 0.0006%),[34] and given the many lifestyle activities shown above to trigger cerebrovascular accidents, it would seem nearly impossible—as this study has done—to attribute the VA dissections reported at indefinite time periods following chiropractic manipulation to the latter. This association, based on a vague recollection of the patient of events in the past, cannot be counted upon to have definitively identified spinal manipulation as a causative event. Identifying the *chiropractor* in this association is even more problematical, as will be shown immediately below.

5. Undetermined identification of caregiver:

Did the 7 cases of VA dissection attributed to cervical manipulation in the study actually follow manipulation by a licensed *chiropractor*? There is no validation of this fact in the study as reported. The actual number of iatrogenic complications specifically ascribed to chiropractic has been shown to be significantly overestimated due to the fact that the practitioner actually involved is in many cases a nonchiropractor. Rather, a major portion of these accidents have occurred at the hands of an individual with inadequate professional training but incorrectly represented in the medical literature as a chiropractor. One particular review is alarming in that it suggests that for many years chiropractors have been over-represented (possibly in a systematic manner) in the literature as having brought on VAs.[37,38]

ANALYSIS IN THE LARGER CONTEXT:

1. Comparative safety:

Risks are inherent in every medical procedure or lifestyle activity that we encounter. In terms of interventions of the spine, chiropractic has been shown to be many orders of magnitude *safer* than medication or surgery. Assuming that each patient receives an average of 10 manipulations in treatment,[61] death rates following cervical manipulation calculate to anywhere between *1/100-1/400* the rates seen in the use of non-steroidal anti-inflammatory drugs (NSAIDs) for the same condition.[35,39] Death rates from lumbar spine operations have been reported to be 300 times higher than the rate produced by cerebrovascular accidents in spinal manipulation;[40,41] for cervical surgeries, recent death rates have been estimated to be *700-fold* greater.[40] As Rome has pointed out,[31] risks for "virtually all" medical procedures ranging from the taking of blood samples,[42] use of vitamins,[43] drugs,[43] "natural" medications,[44] and vaccinations[45] are routinely accepted by the public as a matter of course.

How risks are *interpreted* is another matter. The VA rate for chiropractic as described above, while extremely low, does represent a challenge to be improved upon. On the other hand, as Rome points out,[31] such phenomena as (i) patient informed consent, (ii) "low and *acceptable* rates of complications" stated in a policy by the Australian College of Ophthalmologists,[46] or (iii) "trading off" risks of surgeries and stroke as stated in a recent study of endarterectomies[47] all

attest to the fact that certain levels of risk have been habitually accepted in our society until improvements can be made. Why should chiropractic be singled out as having an unacceptable risk?

In his distinction of specific provider types associated with cerebrovascular accidents, Terrett has identified 34 deaths associated with manipulation over 61 years worldwide.[37] For the sake of comparison, 12,000 deaths per year from unnecessary surgery, 7,000 deaths per year from medication errors in hospitals, about 80,000 deaths per year from nosocomial infections in hospitals, and 106,000 deaths per year from nonerror, adverse effects of medications have been recently reported with regard to conventional medicine.[48-50] These data are presented simply to prevent our losing perspective on the entire issue of risk/benefit ratios raised by the study published in *Neurology*.[1]

This discussion would not be complete without considering "acceptable" *lifestyle* risks, which should be common knowledge if we are to evaluate the safety of any healthcare intervention—chiropractic or otherwise. **Attachment 2** from the study of Dinman[51] clearly indicates that the risk of death per person per year in many of the activities that we accept as normal and engage in are for the most part many orders of magnitude greater than those seen in serious VA complications following chiropractic manipulation. Once again, we must be skeptical if cervical chiropractic manipulation seems to have been singled out as a particularly conspicuous and noxious threat to our livelihood.

2. Actual forces exerted upon the VA:

From a mechanistic viewpoint, the most direct means of assessing the effects of spinal manipulative therapy upon the integrity of the VAs would be to directly measure how the forces anticipated during manipulations might be transmitted through the various skeletal and soft-tissue layers of the cervical milieu to the region of the VA, and how such forces compare to the limits of arterial integrity assessed by deliberately stretching the VA until it ruptures. Such a study was recently accomplished at the University of Calgary upon the VAs excised from unembalmed postrigor patients who had died within the past 72 hours.

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In this investigation, the distal C0-C1 and proximal C6-subclavian loops of the VAs were exposed and fitted with a pair of piezoelectric ultrasonic crystals. Strains between each crystal pair were recorded during range of motion testing, diagnostic tests, and a variety of procedures employed in spinal manipulation. Afterwards, the VA was dissected and strained on a materials testing machine until mechanical failure occurred. For manipulation, the elongations of the C0-C1 and C6-subclavian artery segments of the VA were 6.2% and 2.1% respectively. For normal head rotation, on the other hand, these elongations were respectively 12.5% and 4.8%. The elongations of these same regions needed to reach VA failure were 53.1% and 62.3% respectively. Two conclusions are readily apparent: (i) the values measured during spinal manipulative therapy were **less** than those recorded during range of motion and diagnostic testing; and (ii) the VA strains measured during spinal manipulation were **less than 1/9 those needed to achieve arterial failure**.[52]

The implications of this study shed considerable light upon the controversy regarding VADs and spinal manipulation. First it is evident that the forces experienced during spinal manipulation are virtually an order of magnitude below those needed to produce an arterial failure in a single event. Secondly, it is apparent that *routine neck maneuvers* during the assessments (rather than the manipulations) registered greater forces in the region of the VAs. This immediately raises the possibility that spontaneous rather than induced cerebrovascular accidents (CVAs) are likely to occur in the VA, an issue which will be explored in depth in the following section.

There are a number of significant cautionary notes that must be sounded to this study, however:

1. The portion of the artery most commonly involved in VA dissections associated with spinal manipulation (C1-C2, as pointed out earlier) was not measured; rather, the entire VA was used to obtain mechanical failure points;[53]

2. Stretch by tensile forces rather than compression by combined forces (particularly at the C2 foramen, proposed to be the actual force causing damage during manipulation[53]) was measured, which may not reflect the suspected type of artery deformation occurring in patients;

3. The strain created to the thrust side VA when the neck is fully rotated contralaterally, representing the most forceful manipulation, was not measured;[53]

4. The ranges of motion from the 80-99-year old cadavers would be expected to be more restricted than those more typical of younger patients seen in chiropractic offices, limiting the strains on the VAs that were measured by the researchers and perhaps not representative of those seen in actual practice;[52]

5. There were wide variations in force ranges (4-18N) and of strains (31%-75%);[52]

6. Preparing the arterial specimens in ultrasound gel may have artificially increased their flexibility;

7. One may question whether the overall arterial failures observed bear compelling resemblance to the intimal tearing experienced in vivo during arterial dissections; and finally

8. Since arterial dissections may well represent the culmination of *multiple* arterial insults as outlined in the ensuring text, it is necessary that this experiment be repeated to assess arterial integrity after dozens and perhaps hundreds of applied stretches to the VA.

3. Spontaneous arterial dissections:

The most compelling information that needs to be brought forward to bring the debate about cervical manipulations onto a level playing field pertains to the fact that a significant number and most likely the majority of VADs happen to be spontaneous cervical artery dissection (sCADs). As demonstrated in numerous reports addressing 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.

Prevalence:

As shown in **Attachment 3**, the annual incidence of spontaneous VADs in hospital settings has been estimated to occur at the rate of 1-1.5 per 100,000 patients.[54] The corresponding VAD incidence rate in community settings has been reported to be twice as high.[55,56] Using an estimated

value of 10 from the literature to represent an average number of manipulations per patient per episode,[61] it becomes apparent that the proposed exposure rate for CVAs attributed to spinal manipulation is equivalent to the spontaneous rates for cervical arterial dissections as reported.[54-56] 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.

Association of homocysteine and arterial fragility:
For over 30 years, the amino acid homocysteine has been implicated as a key component of atherosclerotic disease.[62-70] More direct observations point toward the disruption of the structures 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.[71]

2. Homocysteine activates metalloproteinases[71] and serine elastases,[72] 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.[71,72]

3. Homocysteine has been shown to block aldehydic groups in elastin, inhibiting the cross-linking needed to stabilize elastin.[73]

4. The cross-linking of collagen may also be impaired by homocysteine.[74]

5. Experimentally elevated levels of homocysteine produce patchy desquamation of 10% of the aortic surface in baboons.[68]

6. Endothelium-dependent and flow-mediated vascular dilation is impaired in individuals with elevated levels of homocysteine.[70]

7. In cell culture experiments, addition of homocysteine into the medium induces cell detachment from the endothelial cell monolayer.[75]

Yet even a tighter coupling between sCADs and increased amounts of homocysteine have been shown 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.[76]

2. Cervical artery dissection (CAD) patients yield average homocysteine levels of 17.9 micromoles/L while asymptomatic patients report an average of 6.0 micromoles/L.[77]

3. Homocysteine levels exceeding 10.2 micromoles/L are associated with a doubling of vascular risk.[78]

4. A genetic defect in humans involving tetrahydrofolate reductase, the enzyme which produces the methyl-donating cofactor required to convert homocysteine to methionine, is associated with elevations in the rates of sCADs.[76] This metabolic block would be expected to cause homocysteine to accumulate intracellularly.[79]

The striking association of homocysteine with sCAD raises the possibility that a relatively simple diagnostic test is at hand for determining patients at risk for sCAD and who would accordingly be advised to avoid cervical manipulation. Until recently, the gold standard methodology for determining plasma homocysteine has been high pressure liquid chromatography, gas chromatography, and mass spectrometry.[80-82] Fortunately, this cumbersome technology has recently been correlated with a much simpler enzyme conversion immunoassay (EIA).[83] An even more rapid assay method by means of an automated analyzer is also available, requiring only microliter amounts of reagent and sample.[84] This essentially means that homocysteine levels can be determined in any number of clinical reference laboratories already established to measure

blood analytes.

To date, the assessment options for vertebrobasilar artery risk each have significant drawbacks and as a whole have been unable to identify any particular factor that is useful for screening.[85,86] Provocation tests in particular are problematic in that in several aspects they replicate the risks associated with cervical manipulation by requiring the placement of the head and neck in extreme extension and rotation[87] False negative findings compared to angiograms have been reported;[88] reliability and validity have not been reliably tested;[85] and the suggestion has been made that these tests be de-emphasized.[89] In the midst of this disorder, determining homocysteine levels as a predictor of arterial fragility seems to be a plausible, rapid and inexpensive procedure that is no more invasive than a routine blood glucose determination.

CONCLUSIONS:

Thus it would appear that the tearing of the arterial wall in a dissection is both *cumulative* and *spontaneous*: cumulative in that repeated, low-grade insults to the artery would most likely be required to yield a dissection; and spontaneous in that these more minor impositions occur by dint of any number of self-imposed maneuvers as well as any by a practitioner—making it extremely difficult if not impossible to distinguish between the two. Finally, spontaneous dissections appear to correlate with the fragility of the arterial wall, which may be attributable to inborn errors of metabolism and may be detectable by means of a homocysteine assay.

Regarding those studies mentioned above which appear to discredit the wisdom of cervical manipulation,[1-6] there appear to be a number of common fallacies: (i) They fail to disclose that the majority of vertebrovasilar accidents (VBAs) are spontaneous, cumulative, or caused by factors other than spinal manipulation; (ii) They fail to disclose the potential benefits of the procedure, violating medicine's own ethic of accurately reporting true *risk-benefit ratios*; (iii) They fail to place the risks of manipulation in the context of those produced by other medical treatments or lifestyle activities; (iv) They fail to indicate the actual frequency of manipulations administered; (v) They fail to account for the possibility that patients undergoing CVAs are reported more than once; (vi) They fail to report the rates of CVAs following manipulation by parties *other* than licensed chiropractors; and (vii) They incorrectly assume that patients undergoing adverse events

following a manipulation might not have reported such instances to either the attending chiropractor or an appropriate authority.

Many signs point to intrinsic aberrations of arterial structure underlying CVAs, many brought on by elevated levels of homocysteine. When applied to cervical manipulations, the body of evidence outlined in this discussion suggests that the inherent fragility of the arterial wall of the cerebrovascular system rather than any trauma associated with maneuvers by the attending physician is the major culprit regarding arterial dissections. The determination of homocysteine levels as a clinical tool would appear to afford the chiropractic physician a means to bring the actual risks of CVAs to even lower levels than those previously reported. In this regard, homocysteine determinations currently appear to be the most plausible means for assessing patients who are most at risk for experiencing CVAs from routine activities, let alone from cervical manipulations. (With regard to the topics of spontaneous vertebral artery dissections and the possible role of homocysteine as a proposed indicator of patients at risk, I have published more detailed presentations elsewhere.[91,92])

The actual risk of CVAs that can be directly attributable to spinal manipulation may be reduced to far less conspicuous levels when compared to everyday lifestyle risks and those brought on by medical treatments widely accepted by the public. Certainly the propagation of risk estimates attributable to visits to the chiropractor's office without adequate justification from data does not perform a useful service to the public; indeed, it does just the opposite. CVAs have been listed as only the *fifth* most common cause of chiropractic malpractice lawsuits, an unlikely ranking if chiropractors were conclusively found at fault for the majority of CVAs reported. [90]

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ATTACHMENT 1:

NONMANIPULATIVE MANEUVERS ASSOCIATED WITH CVAS[38]

Childbirth
By surgeon or anesthetist during surgery
Calisthenics
Yoga
Overhead work
Neck extension during radiography
Neck extension for a bleeding nose
Turning the head while driving a vehicle
Archery
Wrestling
Emergency resuscitation
Star gazing
Sleeping position
Swimming
Rap dancing
Fitness exercise
Beauty parlor stroke
Tai Chi

ATTACHMENT 2:

VOLUNTARY RISKS[51]

Voluntary Risk	RISK OF DEATH/PERSON/YEAR
Smoking: 20 cigarettes/day	1 in 200
Drinking: 1 bottle of wine/day	1 in 13,300
Soccer, football	1 in 25,500
Automobile racing	1 in 1,000
Automobile driving (United Kingdom)	1 in 5,900
Motorcycling	1 in 50
Rock climbing	1 in 7,150
Taking contraceptive pills	1 in 5,000
Power boating	1 in 5,900
Canoeing	1 in 100,000
Horse racing	1 in 740
Amateur boxing	1 in 2 million
Professional boxing	1 in 14,300
Skiing	1 in 4,350
Pregnancy (United Kingdom)	1 in 4,350
Abortion: legal <12 wk	1 in 50,000
Abortion: legal >14 wk	1 in 5,000

ATTACHMENT 3:

RATES OF STROKE COMPARED TO INCIDENCE OF ARTERIAL DISSECTIONS

ATTRIBUTED CAUSE	RATE (PER MILLION)
Spontaneous, hospital-based[54]	10-15
Spontaneous, community-based[55,56]	25-30
Cervical manipulation[57]	25
Cervical manipulation[58]	10-20*
Cervical manipulation[59]	0
Cervical manipulation[34]	6.4*
Cervical manipulation[60]	1.7*

*Corrected to represent the average incidence per patient, assuming the average number of manipulations per patient to equal 10, as reported in the literature.[61]

