

SECOND MOMENT CONSULTING

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9 February 2005

CUPRON STUDY

I was asked to analyze the effectiveness of Renfro Cupron® socks upon a variety of podiatric conditions: erythema, itching and burning, scaling, vesicular eruptions, fissuring, drainage, odor and edema. One group of patients was studied; the results were compared to the experience the podiatrist had with patients with similar conditions who were not treated with Cupron® socks.

RESULTS:

The following results are all considered statistically significant, meaning that there is credible medical evidence that Cupron® treatment is effective in the period of follow up studied, since the confidence interval of all the results did not include 0 and the p-values for all results were <0.001.

Demographics:

There were 56 patients in all, 17 women and 39 men. Average age of the group was 58 with a standard deviation of 16 years (range 21-85 years). Twenty-one (21) were diabetic, 21 were older than 65, and 24 were followed more than one time.

Variables:

Seven measures were studied: erythema, burning and itching, edema, scaling, vesicular eruptions, fissuring, drainage and odor. Only scaling was present in all 56 patients, with erythema in 51 (see table). Edema (6), Odor (5), and drainage (3) were the least common variables. "Long range follow-up referred to having been evaluated more than one time after use of the socks. There was a three level ordinal scale used: present, improvement, and resolved. Movement along this scale (from "present" to "improved" or from either of the first two to "resolved") was considered a positive sign, movement the other way (from "improved" to "present") considered a negative sign. If a patient was considered resolved on the first visit after wearing the socks, that individual could at best be scored a "same" for long-term follow-up. Therefore, "same" could be equally considered to be "holding improvement". The average length of time in the long term section was defined as being the time between the first visit and the date when the last comment was made about the patient. Only patients who had a specific problem at the outset of the study were counted later. In no instance, did a patient who had no specific problem develop one. In the instances of edema, odor, and drainage, the sample sizes were too small to draw any conclusions, although the results were tabulated.

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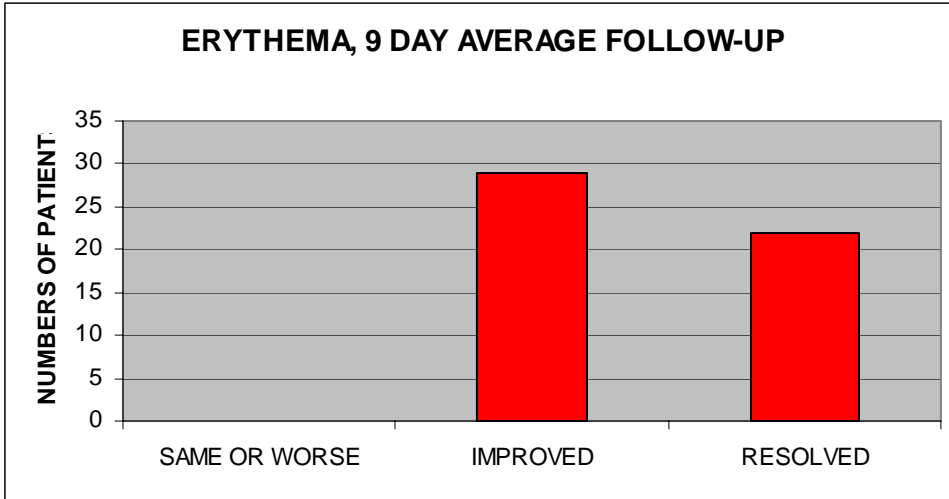
σ^2

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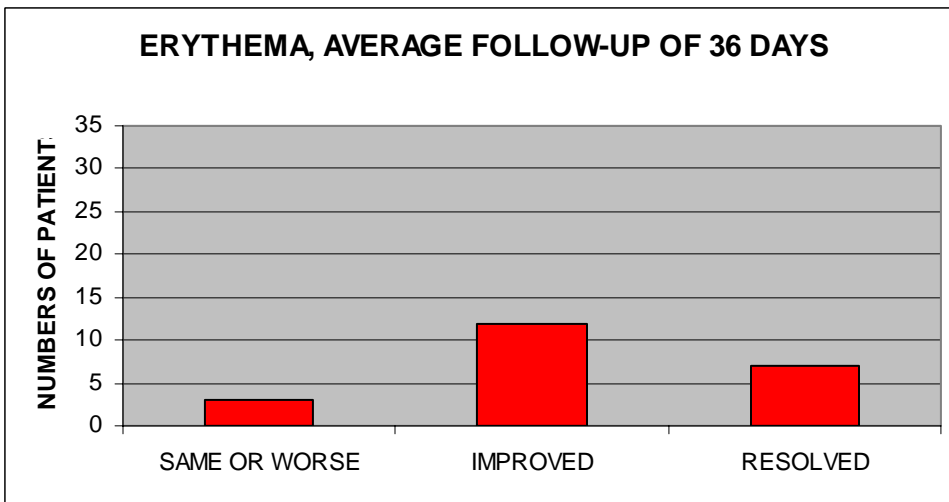
A. ERYTHEMA (51 patients):

All 51 patients improved; 22 (42%) resolved completely over an average period of 9 days (range 4-28 days). The 95% confidence interval for resolution was (0.29, 0.58). This result means that while we don't know the per cent of complete resolution for the entire population (the parameter), we are highly confident it lies in the interval between 29% and 58%. If we know in advance that no patient would normally improve without other treatments in this time frame, than the results obtained are highly significant; that is, not due to chance.



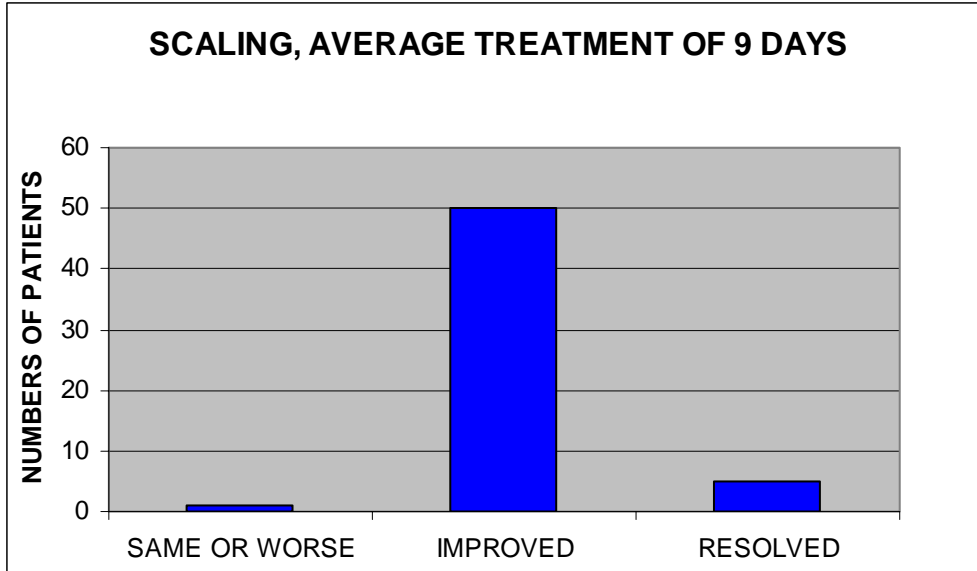
A1. Longer term study (22 patients):

Nineteen (86%) maintained their improvement or resolved, 95% CI (0.65, 0.97). Three patients (14%) did not maintain improvement or reverted to "present", 95% CI (0.03, 0.34). The average length of follow-up was 36 days. Diabetics and patients older than 65 shared in the improvement, both early and long-term.



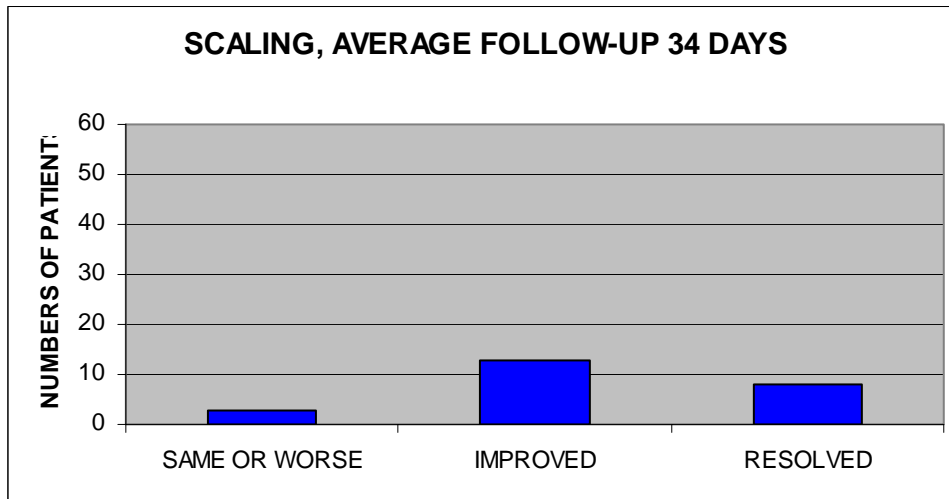
B. SCALING (56 patients):

Fifty-five (55) of the 56 improved (98%), 5 resolved (9%), and 1 stayed the same. The 95% confidence interval for some improvement is (0.90, 1.00); for resolution (0.03, 0.20). Both of the p-values are highly significant for efficacy.



B1. Longer term study (24 patients):

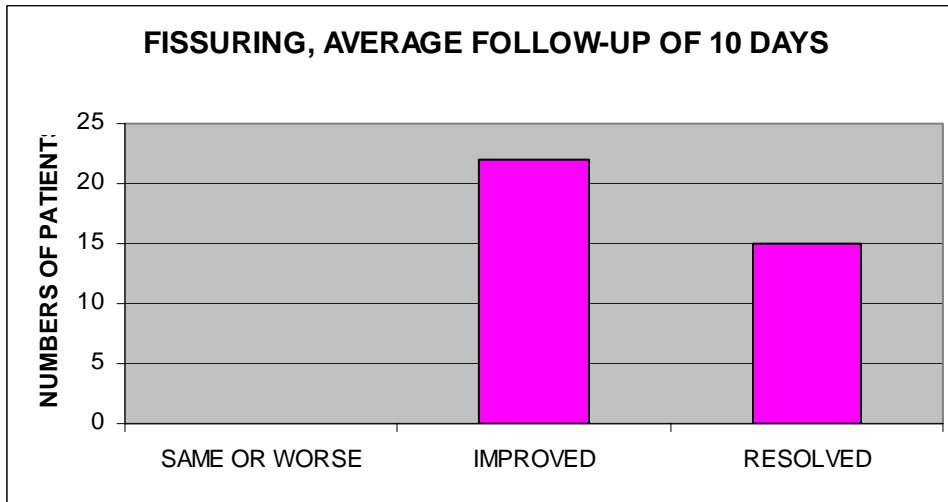
Twenty-one (88%) held improvement or resolved, 3 reverted with an average follow-up of 34 days. The 95% confidence interval is (0.68, 0.97) with a p-value <0.001. Again, diabetics and elderly shared in the improvement.



Note: the follow-up graph has the same scale as the former graph to facilitate comparison.

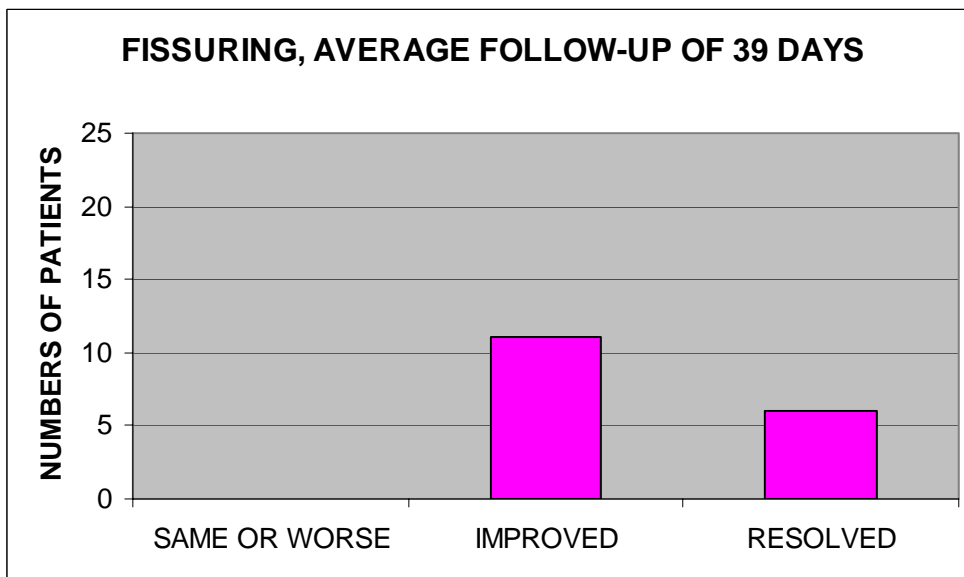
C.FISSURING (37 patients):

All 37 patients improved; 15 (40%) resolved completely with an average follow-up of 10 days, 95% CI (0.25, 0.58). This is highly significant.



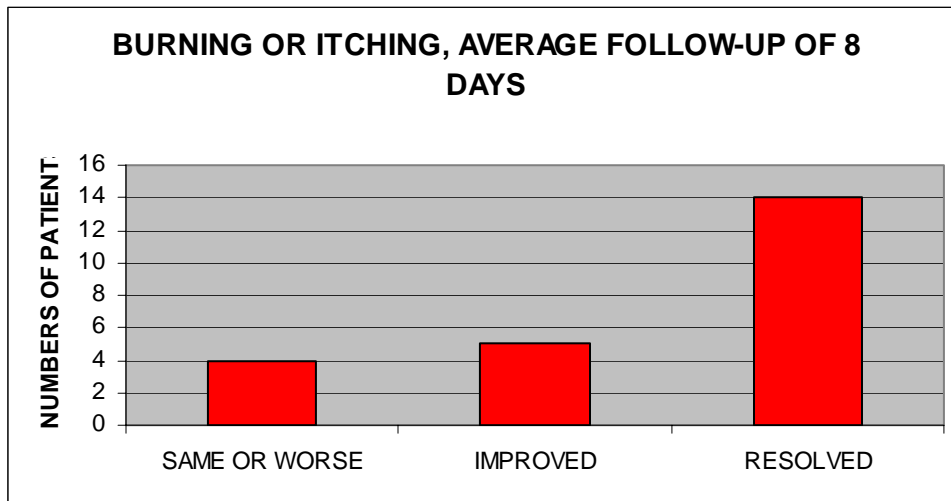
C1. Longer term study (17 patients):

All 17 patients improved, 6 (35%) resolved completely in an average follow-up of 39 days, 95% CI (0.14, 0.62). Again, diabetics and elderly shared in the improvement.



D. BURNING OR ITCHING (23 patients):

Nineteen of the 23 improved (83%), four stayed the same or reverted in the average follow-up period of 8 days. The 95% confidence interval is (0.61, 0.95) with a p-value of 0.003, again highly significant.

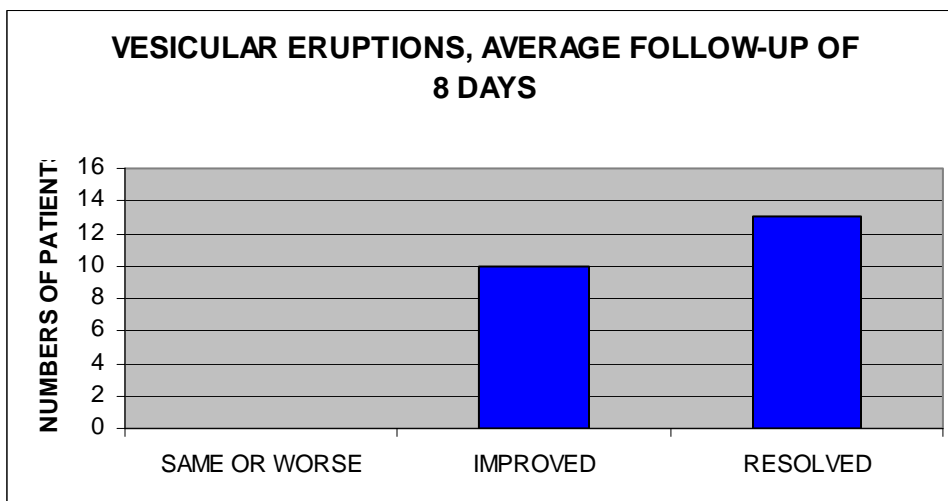


D1. Longer term study (8 patients):

All 8 patients were unchanged over an average follow-up of 46 days, meaning that their initial improvement was maintained. The numbers were too small to study diabetics and elderly.

E. VESICULAR ERUPTIONS (23 patients):

All 23 patients improved; 13 (56%) resolved completely, 95% CI (0.34, 0.76).



E1. Longer term study (10 patients):

All 10 patients maintained their improvement or resolved (6) over an average follow-up of 45 days. The proportions were similar for both diabetics and patients over the age of 65.

F. EDEMA (6), DRAINAGE (3), AND ODOR (5):

Three patients with edema improved; 1 resolved. All three patients with drainage improved; 2 resolved. Three of the five patients with odor improved; two of them resolved.

The attached table summarizes the data. Again, the statement “worse” means that the patient went from “resolved” or “improved” to “present”.

DISCUSSION:

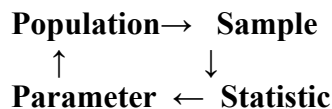
The purpose of the study was to see if patients with a variety of podiatric ailments would improve only by wearing Cupron® socks. One issue in the treatment of the above conditions is compliance in obtaining and using the treatment (special socks). A related issue is the proper application of treatment (special socks) on the plantar aspect of the feet and in the interdigital areas.

1. I assumed the following in the analysis of the data provided:
 - a. The patients were a reasonable, representative sample of the population of patients with these conditions. There was no information received that would contradict this assumption. There were men, women, elderly, young, diabetic, and non-diabetic patients.
 - b. The patients were independent of one another; that is, the selection of one individual had no effect upon the selection of another.
 - c. The definitions of improvement and resolution were constant for each patient.
 - d. The sample size was known and appropriate to perform analysis.
 - e. Outcomes could be defined as dichotomous.The presence of these assumptions allowed a binomial probability distribution to be used.

2. There was no control group reported; however, I received information stating that the podiatrist believed it unlikely that any patient would have resolved or improved in the time frame of the study only by wearing his or her regular socks. Given such information, all of the above results, would be considered statistically significant, meaning that there is medical evidence that Cupron® treatment is effective in this period of follow-up.

It is important to understand the vocabulary used in describing the study:

- *Population*: the group about which one wishes to learn. In this instance, the population are all patients with the above listed foot conditions.
- *Sample*: a subset of a population.
- *Random sample*: A subset chosen where each member of the population has a defined, non-zero probability of being chosen.
- *Parameter*: a numerical measure of the population.
- *Statistic*: a numerical measure of the sample.
- *p-value*: the probability that we would obtain the specific sample statistic (or one more extreme) if the null hypothesis (hypothesis of no change) were true. In the context of this study, a p-value of less than 0.001 means that the probability of obtaining these results by chance alone is less than 1 in 1000. Typically, 1 in 20 is considered the “cut-off” point. Minitab software does not compute p-values to four decimal places, so many of the values obtained here are even smaller.
- A *confidence interval* contains a range of plausible values for the parameter. We call it a confidence interval, because while unknown, the parameter does exist, and the interval either contains or does not contain the parameter. It is NOT a probability question. **For this study, if we assume that no patient would improve in the time frame studied with conventional treatment then so long as the interval does not contain 0, the results are significant, since no plausible value of the parameter is 0. If some other proportion were postulated for improvement, then any interval that did not contain that particular value would be considered significant. In this study, with the above information, all areas reached statistical significance.**
- *Circle of inference*: We sample from a population, obtain a result (a statistic), and use that value to infer something about a parameter which is part of a population.



It is important to recognize that we can seldom identify all members of a population, so that its numerical measure, a parameter, remains unknown.

For this study, since we cannot know all members of the population, the result of the sample, the proportion improved (or resolved), is used to say a similar proportion of the population would be improved as well. If the sample is appropriately chosen, then the estimate has value. We must realize, of course, that other samples would lead to other results, so that there is a *range* of plausible values that samples could conceivably have, and our sample result was one of those potential values, as described above.

CONCLUSION:

Compared to historical controls, patients with Cupron ® socks had significant improvement or resolution in the following conditions:

Erythema	Vesicular eruptions
Burning/itching	Fissures
Scaling	Drainage
Edema	Odor

Moreover, since nearly 40% (19 of 51) of the group was either diabetic or older than 65 (10 were both diabetic and older than 65), this study is statistically significant for improvement or resolved for all the above conditions for people with diabetes, including elderly diabetics.

Michael S. Smith, MD MS

SUMMARY AND AUTHOR'S BACKGROUND

Michael S. Smith is a board certified neurologist with a Master's Degree in Experimental Statistics. He practiced neurology for 17 years, was medical director of St. Mary's Hospital (Tucson) for 5 years and Senior Medical Director (Quality) for Carondelet Health Network in 1998.

CURRICULUM VITAE

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PLACE AND DATE OF BIRTH: Berkeley, California 5 December 1948

EDUCATION:

1966-1970	Dartmouth College, Hanover, NH A.B. Chemistry (<i>Summa cum laude</i>)
1970-1974	University of Colorado Medical School, Denver M.D. (<i>Magna cum laude</i>)
1998-2000	New Mexico State University, Las Cruces, NM, M.S. (Experimental Statistics)

ACADEMIC HONORS:

Phi Beta Kappa, Alpha of New Hampshire, 1969

Honorable Mention, Chemical and Engineering News, 1970 Merit
Award Program

Highest Distinction in Chemistry (1970)

Lange Book Awards, 1972-73; 1973-74

Alpha Omega Alpha, 1973

Merck Book Award, 1974

INTERNSHIP: 1974-1975: Intern, Medicine, Presbyterian Medical Center,
Denver

RESIDENCY: 1977-1980: Neurology, University of Arizona, Tucson.
1979-1980: Chief Resident in Neurology

POSITIONS:

1979-1981:	Assistant Professor, Department of Neurology, University of Arizona
1981-1990:	Adjunct Associate Professor of Neurology, University of Arizona
1981-1992:	Member, Neurological Associates of Tucson
1986-1991:	President, Neurological Associates of Tucson
1992-1998:	Medical Director, St. Mary's Hospital, Tucson, AZ
1995-1998:	Medical Director, Holy Family Center, Tucson, AZ
1998	: Senior Medical Director (Quality) Carondelet Health Network, Tucson AZ
1999-Present	Consultant in quality, statistics, and process improvement (Second Moment Consulting)

MILITARY SERVICE RECORD

1971-1975 Ensign, Lieutenant (j.g.), U.S. Naval Reserve Unit
49-28, Denver, CO
1975-1977 Lieutenant, Medical Corps, U.S. Naval Reserve
1975-1977 Medical Officer, USS St. Louis (LKA-116)
1976-1977 Medical Officer, Amphibious Squadron SEVEN
5 July 1977 Honorable Discharge

MEMBERSHIP IN PROFESSIONAL SOCIETIES

American Academy of Neurology (1978-2004), Fellow (1992)
Pima County Medical Society (1981)
Board Member, 1994-97, 1999-2003.
Secretary-treasurer, 2003-
Rose Marie Malone Award for service to organized
medicine, 2004.
Arizona Medical Association (1981-2003)
Southern District Director, 1995-1997, 2000-2001, Vice-
President, 1997-1998, Secretary, 2001-2002, Treasurer,
2002-2003.
American Statistical Association (1998)

LICENSURE AND CERTIFICATION

National Board of Medical Examiners (139770), July 1975
Arizona (9813), April 1977
New Mexico (83-303), November 1983
American Board of Psychiatry and Neurology (23519), April 1982
Fellow, American Academy of Neurology (1992)
Graduate, Advanced Training Program (ATP) of Intermountain
Health Care, Salt Lake City, Class 9, August-December 1996

VOLUNTEER SERVICE

Volunteer, U.S. Forest Service, Kawishiwi Ranger District,
Superior National Forest, Ely, Minnesota, 1 June-15
October 1992.
Volunteer Service 1993-1997, 1999.
Adopt a Highway, Miles 38-40, Az Rte. 83, 1992-present (solo).
Tutor (math) Sabino HS and Canyon del Oro HS, 2003-.

NON-MEDICAL ASSOCIATIONS

Tucson Amateur Astronomy Association, (1983); Chief Observer
1985-6.
American Association of Variable Star Observers, (1985).
International Occultation Timing Association, (1988).

COLUMNIST, ARIZONA DAILY STAR (morning) for amateur astronomy: *UNDER DARK SKIES*: November 1984-September 1990 (weekly), September 1990-April 1999, (biweekly), April 1999-August 2004 (weekly).

Editor, AAVSO Photoelectric Photometry Journal, 1994-1995.

Columnist, Sombrero (Pima County Medical Society Journal), *Reality Check*, 2003-.

TEACHING:

University of Arizona, Neurology 803 (Clinical Instruction to Undergraduate Medical Students), 1977-1981.

Neuroscience teaching to first year medical students, 1981-1988

Neuro-ophthalmology teaching to third year medical students, 1981-90.

New Mexico State, Experimental Statistics 251, Spring, Fall 1999, Spring 2000.

Pima Community College, Tucson, Math 167/Business 205 (Statistics), Fall 2000.

University of Phoenix, Instructor, Statistics, May, 2001-Present.

Reader, AP Statistics Examinations, Lincoln, NE, 2003-2004.

WRITING HONORS:

Honorable mention, Writer's Digest, Feature Article contest, 2003. ("Lunar Phases for Writers and Editors," 17th place, 1800 entries)

Winner, Creative Expression Award ("A Wise Owl"), American Academy of Neurology, 2003 (presented at the 56th annual meeting, 2004)

PRESENTATIONS:

Smith MS: The Solvolysis of Phenyl-substituted benzhydryl chlorides. NE Section of the American Chemical Society, MIT, Boston, 14 May 1970.

Smith MS, Laguna, JF: Upward Gaze Paralysis after Unilateral Pretectal Infarction: CT correlation. Fifth Annual Rocky Mountain Neuro-ophthalmology course, Jackson, WY, 15 February 1979.

Smith MS, Buchsbaum, HW, Masland, WS: One and a Half Syndrome: Report of a case with CT correlation. Fifth Annual Rocky Mountain Neuro-ophthalmology course, Jackson, WY, 15 February 1979.

Angevine JB, Jr., Smith MS: Recent Advances in Forebrain Anatomy. Barrow Neurological Institute, Phoenix, AZ, 7 February 1980.

Smith MS: Total vertical gaze paralysis with normal mental function. Sixth Annual Rocky Mountain Neuro-ophthalmology course, Santa Fe, NM, 22 February 1980.

Smith MS, Angevine, JB, Jr., Sibley, WA: Total vertical gaze paralysis with normal mental function. Ether Dome, Massachusetts General Hospital, Boston, MA, 7 September 1980.

REVIEWER: American Association of Physicians and Surgeons (2003-).

BIBLIOGRAPHY

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3. Smith MS. Making averaging easier. *The Arithmetic Teacher* 29(4): 40-41, December 1981.
4. Smith MS. The Naval Officer/Medical Officer Quandary. *U.S. Naval Institute Proceedings*, September 1979, pp. 42-45.
5. Smith MS, Laguna JF. Neurological Complications of Infectious Mononucleosis, *Ariz Med* 36: 442-44, 1979.
6. Labadie EF, Smith MS. Tentorial Meningioma: Diagnosis by Coronal Plane Computed Tomography. *Ariz Med* 36: 594-95, 1979.
7. Smith MS, Buchsbaum HW, Masland WS. One and a Half Syndrome: Occurrence after Trauma with CT Correlation. *Arch Neur* 37: 251, 1980.
8. Bamford CR, Smith MS, Sibley WA. Horner's Syndrome. An Unusual Manifestation of Multiple Sclerosis. *Can J Neuro Sci* 7: 65-66, 1980.
9. Laguna JF, Smith MS. Aberrant Regeneration in Idiopathic Oculomotor Palsy. *J Neurosurg* 52: 854-56, 1980.
10. Smith MS. CT Use Statistics in a Community Hospital. *Ariz Med* 37: 340-42, 1980.
11. Smith MS, Laguna JF. Upward Gaze Paralysis after Unilateral Pretectal Infarction: CT Correlation. *Arch Neur* 38: 127-29, 1981.
12. Smith MS, Laguna JF. Confusion, Dysphasia, and Asterixis Following Metrizamide Myelography. *Can J Neuro Sci* 7: 309-11, 1980.

13. Angevine, JB, Jr., Smith MS. Recent Advances in Forebrain Anatomy and Their Clinical Correlates. In: *New Perspectives in Cerebral Localization*. RA Thompson, ed. Raven Press, New York, 1981, pp. 1-21.
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16. Rothrock JF, Smith MS. Wernicke's Encephalopathy Following Gastric Stapling. *J Clin Neuro-ophth* 1: 195-98, 1981.
17. Oommen, KJ, Smith MS, Labadie EL. Pontine Hemorrhage Causing One and a Half Syndrome with Facial Paralysis. *J Clin neuro-ophth* 2: 129-32, 1982.
18. Smith MS. How to Teach (and learn) Astronomy? Write a Column! *Astronomy* 15(2), 26-28, 1987.
19. Smith MS. Getting Sued Kept Me in Medicine. *Medical Economics*, December 1987.
20. Smith MS. A Beginner's story: Do These Mistakes Sound Familiar? *Intl Amat-Prof Photometry Comm*. No. 44, 40-41, June 1991.
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22. Sibley WA, Bamford CR, Clark K, Smith MS, Laguna JF: A Prospective Study of Physical Trauma and Multiple Sclerosis. *J Neur Neurosurg Psych* 54: 584-89, 1991.
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24. Percy JR, Wong, N, Smith MS, and 15 others. Photometric Surveys of Suspected Small-Amplitude Red Variables. III. An AAVSO Photometric Photometry Survey, *Astr. Soc. Pac*, 106:611-615, 1994.
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38. Smith, MS. We Don't Deserve Tort Reform, *Medical Economics*, October 10, 2003, pp. 71-72.
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