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## SIGNIFICANCE OF MULTIPLE INFERENCE TESTS

To the Editor:

A methodological issue that potentially confounds research findings arises in articles such as that by deGruy et al (*deGruy F, Crider J, Hashimi DK, et al: Somatization disorder in a university hospital. J Fam Pract 1987; 25:579-584*). Researchers are faced with the dilemma of deciding how many variables to include in a study. This dilemma in medical research is too often resolved in favor of having a relatively large number of study variables.

As the number of variables increases, so does the number of hypotheses that will be tested, either formally or implicitly.<sup>1</sup> Using the traditional .05 significance (probability) level, the researcher may have a false sense of security that there are only five chances out of 100 per hypothesis (variable) of asserting that there is a significant difference or association when the observed results are actually due to chance variation. In fact, the more hypotheses tested, the greater the probability of obtaining spurious significance (ie, false-positive results).<sup>1,2</sup>

Performing multiple inferential tests on study variables has been criticized for inflating the probability level used to test an hypothesis.<sup>1,2</sup> In the case of the deGruy et al article, the 16 separate statistical tests of study variables yield a maximum probability level inflated to .55 (1 to .95), if study variables are assumed to be uncorrelated.<sup>1,2</sup> Thus, there would be 55 chances out of 100 that at least one of the statistical tests would be "significant" when in fact no difference or association existed between categories of somatization patients or

between these patients and matched controls. This problem may be resolved with the use of various multivariate statistical techniques or by a more parsimonious approach to variable inclusion.

Indeed, physicians in the clinical practice of medicine would hardly place faith in a diagnostic procedure that has a specificity of 55%. Researchers must therefore be aware of both the sensitivity and specificity of their statistical measures. The prudent use of statistical techniques enhances our understanding of the clinical aspects of family practice only to the extent that spurious results are not reported as meaningful.

William H. Replogle, PhD  
F. J. Eicke, EdD

Department of Family Medicine  
University of Mississippi Medical  
Center, Jackson

## References

1. Cohen J, Cohen C: Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. Hillsdale, NJ, Lawrence Erlbaum Associates, 1975, p 159
2. Hair JF, Anderson RE, Tatham RL: Multivariate Data Analysis with Readings. New York, Macmillan, 1987, p 150

*The preceding letter was referred to Dr deGruy, who responds as follows:*

Drs Replogle and Eicke point out that multiple inferential tests within a data set increase the likelihood of ascribing spurious significance to the results: I agree. This fact should cause us to seek alternative approaches; otherwise, we should interpret the results cautiously and in a particular way. They also point out that two alternatives are to select variables more parsimoniously and to use multivariate analytic techniques. Again, I

agree. These cogent observations provoke me to reflect on their application to this study.

In the past 10 years, the statistical literature has begun to devote more attention to the utility of multivariate analysis of categorical data; increasingly, researchers and statistical authorities are adopting these as the methods of choice, although a review of the papers published in *The Journal of Family Practice* for the previous 2 years reveals that these tests have not found their way into our literature.

The data that we presented in Table 1 could be analyzed using log linear analysis; this method is certainly an elegant and valid way of describing significant "predictors" of somatization disorder. It was not used in this study for three reasons: it produces results similar to those published, it would require an additional table to describe the distribution of the study sample, and the results are less understandable to the general readership. Perhaps I underestimate the readership. As to limiting the number of variables, one could hardly argue here for omission, as those variables shown represent only the most basic demographic description of this sample.

Table 2, on the other hand, does not lend itself well to multivariate analysis but could contain fewer variables. Note that these variables are conceptually related to one another; in fact, they display high multicollinearity and therefore raise the overall probability of a chance significant finding much less than if they were independent. It is their lack of significance that is significant here. This panel of variables was intentionally made inclusive because they say something collectively beyond their individual (lack of) significance. This table says, "there are many ways to

see that these patients' hospital experience was similar." I acknowledge that there are other ways to demonstrate this finding.

How then might one interpret a study with many univariate comparisons?

1. Regard all findings as tentative until they are corroborated.

2. Consider the actual *P* values. Significance at the .001 level is much less likely to be due to chance, even in the context of 32 independent comparisons, than significance at the .05 level standing as an isolated comparison.

3. Consider the pattern of findings. A clinical analog to our study might be a serum chemistry panel, wherein 16 separate determinations are made on a blood sample. If the normal range is defined as that within which 95% of the population falls, then if one assumes normal, independent distribution of values on these determinations, there is a 55% likelihood that a well person will have at least one test in the abnormal range. Such an isolated abnormality would be properly regarded with skepticism. One would lose a great deal of information, however, by concluding only that a chemistry panel with such characteristics has a specificity of 45%. If a subset of related tests within this panel, such as the liver function tests, were largely abnormal (as in Table 1), or altogether normal (as in Table 2), then one might draw inferences about the condition of the liver with somewhat more assurance.

But I do not wish to distract from the important point made by Drs Rople and Eicke that the practice of performing multiple inferential tests in a single study renders the results difficult to interpret. I believe they are correct in admonishing us to avoid this practice when possible. I anticipate that multivariate analysis of categorical data will soon become standard practice in our clinical literature.

Frank deGruy, MD, MSFM  
Department of Family Practice  
University of South Alabama  
Mobile

## OFFICE PROCEDURES

To the Editor:

The commentary by Drs Ruane and Hudson deserves commendation for the skillful articulation of extremely complicated issues.<sup>1</sup> The endometrial sampling example may have many interpretations, but when these authors state, "We would interpret this finding as evidence that most family physicians have found that including this procedure in their practices does not add materially to the quality of the care their patients receive," I feel that they have looked at the half-full glass and found it empty.

An alternative interpretation might be that we have "a lost generation" of family physicians who cannot perform simple diagnostic procedures in the office. An 11% skill prevalence may be predictable given that comprehensive office-based training has been an educational orphan.<sup>2</sup> Even the family physicians in the study by Rosenthal et al utilized equipment and techniques that do not reflect the current state-of-the-art improvements. The Vabra aspirator requires special suction equipment. The Novak curette can be replaced by the Unimar pipelle, which is less traumatic. This 3.1-mm soft plastic instrument requires no suction equipment, and it has almost eliminated failed procedures resulting from cervical stenosis.<sup>3,4</sup> Paraphrasing Ruane and Hudson slightly, I would suggest that flexible sigmoidoscopy, colposcopy, and obstetric ultrasound are highly effective procedures that assist in placing primary diagnostic data into the hands of the primary care physician. The atrophy of procedures in the office (and subsequent fragmentation of health care) has been at least partially the result of our blind faith in subspecialist medicine. An equal contribution to this problem of procedural skill atrophy has been an overworked and understaffed residency faculty. Flexible sigmoidoscopy was an example for which procedural costs were dramatically reduced in comparison with subspecialists' fees.<sup>5,6</sup>

Since our specialty is one of breadth, our claim for patient care excellence must be supported by the use of simple and safe diagnostic procedures in the office. Why should we remain in diagnostic darkness?

Wm. MacMillan Rodney, MD  
Department of Family Medicine  
University of Tennessee  
Memphis

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- Rodney WM, Richards E, Morrison JD, Ounanian LL: Constraints on the performance of minor surgery by family physicians: Study of a "mock" skin biopsy procedure. *Fam Pract* 1987; 4:36-40
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- Rodney WM, Felmar E: Why flexible sigmoidoscopy instead of rigid sigmoidoscopy? *J Fam Pract* 1984; 19:471-476
- Rodney WM: Procedural skills in flexible sigmoidoscopy and colonoscopy for the family physician. *Prim Care* 1988; 15(1):79-91

*The preceding letter was referred to Drs Ruane and Hudson, who respond as follows:*

Doctor Rodney's comments are well taken. Clinical care in our office includes flexible sigmoidoscopy, endometrial biopsy, and many other diagnostic and therapeutic services. We support family physicians performing procedures that enhance patient care. Further, we believe that good research by family physicians in the family practice office can better establish reasonable and cost-effective strategies for management of many problems than have been promulgated by organ system or procedural specialists. Our point is that we must critically examine the evidence that the procedure will enhance the health of our patients. Criteria promulgated by Frame<sup>1</sup> in his review of screening procedures provide an excellent framework for such analysis.

As performing procedures has enriched our colleagues, we need to face squarely the temptation that remunerative procedures present. Endometrial biopsy is not likely to be overused for financial gain, although the rate reported by some physicians seems to exceed that which would be expected using prudent indications. Another heavily promoted procedure, colposcopy, its variant "androscope,"<sup>2</sup> and the treatment programs that they seem to dictate have such potential. Their use as screening procedures should be critically evaluated both scientifically and economically.

In a recent report<sup>3</sup> the Centers for Disease Control noted the propensity for fatal cervical cancer to strike the poor and unscreened. They commented, "Thorough screening with the Pap test [once every three years would reduce cervical cancer mortality] by an estimated 70-95%." In the face of this information, we believe that family practice as a specialty should temper its enthusiasm for expensive and unproductive screening and treatment programs and focus on means of responding to real unmet needs.

*Thomas J. Ruane, MD  
James W. Hudson, MD, MPH  
Department of Family Practice  
Michigan State University  
East Lansing*

**MNEMONIC FOR CROUP SCORING**

To the Editor

I have devised the following mnemonic for croup scoring and added a couple of sources together for the scoring system itself. I hope it will be of help to your readers.

*Charles W. Webb, MD  
Owosso, Michigan*

**References**

1. Frame P: A critical review of adult health maintenance. Part 1: Prevention of atherosclerotic diseases. *J Fam Pract* 1986; 22: 341-346
2. Pfenninger JL: Androscope: A technique for examining men for condyloma. *J Fam Pract* 1989; 29:286-288
3. Chronic disease reports: Deaths from cervical cancer—United States, 1984-1986. *MMWR* 1989; 38:652

**OBSTETRIC PRIVILEGES IN FAMILY PRACTICE**

To the Editor:

In response to Dr Renfroe's comments (Letters to the Editor column, *J Fam Pract* 1989; 29, 607) on our article on obstetric privileges for family physicians, he is correct in noting a discrepancy in the annotations of the article, provided in the table of contents, and the data presented in the article itself. The annotation is misleading, but we cannot claim authorship of the synopsis.

Dr Renfroe also comments upon the unclear use of the "standardized normal Z-test" for the analysis of the data in the survey. He is correct in stating that the use of a chi-squared statistic to compare all of the regions simultaneously is adequate. However, that was not the purpose of our analysis.

We attempted to compare each region to any other one region by the use of the "boxes" used to compare any pair of statistics in the column. We believed this would allow the reader to compare the obstetric privileges of family physicians in any one region with the obstetric privileges of family physicians in any other one region.

*Gordon Schmittling  
Division of Research and  
Information Services  
American Academy of Family  
Physicians  
Kansas City, Missouri*

The Editor replies:

Dr Renfroe is quite correct in pointing out an inadvertent error in the annotations of the Table of Contents with reference to the paper by Schmittling and Tsou (*Obstetric privileges for family physicians: A national study. J Fam Pract* 1989; 29: 179-184) on obstetric privileges for family physicians. The authors are not responsible for this error, as the editorial staff prepares the annotations. In this instance the 90% figure for the survey population should have referred to hospital admitting privileges, not obstetric privileges as such (the figure for obstetric privileges was 28%). The editorial office regrets this oversight and thanks Dr Renfroe for his observant correction.

MNEMONIC FOR CROUP SCORING				
Mnemonic		Croup Score		
		0	+1	2+
Remain	<i>Retractions</i>	None	Supra or substernal; nasal flaring	Intercostal and nasal flaring
Calm	<i>Color</i>	Normal	Peripheral cyanosis	Generalized cyanosis
Coughing	<i>Cough</i>	None	Hoarse cry	Severe paroxysms; bark
Makes	<i>Mental Status</i>	Normal	Anxious, restless or obtunded	Delirious or comatose
Stridor	<i>Stridor</i>	None	Audible only when excited or with stethoscope (inspiratory)	Audible when quiet and without stethoscope (inspiratory or expiratory)
Appear	<i>Air Entry</i>	Normal	Decreased, harsh rhonchi	Delayed, minimal heard with stethoscope

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## PRESCRIPTION-WRITING ERRORS

To the Editor:

We read with interest "Prescription-Writing Patterns and Errors in a Family Medicine Residency Program" (*J Fam Pract* 1989; 29:290-295) by Shaughnessy and Nickel. They state, "No other studies of prescription-writing errors have been reported." We would like to bring to the attention of the readership another article published in the Journal entitled "Computerized Prescription Inventory Program for the Education of Residents (PIPER)."<sup>1</sup> Our study, very similar to the one described in this report, used carbonless copies of the prescriptions written by residents. A total of 1,273 prescriptions were collected. The number of prescriptions written per patient visit averaged 0.62, which was similar to the 0.69 reported by the authors. In reviewing these prescriptions, we found 6% of prescriptions did not meet the established criteria. Our criteria were more lenient than the criteria of Shaughnessy and Nickel. For example, a prescription written for a nonprescription product was not considered an error in our study.

The educational component of our study involved a written report to each resident who was monitored. This report provided a comparison for group discussions concerning the residents' prescribing habits. Residents individually received copies of the incomplete prescriptions for review. Recommendations for improvement were made to each resident by the faculty. Prior to the second collection of data, these recommendations were reiterated in writing. The major areas of counseling involved complete entry of data on the prescription blank, inappropriate generic prescribing, and appropriate use of alternative agents within a therapeutic class. Since the publication of our article, we have collected data on the effect of counseling on prescribing. Incomplete data entry on

the prescription blank decreased from 4.4% to 2.1%. Inappropriate generic prescribing of Lanoxin, Dilantin, and sustained released theophylline preparations decreased from 79% to 50%.

The most important counseling effort in our study was directed toward the appropriate use of agents within a therapeutic class. The residents were counseled on medications that are considered equal in efficacy but are lower in cost, administered less frequently, or have a more favorable side effect profile. The counseling has involved different medications for each resident but commonly has included nonsteroidal anti-inflammatory (NSAI) agents. The most frequent prescribed NSAI agents were naproxen and naproxen sodium. The residents were encouraged to prescribe the less expensive alternative ibuprofen. The ratio of prescriptions for naproxens to ibuprofen changed accordingly from 28:3 pre- to 6:36 postcounseling.

In their recently reported study, Shaughnessy and Nickel stated that these "data will be used as a baseline to evaluate a teaching method that will attempt to improve resident knowledge of medication costs." We would like to encourage them to continue with this very important study. We have found from experience that residents are quite amenable to this type of counseling. This may be the only place in their training that they will receive direct feedback on their prescribing.

Geraldine D. Anastasio, PharmD  
J. Lewis Sigmon, Jr., MD  
Department of Family Practice  
Charlotte Memorial Hospital and  
Medical Center, Inc  
Charlotte, North Carolina

### Reference

1. Anastasio GD, White TR, Fries JC: Computerized prescription inventory program for the education of residents (PIPER). *J Fam Pract* 1986; 23:598-600

**CARAFATE**<sup>®</sup>  
(sucralfate) 1gm Tablets

### BRIEF SUMMARY

#### CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

#### PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

**Drug Interactions:** Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be non-systemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

**Pregnancy:** Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children have not been established.

#### ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

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